Spatial Analysis of Ocular Dominance Patterns in Monocularly Deprived Cats

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Monocular deprivation during a critical period in postnatal development leads to a shift in functional and anatomical ocular dominance at the expense of the deprived eye. We analyzed the complete two-dimensional pattern of [^{3}H]proline-labeled afferents in primary visual cortex (area 17) of cats monocularly deprived of vision at eye opening. Substantial shrinkage of deprived eye territory in favor of the normal eye extended into optic disc and monocular segment representations. However, small domains of deprived eye afferents were distributed evenly over the entire visual field representation. Interestingly, normal and deprived eye afferents overlapped extensively in the ipsilateral and in the peripheral contralateral visual field representation of the deprived eye, so that ipsi- and contralateral ocular dominance patterns are not at all complementary. We suggest that this could be the result of both an earlier maturation of crossed versus uncrossed visual pathways and of a maturational gradient within area 17 leading to a lower vulnerability of the central visual field representation to monocular deprivation. Quantitative analysis, using a triangulation algorithm which confirmed previously described larger spacing of adjacent ocular dominance columns in strabismic cats, revealed no difference in spacing of ocular dominance domains in area 17 between monocularly deprived and normals cats. In addition, column spacing was very similar in the same animal and in littermates, indicating that the genetic influence on columnar layout is stronger than previously assumed.

Introduction

One of the classic examples for activity- and experience-dependent cortical development is the deprivation-induced reorganization of ocular dominance columns. When one eye of a kitten is closed during a critical period of early postnatal life and the visual cortex investigated a few months later, only very few cells can be driven by the deprived eye (Wiesel and Hubel, 1963; Hubel and Wiesel, 1970), so that the visual cortex appears almost entirely dominated by the open eye. Anatomical experiments using the transneuronal transport of [^{3}H]proline have provided additional insight into the deprivation-induced cortical wiring changes. When a cat is born, geniculocortical afferents serving the two eyes are overlapping in the input layer IV of primary visual cortex (area 17) and subsequently segregate into the adult pattern of ocular dominance columns (LeVay and Gilbert, 1976; LeVay *et al.*, 1978; Rathjen and Löwel, 2000; Crair *et al.*, 1998, 2001) between the second and fourth postnatal weeks. During the critical period starting around the third week of life, the pattern of ocular dominance columns is susceptible to activity- and experience-dependent modifications (Stryker, 1986, 1991). In monocularly deprived animals, the domains innervated by the open eye are wider than normal, whereas the domains representing the deprived eye are severely shrunken (Hubel *et al.*, 1977; Shatz and Stryker, 1978; Antonini and Stryker, 1993). Although ocular dominance patterns of monocularly deprived animals have been described (Shatz and Stryker, 1978; Mower *et al.*, 1985; Hata *et al.*, 2000) their layout in the entire visual field representation has not yet been analyzed in detail. We therefore reconstructed the overall two-dimensional pattern of ocular dominance columns in visual cortical flat-mounts of monocularly deprived cats by transneuronal labeling of afferents with [^{3}H]proline (Grafstein, 1971; Löwel and Singer, 1987). By comparing labeling patterns of both deprived and non-deprived eye domains we were able to describe as yet unknown differences in domain layout in different visual field representations.

What are the mechanisms governing the development of ocular dominance columns? It is generally assumed that the deprivation-induced reorganization of ocular dominance columns is driven by activity-dependent competition between the geniculocortical afferents of the two eyes (Stryker, 1986, 1991; Goodman and Shatz, 1993), whereby the temporal patterning of neuronal activity conveys the essential information (Stryker and Strickland, 1984). Whether competition can also change the initial columnar layout, i.e. the spacing of adjacent columns, or whether this is determined and maintained by activity-independent factors intrinsic to the cortex is still a matter of debate (Jones *et al.*, 1991). Larger than normal spacing in strabismic cats (Löwel, 1994) and in cats raised with alternating monocular occlusion (Tieman and Tumosa, 1997) suggested that the degree of correlation between activity patterns conveyed by the two eyes may influence periodicity as predicted by theoretical work (Goodhill, 1993; Goodhill and Löwel, 1995). Although this correlation could be reduced in monocularly deprived as compared to normal cats, it is less clear from a theoretical point of view whether this factor plays a role for their columnar layout (Goodhill and Willshaw, 1994; Goodhill and Löwel, 1995; Wolf *et al.*, 2000). We therefore complemented our qualitative description of the ocular dominance patterns with a quantitative analysis of pattern layout to decide this question empirically. In particular, using a two-dimensional, nearest-neighbor analysis for quantitative measurements, we assessed the spacing of deprived eye columns statistically and, for comparison, reference columns of normal and strabismic cats which have been published previously (Löwel and Singer, 1987, 1992, 1993a,b; Löwel, 1994; Schmidt *et al.*, 1997; Löwel *et al.*, 1998).

Materials and Methods

The present study is based on 17 cats from our institute's colony (see Table 1). Four cats from three different litters (MD1/MD2, MD3 and MD4) had one eye sutured before natural eye opening. In eight cats from five different litters (S1/S2, S3/S4, S5, S6, S7/S8), divergent strabismus was surgically induced at the age of 17–18 days. Five cats from three different litters (N1/N2, N3/N4, N5) were normally raised controls. At the age of 3–4 months, ocular dominance columns of four monocularly deprived (MD1, MD2, MD3, MD4), four strabismic (S3, S4, S7, S8) and two normally raised cats (N3, N4) were anatomically labeled by intraocular injections of the transneuronal tracer [^{3}H]proline (Grafstein, 1971; Löwel and Singer, 1987). In six strabismic and three normally raised cats, ocular

Cerebral Cortex Aug 2002;12:783–796; 1047–3211/02/$4.00

Table 1
List of all cats used in the quantitative analysis of ocular dominance columns

Cat	Hemisphere	Mean spillover ratio (%)	No. of sections	Age 1 (days)	Age 2 (days)	Weight (g)	Injected/ stimulated eye	Median distance (mm)	Length of area 17 (mm)
MD1	left, ipsi D	48	60	8	78	1150	proline in non-deprived right eye		38
	right, contra D	28	56					0.844	40
MD2	left, ipsi D	16	66	8	78	1250	proline in deprived left eye	0.883	40
	right, contra D	45	67					0.890	40
MD3	left, contra D	47	49[d]	10	112	1800	proline in deprived right eye	0.856	34
	right, ipsi D	28	57					0.860	35
MD4	left, contra D	40	57	9	98	1300	proline in deprived right eye	0.866	38
	right, ipsi D	25	59					0.875	36
N1[a]	left		60		67	850	stimulation right eye, 2-DG	0.915	40
	right		57					0.951	35
N2[a]	left		62		74	1080	stimulation left eye, 2-DG	0.934	40
	right		59					0.964	40
N3[a]	left		70		84	1200	proline in right eye	0.754	33
	right		65					0.758	33
N4[a]	left		58		84	1200	proline in right eye	0.718	32
	right		65					0.737	32
N5[b]	left		61		87	1150	stimulation right eye, 2-DG	0.849	37
	right		60					0.884	36
S1[a]	left		64	18	56	840	stimulation right eye, 2-DG	0.925	39
	right		58					1.002	38
S2[a]	left		65	18	91	1510	stimulation right eye, 2-DG	0.894	39
	right		59					0.930	39
S3[a]	right		60	18	60	980	proline in right eye	0.987	38
S4[a]	left		62	18	63	1000	proline in right eye	0.917	37
S5[a]	left		53	18	70	940	stimulation right eye, 2-DG	0.992	35
	right		52					0.988	34
S6[a]	left		54	18	70	1120	stimulation right eye, 2-DG	0.969	35
	right		56					1.015	
S7[c]	left		69	18	103	1160	proline in left eye	0.934	39
	right		64					0.870	39
S8[c]	left		58+	18	103	1450	proline in right eye	0.894	40
	right		60					0.875	39

MD, monocularly deprived cats; N, normally raised cats; S, strabismic cats. Animals labelled with [a], [b] and [c] have already been the subjects of previous publications [a]cats N2–N5 and S1–S6 from (Löwel, 1994); [b]cat CC from (Schmidt *et al.*, 1997); [c]cats BO1-2 from (Löwel *et al.*, 1998)]. Abbreviations: Cat, 'name' of the animal. Hemisphere, hemisphere used for the analysis of column spacing: contra D, hemisphere contralateral to the deprived eye; contra I, hemisphere contralateral to the injected eye. Mean spillover ratio, mean spillover ratio calculated from three values from different eccentricities. No. of sections, no. of cortical flat-mount sections; [d]last section still within grey matter (excluded from quantitative analyses). Age 1, age (in days) of the cats at the beginning of the experiment; age 2, age (in days) at the end of the experiment. Weight, body weight (in g) of the cats. Injected/stimulated eye, eye either receiving an injection of [^{3}H]proline or being stimulated visually during a 2-DG experiment. Median distance, median spacing between ocular dominance columns in area 17 as assessed by two-dimensional nearest neighbor analysis. Length of area 17, maximal anterior–posterior extension (in mm) of area 17.

dominance columns were functionally labeled with [^{14}C]2-deoxyglucose — 2-DG (Sokoloff *et al.*, 1977) — after monocular stimulation in both awake (S1–4, N1, N2, N5) and anesthetized and paralyzed conditions (S5, S6) (Löwel and Singer, 1993a,b). 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 for layer IV. Proline-labeled domains are restricted to cortical layer IV (LeVay and Gilbert, 1976), whereas 2-DG-labeled domains extend in columns through all cortical layers (Löwel and Singer, 1993b). All normal and strabismic cats have been subjects of previous studies (Löwel and Singer, 1987, 1992, 1993a, b; Löwel, 1994; Schmidt *et al.*, 1997; Löwel *et al.*, 1998).

Autoradiographic Labeling with [^{3}H]proline and [^{14}C]2-deoxyglucose

For all surgical procedures, a short-term anesthesia was induced with an i.m. injection of ketamine hydrochloride (15 mg/kg; Ketavet, Upjohn GmbH, Heppenheim) and xylazine hydrochloride (2.5 mg/kg; Rompun, Bayer, Leverkusen). All monocularly deprived (MD) cats had one eye sutured at the age of 8–10 days (the left eye in cats MD1 and 2; the right eye in cats MD3 and 4). To this end, the distal lid margins of this eye were excised and then sutured. A small opening at the medial canthus was left for drainage of wound secretion and application of antibiotic ointment (Gentamicin, Hoechst). In cats S1–S8, exotropic squint was induced at the age of 18 days, as previously described (Löwel and Singer, 1992; Schmidt *et al.*, 1997). For transneuronal labeling of ocular dominance columns cats received eye injections at ages between 2 and 4 months. Skin and sclera were incised beneath the upper bone margin of the orbit and some vitreous humor was aspirated with a syringe. [^{3}H]proline (2.5 mCi, sp. act. 93–95 Ci/mmol; Amersham, Braunschweig), dissolved in NaCl (50 µl), was injected with a Hamilton pipette into the non-deprived (right) eye of cat MD1 and into the deprived eye of cats MD2 (left), MD3 (right) and MD4 (right). Cats S3, S4, S8, N3 and N4 had their non-squinting or normal (right) eyes, cat S7 its squinting (left) eye injected. The cut was carefully closed with metal clips. After 12–14 days, the time the tracer needs for transneuronal transport from the retina to the visual cortex, the cats were anesthetized as described above and then given a lethal dose of i.p. pentobarbital (180 mg/kg; Nembutal, WDT, Hannover).

At age 2–3 months, cats S1–S4, N1, N2 and N5 had a venous catheter implanted into the humeral vein under mask anesthesia with a mixture of N_2O/O_2 (70%/30%) and halothane (1–2%) and one eye occluded with a black contact lens provided with additional black tape coverage (Löwel and Singer, 1993b). After full recovery from anesthesia (~5 h), [^{14}C]2-deoxyglucose (100–120 µCi/kg, sp. act., 300–310 mCi/mmol; Amersham) was injected i.v. and the cats were allowed to freely move around in the laboratory for effective monocular stimulation. Strabismic cats S5–S8 were also prepared for a 2-DG experiment under anesthetized and paralyzed conditions (2-DG data of cats S7 and S8 were not used in the following analyses; details of anesthesia and stimulation are provided in the original papers: S5/6 (Löwel *et al.*, 1987; Löwel and Singer, 1993b) and S7/8 (Löwel *et al.*, 1998). Cats S5 and S6 were stimulated monocularly through the right eye, while the left eye was covered with a black contact lens and an additional black patch. Visual stimulation consisted of moving square wave gratings covering 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 s in 45° steps (spatial frequency, 1, 0.5 and 0.15 cycles/degree; velocity 2 degree/s) (Löwel and Singer, 1993b).

Histological Procedures

The occipital poles of the brains of both proline and 2-DG injected cats containing visual cortices and lateral geniculate nuclei (LGN) were removed. The LGN were frozen in methylbutane cooled to −35°C. The non-fixated cortices were flat-mounted (Freeman *et al.*, 1987; Löwel *et al.*, 1987) before freezing them on dry ice. To provide landmarks for later reconstruction, three or more holes were melted into the tissue with hot needles before cutting 26 µm thick serial cryostat sections at −16°C. Blocks containing the visual cortex were cut parallel to the cortical surface; those containing the LGN were cut in the frontal plane. Sections were mounted on glass slides, dried on a hot plate and exposed to X-ray films for either 3 weeks to visualize 2-DG labeling (Structurix D7W, Agfa Gevaert) or for 8–16 weeks to visualize proline labeling (Hypofilm-^{3}H, Amersham, Braunschweig). In the case of double-labeling, sections were first exposed to reveal ^{14}C-labeling and then postfixed with 4% paraformaldehyde, washed to remove all 2-DG and then re-exposed to ^{3}H-sensitive film (Löwel *et al.*, 1988).

Even after preparing flat-mounts, single sections never contained the complete pattern of [^{3}H]proline-labeled layer IV afferents. To obtain the overall two-dimensional distribution of ocular dominance columns, a photomontage of all label-containing regions was made (Löwel and Singer, 1987).

Spillover Estimation

Since we used X-ray films instead of photo emulsions, we could not evaluate spillover on the original sections by counting silver grains in LGN neurons (LeVay *et al.*, 1978). To get a rough estimate of the contribution of spillover of radioactive label in the LGN laminae to cortical labeling, we made optical density measurements on proline-autoradiographs of the LGN sections at three different horizontal eccentricities. Spillover was then computed as described previously (LeVay *et al.*, 1978) as follows. We determined the relative density of labeling in laminae A and A1 after subtracting the density of background label (depicted from unlabeled tissue parts). Subsequently, we computed the amount of label in the lamina (A or A1) which is not supposed to be innervated by the injected eye in relation to labeling in the other laminae (A1 or A, respectively) innervated by the injected eye (Table 1). Since we did not differentiate between label in ganglion cell bodies and fibers of passage, our measurements may have overestimated actual spillover.

Quantitative Analysis

In addition to the qualitative description, we quantitatively analyzed the patterns of ocular dominance in monocularly deprived cats using a two-dimensional, nearest-neighbor analysis (Shapiro *et al.*, 1985; Murphy *et al.*, 1998). For comparative reasons, we reanalyzed previously published ocular dominance patterns of normally raised and strabismic cats with the same algorithm.

Autoradiographs were digitized in 18.75-fold magnification with an image processing system (Imago II, Compulog) and displayed in grey values between 0 and 255. Subsequently, the centers of ocular dominance columns were determined as the local minima of grey values (the pixel with the darkest labeling) in the images. To obtain plausible minima, images were converted to floating point arrays and low-pass filtered using a Butterworth filter of third order at a cutoff of 25 pixels (550 µm). This particular cutoff was located above 95% of the area-under-the-curve of the one-dimensional power spectra in all analyzed images in order to assure that filtering operated outside the signal's range of spatial frequencies. One-dimensional power spectra resulted from averaging the power over iso-frequencies in two-dimensional power spectra obtained by fast Fourier transformation of the images. After filtering, local minima were computed by comparing the value of each pixel with the immediately surrounding pixels.

Next, Delaunay triangulations were applied to determine the nearest-neighboring columns (Shapiro *et al.*, 1985). This algorithm tries to find the largest point (local minimum)-free circle with a columnar center inside its convex hull (Guibas and Stolfi, 1985). Voronoi polygons connecting all centers with the nearest-neighboring centers immediately outside the circle were fitted to the image and all distances were counted. To get as many counts as possible, we analyzed the labeling pattern in the entire area 17. Very long distances occurring as border artefacts at the outer envelopes and distances accidentally crossing more than two labeled column diameters were interactively removed from the data set as 'non-sense' distances. All other distances of one hemisphere were counted and entered the statistical analysis (200–1200 per hemisphere). Since distance distributions in single hemispheres did not always reveal a single maximum, we discarded the maximum as a descriptive value (see Fig. 1). We chose the median rather than the mean of the distance distributions for statistical comparison in order to avoid possible influences of asymmetric extreme values: some distance distributions had remained with a small positive right tail, although we had corrected for 'non-sense' distances.

To determine the influence of rearing condition on ocular dominance spacing, we tested in pairwise comparisons using the Mann–Whitney *U*-test whether median distance distributions of the three rearing groups were different. Furthermore, we investigated the relationship of median distance with litter membership, age and weight of the cats at the end of the experiment and length of area 17 (Löwel, 1994) by computing correlation coefficients in the case of continuous parameters and/or by analysis of variance (ANOVA). As an indication of the size of area 17, its length was determined by measuring the maximal length of the area showing ocular dominance columns on the autoradiographs in an anterior–posterior direction.

Results

Using flat-mount sections and photomontage reconstruction of all [^{3}H]proline label-containing regions, we were able to analyze the overall ocular dominance layout of monocularly deprived cats in the entire visual field representation. In addition, patterns of monocularly deprived cats were compared with patterns previously obtained in strabismic and normally raised control cats.

Qualitative Observations

Layout of ocular dominance columns of the deprived eye

In three monocularly deprived cats (MD2, 3 and 4), [^{3}H]proline was injected into the deprived eye. On the bright-field reproductions of the proline-autoradiographs, labeled regions appeared dark grey to black (Figs 1 and 2). The dark domains innervated by the deprived eye were shrunken and the unlabeled light grey regions representing the non-deprived eye were enlarged compared to the pattern observed in normally raised cats — compare Figures 1*A*,*B* and 2*A*,*B* with 4*B* and previously published images (Löwel and Singer, 1987).

The two-dimensional reconstructions clearly demonstrate that deprived eye afferents appear as 'dark islands in a light grey sea', i.e. as isolated patches on a background of non-deprived eye afferents. This is particularly obvious in hemispheres ipsilateral to the injected eye (Figs 1*A* and 2*A*). There are almost no continuous bands of undulating width that are typical for normal and especially squinting cats (Fig. 4*A*). In these animals, beaded bands are a typical feature of ocular dominance columns and frequently run perpendicular to the 17/18 border. Monocularly deprived cats seem to preserve only some residuals of this pattern; for example, some continuous courses crossing the area 17/18 border can be observed in cat MD3, in the hemisphere contralateral to the deprived eye (Fig. 2*B*).

Deprived eye afferents occupy more cortical territory in the contralateral compared to the ipsilateral hemisphere (compare Figs 1*A* and 1*B*, and 2*A* and 2*B*): in contralateral hemispheres, there are at least some continuous (beaded) bands, whereas ipsilaterally, only isolated islands of deprived eye domains are visible.

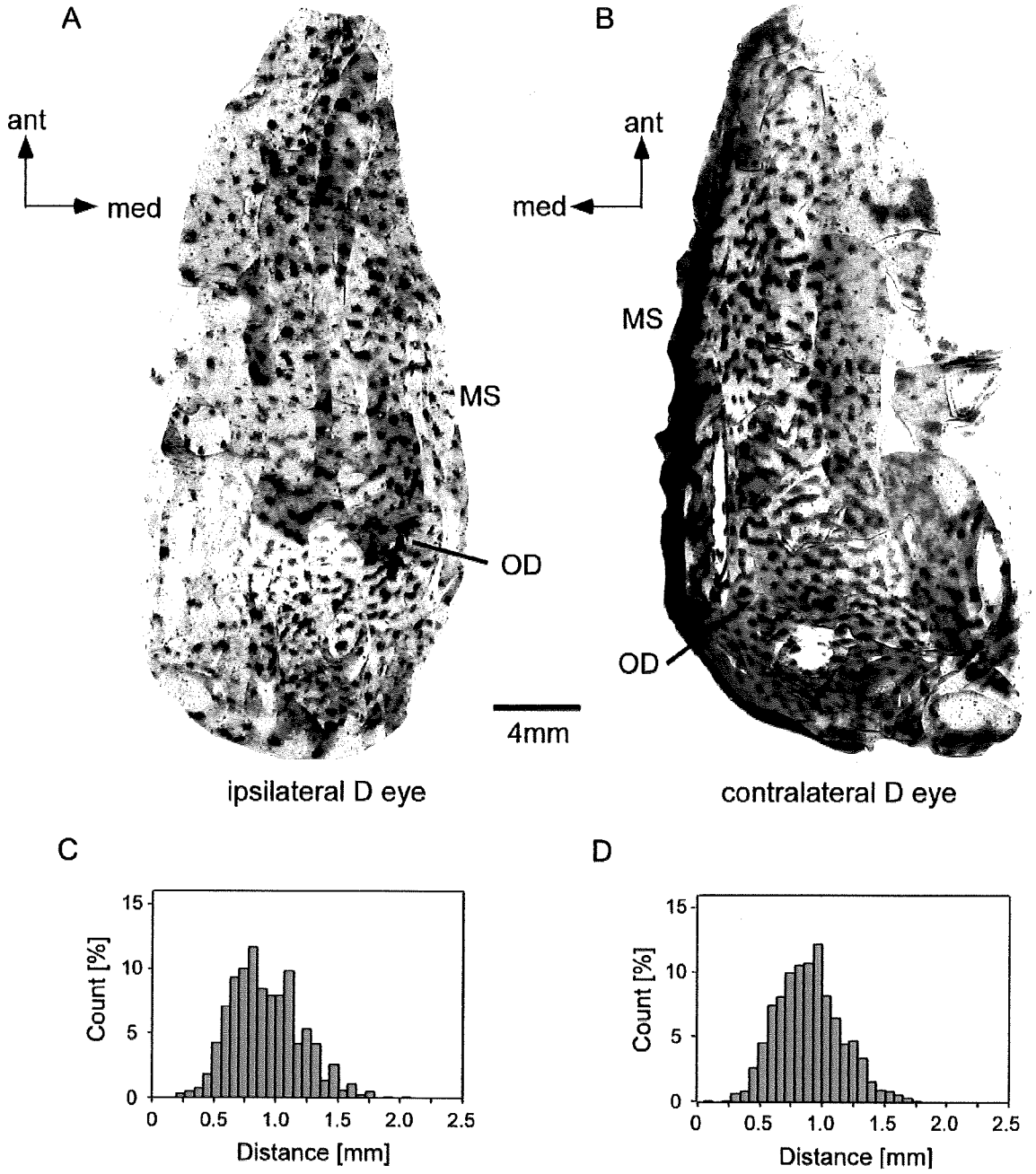

Figure 1. Overall pattern of ocular dominance columns in the primary visual cortex (area 17) of a monocularly deprived cat (MD2): photographic reconstruction of the [^{3}H]proline-labeled columns of the deprived eye in layer IV. Layout of the geniculocortical afferents in the hemisphere ipsilateral (left, *A*) and contralateral (right, *B*) to the injected (deprived) eye. (*A*) Deprived eye afferents appear as patchy 'islands in a light grey sea' that are smaller than normal (compare with Fig. 4*B*). Note, that the optical disc (OD) representation identifiable as a dark elongated slab is also narrower than normal (compare with Fig. 4*A,B* and see also Fig. 5). (*B*) Pattern of deprived eye columns contralateral to the injected (deprived) eye. Note that the monocular segment (MS) indicated by uniform dark labeling at the medial border of the hemispheres is very narrow. (*C, D*) Histograms of all column distances measured by nearest-neighbor analysis of the patterns in (*A*) and (*B*), displayed in percentage of counts. Note that there is no unambiguous peak position in the left histogram. Abbreviations: ant, anterior; med, medial; MS, monocular segment; OD, optical disc.

Single columns in the reconstructed images have variable sizes (see, for example, Fig. 1*A*), regardless of their eccentricity in the visual field representation. Consistent with previous investigations (Shatz and Stryker, 1978) we observed that deprived eye domains are wider at the base of layer IV compared to more superficial regions, leading to a pyramidal shape of ocular dominance columns in the vertical plane. We therefore ascribe irregular patch sizes on the flat-mount sections to differences in section depth and angle, rather than to true differences in column diameter.

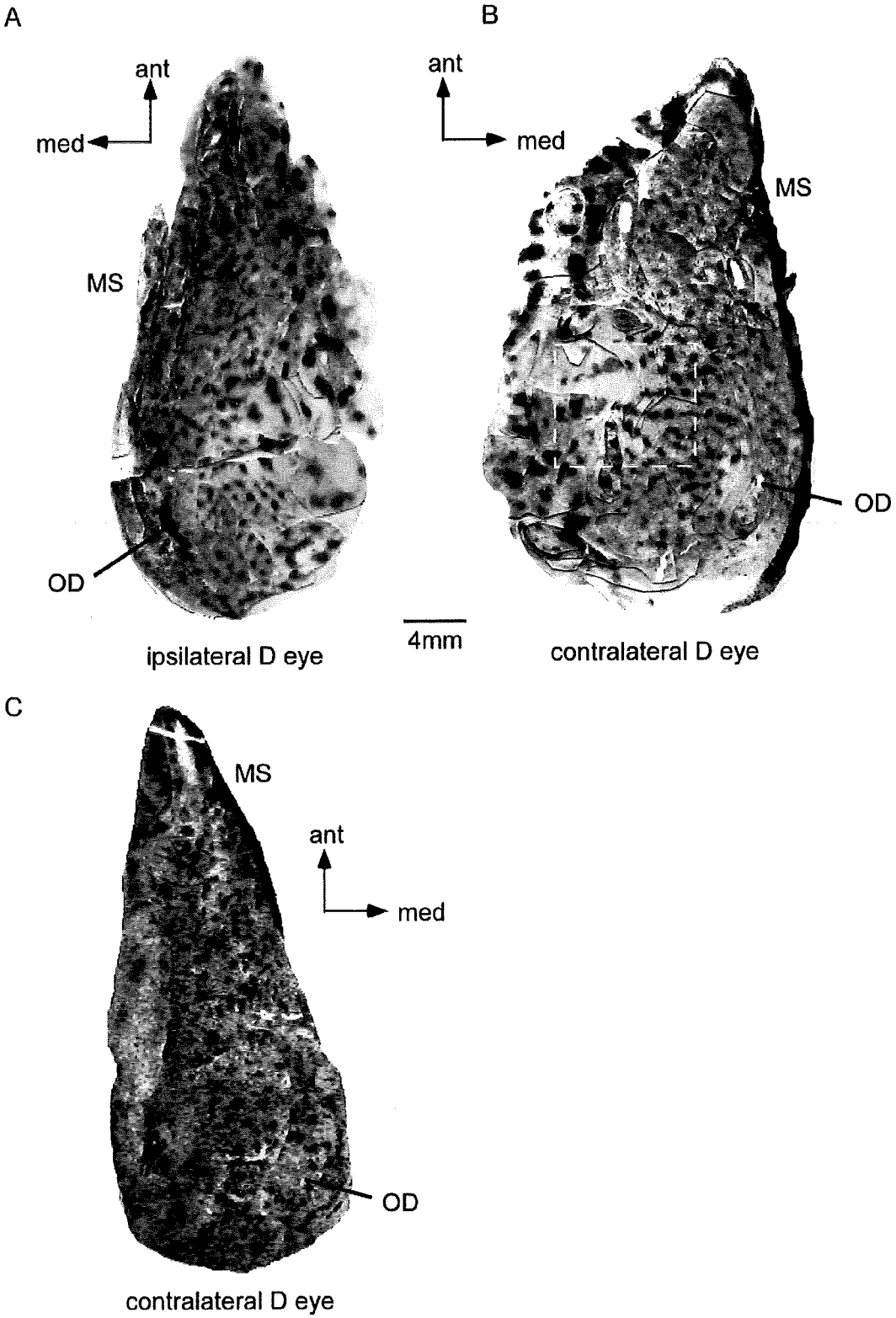

Figure 2. Photographic reconstructions of the [^{3}H]proline-labeled deprived eye columns in cats MD3 (*A*,*B*) and MD4 (*C*). Layout of the geniculocortical afferents in the hemisphere ipsilateral (right, *A*) and contralateral (left, *B*) to the injected (deprived) eye in cat MD3 and contralateral (left, *C*) to the injected (deprived) eye in cat MD4. The right hemisphere of MD4 (ipsilateral to the deprived eye) was not reconstructed because it broke into pieces during cutting. Beaded bands crossing the 17/18 border (dashed white line) are visible within the white dashed frame in (*B*). Note that deprived eye afferents are smaller than normal in all monocularly deprived cats (compare with Fig. 4*B*; see also Fig. 1*A*,*B*). Abbreviations as in Figure 1.

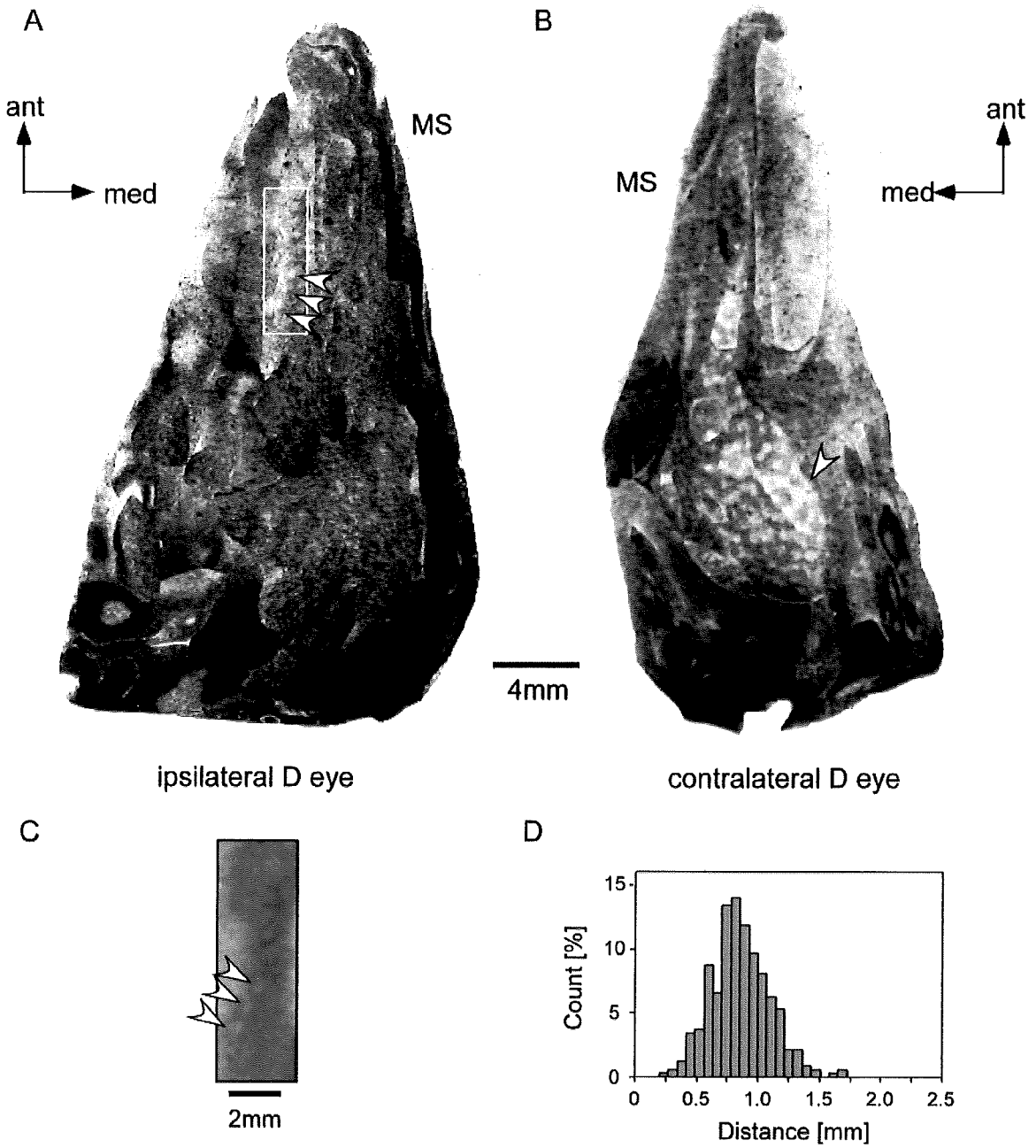

Figure 3. Overall pattern of the non-deprived eye columns in the visual cortex of the monocularly deprived cat MD1: photographic reconstruction of the [^{3}H]proline-labeled columns in layer IV. (*A*) Pattern in the left cortex, contralateral to the injected (non-deprived) eye (ipsilateral to the deprived eye). Labeling of the non-deprived eye's domains is rather homogeneous. Only some faint light grey islands of deprived eye afferents are visible in the anterior third of the pattern (white frame). (*B*) Pattern of non-deprived eye afferents in the right hemisphere of cat MD1, ipsilateral to the injected (non-deprived) eye (contralateral to the deprived eye). In the central visual field representation (center region of the photographic montage), deprived eye afferents are visible as pale, lightly labeled patches, usually surrounded by darker-labeled, non-deprived eye domains. Most centrally, however, there are a few dark, non-deprived eye domains surrounded by pale, deprived eye domains (indicated with the white arrowhead). Note that labeling in more peripheral visual field representations is rather homogeneous. (*C*) Enlarged version of the framed region in (*A*), reproduced from the original proline-autoradiograph, to visualize a couple of light grey columns aligned in a roughly anterior–posterior direction. The three posterior columns are marked by white arrowheads in both pictures (*A*) and (*C*). Note that the monocular segment (MS) of the non-deprived eye [black band at the medial (right) border of the hemisphere] is much wider compared to the deprived eye's MS in Figs 1*B* and 2*B,C*. (*D*) Histogram of the distribution of column distances of the pattern in (*C*). Abbreviations as in Figure 1.

Layout of Ocular Dominance Columns of the Normal (Non-deprived) Eye in Monocularly Deprived Cats

Cat MD1 had received a [^{3}H]proline injection into the non-deprived eye. Reconstruction of the pattern of afferences revealed an almost homogeneous dark labeling of both areas 17 and 18 in the hemisphere ipsilateral to the deprived eye (contralateral to the non-deprived/normal eye; Fig. 3*A*). Only some faint patches corresponding to unlabeled deprived eye afferents are

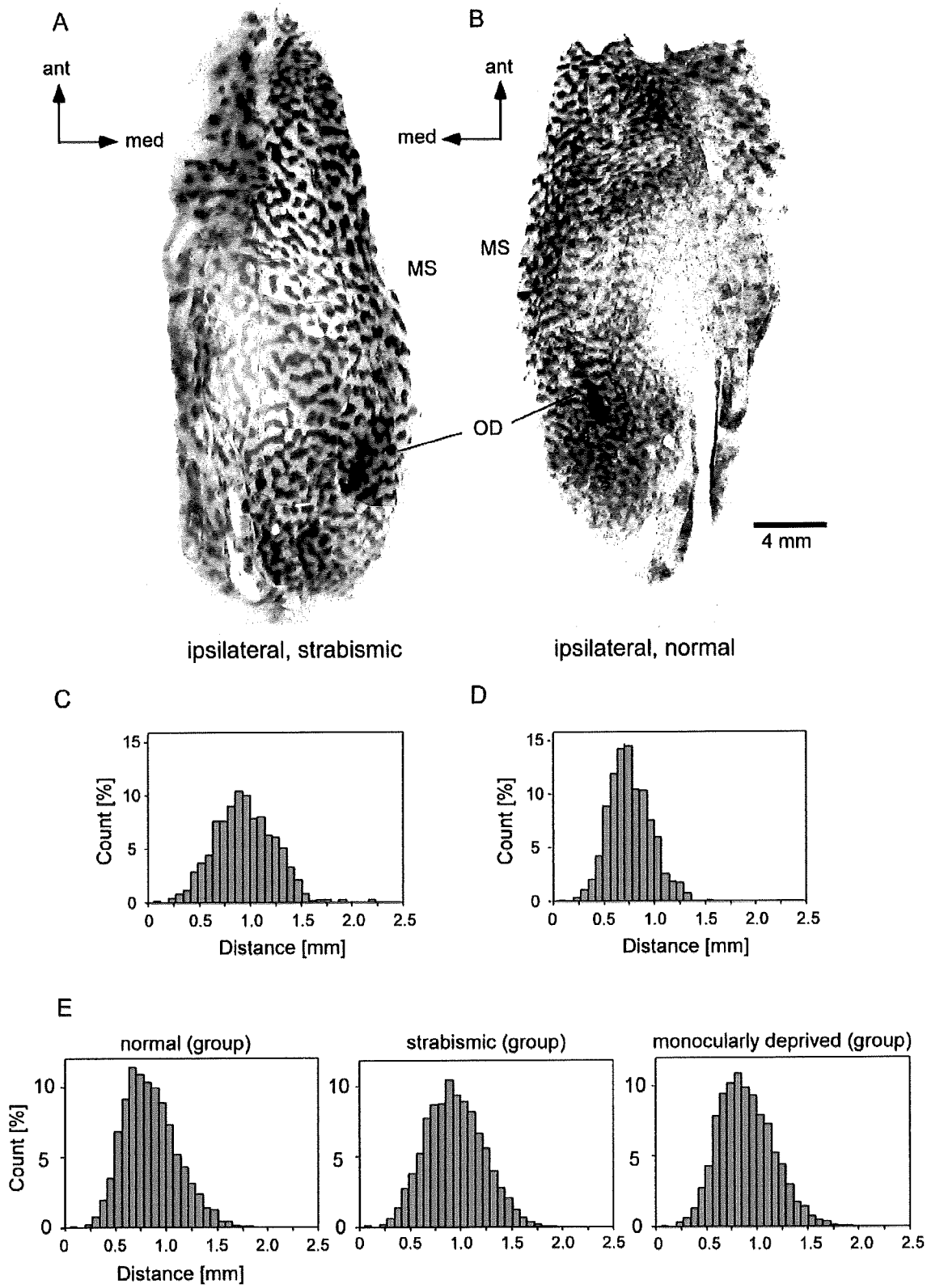

Figure 4. Overall pattern of ocular dominance columns in a strabismic (*A*) and [reproduced from Löwel (Löwel, 1994)] a normally raised cat (*B*). (*A*) Proline-labeling in the left hemisphere of cat S7, ipsilateral to the injected eye. (*B*) Ocular dominance columns in the right hemisphere of cat N2, ipsilateral to the injected eye. (*C*, *D*) Histograms of distance distributions of the patterns in (*A*) and (*B*). Note that the distribution of columnar distances of the strabismic cat is broader than that of the normal cat. (*E*) Summary histograms of the distance distributions of 10 normal (left), 14 strabismic (middle) and seven monocularly deprived hemispheres (right). Abbreviations as in Figure 1.

visible in the center of the anterior third of the labeled area (see Fig. 3C). Even after shorter exposure times of the autoradiographs, patterns of interdigitating ocular dominance columns could not be visualized in other regions.

In contrast, in the hemisphere ipsilateral to the injected eye (contralateral to the deprived eye), proline labeling shows clear undulations in the central part of area 17. This indicates that labeled afferents of the non-deprived eye are segregated and interdigitating with deprived eye afferents (Fig. 3B). The medial part of that region is characterized by unlabeled deprived eye 'islands surrounded by dark sea'. At the lateral site of the patterned region, which presumably corresponds to the most central visual field representation, non-deprived eye afferents even appear as dark and isolated patches, completely surrounded by unlabeled deprived eye afferents (Fig. 3B, white arrow). Thus, in localized regions of the central visual field representation, deprived eye afferents are able to preserve their contralateral bias. In the peripheral visual field representation, however, labeling is as continuous as in the other hemisphere (compare with Fig. 3A). Therefore, there is pronounced overlap between the afferents representing the two eyes which is not obvious after deprived eye injections (Figs 1 and 2). Contralaterally, non-deprived eye afferents overlap with deprived eye domains largely throughout area 17, while ipsilaterally, overlap is increasing towards peripheral visual field representations.

Optic Disc and Monocular Segment (MS)

Both optic disc and MS representations show marked alterations in monocularly deprived compared to normally raised animals (Fig. 5). The optic disc representations identifiable as demarcated oval regions are homogeneously labeled on the ipsilateral and pale, nearly label-free on the contralateral side of a proline injection (Löwel and Singer, 1987). In monocularly deprived cats, the optic disc representations appear as a rather narrow, darkly labeled slab (Figs 1A, 2A and 5A,B) and measure 0.4–0.6 × 2.0–2.9 mm, a value much smaller than 0.8–0.9 × 2.6–2.9 mm usually observed in normally raised cats (Figs 4B and 5C) (Löwel and Singer, 1987). Assuming an ellipsoid shape, optic disc representations of deprived eyes thus occupy up to 50% less cortical territory than those of normal eyes in normally raised cats.

The MSs are indicated by uniform labeling at the medial border of contralateral hemispheres and by the absence of labeling at comparable eccentricity on ipsilateral sides (Löwel and Singer, 1987). In monocularly deprived cats (Figs 1B and 2B,C), the MS, although clearly visible as a dark band in the contralateral hemisphere, is much narrower than in normally raised cats: on average, in cats MD2–4, MSs measure 0.6 mm in width at the narrowest and 1.0 mm at the broadest parts, while their width in normally raised cats ranges from 1.9 to 3.0 mm (Löwel and Singer, 1987; Löwel, 1994). In contrast, the MS of the non-deprived eye in cat MD1, which is depicted as the stripe more heavily labeled than the remaining part of area 17, measures 2.4–3.7 mm in width (Fig. 2A). It is therefore not only larger than the deprived eye's MSs, but probably even larger than MSs in normally raised cats.

Spillover in the LGN Laminae

Spillover between laminae A and A1 ranged from 16 to maximal 40% in ipsilateral nuclei and from 30 to 50% in nuclei contralateral to the injected eye (mean values; see Table 1). There was no difference between cats with deprived eye or non-deprived eye injections. Although we may have overestimated spillover (see Materials and Methods), average spillover ratios of four cats (ipsi, 24%; contra, 45%) were in the range of ratios observed previously (LeVay *et al.*, 1978) for that age group (65–95 days; ipsi, 14–23%; contra, 37–48%).

Quantitative Analysis of Intercolumnar Spacing

Since distance distributions measured by nearest-neighbor analysis from different hemispheres were rather symmetric and differed only slightly in shape (see Figs 1C,D, 3D and 4C,D for individual examples and Fig. 4E for summary histograms), we compared average values rather than distributions. For inter-individual comparisons, the medians (see Materials and Methods) of the counted distances of each hemisphere (seven monocularly deprived, 10 normal and 14 strabismic hemispheres) are plotted in Figure 6A. The pattern of afferents in the left hemisphere of cat MD1 revealed too few discernible columns and was discarded from quantitative analysis.

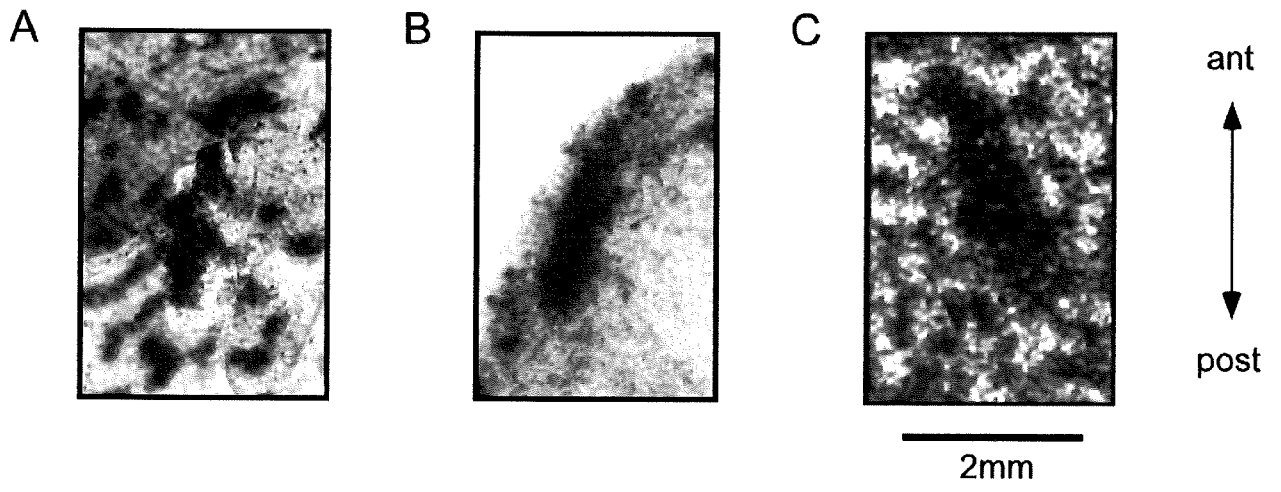

Figure 5. The optic disc representations in visual cortical layer IV of two monocularly deprived cats (*A*, MD2, enlarged detail from Fig 1*A*; *B*, MD3, enlarged detail from Fig. 2*A*) and a normally raised control animal (*C*, N2, enlarged detail from Fig. 3*B*). Photographs from [^{3}H]proline autoradiographs after ipsilateral eye injections.

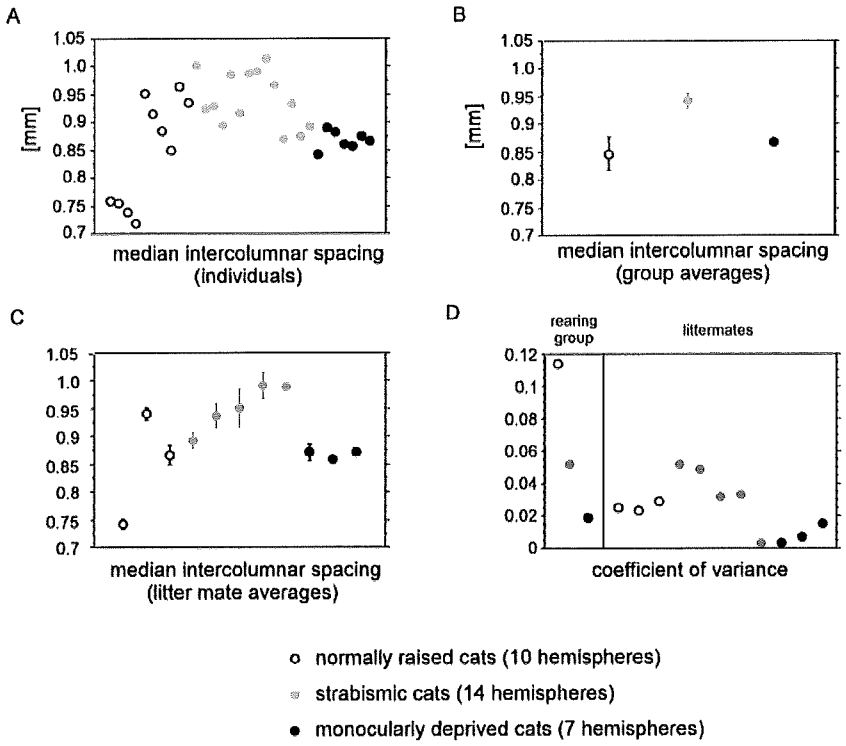

Figure 6. Nearest-neighbor analysis of ocular dominance patterns in normal, strabismic and monocularly deprived cats (31 hemispheres of 17 cats). Color code as indicated at the bottom. Error bars display the standard error of the mean. (*A*) Medians of the distance distributions for each individual hemisphere. (*B*) Rearing group averages of median intercolumnar distances. Although individual values in (*A*) overlap, the group of strabismic cats has a significantly higher spacing compared to normally raised (Mann–Whitney U, $P = 0.019$) and monocularly deprived animals (Mann–Whitney U, $P = 0.012$). (*C*) Littermate averages of median intercolumnar distances. (*D*) Relative variance of median intercolumnar distance within rearing groups (left) and within litters (right). Note that, in contrast to the normal control group, relative variance within the strabismic and monocularly deprived groups is not higher than within single litters.

Spacing and Rearing

Median spacing ranged from 843 to 890 μm in monocularly deprived cats, from 718 to 988 μm in normal cats and from 870 to 1015 μm in strabismic cats. The largest values were observed in strabismic cats, the smallest values in normally raised cats. Spacing measurements overlapped between all three groups (Fig. 6*A*). To test the hypothesis that columnar spacing is different in animals with different visual experience, distance distributions of rearing groups were compared pairwise using the Mann–Whitney U-test. Intercolumnar spacing in the group of strabismic cats (n = 14 hemispheres of seven cats; average, 942 μm) was significantly higher than in normally raised controls (n = 10 hemispheres of five cats; average, 847 μm; Mann–Whitney U, $P = 0.019$) and monocularly deprived animals (n = 7 hemispheres of four cats; average, 868 μm; Mann–Whitney U, $P = 0.012$). However, spacing in monocularly deprived animals did not differ significantly from that in normally raised animals (Mann–Whitney U, $P > 0.999$; Fig. 6*B*).

Spacing and Litter Membership

Column spacing turned out to be strongly influenced by membership of a specific litter (ANOVA, $F = 19.26$; $P = 0.0001$, Fig. 6*C*). Testing the interdependency of the two parameters 'rearing condition' and 'litter membership' was, however, not possible since litter members were always subjected to equal rearing conditions. To nevertheless get an estimate of how litter membership might have influenced our previous analyses, we computed the relative variance of median column spacing within litters and compared it to the variance within the three rearing groups. The respective coefficients of variance (CoV) were determined by dividing the standard deviation by the mean of the median distances for each group separately (Fig. 6*D*). The CoV among median distances is largest within the normal control group (0.114) as compared to a relatively small coefficient within all different litters (0.034). The group of squinters (0.052) shows less than half of the intra-group variance of normal animals. Among monocularly deprived cats, relative variance is orders of magnitude smaller than in the normally raised cats (0.019) and below the average variance within litters (0.034). These data suggest that genetic relationship has a pronounced influence on the intercolumnar distance, at least in the sense that littermates reacted very similarly to a specific type of altered visual experience.

Interhemispheric differences in column spacing vary between 4 and 77 μm (mean, 28 μm) in individual cats and the direction of the difference is not eye-specific in squinting or monocularly deprived cats. Differences are largest among squinters, in agreement with the rather broad distribution of distances in these cats. Still, interhemispheric differences in individuals tend to be smaller than differences between group averages of squinting and normal cats (95 μm) or monocularly deprived cats (74 μm).

Spacing and Weight/Age and Length of Area 17

To exclude the possibility that our observation of the influence of rearing and litter membership on spacing resulted from a sampling artefact with regard to age, body weight or area length

in our cat population, we computed correlation coefficients between these parameters and intercolumnar spacing. None of the interactions disturbed the relation with the factors 'litter membership' or 'rearing' (data not shown) and only significant observations are described. Column spacing seemed to be smaller in older and heavier cats as compared to younger, less heavy cats (ANOVA: age, $F = 7.41$, $R = -0.45$, $P = 0.01$; weight, $F = 4.9$, $R = -0.38$, $P = 0.003$). The length of area 17 was positively correlated with intercolumnar spacing in normal cats (ANOVA: $n = 10$, $F = 158$, $R = 0.98$, $P = 0.0001$), thus indicating larger column spacing in larger areas in adulthood. Interestingly, this strong relationship was not observed in cats with abnormal visual experience (ANOVA: $n = 20$, $F = 1.5$, $R = -0.28$, $P = 0.23$).

Discussion

Overall Pattern of Ocular Dominance Columns in Monocularly Deprived Cats

In agreement with former studies in monkeys and cats, domains serving the deprived eye occupied much less territory than those serving the normal eye (Hubel *et al.*, 1977; Shatz and Stryker, 1978; LeVay *et al.*, 1980; Hata and Stryker, 1994; Horton and Hocking, 1997; Crawford, 1998; Hata *et al.*, 2000). This is compatible with electrophysiological recordings showing that only 21% of the neurons in layer IV — 7% in other layers — are dominated by the deprived eye (Hubel and Wiesel, 1970; Blakemore and Van Sluyters, 1974; Shatz and Stryker, 1978; Movshon and Van Sluyters, 1981).

Interestingly, shrinkage of deprived eye territory extended also into exclusively monocularly driven domains, such as the representations of the optical disc and of the MS. The same observation was previously made in primary visual cortex of monocularly deprived macaque monkeys (von Noorden *et al.*, 1976; Horton and Hocking, 1997). Part of this shrinkage may be explained by competition of deprived and non-deprived eye afferents at the borders of these monocular representations, whereby the open eye gains more cortical territory than normally (Antonini and Stryker, 1998). In addition, sensory disuse could have interfered with the stabilization and elaboration of geniculocortical axons. This observation is interesting given that electrophysiological studies so far showed that the deprived pathway is impaired only within the representation of the binocular part of the visual field (Sherman, 1973; Sherman *et al.*, 1974; Sherman and Guillery, 1976; Wilson and Sherman, 1977). Support for the shrinkage by disuse hypothesis comes from investigations in binocularly deprived cats which revealed that sensory disuse, in the absence of competition, is sufficient to impair cortical functions (Wiesel and Hubel, 1965). The present results complement these observations and suggest an influence of sensory disuse on geniculocortical connectivity.

In agreement with a previous suggestion (Shatz and Stryker, 1978), our data indicate that overlap between afferents representing the two eyes in layer IV is greater in monocularly deprived cats compared to normally raised animals. This observation is supported by electrophysiological studies showing that in deprived eye domains, monocular neurons with different eye dominance are intermingled and that even some binocularly driven cells occur (Shatz and Stryker, 1978). This overlap further correlates with electrophysiological recordings describing a substantial amount of functionally binocular neurons also outside layer IV in monocularly deprived cats (Shatz and Stryker, 1978; Freeman and Ohzawa, 1988).

Eccentricity Dependent Variations of Intercolumnar Competition?

In all monocularly deprived cats, density of labeling was higher contralateral than ipsilateral to the injected eyes. This is in accordance with previous anatomical (Hubel *et al.*, 1977; Shatz and Stryker, 1978; LeVay *et al.*, 1980; Horton and Hocking, 1997), electrophysiological (Hubel and Wiesel, 1962; Blakemore and Pettigrew, 1970; Albus, 1975; Shatz and Stryker, 1978) and 2-deoxyglucose (Löwel *et al.*, 1993a, b) studies, which all report a prevalence of the contralateral eye representation. This bias may also explain the observation that unlabeled deprived eye patches are hardly discernible in the hemisphere contralateral to the labeled normal eye (Shatz and Stryker, 1978). In this study we noted, in addition, that segregation of afferents from the two eyes was less pronounced in the representation of the peripheral visual field. We are confident that the lack of distinct columns in the peripheral visual field representation contralateral to the injected normal eye of cat MD1 does reflect a decreased segregation of non-deprived eye afferents and is not the result of methodological artefacts. Labeling in cat MD1 is comparable to that in other cats, as indicated by a similar quality of staining in the LGN autoradiographs and by the good expression of columns in the cortex ipsilateral to the injected eye. With proline labeling, the density of cortical labeling is often weaker in regions representing the central than the peripheral visual field (LeVay *et al.*, 1978; Löwel and Singer, 1987). Therefore, one could argue that fading of contrast in the periphery might be due to saturation when exposure times are chosen that render optimal contrast in the center. However, on unsaturated films an increase in label density should not eliminate contrast. Moreover, peripheral label in cat MD1 appeared homogeneous even after short exposure times. We therefore exclude saturation as a cause of the eccentricity effect.

Another process mimicking reduced segregation is spillover of radioactive tracer across LGN laminae from labeled fibers of the contralateral eye that pass through lamina A1 and terminate in lamina A (LeVay *et al.*, 1978; Shatz and Stryker, 1978). Our measurements indicated that such spillover had occurred, but did not differ between deprived or non-deprived eye injections (LGN autoradiographs, not shown). Since we measured spillover on films and not directly on sections, we may have overestimated its magnitude (see Materials and Methods) by including labeled fibers of passage and not only cell bodies (LeVay *et al.*, 1978). Thus 'spillover' ratios most probably did not exceed 50% and this ratio should not have prevented the visualization of segregated afferents.

Taken together, the arguments suggest that the lack of modulation in labeling intensity at large eccentricities and contralateral to non-deprived eye injections reflects low or absent segregation of afferents. This eccentricity dependent difference in labeling pattern was not observed after deprived-eye injections. Thus, in contrast to normally raised cats (Hata and Stryker, 1994) and monocularly deprived monkeys (LeVay *et al.*, 1980; Horton and Hocking, 1997), (i) geniculocortical afferents of the two eyes in monocularly deprived cats are not complementary and (ii) their overlap seems to be expressed to varying degrees on contra- and ipsilateral sides. When studying plasticity of geniculocortical afferents and its pharmacology, it might thus be important to consider that layout differences between ipsi- and contralateral eye afferents and between central and peripheral visual field representation can be observed in monocularly deprived cats, especially ipsilateral to the open eye, even without pharmacological intervention.

Complementary support for an eccentricity dependent

variation in the segregation of OD columns comes from one macaque monkey who was monocularly deprived by lid suture very early on (at 1 week of age). After a non-deprived eye injection, segregated ocular dominance columns appeared also predominantly in the representation of the fovea and faded completely towards the periphery — monkey 3 (Horton and Hocking, 1997). In animals deprived at successively later ages, this trend became less and less evident [see also (LeVay *et al.*, 1980)]. This observation had been attributed mainly to a difference in column spacing between foveal and more peripheral visual field representations: in the macaque fovea, columns are widely spaced, whereas in the periphery columns are much more narrowly spaced. Thus, spreading of non-deprived eye afferents into deprived eye domains was suggested to prevent the visualization of domain segregation assuming an equal radius of the spread of non-deprived afferents in central and peripheral regions. In principle, this might also be an explanation for the lack of segregation we observed in the peripheral visual field representation of monocularly deprived cats.

However, we did not find a clear difference in column spacing between central and peripheral visual field representations in cat area 17 (data not shown), as has been reported for monkey primary visual cortex. Thus, differences in column spacing most likely do not account for the observed retinotopic gradient in segregation in cat MD1. Alternatively, an eccentricity dependent gradient in cortical maturation might explain our observations. In cats, geniculocortical afferents start to segregate around eye opening and thus ~1–2 weeks after birth (LeVay *et al.*, 1978; Crair *et al.*, 2001), so that the developmental scenario is different from that in the monkey, who is already born with columns (Rakic, 1977, Horton and Hocking, 1996a; Crowley and Katz, 2000). Once ocular dominance columns are laid out, non-deprived eye afferents may no longer be able to invade the center of a deprived eye domain, but if they have not yet left the deprived eye's territory in the course of the normal segregation process, non-deprived eye projections may stabilize. This would imply that the retinotopic gradient we observed in the segregation of non-deprived eye afferents reflects delayed maturation of domains devoted to the peripheral visual field.

Indirect support for this hypothesis comes from data by Hata *et al.* who mapped a large part of the ocular dominance pattern of a monocularly deprived cat after proline injection into the non-deprived eye (Hata *et al.*, 2000). The authors began deprivation (lasting only 2 weeks) long after columns have been formed in cats (PND 35–38). In this study, the size of the region containing well-segregated columns was much larger than in our case, indicating that segregation of the non-deprived eye extended much further into peripheral visual field representations. This is what one expects if deprivation time has either been too short for non-deprived eye afferents to invade the deprived-eye columns and/or, more likely, if new outgrowth of non-deprived eye afferents into already stabilized peripheral ocular dominance centers of the deprived eye has no longer been possible. Thus, the difference between the data Hata *et al.* and our study is compatible with a maturational gradient between central and peripheral visual field. To our knowledge, there is no other evidence yet that segregation starts earlier in the central part of area 17. However, there is evidence from other parts of the visual system supporting such a gradient. The orienting response of kittens, which probably involves the superior colliculus, matures later in the more peripheral than in the central visual field (Sireteanu and Maurer, 1982). Also, peripheral regions of the kitten's retina which is immature at birth, mature later than central regions (Donovan, 1966; Johns *et al.*, 1979). The central part is fully developed by 4–5 weeks, but peripheral parts continue to mature until 9 weeks postnatally (Donovan, 1966).

The fact that in our cats clearly segregated deprived eye columns are especially prominent in the hemisphere contralateral to the deprived eye is consistent with an earlier maturation of the domains of the contralateral eye (Crair *et al.*, 1998; Rathjen and Löwel, 2000). This is also in agreement with previous studies in cat suggesting an earlier maturation of the crossed versus the uncrossed pathways (Singer and Tretter, 1976; Anker, 1977; Singer, 1978).

Ocular Dominance Column Spacing

In a previous study in our laboratory, intercolumnar distances were investigated by one-dimensional Fourier measurements along vectors perpendicular to the columnar boundaries (Löwel, 1994). Since in normal and especially strabismic cats, a clear alternation of left and right eye columns is mainly observed in the anterior–posterior axis, a one-dimensional analysis is adequate to measure intercolumnar distances in these animals. However, patterns produced by proline injections into monocularly deprived cats revealed discontinuous patches and fewer bands with distinct orientations, making one-dimensional measurements inadequate. We decided to analyze the ocular dominance patterns with a nearest-neighbor analysis using Voronoi triangles, as detailed in Materials and Methods and elsewhere (Murphy *et al.*, 1998), because this method — in contrast to two-dimensional Fourier transformations — allows the determination of column spacing, even from small layer IV fragments common in proline experiments and the performance of quantitative measurements directly on the original autoradiographs, thus minimizing artefacts.

Rearing

One major finding of the quantitative analyses was that column spacing in monocularly deprived cats was not significantly different from that in normally raised cats. This observation is in agreement with measurements in visually deprived cats (Jones *et al.*, 1996) and monkeys (Crawford, 1998; Murphy *et al.*, 1998) revealing no differences between different rearing groups. It is consistent with theoretical predictions by (i) an elastic net model assuming decreased competitive strength of the deprived eye (Goodhill and Willshaw, 1994) and (ii) models reproducing a squint-induced increase in column spacing, including reduced inter-eye correlations (Goodhill and Löwel, 1995; Wolf *et al.*, 2000). However, with only spontaneous activity driving the deprived eye afferents, assumptions about inter-eye correlations are difficult to deduce. In the modeler's context, the present results only indicate that reduced inter-eye correlations at least do not prevail over reduced intra-eye correlations in their effect on column spacing.

The re-evaluation of previously published ocular dominance patterns with two-dimensional, nearest-neighbor analysis confirmed the observation of an increased column spacing in the strabismic animals compared to the normally raised controls (Löwel, 1994). It is in agreement with a study in which cats were raised with alternating monocular occlusion (Tieman and Tumosa, 1997), a preliminary report of strabismic monkeys (Roe *et al.*, 1995; Murphy *et al.*, 1998) and developmental models including reduced inter-eye correlations (Goodhill, 1993; Wolf *et al.*, 2000).

However, the new observation that belonging to the same litter has a very strong influence on column spacing introduces a new perspective on the data set.

Litter Membership

Inter-individual variability was particularly high among normal cats, in agreement with data from normal macaque monkeys (Horton and Hocking, 1996b). In contrast, ocular dominance spacing was very similar (low variance) in the two hemispheres of the same animal and in cats from the same litter. Thus, litter membership and therefore probably genetic factors may play a major role for column spacing. Supporting this idea, a substantial genetic influence on the spacing of orientation columns has recently been observed in cat area 17 (Löwel *et al.*, 2000).

Since all cats reared with different kinds of visual experience were also littermates, it cannot be excluded that this fact contributed significantly to the consistently wider column spacing in the strabismic group. It is noteworthy in this context that three cats, a strabismic litter, S7/8 (Löwel *et al.*, 1998) and one normal cat, N5 (Schmidt *et al.*, 1997), which had not been included in the former analysis (Löwel, 1994), have overlapping spacing values (Table 1).

Age/Weight

Although our youngest cats were already 6–7 weeks old and thus at an age at which ocular dominance layout already appears adult-like (LeVay *et al.*, 1977; Rathjen and Löwel, 2000; Crair *et al.*, 2001), we observed a slight decrease of column spacing with increasing age and body weight. Though indicating that the pattern layout might still change to a limited extent between 8 and 16 weeks of age, this did, however, not affect our above conclusions because different rearing groups behaved similarly.

Length

In normally raised, but not in strabismic and monocularly deprived cats, larger spacings usually occurred in larger areas, which may keep the number of modules analyzing the visual field with the two eyes independent of area size. One explanation could be that a constant relationship between monocular resolution of the visual field and area size needs to be maintained only in cats with binocular receptive fields (normals) in order to ensure a monocular sampling frequency of the visual field, which is invariant of the individual brain size. Further experiments are, however, needed to settle the issue of a possible interaction between area size, column spacing and rearing condition.

Since none of the investigated litters were reared with different paradigms, the present data do not allow one to clearly distinguish between 'pure' effects of rearing and litter membership on column spacing and their interference with age, weight and area size, but the genetic influence seems to be extraordinary high and thus overshadows any other influence. To decide this issue finally, different rearing conditions must be applied to members of the same litter (Rathjen *et al.*, 1999) and a large number of cats must be investigated because effects might be very small.

Mechanisms

Although deprived eye domains in area 17 of monocularly deprived cats are clearly smaller than normal, it is surprising how much territory is still innervated by the deprived eye. Assuming a competitive process, the amount of territory taken by one eye might depend on several factors, such as the overall activity of the afferent fibers, the synchronicity between the activity of the two eyes and the initial density of the afferent fibers of the two eyes. Since afferent activity of the deprived eye is strongly reduced and unstructured, the afferents of the monocularly deprived eye probably cannot greatly benefit from activity- or experience-dependent competition. Thus, one explanation for the even distribution of the small deprived eye columns throughout the visual field representation might be that ocular dominance segregation had started before the onset of visual experience (Crowley and Katz, 2000) and local terminal density was already particularly high, with only few terminals of the other eye around.

In this respect, it is also very interesting that in monocularly deprived cats, functionally intact domains of the deprived eye domains have been found to be co-localized with pinwheel center singularities (Crair *et al.*, 1997b). This co-localization was even stronger than that observed between peaks of monocularity and singularities in normal (Crair *et al.*, 1997a) or strabismic cats (Löwel *et al.*, 1998). Specific visual response properties of the neurons in pinwheel center singularities, among other reasons, have been suggested to account for this observation (Crair *et al.*, 1997a). As the remaining functional domains coincide with the anatomically defined patches of the deprived eye afferents, it is possible that those regions differ from the surrounding cortex with respect to their thalamocortical input pattern and/or to other intrinsic, molecular cues.

Conclusions

Taken together, the qualitative analyses indicate that: (i) shrinkage of deprived eye territory is present throughout area 17, extends even into the MS and the optic disc representation and thus into regions without, or with at least reduced, binocular competition; (ii) there is extensive (more than normal) overlap of non-deprived and deprived eye afferents throughout area 17 in hemispheres contralateral to the non-deprived eye and in the visual field periphery of hemispheres ipsilateral to the non-deprived eye; and (iii) the eccentricity dependent gradient in the degree of overlap between normal and deprived eye afferents suggests a maturational gradient with the central visual field representation maturing earlier than the periphery. The quantitative analyses indicate that: (i) monocular deprivation does not influence the average column spacing in area 17 of cats and (ii) littermates have very similar column spacing, suggesting a pronounced genetic influence on ocular dominance column spacing.

Acknowledgements

We are very grateful to Gerd Bink for his valuable help, to Margitt Ehms-Sommer for the superb photographic reproductions, to Monika Sum, Evelyn Raulf, Sandra Schwegmann and Petra Janson for excellent technical assistance and to Ralf Galuske, Sonja Grün, Jan-Hinrich Schröder and Fred Wolf for helpful discussions of the manuscript.

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References

Albus K (1975) Predominance of monocularly driven cells in the projection area of the central visual field in cat's striate cortex. Brain Res 89:341–347.

Anker RL (1977) The prenatal development of some of the visual pathways in the cat. J Comp Neurol 173:185–204.

Antonini A, Stryker MP (1993) Rapid remodeling of axonal arbors in the visual cortex. Science 260:1819–1821.

Antonini A, Stryker MP (1998) Effect of sensory disuse on geniculate afferents to cat visual cortex. Vis Neurosci 15:401–409.

Blakemore C, Pettigrew JD (1970) Eye dominance in the visual cortex. Nature 225:426–429.

Blakemore C, Van Sluyters RC (1974) Reversal of the physiological effects of monocular deprivation in kittens: further evidence for a sensitive period. J Physiol 237:195–216.

Crair MC, Ruthazer ES, Gillespie DC, Stryker MP (1997a) Ocular dominance peaks at pinwheel center singularities of the orientation map in cat visual cortex. J Neurophysiol 77:3381–3385.
Crair MC, Ruthazer ES, Gillespie DC, Stryker MP (1997b) Relationship between the ocular dominance and orientation maps in visual cortex of monocularly deprived cats. Neuron 19:307–318.
Crair MC, Gillespie DC, Stryker MP (1998) The role of visual experience in the development of columns in cat visual cortex. Science 279: 566–570.
Crair MC, Horton JC, Antonini A, Stryker MP (2001) Emergence of ocular dominance columns in cat visual cortex by 2 weeks of age. J Comp Neurol 430:235–249.
Crawford ML (1998) Column spacing in normal and visually deprived monkeys. Exp Brain Res 123:282–288.
Crowley JC, Katz LC (2000) Early development of ocular dominance columns. Science 290:1321–1324.
Donovan A (1966) The postnatal development of the cat retina. Exp Eye Res 5:249–254.
Freeman B, Löwel S, Singer W (1987) Deoxyglucose mapping in the cat visual cortex following carotid artery injection and cortical flat-mounting. J Neurosci Methods 20:115–129.
Freeman RD, Ohzawa I (1988) Monocularly deprived cats: binocular tests of cortical cells reveal functional connections from the deprived eye. J Neurosci 8:2491–2506.
Goodhill GJ (1993) Topography and ocular dominance: a model exploring positive correlations. Biol Cybern 69:109–118.
Goodhill GJ, Löwel S (1995) Theory meets experiment: correlated neural activity helps determine ocular dominance column periodicity. Trends Neurosci 18:437–439.
Goodhill GJ, Willshaw DJ (1994) Elastic net model of ocular dominance: overall stripe pattern and monocular deprivation. Neural Comp 6:615–621.
Goodman CS, Shatz CJ (1993) Developmental mechanisms that generate precise patterns of neuronal connectivity. Cell 72:77–98.
Grafstein B (1971) Transneuronal transfer of radioactivity in the central nervous system. Science 172:177–179.
Guibas L, Stolfi J (1985) Primitives for the manipulation of general subdivisions and the computation of Voronoi diagrams. ACM Trans Graphics 4:74–123.
Hata Y, Stryker MP (1994) Control of thalamocortical afferent rearrangement by postsynaptic activity in developing visual cortex. Science 265:1732–1735.
Hata Y, Ohshima M, Ichisaka S, Wakita M, Fukuda M, Tsumoto T (2000) Brain-derived neurotrophic factor expands ocular dominance columns in visual cortex in monocularly deprived and nondeprived kittens but does not in adult cats. J Neurosci 20:RC57.
Horton JC, Hocking DR (1996a) An adult pattern of ocular dominance columns in striate cortex of newborn monkeys prior to visual experience. J Neurosci 16:1791–1807.
Horton JC, Hocking DR (1996b) Intrinsic variability of ocular dominance column periodicity in normal macaque monkeys. J Neurosci 16: 7228–7239.
Horton JC, Hocking DR (1997) Timing of the critical period for plasticity of ocular dominance columns in macaque striate cortex. J Neurosci 17:3684–3709.
Hubel DH, Wiesel TN (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol 160:106–154.
Hubel DH, Wiesel TN (1970) The period of susceptibility to the physiological effects of unilateral eye closure in kittens. J Physiol (Lond) 206:419–436.
Hubel DH, Wiesel TN, LeVay S (1977) Plasticity of ocular dominance columns in monkey striate cortex. Philos Trans R Soc Lond B Biol Sci 278:377–409.
Johns PR, Russoff AC, Dubin MW (1979) Postnatal neurogenesis in the kitten retina. J Comp Neurol 187:545–556.
Jones DG, Van Sluyters RC, Murphy KM (1991) A computational model for the overall pattern of ocular dominance. J Neurosci 11: 3794–3808.
Jones DG, Murphy KM, Van Sluyters RC (1996) Spacing of ocular dominance columns is not changed by monocular deprivation or strabismus. Invest Ophthalmol Vis Sci 37(Suppl.):1964.
LeVay S, Gilbert CD (1976) Laminar patterns of geniculocortical projection in the cat. Brain Res 113:1–19.
LeVay S, Stryker MP, Shatz CJ (1978) Ocular dominance columns and their development in layer IV of the cat's visual cortex: a quantitative study. J Comp Neurol 179:223–244.
LeVay S, Wiesel TN, Hubel DH (1980) The development of ocular dominance columns in normal and visually deprived monkeys. J Comp Neurol 191:1–51.
Löwel S (1994) Ocular dominance column development: strabismus changes the spacing of adjacent columns in cat visual cortex. J Neurosci 14:7451–7468.
Löwel S, Singer W (1987) The pattern of ocular dominance columns in flat-mounts of the cat visual cortex. Exp Brain Res 68:661–666.
Löwel S, Singer W (1992) Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. Science 255: 209–212.
Löwel S, Singer W (1993a) Monocularly induced 2-deoxyglucose patterns in the visual cortex and lateral geniculate nucleus of the cat. I. Anaesthetized and paralysed animals. Eur J Neurosci 5:846–856.
Löwel S, Singer W (1993b) Monocularly induced 2-deoxyglucose patterns in the visual cortex and lateral geniculate nucleus of the cat: II. Awake animals and strabismic animals. Eur J Neurosci 5:857–869.
Löwel S, Freeman B, Singer W (1987) Topographic organization of the orientation column system in large flat-mounts of the cat visual cortex: a 2-deoxyglucose study. J Comp Neurol 255:401–415.
Löwel S, Bischof H-J, Leutenecker B, Singer W (1988) Topographic relations between ocular dominance and orientation columns in the cat striate cortex. Exp Brain Res 71:33–46.
Löwel S, Schmidt KE, Kim D-S, Wolf F, Hoffsümmer F, Singer W, Bonhoeffer T (1998) The layout of orientation and ocular dominance domains in area 17 of strabismic cats. Eur J Neurosci 10:2629–2643.
Löwel S, Kaschube M, Geisel G, Wolf F (2000) Substantial genetic influence on visual cortical orientation maps. Soc Neurosci Abstr 26:820.
Movshon JA, Van Sluyters RC (1981) Visual neural development. Annu Rev Psychol 32:477–522.
Mower GD, Caplan CJ, Christen WG, Duffy FH (1985) Dark rearing prolongs physiological but not anatomical plasticity of the cat visual cortex. J Comp Neurol 235:448–466.
Murphy KM, Jones DG, Fenstemaker SB, Pegado VD, Kiorpes L, Movshon JA (1998) Spacing of cytochrome oxidase blobs in visual cortex of normal and strabismic monkeys. Cereb Cortex 8:237–244.
Rakic P (1977) Prenatal development of the visual system in the rhesus monkey. Phil Trans R Soc Lond B Biol Sci 278:245–260.
Rathjen S, Löwel S (2000) Early postnatal development of functional ocular dominance columns in cat primary visual cortex. Neuroreport 11:2363–2367.
Rathjen S, Schmidt KE, Löwel S (1999) The development of ocular dominance columns in primary visual cortex of normally raised and strabismic kittens. In: Göttinger neurobiology report (Elsner N, Eysel U, eds), p. 478. Stuttgart: Thieme.
Roe AW, Ghose GM, Smith EL, Chino YM, Ts'o DY (1995) Alterations in striate cortical ocular dominance columns in anisometropic amblyopia. Soc Neurosci Abstr 21:1752.
Schmidt KE, Kim DS, Singer W, Bonhoeffer T, Löwel S (1997) Functional specificity of long-range intrinsic and interhemispheric connections in the visual cortex of strabismic cats. J Neurosci 17:5480–5492.
Shapiro MB, Schein, SJ, deMonasteiro, FM (1985) Regularity and structure of the spatial pattern of blue cones of macaque retina. J Am Stat Assoc 80:803–812.
Shatz CJ, Stryker MP (1978) Ocular dominance in layer IV of the cat's visual cortex and the effects of monocular deprivation. J Physiol (Lond) 281:267–283.
Sherman SM (1973) Visual field defects in monocularly and binocularly deprived cats. Brain Res 49:24–45.
Sherman SM, Guillery RW (1976) Behavioral studies of binocular competition in cats. Vision Res 16:1479–1481.
Sherman SM, Guillery RW, Kaas JH, Sanderson KJ (1974) Behavioral, electrophysiological and morphological studies of binocular competition in the development of the geniculo-cortical pathways of cats. J Comp Neurol 158:1–18.
Singer W (1978) The effect of monocular deprivation on cat parastriate cortex: asymmetry between crossed and uncrossed pathways. Brain Res 157:351–355.
Singer W, Tretter F (1976) Receptive-field properties and neuronal connectivity in striate and parastriate cortex of contour-deprived cats. J Neurophysiol 39:613–630.

Sireteanu R, Maurer D (1982) The development of the kitten's visual field. Vision Res 22:1105–1111.

Sokoloff L, Reivich M, Kennedy C, DesRosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M (1977) The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 28:897–916.

Stryker MP (1986) The role of neural activity in rearranging connections in the central visual system. In: The biology of change in otolaryngology (Ruben RJ, Van De Water TR, Rubel EW, eds), pp. 211–224. Amsterdam: Elsevier Science.

Stryker MP (1991) Activity-dependent reorganization of afferents in the developing mammalian visual system. In: Development of the visual system (Lam DMK, Shatz CJ, eds), pp. 267–287. Cambridge, MA: MIT Press.

Stryker MP, Strickland SL (1984) Physiological segregation of ocular dominance columns depends on the pattern of afferent electrical activity. Invest Ophthalmol Vis Sci 25(Suppl.):278.

Tieman SB, Tumosa N (1997) Alternating monocular exposure increases the spacing of ocularity domains in area 17 of cats. Vis Neurosci 14:929–938.

Von Noorden GK, Crawford MLJ, Middleditch PR (1976) The effects of monocular visual deprivation: disuse or binocular interaction? Brain Res 111:277–285.

Wiesel TN, Hubel DH (1963) Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. J Neurophysiol 26:978–993.

Wiesel TN, Hubel DH (1965) Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. J Neurophysiol 28:1029–1040.

Wilson JR, Sherman SM (1977) Differential effects of early monocular deprivation on binocular and monocular segments of cat striate cortex. J Neurophysiol 40:891–903.

Wolf F, Pawelzik K, Scherf O, Geisel T, Löwel S (2000) How can squint change the spacing of ocular dominance columns? J Physiol Paris 94:525–537.