

Binocular phasic coactivation does not prevent ocular dominance segregation

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1. ABSTRACT

The segregation of geniculo-cortical afferents into ocular dominance columns is an activity-dependent process. It was hypothesized that this process is susceptible to the temporal patterning of the retinal input. Accordingly, asynchronous activation of the two eyes should enhance ocular dominance segregation but synchronous activation should decrease or prevent it. In order to test the second part of the hypothesis, kittens were raised in strobe light which phasically coactivated the retinal inputs during 10 microsecond flashes at 8Hz. Strobe rearing prevents retinal motion signals but allows vision of stationary contours. At the age of 10-14 weeks, ocular dominance columns were labeled either transneuronally by [³H]-proline or by [¹⁴C]-2-deoxyglucose autoradiography. Contrary to the hypothesis, ocular dominance columns were very well segregated and the pattern closely resembled the pattern observed in squinting cats. We conclude that the light flashes were sufficient to enable binocular competition and that ocular dominance segregation was supported by the mismatch of the stationary contours. Our result thus emphasizes a feature-selective mechanism over mere global temporal patterning of retinal signals.

2. INTRODUCTION

One of the classic animal models for activity- and experience-dependent cortical development is the segregation of geniculo-cortical afferents of the two eyes into ocular dominance columns in the visual cortex. In newborn cats, geniculocortical afferents serving the two eyes are overlapping in the input layer IV of primary visual cortex (area 17). Between the second and fourth postnatal week, the geniculocortical afferents segregate into the adult pattern of ocular dominance columns (1-5). The segregation process is susceptible to experience-dependent modifications during the critical period starting around the third week of life (for review, e.g. 6, 7). Several investigations indicated that column formation is driven by activity-dependent competition between the afferents of the two eyes whereby the temporal patterning of the input activity is a key modulating factor of segregation (for review, 8). Accordingly, blocking neuronal activity by intravitreal injection of tetrodotoxin (TTX) was sufficient to prevent column formation at all (9). Reducing neuronal activity by binocular lid suture or dark rearing reduced also the magnitude of segregation (10-12). Reducing neuronal activity conveyed by only one eye from birth (monocular

deprivation) led to a clear expansion of the open eye's domains at the expense of the closed eye domains: the patches of geniculocortical afferents in layer IV serving the deprived eye were smaller, and those serving the non-deprived eye larger, than normal (12-17). Inducing a squint angle in kittens produced a greatly enhanced segregation of afferents and almost exclusively monocular subpopulations of neurons (18, 19). This was interpreted as a result of desynchronizing the activity between the two eyes induced by the squint angle which in turn increases the competition for cortical territory (for review, e.g. 6, 7, 20). Preliminary results of Stryker and Strickland (21) had indicated that the temporal patterning of neuronal activity conveys the essential information for the geniculocortical axons to segregate. When both optic nerves were stimulated asynchronously during the critical period with implanted electrodes, 72% of all neurons became monocular while in the case of synchronous stimulation, almost all neurons became binocular.

In the present study, we aimed to test the hypothesis that correlating the input activity of the two eyes would group the geniculocortical afferents together and thus prevent or decrease the segregation process. To artificially correlate the activity conveyed by the two eyes, we raised kittens in a stroboscopically illuminated environment from birth. This paradigm of "strobe-rearing" prevents the experience of coherent motion but allows normal pattern vision on the basis of stationary contours (22). Previous studies have shown that kittens reared in an environment stroboscopically illuminated at 8Hz develop reduced direction selectivity but normal levels of orientation selectivity (23, 24). In contrast, protocols with lower flash frequencies (2Hz) seem to also profoundly perturb patterned visual input: they result in impaired development of behavioral contrast sensitivity and spatial acuity (25, 26) as well as reduced cortical orientation selectivity and altered receptive field structures (22, 27-29). Since we did not want to confound our experiment with visual deprivation effects we therefore chose the 8Hz protocol. Contrary to our expectation, strobe rearing did not prevent or decrease segregation of geniculocortical afferents but rather enhanced it. As a consequence, the ocular dominance patterns resembled closely those of strabismic cats.

3. MATERIALS AND METHODS

Three cats from two different litters (litter 1: cat ST1 and 2; litter 2: cat ST9) from the colony of the Max-Planck-Institute for Brain Research are included in the present study. The two litters were raised in a dark room illuminated by stroboscopic light of 8Hz flash frequency for 24 hours per day for 11 (litter 1) to 14 weeks (litter 2) from birth. Ocular dominance columns in cats ST1 and ST2 were anatomically labeled by intraocular injections of the transneuronal tracer [^3H]-proline (30, 31) at the age of 13 weeks. Strobe-reared cat ST9 had its ocular dominance columns functionally labeled with [^{14}C]-2-deoxyglucose (2-DG, 32) after monocular stimulation in awake conditions (see 33-34) at the age of 20 weeks. Since monocularly activated 2-DG columns are in precise register with the

termination zones of the afferents from the activated eye in layer IV (34, 35) the two techniques give essentially similar results for layer IV. Proline-labeled domains are restricted to cortical layer IV (1) whereas 2-DG labeled domains extend through all cortical layers (34).

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

For transneuronal labeling of ocular dominance columns by eye injection, a short-term anesthesia was induced with an intramuscular injection of ketamine hydrochloride (15mg/kg; Ketavet, Upjohn GmbH, Heppenheim) and xylazine hydrochloride (2.5mg/kg; Rompun, Bayer, Leverkusen). Skin and sclera were incised beneath the upper bone margin of the orbit and some vitreous was aspirated with a syringe. 2.5mCi of [^3H]-proline (Amersham, Braunschweig; specific activity 92-94 Ci/mmol), dissolved in a volume of 50 μl NaCl, was injected with a Hamilton pipette into the right eye. The cut was carefully adapted 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 before and then given a lethal dose of pentobarbital (180mg/kg, Nembutal, WDT, Hannover) intraperitoneally. Cat ST9 had a venous catheter implanted into the humeral vein under mask anesthesia with a mixture of $\text{N}_2\text{O}/\text{O}_2$ (70%/30%) and halothane (1-2%) and one eye occluded with a black contact lens provided with an additional black tape coverage. After full recovery from anesthesia (about 5 hours), [^{14}C]-2-deoxyglucose (Amersham; 100-120 $\mu\text{Ci/kg}$; specific activity, 290 mCi/mmol) was injected intravenously and the cat was allowed to move freely around the laboratory so that it received effective monocular stimulation. After 45 minutes, the animal received a lethal dose of pentobarbital (180mg/kg, Nembutal, WDT, Hannover) injected intravenously.

3.2. Histological procedures

The occipital poles of the brains of both proline and 2-DG injected animals containing both visual cortices and lateral geniculate nuclei (LGN) were removed. The LGN blocks were frozen in methylbutane cooled to -35°C . The visual cortices were flat-mounted (36, 37) before the tissue was frozen on dry ice. To provide landmarks for later reconstruction, three or more holes were melted in the flat-mounts with warm needles. Subsequently, 26- μm -thick serial sections were cut: 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 then exposed to X-ray films for either 3 weeks to visualize 2-DG labeling (Structurix D7W, Agfa Gevaert) or for 8 to 16 weeks to visualize proline labeling (Hypofilm- ^3H , Amersham, Braunschweig). The transneuronal tracer [^3H]-proline labels the geniculocortical afferents in layer IV of the visual cortex. Single sections never contained the complete pattern of [^3H]-proline labeled columns even after preparing flat-mounts. To obtain the overall two-dimensional distribution of ocular dominance columns a photomontage of all label-containing regions was made (see 17, 37).

3.3. Quantitative analysis

In addition to the qualitative description of ocular dominance patterns, we quantitatively analyzed the patterns using a 2-dimensional nearest neighbor analysis to determine the distance between adjacent columns (for details see 17). Autoradiographs were digitized and low-pass filtered using a butterworth filter of third order at a cutoff of 25 pixels ($\approx 550 \mu\text{m}$). The centers of ocular dominance columns were determined in the images as the local minima of gray values (the pixel with the darkest labeling). Next, Delaunay triangulations were applied to determine the nearest neighboring columns (38). This algorithm tries to find the largest point (local minimum)-free circle with a columnar center inside its convex hull (39). Voronoi polygons connecting all centers with the nearest neighboring centers were fitted to the image. To get as many counts as possible we analyzed the labeling pattern in the entire area 17. All measurable inter-columnar distances of one hemisphere were counted (200-800 per hemisphere) and the median determined. Further, in order to compare the sharpness of ocular dominance segregation in strobe-reared cats with strabismic and normal animals we performed one-dimensional density measurements from the unprocessed autoradiographs in hemisphere pairs of each group. Density was measured along a representative vector on the raw autoradiograph. The maximal amplitude was determined from the grey values of monocular segments and optic disks. Grey level amplitudes ranged from 65 to 80. For comparison, the profiles were clipped equally and plotted around their mean.

4. RESULTS

4.1. Qualitative observations of visual abilities

When the kittens were taken out of the dark room and strobe-rearing was stopped at the age of 11 to 14 weeks, all cats had developed a small divergent squint angle and a rotatory nystagmus. The nystagmus disappeared after about one week. Coarse psychophysical testing revealed that, unlike normal cats, the strobe-reared cats did not display a threatening response, that means they did not react to an object (a hand) being moved very fast towards their faces from the frontal direction. They were harder to motivate to follow objects and hesitated longer than normal kittens of the same age group to jump to the floor from 1.5m height. Otherwise, they did not demonstrate any obvious visual impairment as expected from previous studies using the same strobe-rearing paradigm (22).

4.2. Layout of ocular dominance columns in strobe-reared cats

We analyzed the complete two-dimensional pattern of [^3H]-proline labeled geniculocortical afferents in primary visual cortex (area 17) of our strobe-reared cats. On the bright-field reproductions of the autoradiographs [^3H]-proline appears dark gray to black (Figure 1 and 2). The [^3H]-proline labeling was restricted to sections located in a depth of 700-1000 μm corresponding to visual cortical layer IV. Both areas 17 and 18 were labeled. Contrary to our initial expectation, the two-dimensional reconstructions of layer IV clearly demonstrated dark gray domains of the

injected eye alternating with light gray domains of the other eye in both hemispheres. Ocular dominance domains of the injected eye were very sharply delineated. The labeling patterns were very similar to those previously observed in squinting cats (for comparison, see Figure 2) and visibly different from patterns in normal cats. In the latter, the contrast between labeled and unlabeled ocular dominance domains is much lower indicating a less pronounced segregation of the afferents of the two eyes (14, 31, 40). In the strobe-reared animals, the labeling pattern consisted of continuous bands of undulating width and thus very much resembled the patterns observed in squinting cats whereas the pattern in normal cats shows much more discontinuous patches of label (Figure 3). 2-DG labeled ocular dominance columns in the third cat ST9 basically revealed a similar layout with the difference that they extended through all cortical layers. There was also no obvious difference in the column layout in superficial layers of strobe-reared cats as compared to normal and strabismic animals.

As previously observed in both normal and squinting cats, spacing between ocular dominance domains was wider in area 18 compared to area 17. Furthermore, in the representation of the central visual field, domains tended to cross the area border at a perpendicular angle. In the peripheral visual field representation, domains were more beady and irregular and - as in all other cats independently of the visual experience (14, 17-19, 31) - the contralateral eye occupied more cortical territory. Thus, in the hemisphere contralateral to the injected eye, labeled domains tended to encircle unlabeled domains of the ipsilateral eye producing a honeycomb-like structure. In contrast, in the hemisphere ipsilateral to the injection, labeled domains appear more like dark gray islands in a light gray sea.

4.3. Sharpness of ocular dominance segregation

Sharp segregation of geniculocortical afferents into distinct ocular dominance columns was also illustrated by optic density measurements on the [^3H]-proline autoradiographs (Figure 4). In general, in hemispheres ipsilateral to the eye injection, amplitudes between labeled and un-labeled domains tended to be smaller than on the contralateral side. In all stroboscopic animals, the optic density profiles were very steep, similar to strabismic animals, and thus clearly different from the more shallow profiles of normally raised animals. Ocular dominance domains are thus more sharply segregated in both stroboscopically raised and strabismic cats compared to normally raised animals whose response profiles show much smaller dynamics between labeled and unlabeled domains.

4.4. Optic disc and monocular segment

Both optic disc and monocular segment (MS) representations were as clearly developed as in normal cats and as strongly contrasted as in squinters (compare Figures 1, 2 and 3). The optic disc representations correspond to homogeneously labeled oval regions on the ipsilateral hemisphere and to nearly label-free oval regions on the contralateral side of a proline injection. On average, optic disc representations in six hemispheres of strobe-reared

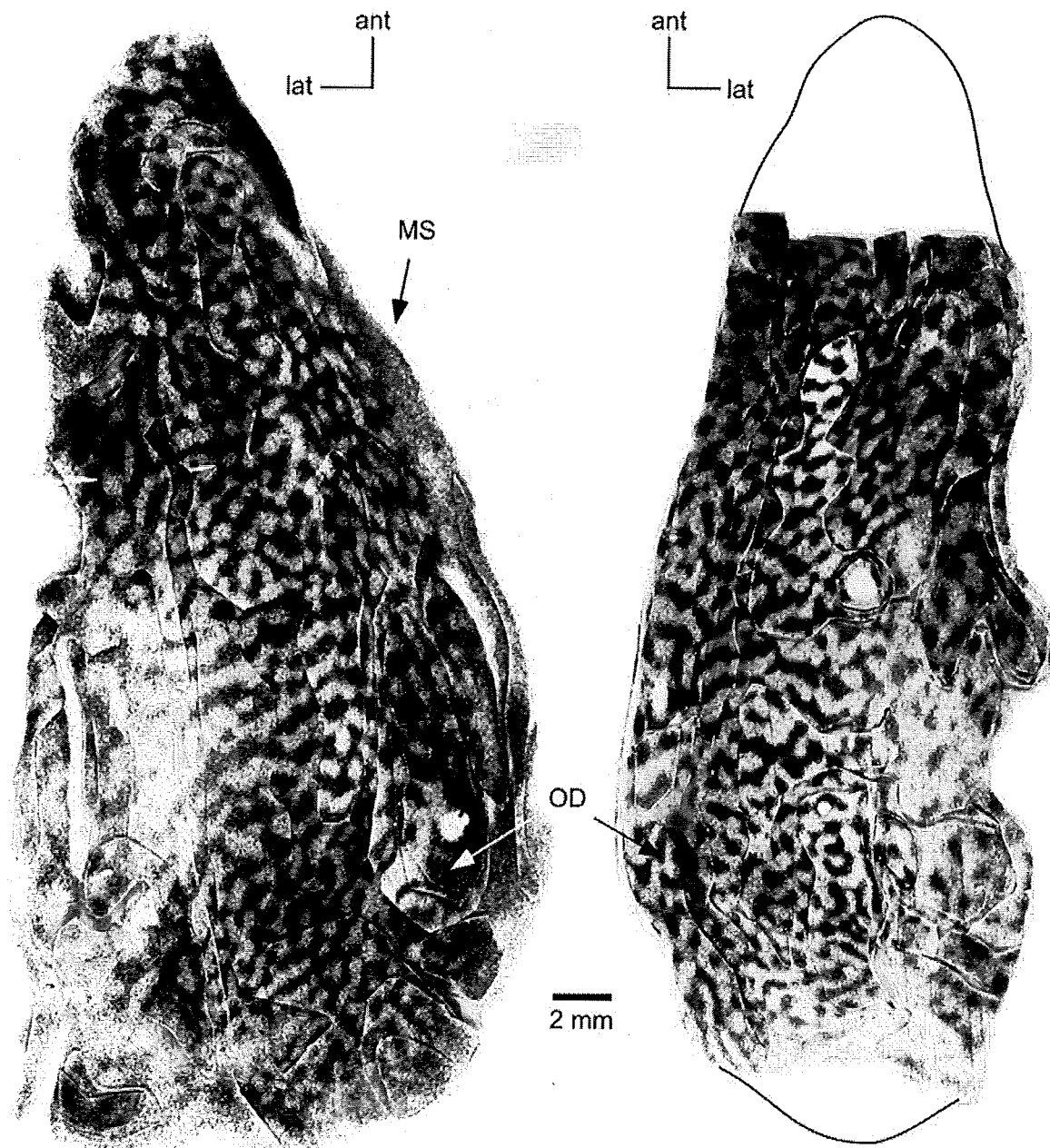


Figure 1. Overall pattern of ocular dominance columns in the primary visual cortex (area 17) of a strobe-reared cat (ST1): photographic reconstruction of the [^3H]-proline labeled columns in layer IV. Layout of the geniculocortical afferents in the hemisphere contralateral (left, A) and ipsilateral (right, B) to the injected right eye. Note the similarity of the patterns to the OD patterns in Figure 2. Abbreviations: ant = anterior; med = medial; MS = monocular segment; OD = optical disc.

rats measured $0.8 \times 3.5\text{mm}$, a value similar or slightly larger to $0.8\text{-}0.9 \times 2.6\text{-}2.9\text{mm}$ usually observed in normally raised cats (17, 31). Monocular segments are indicated by uniform labeling at the medial border of contralateral hemispheres and by the absence of labeling at comparable eccentricity on ipsilateral sides (31). On average, monocular segments measured 1.4mm in width at the most narrow and 2.2mm at the broadest parts. In normally raised cats the width ranges from $1.9\text{-}3.0\text{mm}$ (19, 31).

4.5. Quantitative analysis of intercolumnar spacing

Intercolumnar distances of ocular dominance patterns of strobe-reared cats were measured using the nearest-neighbor analysis (17) and compared to the values taken from a sample of monocularly deprived, normally raised and strabismic cats published previously (17). For interindividual comparisons the median of the counted distances of one hemisphere was chosen. These median intercolumnar distances from the three strobe-reared cats

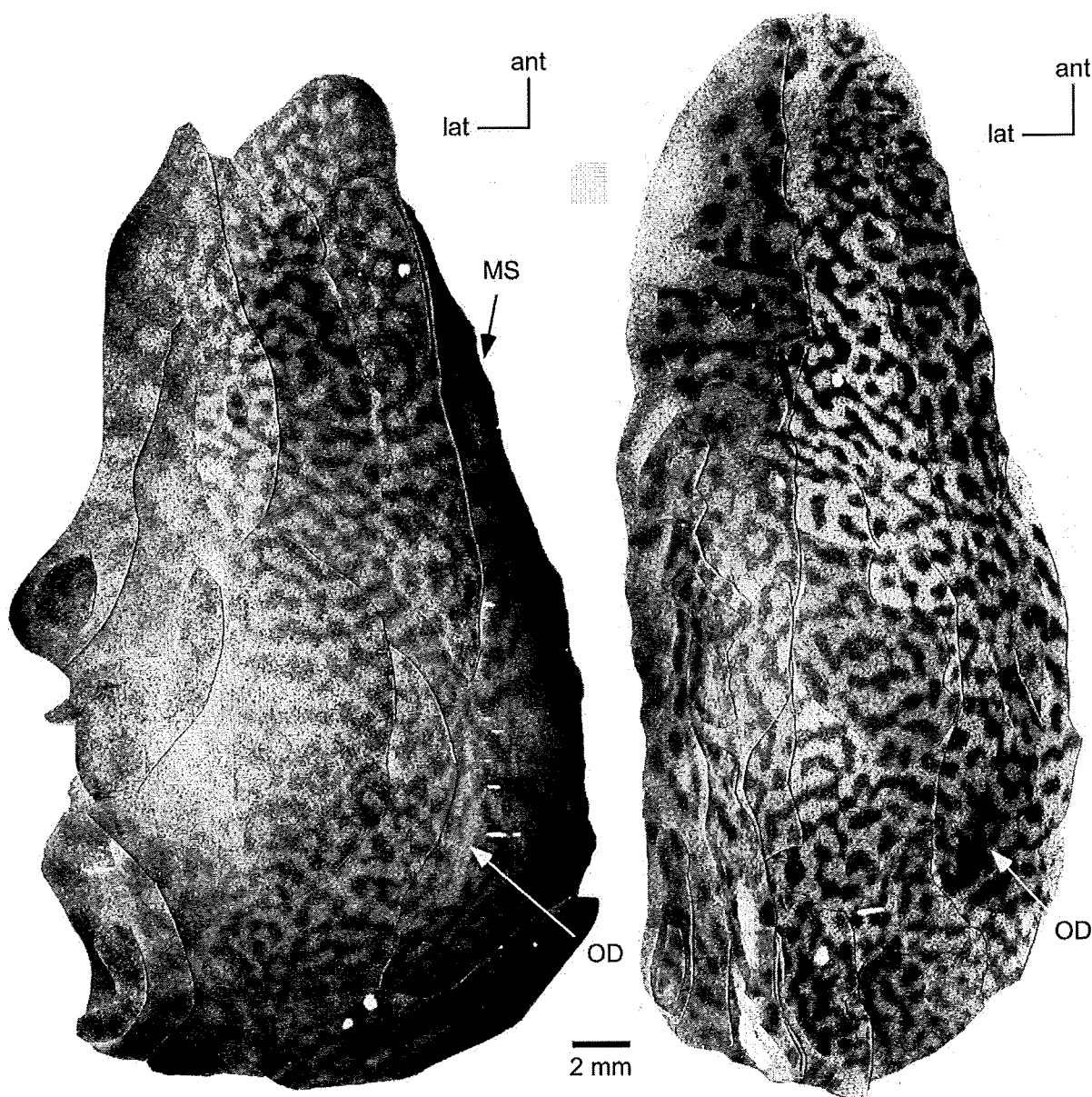


Figure 2. Overall pattern of ocular dominance columns in primary visual cortex of two squinting cats after labeling with [^3H]-proline. Layout of the geniculocortical afferents in a hemisphere contralateral (left, A) and ipsilateral (right, B) to the respective injected eye. Abbreviations as in Figure 1.

are plotted in Figure 5A. As described previously, values from hemispheres of the same animal are within the same range. Furthermore, values from the two littermates ST1 and ST2 are more similar to each other than to ST9.

On average, in strobe-reared cats, median spacing ranges from $780\mu\text{m}$ to $1050\mu\text{m}$ (for comparison: from $843\mu\text{m}$ to $890\mu\text{m}$ in monocularly deprived cats ($n=4$), from $718\mu\text{m}$ to $988\mu\text{m}$ in normal cats ($n=5$) and from $870\mu\text{m}$ to $1015\mu\text{m}$ in strabismic cats ($n=8$); Figure 5B). Although the mean spacing in the strobe-reared group is located at the higher end of the sample as are the strabismic cats,

interindividual variability in the strobe-reared cats is quite large and extends over the whole range. In conclusion, spacing measurements overlap between all four rearing groups (Figure 5B, error bars of SEM) and spacing did not differ significantly between the four rearing groups (Kruskal-Wallis, $p = 0.21$).

5. DISCUSSION

In the present study, we have investigated the complete two-dimensional layout of ocular dominance patterns of strobe-reared cats by transneuronal labeling

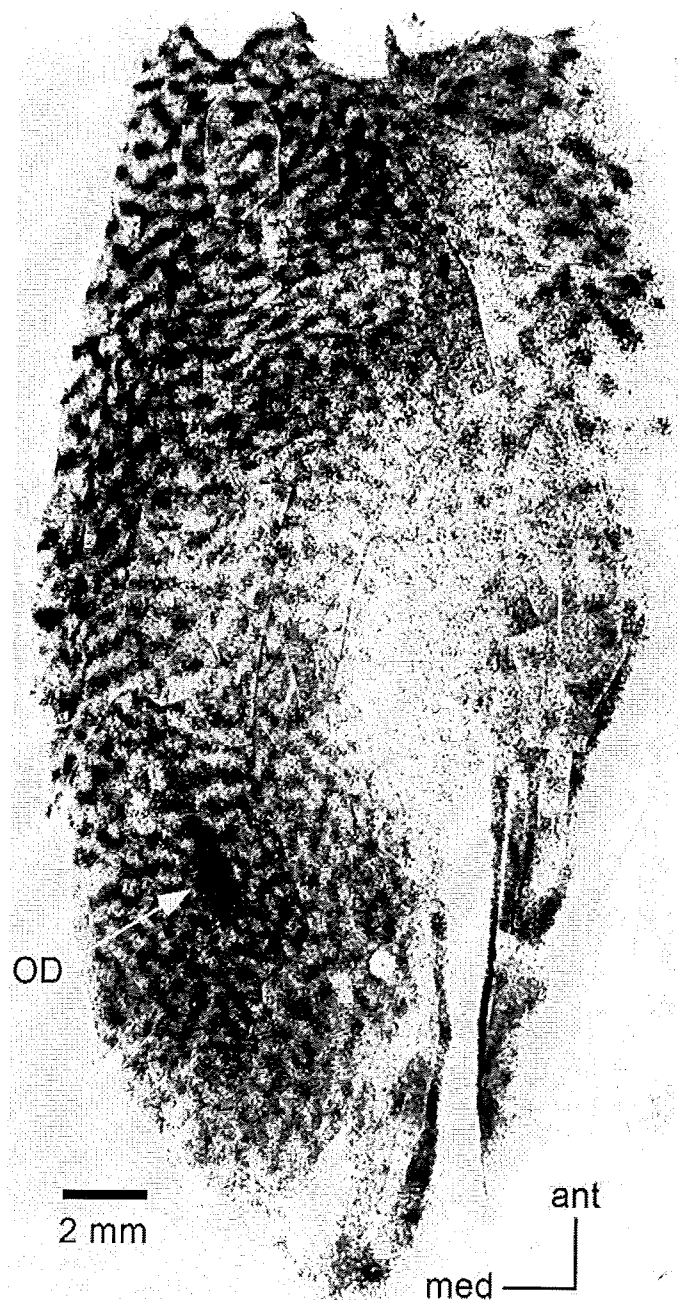


Figure 3. Overall pattern of [^3H]-proline labeled ocular dominance columns in the primary visual cortex of a normal cat. Layout of the geniculocortical afferents in a hemisphere ipsilateral to the injected eye. Abbreviations as in Figure 1. (Figure reproduced with permission from 17 and shown for comparison).

with [^3H]-proline or 2-deoxyglucose autoradiography and also analyzed the spacing of the domains quantitatively. To our surprise, phasic coactivation of the two eyes by strobe-rearing did not prevent ocular dominance column segregation but rather enhanced it as was previously observed with strabismus. The spacing between adjacent domains was not significantly different from normally raised cats. However, as in squinting cats, column spacing tended to be in the upper range of our previously investigated cat population (17).

Strobe illumination creates an environment where patterned visual input is allowed only for short flashes, which phasically coactivate the two eyes. Preliminary evidence of enhanced binocularity after synchronous electrical stimulation of both optic nerves had indicated that the temporal patterning of the input is a critical parameter for ocular dominance segregation (21). However, simultaneous activation of the eyes by the strobe flashes did not prevent ocular dominance segregation but rather enforced the formation of separated domains. Thus, a likely

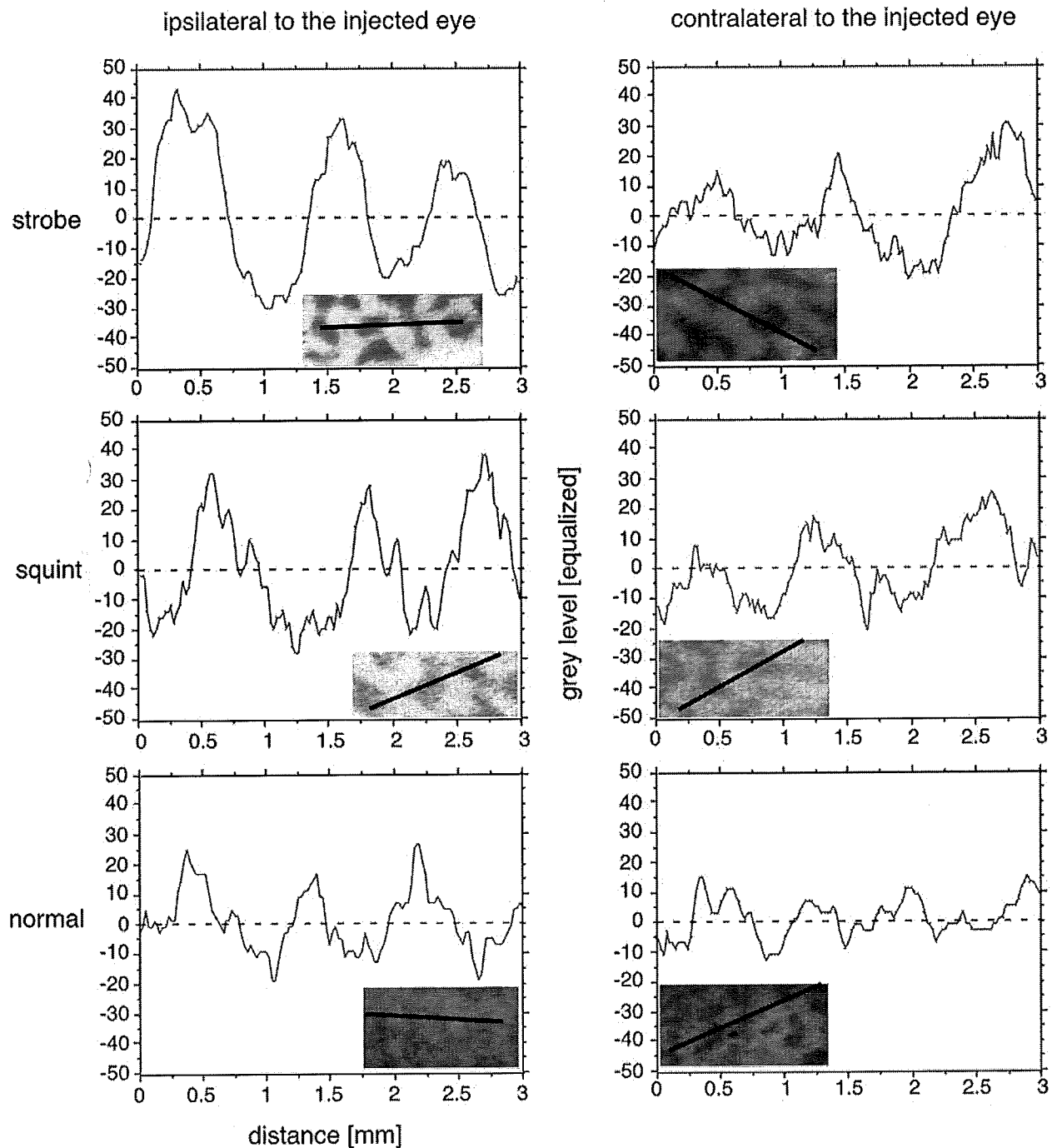


Figure 4. Density measurements on the unprocessed autoradiographs of the strobe-reared, strabismic and normal cats illustrated in Figures 1, 2, and 3. Label density was measured along the vectors depicted in the insets (raw autoradiographs). All spectra were clipped equally and plotted around their respective mean. Positive values correspond to light grey levels (between mean and 255), negative to dark grey levels (between mean and 0). Note, that the dynamics is smallest for the normal cat.

explanation is that spatial interactions limited to the duration of the very short $10\mu\text{s}$ flashes were not sufficient to perform and learn correct vergence movements. As we have observed, all our strobe-reared animals developed a divergent squint angle (and a nystagmus), indicating that vergence movements indeed did not develop normally. This

confirms previous observations of squint and abnormal eye movements in strobe reared kittens (27, 41-42).

2Hz strobe rearing was associated with an increase of monocular neurons in supragranular layers as in squinting cats (27-28). Indeed, also with 8Hz strobe

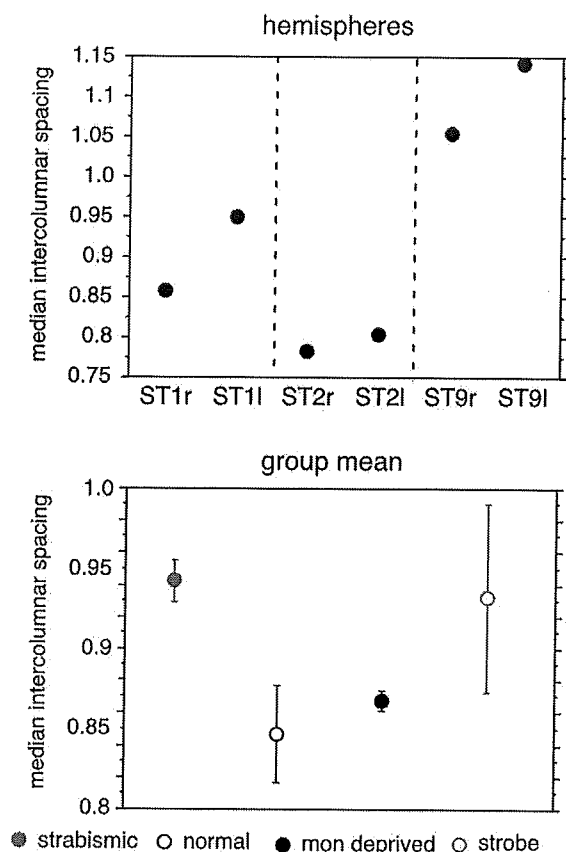


Figure 5. Nearest neighbor analysis of ocular dominance patterns in strobe-reared cats (6 hemispheres of 3 cats) (A) and strabismic ($n=5$), normal ($n=4$) and monocularly deprived ($n=4$) cats for comparison (B, values taken from Schmidt et al., 2002). (A) Medians of the distance distributions for each individual hemisphere. Note that values of the same hemisphere tend to be similar. (B) Rearing group averages of median intercolumnar distances of strabismic, normal, monocularly deprived and strobe-reared cats. Note that the values taken from strobe-reared cats overlap with the values of other rearing groups.

rearing, the ocular dominance pattern we observe is in many aspects very similar to the pattern previously observed in squinters (18-19). Squint induction is known to enhance the segregation of geniculocortical afferents into ocular dominance domains. This is usually interpreted as the outcome of a competition for cortical territory by the geniculocortical afferents of the two eyes. Due to the misalignment of the optical axes in strabismus, the visual input delivered by the two eyes is desynchronized which impedes the development of binocular neurons. Therefore, the enhanced segregation we observe in strobe-reared cats could be a result of the induced squint angle.

Stroboscopic light flashes are known to synchronize cortical responses (43). However, very precise synchronizations in the millisecond range are induced only at flash frequencies higher than 20Hz whereas lower flicker frequencies also induce rate

covariations. It is thus possible that the 8Hz stroboscopic illumination used in the present experiments was not sufficient to induce neuronal synchronization in the millisecond range. Thus, our result supports the interpretation that the segregation mechanism for ocular dominance is dependent on millisecond precision. Obviously, the light flashes were sufficiently long to enable binocular competition at the cortical level. They were, however, most probably not long enough to promote the development of normal vergence movements, which resulted in optically induced strabismus (27). As strobe rearing prevents retinal motion signals (and vergence movements) segregation of ocular dominance domains must have been supported already by the mismatch of responses to stationary contour borders. This also indicates that the segregation mechanism for geniculocortical afferents is feature sensitive and not simply dependent on the global patterning of retinal input (21), emphasizing the role of postsynaptic responses of feature selective cortical cells in ocular dominance segregation (44).

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Binocular phasic coactivation during development

Key Words Visual cortex, Area 17, Postnatal development, Strobe rearing, Ocular dominance column, [^3H]-proline, Column spacing

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