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Two-dimensional analysis of the spacing of ocular dominance columns in normally raised and strabismic kittens

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Abstract In the primary visual cortex of cats, ferrets and macaque monkeys, the thalamocortical afferents conveying signals from the two eyes terminate in alternating regions of layer IV known as ocular dominance columns. Previous experiments have indicated that the periodicity of these columns can be influenced by visual experience: compared to normally raised animals both strabismic cats and cats raised with alternating monocular exposure displayed an increased spacing of adjacent ocular dominance columns in the primary visual cortex (area 17). However, recently it was shown that the formation of ocular dominance columns begins much earlier than previously supposed, indicating that early visual experience might only have a limited influence on the development of the spatial pattern of ocular dominance columns. We therefore visualized the complete pattern of ocular dominance columns in area 17 of normally raised and strabismic kittens during early postnatal development (age 3–6 weeks), particularly focussing on littermates. In addition, we used a previously developed spatial analysis (period statistics) to quantify columnar spacing two-dimensionally. We observed a pronounced interindividual variability in both normally raised and strabismic animals, with column spacings ranging from 783 to 1362 μm . In contrast to previous reports, there were no significant differences in columnar periodicity between normally raised and strabismic cats. These data indicate that rearing has less influence on column spacing while the interindividual variability is much greater than previously supposed, suggesting that genetic differences have an influence on column spacing.

Keywords Area 17 · Columnar spacing · 2-Deoxyglucose · Ocular dominance columns · Strabismus

Introduction

It is generally assumed that the formation of ocular dominance columns is the result of a competitive self-organizing process (e.g., Constantine-Paton 1983; Stryker 1991), whereby the relative columnar sizes are determined by the balance between the activities of the two eyes. When neuronal activity is reduced in one eye (monocular deprivation), projections from this eye occupy much less than their normal share of territory in layer IV, while those from the open eye expand (Wiesel and Hubel 1965; Shatz and Stryker 1978; Schmidt et al. 2002). In strabismic animals, in which the activities of both eyes are equally strong but decorrelated, the formation of alternating ocular dominance columns is enhanced (Shatz et al. 1977; Löwel 1994) and neurons become responsive almost exclusively to stimulation of either the left or the right eye (Hubel and Wiesel 1965).

While the periodicity of the ocular dominance columns has been ascribed to factors intrinsic to the cortex such as cortical interactions or intrinsic to the afferents such as the spread of the afferent terminals (e.g., Miller et al. 1989; Miller and Stryker 1990; for a review of models see Swindale 1996), Goodhill (1993) suggested that the columnar periodicity is determined by the degree of correlation between the eyes' inputs: The stronger the correlation between the eyes, the more often the tendency to form connections with afferents representing corresponding points within both eyes will win over the tendency to form connections with afferents from neighboring cells of one retina, leading to an increased alternation of ocular dominance columns. Hence, in the case of strabismus, which decorrelates the eyes' inputs, the columnar spacing should become enlarged. Support for this suggestion was first supplied by a study by Löwel (1994), showing that the mean spacing of ocular domi-

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nance columns was increased by about 30% in strabismic compared to normally raised cats (see also Goodhill and Löwel 1995). Further support for experience-dependent changes in the spatial periodicity of ocular dominance columns was reported by Tieman and Tumosa (1997): although the effect was less striking, the spacing of ocular dominance columns was 11% wider in cats raised with alternating monocular exposure than in normally raised animals (but see Jones et al. 1996).

Recent experiments have shown that the formation of ocular dominance columns begins earlier than previously supposed. There is evidence that functional ocular dominance columns emerge during the second postnatal week and can already appear adult-like 2 weeks later (Crair et al. 1998; Rathjen and Löwel 2000). In addition, anatomically, the segregation of the thalamocortical afferents seems to begin at the end of the second postnatal week (Crair et al. 2001; see also Crowley and Katz 2000). It is therefore possible that a basic pattern of ocular dominance columns is already fixed at around 2 weeks of age and that visual experience may only have a limited influence on the development of the spatial pattern of ocular dominance columns.

We therefore measured the spacing of the ocular dominance patterns, as revealed by 2-deoxyglucose autoradiography, using two-dimensional period statistics in kittens between 3 and 6 weeks of age. As far as possible pairs of littermates were used. In contrast to previous reports, we found no significant differences in ocular dominance periodicity between strabismic and normally raised kittens. Some of these results have been reported in abstract form (Rathjen et al. 1999).

Materials and methods

To visualize ocular dominance columns in the primary visual cortex (area 17) we used the 2-deoxyglucose (2-DG) technique (Sokoloff et al. 1977; Löwel and Singer 1993). A total of 18 kittens (including five pairs of littermates) were used from our institutes' colonies. In nine kittens, divergent strabismus was induced surgically at postnatal days 14 or 15 (P14 or P15). At an age of 3–6 weeks, the kittens were subjected to a 2-DG experiment while being allowed to move freely around in the laboratory for effective monocular stimulation. Some of these animals had been used in a previous study on the development of functional ocular dominance columns (Rathjen and Löwel 2000). All animal experiments were performed according to the German Law on the Protection of Animals and the corresponding NIH regulations ("Principles of laboratory animal care," NIH publication no. 86–23, revised 1985).

Squint induction

For the induction of strabismus, anesthesia was induced with ketamine hydrochloride (20 mg/kg) mixed with xylazine hydrochloride (1.5 mg/kg), injected intramuscularly. A divergent squint angle was induced by transecting the tendon of the medial rectus muscle of the left eye. To ensure that the kittens were strabismic, we used the corneal reflex method (Sherman 1972; von Grünau 1979) to determine eye alignment. For this purpose, the kittens were restrained manually and at least three flashlight snapshots of the animals' faces were taken weekly until the 2-DG experiment was performed. The distances between the corneal reflexes and the

pupils were measured on the photographs: the ratio of the reflex distance over the pupillary distance is a reliable indicator of eye alignment (Sherman 1972; Sireteanu et al. 1993). The ratios of the examined animals were always below 0.93 (0.81–0.92) and thus in the range of exotropic strabismus throughout the critical period (see Sireteanu et al. 1993).

Surgical and histological procedures

For the application of 2-DG a venous catheter was implanted with the animals under either halothane anesthesia using an inhalation mask (1% halothane in a mixture of 70% nitrous oxide and 30% oxygen) or Saffan anesthesia (15 mg/kg, i.m. injectable steroid, Pitman-Moore Ltd.). After full recovery from anesthesia, one eye was occluded with a black contact lens and 2-deoxy-D-[U-¹⁴C]glucose (Amersham, specific activity 10.9–11.7 GBq/mmol) was injected intravenously at a dose of 3.7–4.2 MBq/kg. After 45 min, the animals received a lethal dose of pentobarbital, injected intravenously. The brains were removed and the visual cortices flat-mounted prior to freezing the tissue on dry ice (Freeman et al. 1987). Subsequently, 25- μ m-thick serial cryostat sections (at -17°C) were cut parallel to the cortical surface. The sections were mounted on glass slides, immediately dried on a hot plate and exposed to X-ray film (Agfa Structurix) for 3–4 weeks.

Image processing and quantitative analyses

Representative 2-DG autoradiographs of supragranular flat-mount sections of the visual cortical hemispheres were digitized in 8-bit gray scales with a resolution of 20.48 pixels/mm using an image processing system (Imago II, Compulog). The columnar spacing was determined on the digitized images by using period statistics, a previously developed technique for the 2D spatial analysis of columnar patterns (Scherf et al. 1994). Period statistics is a simple but robust method for detecting the typical periodicity length of the ocular dominance pattern while ignoring waveform and absolute amplitudes. First, an artifact-free region of interest including only columnar activation patterns within the binocular zone of area 17 (excluding artifacts such as air bubbles or folds) was defined and then the local period lengths were evaluated in that region as follows. The images were high-pass filtered by subtracting the local mean density of gray values. For every pixel, this local mean density was estimated as the average of the gray values in a square region of linear size (5 mm) centered on the respective pixel. In the filtered images, we identified all crossings through the local average along rows and columns of pixels. Crossings with positive and negative slope were stored separately. From these points the histograms of the distances between all pairs of adjacent negative slope zero-crossings and all pairs of adjacent positive slope zero-crossings were calculated in both directions (rows and columns of pixels). This was repeated for rotated versions of the image (rotated in 10° steps up to 170°). Finally, a compound histogram was calculated by averaging the histograms obtained from all image rotations. These compound histograms generally exhibit one clear peak at a well-defined distance of subsequent zero crossings, i.e., there is one most frequently found distance of subsequent zero crossings. This distance was used as the typical periodicity length of an ocular dominance pattern. In order to reduce the influence of noise on the measured periodicity lengths, the calculations described above were performed after preprocessing of the images with a set of gaussian low-pass filters (cutoff wavelengths: 0.1–1.5 mm). Figure 1A shows the influence of the different low-pass filters on the location of the period statistics maxima for a representative 2-DG autoradiograph. As shown in Fig. 1B, there is a pronounced contribution of high-frequency noise to the distribution of the period lengths at lower cutoff wavelengths, while at cutoff wavelengths above 1 mm the signal to be detected is already cut off. Therefore the cutoff wavelength of 0.6 mm was selected for further analyses because there was a plateau in that range in all evaluated 2-DG autoradiographs, indicating that the maxima in that range do not depend sensitively on the preprocess-

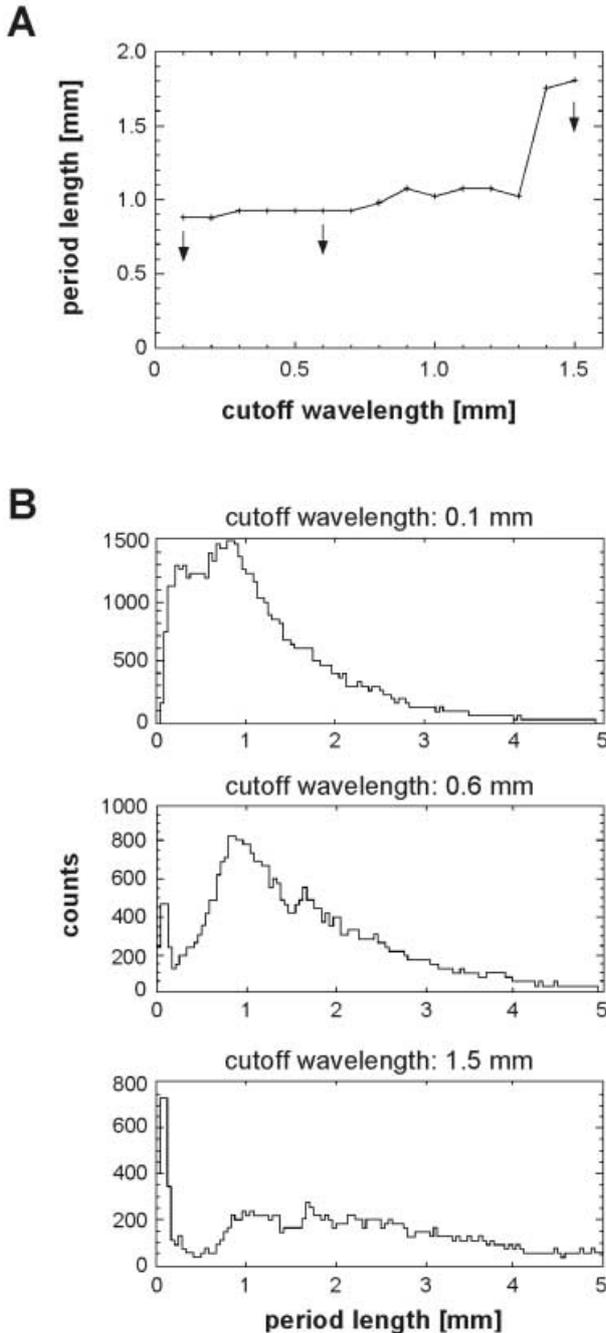


Fig. 1A, B Two-dimensional period statistics as a tool to analyze the spacing of “noisy” biological patterns. **A** Representative example of a period statistics analysis of 2-deoxyglucose (2-DG)-labeled ocular dominance columns from cat area 17. The location of the period statistics maxima of the respective 2-DG autoradiograph depends on the cutoff wavelength of the low-pass filter (*x-axis* cutoff wavelength, mm, of the low-pass filter, *y-axis* period length, mm). The cutoff wavelength of 0.6 mm was selected for further analyses because there was a plateau in that range in all evaluated 2-DG autoradiographs. **B** The effect of applying various low-pass filters on the frequency distributions of period length. Examples of cutoff wavelengths 0.1 mm, 0.6 mm and 1.5 mm (indicated with *downward pointing arrows* in **A**) are given. At 0.1 mm (*upper graph*), there is a pronounced contribution of high-frequency noise to the distribution of the period lengths. At 0.6 mm (*middle graph*), the distribution is displaying a clear peak at around 1 mm while at 1.5 mm (*lower graph*) the signal to be detected (near 1 mm) is already cut off

ing (see Fig. 1A). The spacing of ocular dominance columns was defined as the maximum of the smoothed compound histogram. For every image, this maximum was determined by smoothing the raw compound histogram with a boxcar filter of 3 bins length and determining the maximum bin by simple search. The resulting columnar spacings of the evaluated hemispheres were averaged and displayed for the different age groups. For every hemisphere, one representative 2-DG autoradiograph was analyzed in detail after establishing that across section variability within one hemisphere was small (less than 50–100 μm difference in spacing values within the same hemisphere) compared to the variability across animals (up to 580 μm difference in spacing in different animals).

Results

In all cats, monocular stimulation induced 2-DG-labeled ocular dominance columns that covered the entire area 17 (Fig. 2). The pattern contrast of the ocular dominance columns, however, was fainter in the 3-week-old kittens compared to the older animals (Fig. 2C, D; see also Rathjen and Löwel 2000). Area 17 was reliably discernible by its distinct columnar activation pattern in comparison to surrounding cortical areas. The dark columns represent the open (right) eye input; the pale columns represent the input from the closed (left) eye (the squinting eye in the case of the strabismic kittens). The peripheral visual field representations corresponding to the monocular segment are darkly labeled at the medial border of area 17 in the contralateral hemispheres (right side of left images in Fig. 2A, B), whereas they are lightly labeled on the ipsilateral side (left side of right images in Fig. 2A, B). However, we were not able to delineate the optic disk representations as described previously (Löwel and Singer 1993).

Figure 2A, B shows the 2-DG-labeled ocular dominance patterns of the left and right hemisphere from a pair of 4-week-old littermates. While the kitten in Fig. 2A was normally raised, its littermate in Fig. 2B was raised with a divergent squint angle induced at 2 weeks of age. This comparison shows that there are no obvious differences in pattern layout between ocular dominance columns of normally raised and strabismic kittens. In Fig. 2C, D, the 2-DG-labeled ocular dominance columns of the left hemispheres from two additional pairs of littermates are shown (Fig. 2C: 3-week-old kittens; Fig. 2D: 6-week-old kittens). In each litter, one animal was raised with a divergent squint angle induced at 2 weeks of age and its littermate was normally raised. Like the littermates in Fig. 2A, B, the 2-DG autoradiographs of the related animals do not show striking differences either in the gross layout of the ocular dominance pattern or in the shape of area 17, an observation that holds true for all examined littermate pairs. The ocular dominance patterns in related kittens even display pronounced similarities in pattern layout.

The evaluation of the periodicity of ocular dominance columns using period statistics revealed a high variability both for normally raised and strabismic kittens (Fig. 3). For normally raised animals, the mean spacing was $1042 \pm 136 \mu\text{m}$ (SD) with an observed range from

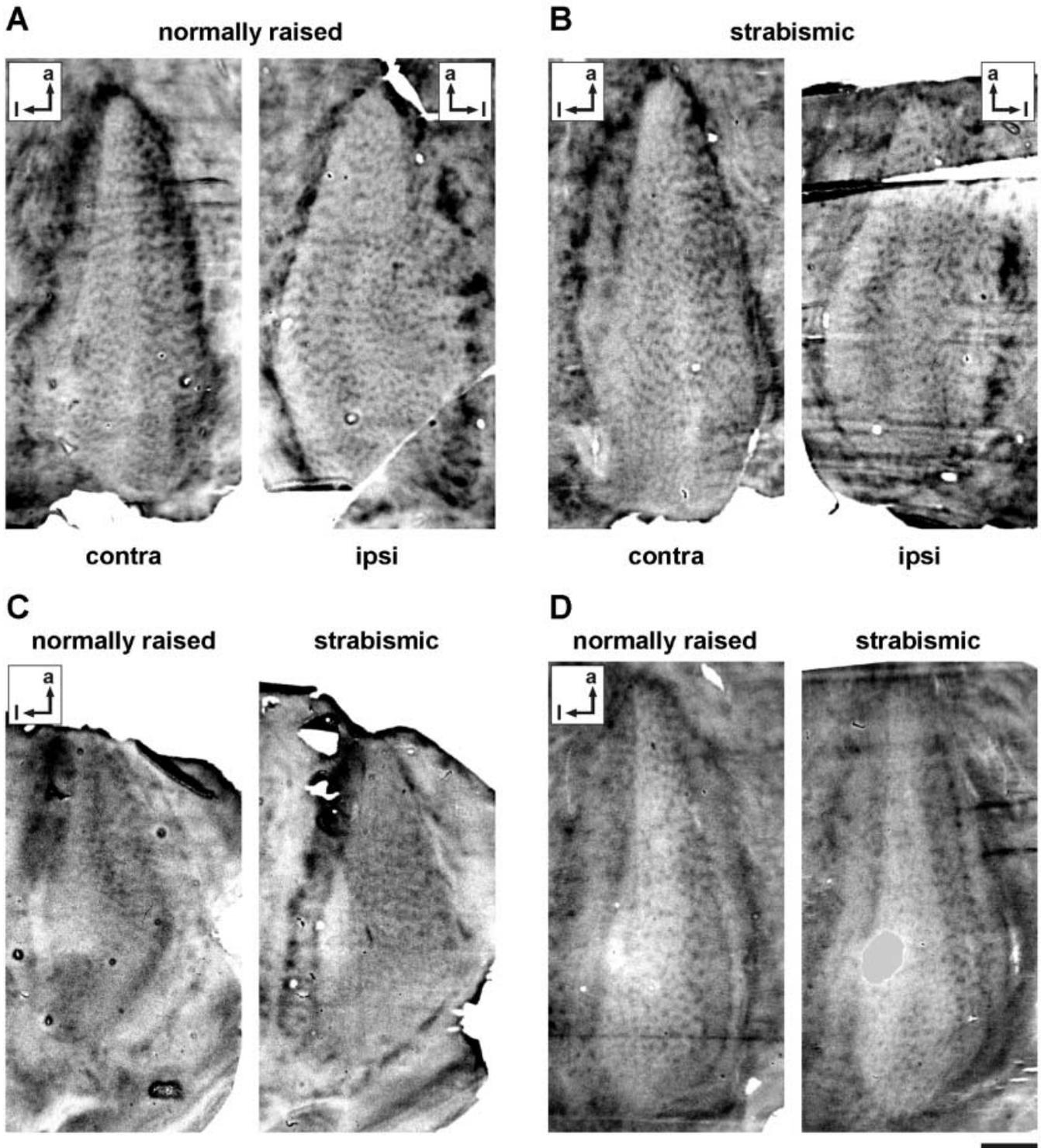


Fig. 2A–D 2-DG-labeled patterns of ocular dominance columns from pairs of littermates. **A, B** 2-DG autoradiographs of supragranular flat-mount sections of unfolded left (*left*) and right (*right*) hemispheres are displayed for 4-week-old kittens. The kitten in **A** was normally raised while its littermate in **B** was raised with a divergent squint angle induced at 2 weeks of age. Both animals had been stimulated through the right eye. Area 17 encompasses the oval-shaped region of the images (containing the patchy activity patterns) that is delineated by darker labeling. The dark patches correspond to activated ocular dominance columns. Note that there are no obvious differences in pattern layout between ocular dominance columns of normally raised and strabismic kittens. **C, D** 2-DG-labeled ocular

dominance columns from two additional pairs of littermates. Animals in **C** were 3 weeks old; those in **D** were 6 weeks old. In each litter, one animal was raised with a divergent squint angle induced at 2 weeks of age (strabismic, *right image* in **C** and **D**) and its littermate was normally raised (*left image* in **C** and **D**). In both cases, the pattern in the left hemisphere (contralateral to the open, right eye) is displayed. Note that due to an artifact, 2-DG labeling is missing in the gray area of the right autoradiograph in **D**. Like the littermates in **A** and **B**, the 2-DG autoradiographs of the related animals do not show striking differences either in the gross layout of the ocular dominance pattern or in the shape of area 17 (*a* anterior, *l* lateral, *contra* contralateral, *ipsi* ipsilateral). Scale bar 5 mm

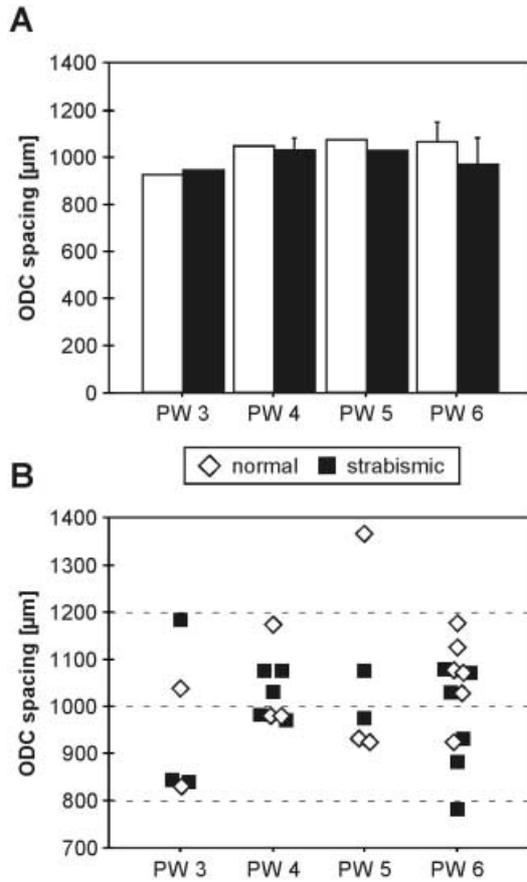


Fig. 3A, B Analysis of the spacing of ocular dominance columns (ODC) in area 17 of normally raised and strabismic kittens aged 3–6 weeks using period statistics. *White bars (A) or diamonds (B)* represent values from normal; *black bars (A) or squares (B)* represent values from strabismic animals. **A** Mean spacing of ODC for 3- (PW 3), 4- (PW 4), 5- (PW 5) and 6-week-old (PW 6) kittens. *Error bars* represent SD ($n \geq 4$). **B** Scattergram of the same dataset illustrating the considerable interindividual variability. Note that there are no significant differences between spacing values of normally raised and strabismic animals

826 μm to 1362 μm . In strabismic kittens, the column spacings ranged from 783 μm up to 1174 μm with a mean value of 987 ± 109 μm (SD). The mean value of all measured spacings was 1013 ± 123 μm (SD). Figure 3 shows the results of the period statistics by presenting calculated mean values for the different age groups as well as a scattergram of the individual data.

The calculation of Mann-Whitney U-tests for the age groups with sufficient entries (4 and 6 weeks) revealed no significant differences between spacing values of normally raised and strabismic animals ($P > 0.1$). The same was true when the sample size was increased by pooling two age groups (3+4 weeks and 5+6 weeks) or when only two categories covering all evaluated ages were formed (all $P > 0.1$). By calculating Spearman rank correlations we found no significant correlations between the weight of the cats or the size of area 17 and the observed ocular dominance column spacings. Figure 4 shows the columnar spacings of all evaluated pairs of littermates.

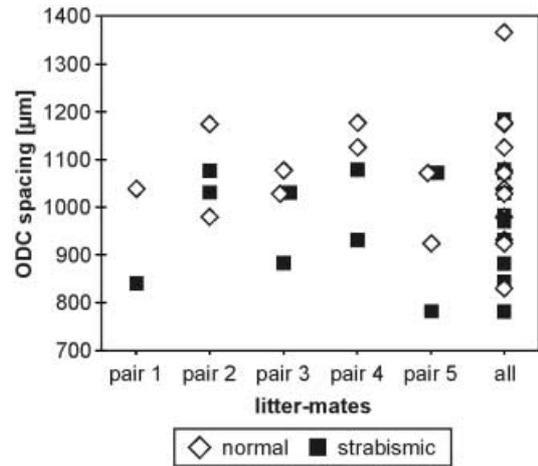


Fig. 4 Spacing of ocular dominance columns (ODC) for the littermate pairs of different ages (pair 1: 3-week-old, pair 2: 4-week-old, pairs 3–5: 6-week-old). For pair 1 the period statistics could only be applied to the left hemispheres. For comparison, the spacing values from all hemispheres are plotted on the right side of the figure. Note that values from normal and strabismic littermates were not consistently different

The itemized list indicates that within related animals the kittens do not show consistent spacing differences compared to their normally raised littermates. This result was independent of the delay between squint induction and the visualization of ocular dominance columns (pair 1: 1 week; pair 2: 2 weeks; pairs 3–5: 3 weeks).

The comparison of spacing values in left and right hemispheres revealed no systematic difference in the ocular dominance periodicities: there was no preference for one of the hemispheres (left or right) to show a wider spacing of ocular dominance columns ($n=12$; chi-square test, $P > 0.1$). This result complements the recent observation of a similar contrast of the 2-DG autoradiographs in ipsi- and contralateral hemispheres throughout early postnatal development (Rathjen and Löwel 2000).

Discussion

The main result of the present study is that strabismus does not seem to influence the spacing of ocular dominance columns in area 17 of kittens aged 3–6 weeks. Using period statistics, a method developed to perform automatized two-dimensional measurements of the space constants of relatively “noisy” biological patterns, we obtained distributions of column spacings in the two experimental groups that nearly completely overlapped and did not display any significant differences between the normally raised and strabismic animals at any of the evaluated ages between 3 and 6 weeks. These results are not easy to reconcile with previous reports, indicating that the decorrelation of activity between the two eyes either by strabismus or by alternating monocular exposure (Löwel 1994; Tieman and Tumosa 1997; but see Jones et al. 1996) leads to an increased spacing of adja-

cent columns in the primary visual cortex of cats. There are several possible interpretations of the observed discrepancy.

First, it is possible that the absence of an increased columnar spacing can be attributed to the difference in the timing of squint induction. In the present study, squint was induced at an age of 14–15 days while the cats in the previous study by Löwel (1994) were 17–18 days old at squint onset. The earlier squint onset was chosen due to theoretical considerations in an attempt to maximize possible squint-induced changes to columnar layout (Hoffsäumer et al. 1995). In a previously published theory, ocular dominance patterns develop from an initial homogeneous state whereby the wavelength of the emerging ocular dominance columns depends on the exact timepoint at which the initial state becomes unstable. Assuming that the instability threshold will be attained faster in strabismic cats compared to normally raised animals, the former should develop larger-sized ocular dominance columns compared to the latter (Wolf et al. 2000). Accordingly, the earlier the divergent squint angle is induced, the more pronounced the effect should be. A similar relation had been observed previously in macaque monkey striate cortex for the effect of monocular deprivation: Horton and Hocking (1997) reported that the earlier monocular eyelid suture was performed (at ages 1–12 weeks), the more severe the degree of column shrinkage. However, in the present study, earlier squint induction did not lead to a more pronounced increase in column spacing as expected theoretically. In contrast, the effect could not be observed at all, which fits the recent observation that ocular dominance columns in strabismic and normal kittens probably emerge at similar times during postnatal development (Rathjen and Löwel 2000). A possible explanation for the conflicting results would be to assume a sensitive period in cortical development during which the spacing of the pattern of ocular dominance columns can be influenced by decorrelated activity of the two eyes. This sensitive period may not start before 2 weeks of age and may last only for several days because functional ocular dominance columns already look adult-like at 4 weeks of age (Rathjen and Löwel 2000). On the one hand, this assumption may appear rather unlikely since first signs of ocular dominance segregation have already been detected in 2-week-old kittens with both optical imaging (Crair et al. 1998) and anatomical methods (Crair et al. 2001). By the same token, squint is not expected to cause a comparable change of the spacing of ocular dominance columns in macaque monkeys because in this species the columnar patterns appear fairly developed at birth (Horton and Hocking 1996a). This is exactly what has been reported recently from a number of laboratories (Tychsen and Burkhalter 1997; Crawford 1998; but see Roe et al. 1995; for the spacing of cytochrome oxidase blobs see Murphy et al. 1998). On the other hand, the observation that orientation domains emerge over a period of only a few days (Chapman and Stryker 1993; Chapman et al. 1996; Crair et al. 1998) makes it conceiv-

able that a possible critical period for column spacings may also last only a couple of days.

Second, it is possible that ocular dominance spacing can still be changed in animals older than 6 weeks. There could be differences in maturation velocities of column systems induced by the different rearing conditions so that ocular dominance column development might not have been finished for all cats during our investigation period. However, to finally decide this issue a longitudinal study of column layout in single animals would be necessary.

Third, our study reveals that the variability of columnar spacings is much larger than previously assumed. Together with the fact that the spacing of ocular dominance columns in strabismic kittens was not different from their normally raised littermates, this indicates that genetic differences might have an influence on columnar spacing or on the susceptibility for activity-related factors. The presented data show that the spacing of ocular dominance columns ranged from 830 to 1360 μm in normally raised and from 780 to 1170 μm in strabismic kittens. In previous analyses of ocular dominance column periodicity, the spacing values were reported to cluster around 800 μm or up to 1100 μm (Löwel and Singer 1987; Löwel et al. 1988; Swindale 1988; Diao et al. 1990; Löwel 1994; Murphy et al. 1996; Tieman and Tumosa 1997). A larger variability has, however, been reported for ocular dominance columns in macaque monkey striate cortex (column width 395–670 μm within six monkeys, indicating an approximate column spacing of 790–1340 μm ; Horton and Hocking 1996b). In the study by Löwel (1994), a range of 500 μm was observed between the smallest column spacing in a normally raised animal (770 μm) and the largest spacing in a strabismic animal (1270 μm). In the present study, this range of column spacings was already observed within the normal cats. In addition and in contrast to the older study in which littermates were always raised together either as squinters or as normal controls (Löwel 1994), we used littermate controls by making one kitten strabismic and raising its littermate normally to guarantee a similar genetic background on which to test the influence of rearing on column spacing. Interestingly, reanalysis of the previous dataset (Löwel 1994) with respect to litter membership revealed that there was a strong similarity of column spacings in littermates compared to the inter-individual variability among normally raised animals (Schmidt et al. 2002). Taken together, these results indicate that it is difficult to disentangle the influence of litter membership and visual experience on column spacings in the previous study (Löwel 1994) and that it is possible that the observed similarity of column spacings in strabismic cats had rather been due to their litter membership than to their particular visual experience. Indeed, a recent study suggests that there is a substantial genetic influence on quantitative features of column layout in cat area 17 because the spacing of orientation columns is much more similar in the two hemispheres of individual brains and in related cats compared to the overall inter-

individual variability in non-related animals (Löwel et al. 2000a, 2000b). Interestingly, a comparison of ocular dominance columns in normal and strabismic squirrel monkeys revealed a tendency for strabismic monkeys to have wider columns, but the authors report that the data are confounded by the tremendous intrinsic variability of column width among normal animals, suggesting the possibility that genetic factors (e.g., parentage, colony origin) may influence column width (Horton et al. 1999).

Despite the ongoing maturation of ocular dominance columns in the first few weeks of life in cats there is new functional and anatomical evidence showing that a pattern of ocular dominance columns starts to be visible already at the time of eye opening in the second postnatal week (Crair et al. 1998, 2001; see also Crowley and Katz 2000). If squint is induced after ocular dominance columns have formed, as might have been the case in the present study, one would not expect to observe a general change in column layout and the spacing should be the same as in normal animals (Wolf et al. 2000). This is indeed what we observed. It may therefore be that in cats as in primates, visual experience selects and maintains the visual circuitry within the existing spatial pattern but is not able to change the basic spatial geometry. An unchanged spacing of ocular dominance columns in strabismic cats could further explain the observation that in these animals the topographic relationship between ocular dominance and orientation maps is the same as in normally raised controls (Löwel et al. 1998).

In summary, our present results demonstrate that strabismus induced at postnatal days 14 or 15 does not alter the periodicity of ocular dominance columns in cats aged 3–6 weeks. More detailed quantitative comparisons between the spacings of genetically related animals are needed to determine how far hereditary components are responsible for the observed considerable variability of the columnar patterns or whether its periodicity is mutable by visual experience. In that case the precise timing of altered visual experience should be crucial in determining whether activity-dependent effects can be observed or not.

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