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Effects of binocular deprivation on the development of clustered horizontal connections in cat striate cortex

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ABSTRACT **Intrinsic horizontal axon collaterals in the striate cortex of adult cats specifically link columns having the same preferred orientation; consequently, retrograde tracer injections result in intrinsic labeling that is sharply clustered. We have previously shown that the normal development of this circuitry involves the emergence of crude clusters from an unclustered pattern during the second postnatal week. Crude clusters are later refined to the adult level of specificity by the selective rearrangement of axonal arbors that initially project to incorrect orientation columns. Here we report that depriving animals of patterned visual experience by binocular lid suture prior to natural eye opening had no discernible effect on the emergence of crude clusters. In contrast, cluster refinement was dramatically affected by binocular deprivation. Injections of retrograde tracers in the striate cortex of animals binocularly deprived for >1 month revealed only crude clusters, indicating that horizontal axon collaterals projecting to incorrect orientation columns were retained well past the age when they normally would have been eliminated. Layer 2/3 pyramidal cells from 6-week-old binocularly deprived animals had abnormal distributions of intrinsic horizontal axon collaterals that mirrored the lack of cluster refinement. The radial clustering of their horizontal collaterals was considerably less precise than normal. These cells, nevertheless, developed many of the features of normal mature arbors, including the distal axonal branches not seen in arbors from younger animals with normal visual experience. Together, these results indicate that axonal rearrangements occurred, but with reduced specificity. Thus, binocular deprivation did not simply arrest the development of this orientation-specific circuit at an immature state but limited the accuracy with which axon collaterals were added or eliminated. We suggest that development of this orientation-specific circuitry, like ocular dominance column segregation, may depend on temporal correlation of activity for regulation of axonal rearrangement. The specificity of rearrangement may be degraded in binocularly deprived cats because they do not experience sharply oriented visual stimuli necessary for concurrent activation of same-orientation columns.**

Pyramidal neurons in layer 2/3 and layer 5 of adult cat striate cortex have long intrinsic axon collaterals that project horizontally for several millimeters and elaborate clusters of finer terminal branches within isoorientation domains (1–4). Because these connections are reciprocal, clustered horizontal connections can be demonstrated either by intracellular filling of individual neurons (2–4) or by injection of retrograde tracers into the cortex (1). The latter method results in distinct clusters of retrogradely labeled cells at intervals of roughly 1 mm surrounding the injection site. Clusters of labeled cells are localized to columns having the same orientation specificity as the injection site (1).

Injections of retrograde tracers during the first postnatal week reveal intrinsic horizontal connections extending up to 2 mm, but which are not clustered (5). Clustering of retrograde label appears during the second postnatal week but is crude (see Fig. 1*a*); many cells between clusters are labeled, indicating aberrant projections to the injection site. By the end of the fourth postnatal week the adult-like pattern of labeling is observed; very few retrogradely labeled cells are present between clusters (see Fig. 1*b*). Thus, cluster development can be considered in two stages: the initial appearance of crude clusters and their subsequent refinement. Cluster refinement is also apparent as a reorganization of the radial distribution of long axon collaterals originating from individual layer 2/3 pyramidal neurons. The transition from crude to refined clusters results from the elimination of axon collaterals projecting to incorrect orientation columns and not from the death of cells making incorrect connections (5).

To determine whether patterned visual activity influences either the normal formation of crudely clustered connections or their refinement, retrograde tracers were injected into the striate cortex of cats whose eyelids were sutured shut prior to natural eye opening. Individual layer 2/3 pyramidal neurons were also intracellularly stained with Lucifer yellow to assess the effects of binocular deprivation on the development of horizontal axon collaterals.

METHODS

Binocular Lid Suture. Kittens that had not yet opened their eyes (all <7 days old) were anesthetized with halothane (2–4% in O_2). Their eyelids were then gently pulled apart and sutured shut by methods used by others (6). Binocular deprivation was maintained until the animals were killed.

Retrograde Tracer Injections. Details of methods for tracer injections and analysis of retrograde labeling have been described (5). Briefly, red or green fluorescent latex microspheres, retrograde neuronal tracers (7, 8), were injected into the striate cortex of cats under halothane anesthesia. Injection sites were typically 100–400 μm in diameter and extended in a column perpendicular to the cortical laminae. Injections were confined to area 17 as evidenced by the distribution and sizes of retrogradely labeled cells in the lateral geniculate nucleus.

Patterns of intrinsic label were analyzed by selecting a representative tangential section through superficial layers (2/3) of flattened striate cortex. The position of each retrogradely labeled cell was digitized to allow computerized calculations of cell densities. Density distributions were determined by a window smoothing method. For the pseudocolored images shown in Fig. 1, the color of each pixel corresponds to the density of labeled cells within a 250 μm × 250 μm square window centered at that pixel. For example, in Fig. 1*a*, the brightest red corresponds to a density of 800 cells per mm^2, the intermediate shade of green corresponds to 400 cells per mm^2, and the darkest blue corresponds to 1

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Abbreviation: P, postnatal day.

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cell per mm^2. Black corresponds to densities of <1 cell per mm^2 and white corresponds to densities of >800 cells per mm^2.

Intracellular Staining. Details of intracellular staining and reconstruction of cells have been described (5). Living tangential slices of cat striate cortex were cut parallel to the cortical laminae at a thickness of 350 μm using a vibratome. Only the most superficial slices (corresponding to layer 2/3) were retained. Individual neurons were intracellularly impaled with a Lucifer yellow-filled microelectrode and iontophoretically filled. Slices were then sectioned at 50 μm and axonal arbors were reconstructed by camera lucida drawing.

Analysis of Interaxon Intervals. The distributions of long horizontal axon collaterals (extending >400 μm from the cell body) were assessed by drawing a circle with a 400-μm radius around the cell body of each reconstructed neuron and recording the positions of axon collaterals crossing this circle. For each cell the angles between every pair of axon collaterals (interaxon intervals) were determined. Any given pair of axons must be 0° to 180° apart, and if their radial positions are determined at random, the actual interaxon interval will occur at any given distance with equal probability. Thus, for an idealized random distribution of radially projecting axons, the distribution of interaxon intervals is flat. Actual distributions of interaxon intervals were compared to one another and to the theoretical random distribution using the χ^2 test.

Because the number of intervals for each cell was small, significant variations were only evident for the few cells having the largest numbers of long horizontal collaterals. Therefore, the values from all cells in a group (normal 3-week, normal 6-week, or 6-week binocularly deprived) were pooled. Statistical comparisons were then made for these pooled distributions. It is important to note that differences between the pooled distributions do not necessarily reflect differences between individual cells within the various groups. Rather, the distributions of pooled interaxon intervals contain information regarding the relative positions of a large population of horizontal axon collaterals from many cells. Pooling of intervals to attain increased population sizes for statistical comparisons is appropriate as long as any observed differences are interpreted as differences between the populations of axon collaterals, not between the distributions for individual cells.

A distance of 400 μm was chosen for this analysis because we were interested only in the distributions of long collaterals that link isoorientation columns (1). In addition to these collaterals, layer 2/3 pyramidal neurons have a cluster of highly branched local collaterals immediately surrounding their somata and sometimes extending up to 300 μm before terminating (see Fig. 2). Thus, it was necessary to assess only the collaterals extending beyond this local region. Long axon collaterals elaborate clusters of collateral branches distant from the cell body (see Fig. 2) and these can occur as close as 500 μm from the cell body. Therefore, selecting a distance of 400 μm for analysis also avoids mistaking these collaterals for the long collaterals responsible for linking clustered regions.

Counts of axon collaterals intersecting a radius at 400 μm from the cell body were used to assess developmental changes in the numbers of long collaterals per cell. This method almost certainly underestimates the number of long collaterals since the entire axonal arbor is not likely to be confined to the 350-μm-thick cortical slice. These counts are useful, however, as a relative measure allowing comparisons between populations of neurons at different ages. Also, the exclusion of axons outside the plane of a slice does not invalidate the analysis of interaxon intervals (see above). This analysis determines the relative positions of pairs of axon collaterals and the random exclusion of some pairs will not systematically change the overall distributions.

RESULTS

Retrograde Labeling. Fig. 1*c* shows the pattern of intrinsic retrograde label observed in a tangential section through superficial layers of flattened cortex after injection of fluorescent latex microspheres in area 17 of a 2-week-old binocularly deprived kitten. The labeled cells were crudely clustered and the overall pattern was indistinguishable from that observed for normal kittens of the same age (compare to Fig. 1*a*). Thus, in agreement with previous reports (9, 10), patterned visual experience was not obligatory for the initial formation of crude clusters.

Although patterned visual activity was not required for the formation of crude clusters, binocular deprivation profoundly affected cluster refinement. The pattern of retrograde label observed for binocularly deprived cats after the fifth postnatal week is shown in Figure 1*d*. Clustering was crude, similar to that observed in normal animals during the second or third postnatal week (compare to Fig. 1*a*). Unlike the sharply defined clusters of retrograde label normally observed at this age (see Fig. 1*b*), numerous cells between clusters were labeled, apparently because they maintained connections to the injection site that normally would have been eliminated. Similar results were obtained from four injections in two binocularly deprived animals at this age (P38–P40). Thus, binocular deprivation altered the development of intrinsic horizontal circuitry such that connections to regions where they normally would have been eliminated by the fourth postnatal week were present during the sixth postnatal week.

Intracellular Staining. The experiments described above indicated that development of horizontal axons was altered by binocular deprivation. To understand which of the changes that occur during the normal rearrangement of individual axonal arbors might have been altered by binocular deprivation, neurons were intracellularly stained with Lucifer yellow in living tangential slices of striate cortex. Our sample was limited to pyramidal cells in layer 2/3 (see *Methods*). In normal adult cats, axonal arbors of individual pyramidal cells have radially clustered long horizontal collaterals projecting away from the cell body that also elaborate clusters of fine collaterals at periodic intervals distant from the cell body (2–4). We have previously reported that this pattern of axonal arborization is observed in 6-week-old cats (see Fig. 2*a*) and that radial clustering results from the specific elimination of long collaterals, whereas distant clusters arise from the specific addition of fine collateral branches (5).

We have increased our sample of cells from normal animals at 3 weeks, when clusters are crude, and 6 weeks, when clusters are refined, to allow quantitative analyses of their axonal arbors (see *Methods*). Consistent with our original report (5), we found that the radial distribution of long collaterals (those extending more than 400 μM, see *Methods*) was unclustered at 3 weeks (Fig. 3*a*), but extremely clustered at 6 weeks (Fig. 3*b*). There was a significant increase in the percentage of collaterals spaced <15° apart and a significant decrease of those spaced 15° to 75° apart. The many closely spaced collaterals correspond to radial axon clusters, whereas the paucity of larger angular separations corresponds to gaps between radial clusters. We were surprised, however, to find that the average number of long horizontal collaterals per cell increased between 3 and 6 weeks, from 5.9 ± 0.8 (mean ± SEM, 15 cells) to 9.2 ± 1.4 (9 cells). Thus, the normal maturation of horizontal axonal arbors involves the addition of collaterals within radial clusters as well as elimination of incorrectly projecting collaterals between clusters

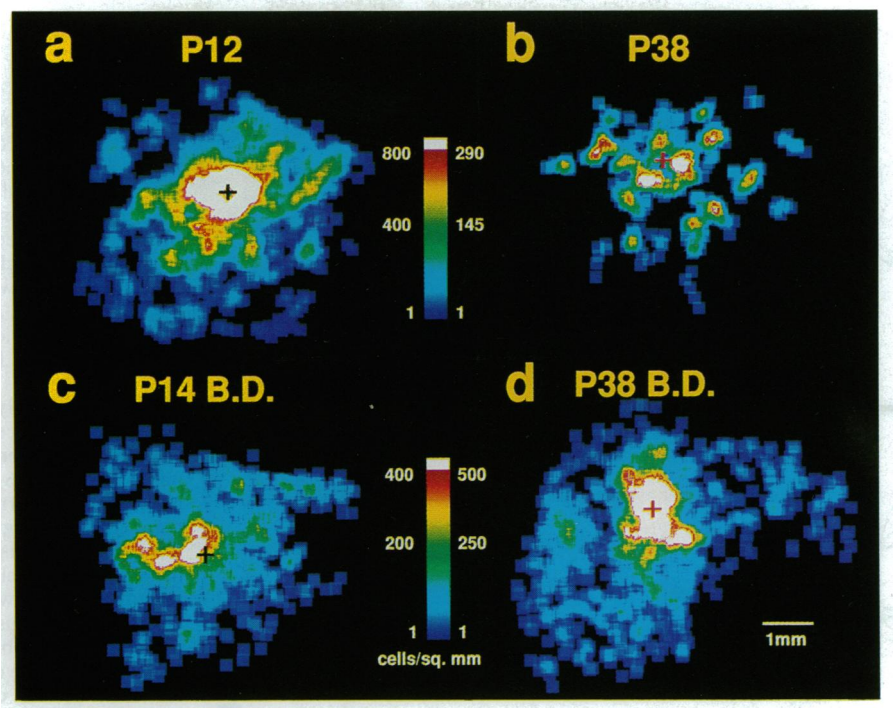

FIG. 1. Intrinsic retrograde label in tangential sections through superficial layers of flattened striate cortex. Each panel shows a pseudo-colored representation of the densities of cells labeled by an injection of fluorescent latex microspheres in area 17. Locations of injection sites are indicated by a cross near the middle of each panel. (*a*) Retrograde label resulting from a microsphere injection in a normal cat at about 2 weeks postnatal (P12). There were high densities of retrogradely labeled cells within clusters spaced roughly 1 mm apart and extending several millimeters from the injection site. Many retrogradely labeled cells between clusters made projections to the injection site, giving the clusters a crude appearance. (*b*) The pattern of retrograde label normally observed after 4 weeks postnatal (in this case P38). Sharply defined clusters with high densities of labeled cells separated by gaps with very low densities give the clusters a refined appearance. Few cells made inappropriate projections to the injection site. (*c* and *d*) Labeling from animals deprived of normal visual experience by binocular lid suture prior to natural eye opening. (*c*) Results from a microsphere injection in a 2-week-old (P14) binocularly deprived (B.D.) kitten. Cells were arranged in the crudely clustered pattern typical for normal animals of this age (compare to *a*). (*d*) Labeling in a 5½-week-old (P38) binocularly deprived (B.D.) cat. Clusters of labeled cells spaced about 1 mm apart were evident but clearly not refined as would normally be observed at this age (compare to *b*). The high density of labeled cells between clusters resulted in a crudely clustered labeling pattern similar to that normally seen during the second postnatal week (compare to *a*). (Bar = 1 mm.)

(see also *Discussion*). Subsequently, fine collateral branches are added at periodic intervals along the long collaterals and specifically within appropriate target regions (5).

The abnormal pattern of retrograde labeling observed in 5- to 6-week-old binocularly deprived animals indicated a persistence of connections to incorrect orientation columns. To determine how this change was manifested at the level of individual axonal arbors, pyramidal cells from 6-week-old binocularly deprived cats were intracellularly stained and analyzed. The axonal arbors of these neurons (Fig. 2 *b–d*) were similar in many respects to neurons observed in normal 6-week-old cats (Fig. 2*a*). They had long horizontal axon collaterals with clusters of finer collateral branches distant from the cell body, and the long collaterals were often radially clustered. The average number of long collaterals per cell was also normal [9.2 ± 1.4 for 6-week-old normal cells (n = 9) vs. 9.1 ± 1.6 for 6-week-old binocularly deprived cells (n = 14)]. However, consistent with the observation that retrogradely labeled cell clusters in binocularly deprived cats were not refined, the radial clustering of long collaterals was substantially less precise than normal. For example, the radial distribution of long collaterals was relatively continuous over a much larger extent (bracketed by arrows in Fig. 2 *b–d*) than observed for normal cells of this age (compare Fig. 2*a*).

Quantitative analyses also indicated a significant difference in the radial distribution of long collaterals from 6-week normal vs. binocularly deprived neurons (Fig. 3*b* vs. Fig. 3*c*). For both groups, the percentage of collaterals spaced <15° apart (radially clustered collaterals) was significantly greater than for either a random distribution or the normal distribution at 3 weeks (Fig. 3*a*), indicating that axon collaterals from normal and binocularly deprived cells underwent some degree of reorganization. In normal animals, however, the percentage of intervals in the 15° to 75° range decreased between 3 and 6 weeks, reflecting the loss of inappropriate projections between radial clusters. But for collaterals from 6-week-old binocularly deprived neurons there was a significant *increase* in the range of 15° to 45°. There were 50% more values in this range than normally observed at 6 weeks. More detailed statistical comparisons are presented in the legend to Fig. 3.

DISCUSSION

In addition to describing the effects of binocular deprivation on development of horizontal intrinsic circuitry we have extended our studies of normal maturation. This involved quantitative analysis of an increased sample of intracellularly stained neurons. Although analysis of the radial positions of long axon collaterals confirmed our original report that radial clusters arise from an initially unclustered distribution (5), we made one finding that differed from the original interpretations made from qualitative observations. Based on very small samples of intracellularly stained neurons from 3- and 6-week-old cats, it appeared that the number of long axon collaterals per cell decreased during cluster refinement. It is now apparent, however, that there is a great deal of variability between cells of a single age and that the *average* number of long collaterals per cell actually increases. Thus, for at least some cells there is a net increase in long collaterals,

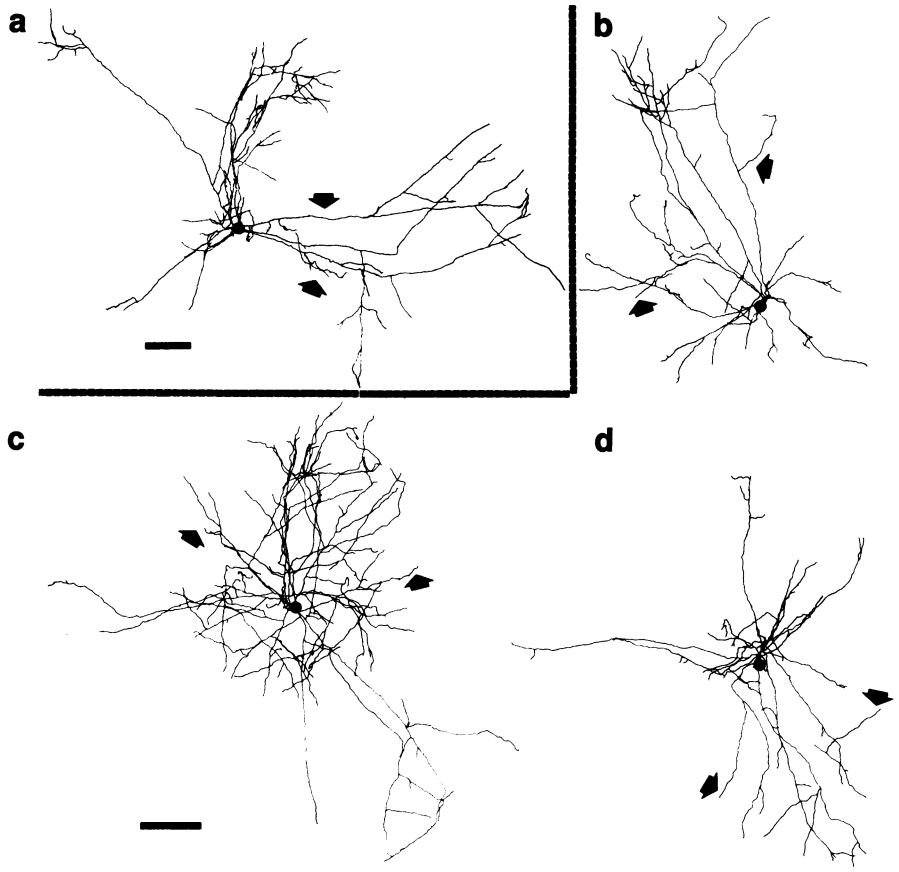

FIG. 2. Horizontal axonal arbors of pyramidal cells from superficial striate cortex of a normal 6-week-old cat (*a*) and 6-week-old binocularly deprived cats (*b–d*). Dendritic arbors are omitted and cell bodies are indicated by filled circles near the center of each figure. (*a*) Normal axonal arbors at 6 weeks had an adult-like appearance with prominent clusters. Clustering was evident in the radial distribution of long horizontal collaterals (one such cluster is bracketed by arrows) and the more highly branched collaterals distant from the cell body. (*b–d*) Horizontal axonal arbors of cells from binocularly deprived, 6-week-old cats. Like neurons from normal 6-week-old cats, these cells had long horizontal collaterals that elaborated clusters of finer branches distant from the cell body. The long horizontal collaterals were also radially clustered, but these clusters were not as tight as normal. Most obvious was the greater radial extent of the clusters; for example, for each of the cells, rather closely spaced long collaterals subtended an abnormally large angle (shown bracketed by arrows at 400 μm from the cell body). This difference was also apparent from quantitative analyses of the distances between pairs of axons shown in Fig. 3. (Bars = 200 μm.)

whereas a net reduction for other cells initially extending large numbers of collaterals cannot be ruled out. At any rate, previous retrograde tracer experiments showed definitively that refinement of clusters results at least in part from the specific elimination of incorrectly projecting axon collaterals (5). We therefore conclude that elimination of incorrectly projecting collaterals and addition of axon collaterals to correct orientation columns normally occur during cluster refinement.

Retrograde tracer experiments showed that crude clusters can emerge even in binocularly deprived cats. This finding is in agreement with previous reports (9, 10). The presence of crude orientation columns in neonatal animals (11–13) and the formation of crude clusters in the absence of normal patterned visual activity suggest that there may be an intrinsic, activity-independent framework designating the presumptive positions of orientation columns (5, 9). Our observations on binocularly deprived cats do not, however, rule out the possibility that spontaneous activity could play an important role in the development of crude columns. If this were the case, manipulations that more profoundly reduce visual cortical activity would have predictable effects on the development of horizontal connections. For example, cortical infusion or intraocular injection of tetrodotoxin (14) initiated during the first postnatal week might prevent the *emergence* of orientation columns and/or clustered horizontal connections.

Although binocular deprivation had no discernible effect on the emergence of a crudely clustered pattern of retrograde labeling, it did prevent the normal refinement of clusters. Binocular deprivation resulted in the maintenance of connections to inappropriate target regions for at least 2 weeks past the time when refined clusters are normally present. Since the normal rearrangement of individual axonal arbors involves the specific elimination of long collaterals, and the specific addition of long collaterals and finer distal collateral branches in correct locations, the presence of incorrect connections could have resulted from the disruption of any of these events. Analysis of intracellularly stained neurons revealed that modifications typical of maturing axonal arbors in normal animals also occurred in binocularly deprived animals. These included reorganization of the radial positions of long collaterals, an increase in the average number of long axon collaterals per cell, and the addition of clusters of finer distal branches. But, since incorrect connections were maintained in binocularly deprived cats and the radial distribution of long collaterals was significantly less clustered than normal, the specificity of these changes must have been reduced. Thus, binocular deprivation does not prevent the maturation of horizontal axonal arbors, but the *specificity* of horizontal axon rearrangements *does* depend on patterned visual activity.

Our results conflict with those reported by Luhmann *et al.* (9, 10) on several counts. We have discussed discrepancies related to the normal development of clustered connections in an earlier report (5) and remain unable to reconcile those differences. Discrepancies related to cluster development in binocularly deprived animals are more easily reconciled. Luhmann *et al.* (10) reported that binocular deprivation had no effect on cluster development during the first 6 postnatal weeks. We, however, observed a lack of refinement of clustered connections in binocularly deprived animals. The inconsistencies between these findings can be attributed to methodological differences. Luhmann *et al.* (10) have not observed cluster refinement in either normal or binocularly deprived animals, probably because they usually used tracers that result in relatively large injection sites. Since the injection sites were large relative to the distances over which orientation columns repeat, labeling between clusters would be expected even after elimination of connections to incorrect orientation columns. In the few cases in which Luhmann *et al.* used fluorescent latex microspheres, the tissue was not sectioned in the tangential plane (10), making subtleties in the degree of clustering impossible to observe without serial

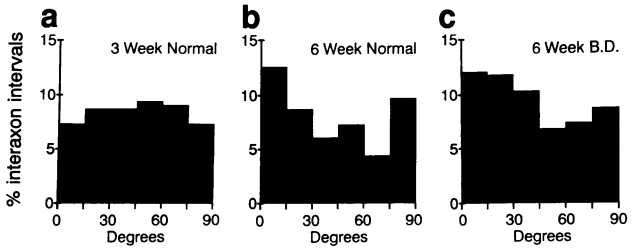

FIG. 3. Histograms showing the distributions of the angles between long (>400 μm) horizontal axon collaterals (interaxon intervals, see text). Interaxon intervals are divided into 15° bins and although the values ranged from 0° to 180°, for clarity only those <90° are shown. Analysis of 15 pyramidal cells from normal 3-week-old cats yielded 287 angles between axon collateral pairs. Their distribution is shown in *a*. Interaxon intervals at this age were distributed evenly over the entire range, reflecting the unclustered distribution of long collaterals. The percentage of values within the 15° bins did not vary significantly ($P > 0.1$, χ^2 test) from random (an even, flat distribution with 8.3% of values in each bin; see text) for any bin. (*b*) Marked radial clustering of long axon collaterals from 6-week-old normal cells. Nine cells yielded 413 angles between axon collateral pairs. The percentage of angles <15° was 52% greater than expected at random ($P < 0.005$) and 73% greater than observed at 3 weeks ($P < 0.025$), reflecting the disproportionate number of closely spaced axons within radial clusters. The gaps between clusters were evident as a paucity of angles between 15° and 75°. The percentage of angles observed in this range was 21% less than expected at random ($P < 0.005$) and 27% less than observed at 3 weeks ($P < 0.01$). (*c*) Distribution of 735 interaxon intervals from 14, 6-week-old binocularly deprived (B.D.) cells. Like the distribution from normal 6-week-old cells, the percentage of interaxon intervals <15° was greater than random and greater than observed normally at 3 weeks. The percentage of intervals <15° was 46% greater than expected at random ($P < 0.005$) and 66% greater than for normal 3-week-old cells ($P < 0.05$). However, unlike normal 6-week-old cells, an increase occurred over the entire range from 0° to 45°. There were 37% more intervals at 0–45° than expected at random ($P < 0.005$) and 39% more than in the normal 3-week-old group ($P < 0.005$). The percentage of intervals at 15–45° was also 50% greater than normally observed at 6 weeks ($P < 0.005$).

reconstruction. In addition, even if the subtle differences between crude and refined clustering of retrograde label could be resolved following large tracer injections, Luhmann *et al.* analyzed their material using an image processing procedure that would tend to eliminate labeling between clusters and therefore obscure this developmental change (10).

We agree with Luhmann *et al.* (9, 10) that binocular deprivation does not prevent the initial emergence of at least a crudely clustered pattern of retrograde labeling. In addition, they have reported that the numbers of clusters resulting from a single tracer injection is decreased in binocularly deprived animals >15 weeks old. We do not yet have any data addressing long-term effects of binocular deprivation.

Visual deprivation by binocular lid suture clearly influences the development of ocular dominance selectivity of neurons throughout the cortical laminae (6, 12) and may also affect the refinement or maintenance of orientation selectivity (12, 15). Previous structural studies of the effects of binocular deprivation in striate cortex have been restricted to analysis of geniculate afferents in relation to ocular dominance; intraocular proline injections have demonstrated that binocular deprivation by either dark-rearing (16) or retinal activity blockade (14) prevents the segregation of afferents into distinct columns. Thus, the failure of ocular dominance selectivity to develop normally in lid-sutured cats could result from effects of binocular deprivation on the development of afferent inputs alone or could also be attributed to additional effects on intrinsic connectivity. Indeed, models of ocular dominance column development suggest an important role for horizontal interactions mediated by intrinsic circuits to establish the columnar pattern (17). Our results demonstrate that in addition to the effects on geniculo-cortical afferents, binocular deprivation also profoundly affects intracortical circuits. Several investigations suggest that binocular deprivation either prevents the refinement or leads to the degradation of orientation selectivity (15). However, because the circuitry that generates orientation selectivity remains obscure, the structural correlates to these deprivation-induced changes have proven difficult to assess. Because horizontal cortical circuitry is intrinsic and closely related to orientation selectivity, the present findings indicate that development of intrinsic circuitry and circuitry related to orientation columns depends on normal visual experience.

Correlated activity has been strongly implicated as a cue for the segregation of ocular dominance columns in striate cortex (18, 19). The development of horizontal connections may also rely on activity correlations for distinguishing between correct and incorrect targets. Cortical columns with similar orientation selectivity would need to be activated synchronously; such a correlation has been demonstrated in the striate cortex of adult cats (20). Similar correlations might also exist between the initially crude columns in newborn cats and could supply the information necessary for recognition of correct vs. incorrect targets by developing axons. Orientation-dependent correlations would probably be degraded by binocular lid suture due to the absence of oriented visual stimuli, resulting in the observed reduction in the specificity of developing intrinsic horizontal circuitry.

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