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Right and left eye bands in frogs with unilateral tectal ablations

(input segregation/retinotectal/synaptic plasticity)

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ABSTRACT **Surgical ablation of a single tectal lobe in *Rana pipiens* can cause regenerating retinal ganglion cell axons to cross to the remaining tectum. These synaptically deprived fibers can obtain termination space in a retinotopic and highly stereotyped manner. Each of the two eyes can share the undisturbed tectum by terminating in mutually exclusive, eye-specific stripes that alternate across the medial–lateral extent of the tectal lobe. Invading axons from the ipsilateral eye must actively displace established synapses from the contralateral eye in order to form these exclusive termination zones because the normal projection to the intact tectum is not severed in these experiments. In animals in which a large proportion of anomalous fibers do not reach the undisturbed tectum, only a few ipsilateral eye bands are observed. Nevertheless, these bands have the same width, periodicity, and orientation as those observed in fully banded preparations. When ipsilateral eye terminal density is extremely low, banding is absent. The completely striped termination pattern of unitectal animals is identical to the pattern previously reported in the dually innervated tecta of three-eyed *R. pipiens*. We theorize that this pattern results from a compromise between two synaptogenic forces that are active in regeneration as well as in development.**

Axons originating from different presynaptic sources often segregate during termination within a single synaptic region. These input segregation patterns can appear as ellipses, annulae, or patches (1–7). However, the most widely known example is the system of interdigitating left and right eye stripes, the ocular dominance columns, produced by alternating layers of the dorsal lateral geniculate in layer IV of cat and monkey visual cortex (3, 4, 8–10).

Recently we reported (11) that similar stripes of visual input can be produced experimentally in the optic tectum of developing *Rana pipiens*. Normally, the optic tectum in these frogs receives direct retinal ganglion innervation from the contralateral eye. However, when a supernumerary eye primordium is implanted in early embryonic stages, the third eye will frequently innervate one of the two tecta along with retinal axons from one of the host's eyes. The presence of a supernumerary optic projection disrupts the normally continuous ganglion cell termination pattern within the superficial tectal neuropil. In these three-eyed frogs the fibers from the supernumerary and normal eyes form approximately 200-μm-wide eye-specific bands of neuropil that alternate across the medial–lateral extent of the doubly innervated optic lobe (11).

We report here that the striped pattern also can be produced in regeneration after the unilateral ablation of one of the two tectal lobes. During regeneration the segregation develops in differentiated nervous tissue between inputs from the left and right eyes of the same animal. Moreover, the segregation involves a period in which surgically undisturbed retinotectal synapses are displaced by axons that invade the remaining tectal lobe from the ipsilateral eye.

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MATERIALS AND METHODS

Partial or complete removal of one tectal lobe was performed on 15 *R. pipiens* under anesthesia induced by immersion in 0.05% Tricaine methanesulfonate (Sigma). Animals ranged in age from Taylor and Kollros stage VI (12) to 4 months postmetamorphosis. The visual projection to the intact tectum remained intact and was able to mediate prey-catching behavior within a day or two of this operation. Survival periods extended from 1 to 10 months. Tectal ablations were verified in serial histological sections.

The central distributions of optic nerve axons were determined in six experimental frogs by using anterograde transport of horseradish peroxidase (HRP) (13, 14). The enzyme (Sigma type VI) was applied to the cut optic nerve as described by Scalia and Colman (13). After survival for 2–3 days the frogs were fixed by intracardial perfusion with phosphate-buffered 1% paraformaldehyde/2% glutaraldehyde, pH 7.4. Brains were postfixed for 2 hr, rinsed in buffer, and then allowed to equilibrate overnight in a buffered mixture of 30% egg albumin, 5% gelatin, and 30% sucrose. This was subsequently hardened with 50% glutaraldehyde. Frozen sections at 30 or 50 μm were developed for HRP (15), mounted serially and poststained with cresyl violet.

For autoradiographic tracing of the visual pathway, 10–15 μCi (1 Ci = 3.7×10^{10} becquerels) of [^{3}H]proline (specific activity, 26 Ci/mmol; New England Nuclear) was injected into the vitreous body of one eye. After 3 days, tissue was processed according to published techniques (16). In four animals, HRP and autoradiography processing were applied to alternate frozen sections.

Activity originating in the terminal arbors of retinal ganglion cells (17) was studied with gold- and platinum-plated tungsten microelectrodes in the undisturbed tectal lobe of two curarized (1 μg/mg body weight, *d*-tubocurarine chloride, Sigma) experimental frogs. These animals were centered in an ophthalmic perimeter, and a 3° light spot presented in darkness was used to elicit action potential activity in one to three units. Recording sites were spaced 200 μm apart across the dorsal surface of the midbrain. Use of an opaque corneal occluder ensured that each eye was driven independently.

RESULTS

Unilateral removal of anuran tectal tissue disrupts the normal, crossed (13) projection from one retina to the perturbed tectal lobe. Consequently, most of the animals examined in this study developed an anomalous projection from the ipsilateral retina to the intact optic tectum. Regenerating axons reached the undisturbed lobe by recrossing the midline at the posterior commissure or immediately caudal to it. A smaller proportion entered the tectum from the ipsilateral optic tract.

Tectal innervation patterns resulting from the ablation procedure are summarized in Fig. 1 along with postoperative

Abbreviation: HRP, horseradish peroxidase.

survival times and the tectal tissue removed. Several generalizations should be noted. First, a minimal survival time of 4 months was necessary before axons from the ipsilateral eye were observed in the undisturbed tectal lobe. Second, in no case did the remaining tectal lobe appear markedly enlarged or distorted due to increased innervation. Finally, and most importantly, only two ipsilateral eye innervation patterns were observed: axon terminals were either in low density and diffusely distributed or they were clustered into highly stereotyped bands.

In Fig. 1 and throughout this report, the term "band" or "banded" refers to a labeled projection that is in register throughout the different laminae of the superficial tectal neuropil. Bands have relatively abrupt borders and an elongated shape with the long axis running rostrocaudally. Fig. 2 illustrates a band and a region of diffuse innervation within a single transverse section.

Consideration of individual animals is necessitated by marked differences in the degree of the ipsilateral eye innervation to the undisturbed optic lobe. In the interest of clarity, however, we group these animals according to the type of the tectal ablation performed.

Complete Unilateral Ablation. Five animals (nos. 5, 12, and 15) survived for more than e months after complete removal of one optic tectum. In two of these animals (nos. 6 and 9), a large number of fibers from the tectally deprived tract were

Frog	Age, months: At oper	Age, months: At death	Label: Left	Label: Right	Ablation	Innervation patterns in other lobe
1	2	3	–	^{3}H	A P	Not labeled
2	4	5	^{3}H	–		Not labeled
3	2	3.3	HRP	^{3}H		Diffuse label; higher density medially
4	2	4	–	^{3}H		Not labeled
5	1	4	–	^{3}H		Some bands; poor anatomy
6	2	6	^{3}H	–		Entirely banded
7	2	6.5	–	HRP		Diffuse label, anterior half
8	XIX	5	–	^{3}H		Banded, posterior half; diffuse label, anterior half
9	2	7	^{3}H	HRP		Entirely banded
10	2	7	HRP	^{3}H		Banded, all but most posterior sections
11	2	7	–	^{3}H		Diffusely labeled
12	VI	5	^{3}H	–		Banded, anterior sections; 3 medial bands, posterior sections
13	2	8	^{3}H	–		Banded, ventrally and laterally
14	2	9	–	HRP		Not labeled
15	2	12	^{3}H	HRP		Diffuse label, anterior half; 1,2 medial bands, posterior half

FIG. 1. Experiments performed on each of the 15 frogs. ^{3}H, proline autoradiography; HRP, horseradish peroxidase; A, anterior tectum; P, posterior tectum. Roman numerals stand for Taylor and Kollros larval stages (12); arabic numerals are age past metamorphosis.

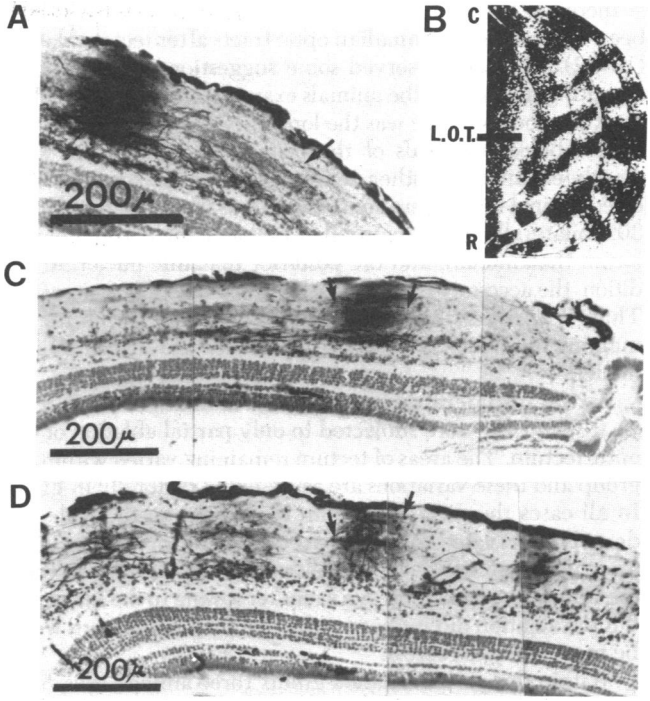

FIG. 2. Termination patterns. (In *A*, *C*, and *D*, scale = 200 μm.) (*A*) Banded and diffuse innervation patterns in a single section of animal 15. HRP label in the regenerated retinal fibers reveals a densely filled band immediately adjacent to a diffusely innervated area (arrow). (*B*) Photographic reconstruction from horizontally sectioned autoradiographs of animal 6. The remaining right tectal lobe is viewed from below. L.O.T., lateral optic tract; C, caudal tectum; R, rostral tectum. (*C* and *D*) Comparison of the stripes in a fully banded preparation (*D*) and a partially banded one (*C*). Band width remains constant within the striped tectum (*D*) despite variable densities of innervation. Arrows delineate band edges where terminal powder is slightly decreased.

able to recross the midline to innervate the undisturbed optic lobe. In both these cases, a periodic pattern of labeled bands extended throughout the intact tectum. Fig. 2*B* is a photographic reconstruction of the ventrolateral surface of the right tectum in one of these animals. Radioactive label from ipsilateral eye terminals can be seen to diverge from the lateral optic tract where it forms stripes that are oriented in a roughly rostral–caudal direction.

In the remaining three animals, only a portion of the regenerating optic tract reached the intact tectal lobe. Complete serial reconstructions of animals 12 and 15 revealed that only parts of the remaining tectum were banded. The anterior pole of the tectal lobe in animal 12 was fully striped but only three ipsilateral eye bands extended into the posterior regions. In animal 15 the optic tract from the ipsilateral eye was filled with HRP and the projection from the contralateral eye was labeled with [^{3}H]proline, allowing direct visualization of both the normal and the recrossed retinal projections. Interdigitating bands of HRP and autoradiographic label were restricted to the medial region of the undisturbed tectum in this frog. The rest of the lobe was filled with dense autoradiographic label from the normal, contralateral eye and only some light, diffuse label from the tectally deprived optic tract.

The existence of unbanded regions in intact optic tecta could reflect either a transient state in the development of a fully banded tectum or the selective loss of optic fibers bound for those tectal regions. The 10-month survival of animal 15 suggests that partial banding is likely to be a final state of regeneration.

Increased innervation to alternate target zones has frequently been observed in mammalian optic tracts after tectal ablation (18–22). We have observed some suggestion of this type of sprouting in many of the animals examined for this study. The most pronounced case was the long-survival animal 15. Here, HRP-labeled terminals of the tectally deprived tract were clearly expanded in other neuropil regions known to receive direct retinal input. Terminal volume was increased by roughly 30% bilaterally in the neuropil of Bellonci, the corpus geniculatum thalamicum, and the posterior thalamic nuclei. In addition, the accessory optic nuclei became bilaterally innervated. Thus, it appears likely that axons that did not reach the remaining tectal lobe sprouted to hyperinnervate alternate visual nuclei.

Partial Unilateral Ablations. Seven animals (nos. 4, 7, 8, 10, 11, 13, and 14) were subjected to only partial ablation of one optic tectum. The areas of tectum remaining varied within this group and these variations are represented pictorally in Fig. 1. In all cases the piece of tectum remaining on that side was densely innervated by all or part of the appropriate eye. The area of tectum removed was seldom an accurate predictor of the number of ipsilateral eye axons recrossing to the intact lobe but the ablation did influence which of the retinal axons would be most likely to recross.

Within this partial ablation group, three animals (nos. 8, 10, and 13) were banded only in the portion of the intact lobe corresponding to the tectal ablation on the opposite side. For example, in animal 10 all but the posterior one-quarter of the left tectal lobe was destroyed. This left tectal remnant was successfully reinnervated by part of the regenerating optic tract. The remaining axons which were forced to cross to the intact tectal lobe were primarily fibers inappropriate to that tectal remnant because only the anterior three-quarters of the undamaged right lobe became densely innervated. In these anterior regions, ipsilateral eye terminals were obvious as tritium-labeled bands. In the posterior one-quarter, diffuse light ipsilateral innervation was indicated by continuously distributed silver grains at densities only slightly above background.

In animal 8, levels of grain density allowed quantification of ipsilateral eye input in both banded and unbanded regions. Grain counts in diffusely innervated tectal sections ranged from 25 to 35 grains per 400 μm^2. These densities varied from 104 to 167 grains per 400 μm^2 within bands and from 35 to 45 grains per 400 μm^2 in interbands. Thus, the density of grains averaged over the entire banded region (that is, band plus interband) was approximately 70–106 grains per 400 μm^2. The average tissue background grain density was 15 grains per 400 μm^2. These numbers substantiate our preliminary observations that segregated regions of the undisturbed tectal lobe receive higher densities of innervation than do the diffusely labeled regions.

Substantial portions of the regenerating tracts remained uncrossed in animals 4, 7, 11, and 14. Only light diffuse label was evident in animals 7 and 11 and no label was seen in the undisturbed lobes of animals 4 and 14.

Visuotectal Mapping. Correspondence between missing regions of one tectum and banding in an identical region of the remaining tectum implies that axons from the ipsilateral eye are regenerating to topographically appropriate regions of the undisturbed lobe. Electrophysiological mapping experiments confirmed this suggestion. In both preparations from which recordings were obtained (animals 5 and 11 of Fig. 1), multiple-unit activity was elicited from either the left or the right eye at most neuropil sites of the undisturbed lobe. Furthermore, these left and right eye receptive fields generally occupied mirror symmetrical positions relative to the verticle meridan (Fig. 3). Such symmetry could be obtained only if both the normal and anomalous projections were organized retinotopically within the doubly innervated optic tectum.

Subsequent autoradiography showed densities of labeled neuropil reminiscent of the striped pattern in animal 5. Unfortunately, much of this brain was destroyed during processing, making full reconstruction impossible. Animal 11, however, had a large tectal remnant and subsequent study revealed that the intact lobe had only diffuse light label from the ipsilateral eye. Thus, the simple presence of fibers from corresponding regions of two retinas is not sufficient to produce bands within tectal neuropil. These results suggest instead that eye-specific segregation is also dependent on the relative densities of the two presumably competing projections.

Characteristics of Eye-Specific Bands. All eye-specific bands were highly uniform in both width and orientation despite great differences in the extent of the striped pattern. All bands ran in a roughly rostral–caudal direction and, all had a measured mean band width of approximately 100 μm. Tissue shrinkage is roughly 45–50% in our paraffin-processed tissue and 40–45% after frozen sectioning. Therefore, the actual width of these bands lies between 150 and 200 μm.

Mean band widths for the animals presented in Fig. 1 were obtained by measuring every labeled band in sections spaced 50 μm apart through the entire midbrain. All had large standard deviations probably due to difficulties in accurately identifying the edges of labeled regions, differences in angle of sections, and the bending and branching of bands. Fig. 4 demonstrates the consistency in the band width distributions with measurements from four different animals. The data shown are from the frogs that had the largest number of bands, but all preparations had similar distributions.

This band width constancy is illustrated in Fig. 2 *C* and *D*, photomicrographs of HRP-filled ipsilateral eye projections in the undisturbed tectum of two different frogs. Fig. 2*C* contains one of the two ipsilateral eye bands observed in the partially banded animal 15. Four ipsilateral eye bands from the fully banded animal 9 are shown at the same magnification in Fig.

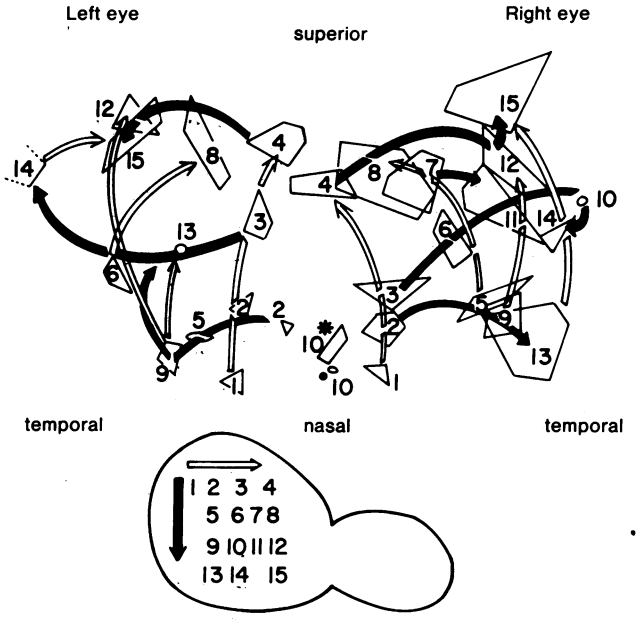

FIG. 3. The visuotectal map of animal 11 at 5 months after partial ablation of its right tectal lobe. Numbered recording sites are represented in a dorsal view of the tecta. Corresponding visual receptive fields for each eye are located at roughly mirror symmetrical positions relative to the vertical meridian.

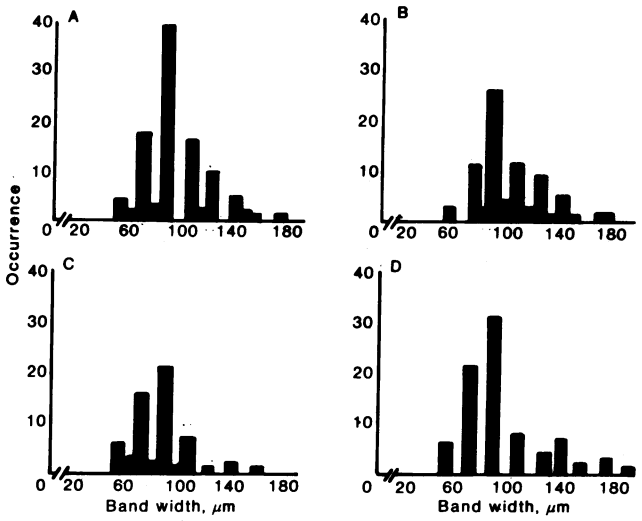

FIG. 4. Measured widths of eye-specific bands. Histograms from four animals are shown. Measurements have been grouped into 8-μm-wide bins which reflect the resolution of the measuring procedure. Mean band width (μm) ± SD: *A*, 97 ± 25; *B*, 99 ± 26; *C*, 87 ± 22; *D*, 97 ± 32.

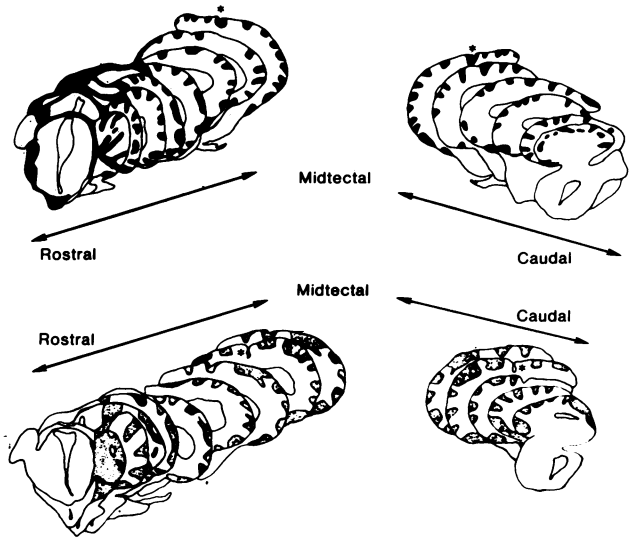

FIG. 5. Camera lucida reconstructions of alternate 50-μm sections from animal 9. (*Upper*) HRP-Labeled ipsilateral eye bands extending from rostral to midtectal levels (*Left*) and from caudal to midtectal levels (*Right*). (*Lower*) Autoradiographic visualization of [^{3}H]proline label in normal contralateral eye axons, similarly presented. Asterisks in each reconstruction mark a dorsal tectal lesion and illustrate the complementary nature of the ipsilateral and contralateral eye bands.

2*D*. The width of the single zone in animal 15 is nearly identical to widths attained in the fully striped tectum of animal 9. Furthermore, in Fig. 2*D*, width remains constant from band to band even though the density of label varies considerably.

When transported in an anterograde direction from the cut end of optic nerve fibers, HRP allows the axon cylinder to be distinguished from termination areas (13, 14). In Fig. 2 *C* and *D*, the axon cylinders are completely and uniformly filled and the termination areas appear to contain fine, powder-like deposits. Close examination of these HRP-labeled zones reveals a gradual decrease of terminal powder density near the edges. This may represent areas of overlap between labeled and unlabeled eye bands.

Fig. 5, camera lucida tracings of all tectal sections from animal 9, illustrates a final characteristic of banding that was invariably observed in preparations in which we labeled the projection from both eyes. In all cases the termination zones of the two eyes were complementary: regions of low grain density in autoradiographs were closely correlated with regions occupied by HRP-filled terminals in adjacent 40- or 50-μm sections. The dorsal lesion marked by an asterisk in the figure is a convenient reference for corresponding points in the two reconstructions. Overlap between the two projections is on the order of 30 μm, but this estimate is approximate because the two projections could not be visualized in the same section. Measurement under high magnification with an eyepiece micrometer has not revealed any consistent difference between the widths of bands in the normal contralateral and the ipsilateral projection.

DISCUSSION

The present results demonstrate that a banding pattern essentially indistinguishable from that seen in three-eyed frogs can be produced by removal of one tectal lobe in late tadpole or postmetamorphic animals. Thus, the cellular interactions that generate rostral–caudally oriented slabs of eye-specific termination areas are active in regeneration as well as in development. Furthermore, these interactions must be quite strong because invading ipsilateral axons displace the surgically undisturbed and functional synapses of the contralateral eye.

However, removal of all or part of one optic lobe fails to produce banded tecta with the consistency that we observed after the addition of a third eye primordium to young embryos (11). This may be because many axons failed to reach the ipsilateral optic tectum.

One previous study subjected full grown *R. pipens* to radical unilateral tectal ablations (21). Degeneration staining of the tectally deprived tract in these animals revealed sparse label in the remaining optic lobe; there was no evidence of banding. The present study suggests that this absence of bands may simply be due to a low density of ipsilateral eye axons in the remaining tectum. In our preparations, ipsilateral label was always much lighter in unbanded as opposed to banded regions. Decreased innervation density was most dramatic with the HRP label (Fig. 2*A*) but it was also apparent as an absolute decrease in autoradiographic grains after [^{3}H]proline injections.

Our findings are consistent with a number of anatomical investigations that mention similar but apparently more variably sized bands or patches of ipsilateral eye terminals in single-tectum *Xenopus*, goldfish, and rats (22–29). In goldfish, segregation of both normal and anomalous projections has been demonstrated after deflections of optic tract fibers onto ipsilateral tecta that were simultaneously deprived of existing retinal input by optic nerve crush (23).

Our results also agree with earlier electrophysiological work on single-tectum frogs and goldfish in which both microelectrode mapping techniques and behavioral testing (30–34) have shown that left and right eyes project retinotopically within the dually innervated lobe. It is likely, however, that extracellular recordings from the superficial tectal neuropil cannot readily provide an accurate assessment of the density or detailed distribution of retinal ganglion cell terminal arbors. It would have been difficult, for example, to distinguish the diffusely distributed ipsilateral projection of animal 11 from the apparently segregated ipsilateral projection of animal 5 on the basis of our electrophysiological analyses alone. In both preparations, most tectal neuropil sites showed some, although not necessarily equally pronounced, activity in response to stimulation of both eyes. There were no obvious changes in magnification factor.

The reasons for this difference in anatomical and electrophysiological data remain obscure. Nevertheless, somewhat similar discrepancies have arisen before and suggest caution when relying on multi-unit physiology alone (22, 35, 36).

Four aspects of the present results may provide clues to the cellular determinants of input segregation: (*i*) all eye-specific terminal zones are elongated in one axis (i.e., they are either bands or ellipses); (*ii*) to our best estimation all bands are close to the same width ($\leq$ 200 μm) and, when two or more are present, they repeat with approximately the same periodicity ($\leq$ 400 μm); (*iii*) a certain critical density of fibers seems to be necessary for banding to occur; and (*iv*) anatomical and electrophysiological data suggest that this segregation is superimposed upon retinotopically organized projections from both eyes. These four properties are also evident in the bands of three-eyed frogs and tadpoles (11).

We suggest that eye-specific bands represent a compromise between two mechanisms that generally work together to establish the normal retinotectal projection. One of these is a graded affinity between particular parts of the retina and particular parts of the tectum (e.g., refs. 37–40). The other is a cooperative interaction between neighboring ganglion cells which causes them to terminate near one another in the tectum. This latter mechanism may or may not be mediated synaptically, but it requires a certain density of fibers and has the net effect of ensuring that only nearest retinal neighbors remain together within the tectal lobe. Experimental support for an ordering mechanism of this type has recently been obtained in the retinotectal system of goldfish where it has been shown to be involved in the fine tuning of the retinotopic termination pattern (28).

In doubly innervated tecta, these two mechanisms oppose one another because high densities of axons from equivalent regions of two retinas must now attempt to innervate the same tectal space. The first mechanism would tend to spread axons according to their retinotectal affinities. The second would encourage clumping of terminals from the same presynaptic sheet. This situation could produce retina-specific termination zones whose widths reflect the relative strengths of the two forces involved. LeVay *et al.* (41) advanced this same system to explain the ocular dominance columns in layer IV of primate visual cortex. They pointed out that, given the two opposing tendencies, the best way for two projections of equal strength to satisfy both would be to form elongated termination zones or bands. Only a banded pattern minimizes the distance between a particular tectal region and axon terminals from corresponding parts of two retinas and, at the same time, minimizes the region of juxtaposition where the two presynaptic populations have to mix (41, 42).

It is possible that the patches, annulae, or ellipses observed in normal projections (1–7) as well as the various induced patterns of ipsilateral termination in single-tectum animals result from differences in the relative strengths of these two forces (42). In short, axon–target cell affinities (neurospecificity) in conjunction with axon–axon interactions based on the physical proximity of presynaptic cell bodies could explain elaborate patterns of input segregation. Although these two phenomena have been widely implicated in synaptogenesis, their cellular bases remain obscure. Multiply innervated frog tecta may offer an approach for study of these mechanisms.

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