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# Axon arbors of X and Y retinal ganglion cells are differentially affected by prenatal disruption of binocular inputs

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ABSTRACT **In the mammalian visual system, the terminal arbors of retinal ganglion cell axons from the two eyes are restricted to mutually exclusive territories within their thalamic target, the lateral geniculate nucleus (LGN). Here we have investigated some of the factors that determine the adult morphology of terminal arbors in the cat's retinogeniculate system. Removal of one eye during prenatal life at a time when retinogeniculate axons from the two eyes are extensively intermixed within the LGN perturbs the subsequent morphological development of some but not all axons from the remaining eye. The presence of terminal arbors qualitatively normal in size, shape, and location within the LGN suggests that for some retinal axons, ongoing binocular interactions throughout prenatal life are not needed for the development of normal arbor morphology. However, many of the axons form arbors of abnormal size or location, suggesting that such features of axon morphology are not intrinsically determined for these axons but may be susceptible to external influences. Electrophysiological studies reveal that the abnormal arbors all belong to the functionally distinct Y class of retinal ganglion cells, whereas the normal arbors all belong to X cells. The different responses of X and Y axons to prenatal enucleation demonstrate that during development subsets of a single neuronal population projecting to the same target in the central nervous system can be under different developmental controls for axon arbor differentiation.**

In adult cats, the retinal projection from the two eyes forms alternating eye-specific layers within the lateral geniculate nucleus (LGN) (1). The anatomical subunits of these layers are the terminal arbors of individual retinal ganglion cells, with the height of each terminal arbor corresponding generally to the thickness of a given layer (2–5). How is this characteristic terminal morphology achieved? During prenatal development, retinal axons from both eyes are initially intermixed within the LGN (6–8) and are morphologically simple with a few short side branches issuing from a main axon. As axons elaborate adult-like terminal arbors, side branches are lost in territories of the LGN where axons from the opposite eye elaborate their terminal arbors, a process that correlates spatially and temporally with the formation of eye-specific layers (6–8). These observations suggest that the overall size, shape, and position of retinal axon arbors within the LGN may be controlled by means of interactions between axons from the two eyes.

To investigate further this suggestion, we have disrupted binocular interactions by removing one eye during fetal life at embryonic day 44 (E44; birth = E65). The consequences of this manipulation were then examined at later times by filling individual retinogeniculate axons with horseradish peroxidase (HRP). We selected E44 for several reasons. First, it is a time when ganglion cell axons from both eyes are extensively intermixed within the LGN (6, 7), so that removal of one set of inputs will have a direct effect on the remaining set. Second, we were particularly interested in comparing the consequences of eye removal at E44 with those known to result from eye removal either at birth, when eye-specific layers are well formed, or at E23, a time when ganglion cell axons have not yet reached the optic chiasm. Previous studies have shown that eye removal at birth causes the inputs from the remaining eye to expand into territory normally reserved for the enucleated eye (9–11). However, when single physiologically identified retinogeniculate axons were injected with HRP, it was found that only one of the two major ganglion cell classes, the Y cells, had expanded axonal arbors in the LGN (12). The X axons (and a small percentage of the Y axons) were appropriately restricted to zones appropriate for their eye of origin. A different pattern of retinogeniculate termination was found when one eye was removed at E23 rather than at birth. During subsequent development in these animals, while axons from the remaining eye filled the entire LGN as expected, it was remarkable to find that all individual axons filled with HRP had terminal arbors of normal height. No axons had abnormally expanded arbors, including those located abnormally in territory normally innervated by the removed eye (13). Due to the fragility of the experimental animals enucleated at E23, axons were filled with HRP at E59, a time when it is not yet possible to distinguish X from Y axons either morphologically or physiologically. In the present experiments, we have attempted to clarify the two sets of divergent observations (following monocular enucleation at birth or at E23) by performing enucleations at an intermediate time (E44) and by then examining the morphology of individual retinogeniculate axons either at E59, when a direct comparison with animals enucleated at E23 is possible, or in adulthood, when axons can also be identified physiologically.

## METHODS

By using previously reported procedures (6), cesarian sections were performed in timed pregnant cats under sterile conditions using inhalation anesthesia. Experiments were done on six fetuses, two of which survived into adulthood. On E44, fetuses were exteriorized, monocularly enucleated, and returned to the womb to undergo further development. To accomplish the enucleation, the extraocular muscles of one eye were dissected away and the globe was removed. The central artery was then cauterized and a pledget of Gel-foam was placed in the orbit. The eyelids were then glued shut and the fetus was returned to its uterine sac (6). We studied retinogeniculate axons in these animals using HRP bulk-

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Abbreviations: LGN, lateral geniculate nucleus; E, embryonic day; HRP, horseradish peroxidase.

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filling methods in E59 fetuses and intracellular injections of HRP into physiologically identified axons in adult cats.

In the first group of experiments, four fetuses were delivered by cesarian section at E59, about 6 days before natural birth, and the terminal arbor morphology of individual retinogeniculate axons within the LGN was examined *in vitro*. To do so, the brain was quickly dissected and a preparation containing the LGN and optic tract was placed in an *in vitro* slice chamber. Glass micropipettes with HRP-coated tips were used to bulk-fill retinogeniculate axons and their terminals. After a survival time of 4–6 hr, the preparation was immersion-fixed overnight and 100-$\mu$m-thick horizontal sections were cut on a vibratome. The sections were then allowed to react for HRP histochemistry using diaminobenzidine with cobalt chloride intensification. Axons filled with HRP were reconstructed by using a camera lucida attachment to a microscope. Complete details of these procedures have been described elsewhere (7, 13).

For the second set of experiments, two animals were delivered at term and then studied electophysiologically at 6 months of age by previously reported methods (5, 12, 14, 15). The cats were anesthetized with 4% halothane and placed in a stereotaxic device. They were then paralyzed with gallamine triethiodide and artificially ventilated with 70% nitrous oxide/30% oxygen. Throughout the experiments, animals received continuous i.v. infusions of gallamine and ketamine hydrochloride. Stimulating electrodes were placed across the optic chiasm and craniotomies were performed over both LGNs (A 6.0, L 9.0). Glass micropipettes filled with 10% HRP in 0.2 M KCl and 0.05 M Tris buffer were beveled to final impedances of 95–105 M$\Omega$ and were used to record single retinogeniculate axons within the LGN or optic tract. Axons were electrophysiologically classified as X or Y by using a standard battery of tests (5, 12). After classification, axons were impaled and HRP was injected iontophoretically into them. At the conclusion of an experiment, each cat was deeply anesthetized with sodium pentobarbital and perfused intracardially with a mixture of 1% paraformaldehyde/2% glutaraldehyde. The brains were stored overnight in phosphate buffer with 30% sucrose and then sectioned parasagittally at 100 $\mu$m on a freezing microtome. Sections were allowed to react for HRP histochemistry using diaminobenzidine with cobalt-chloride intensification (16). Axons were identified with the aid of Sanderson's (17) maps and reconstructed using a microscope with a camera lucida attachment.

## RESULTS

**Experiments Performed at E59.** On E44, ganglion cell axons from the two eyes are intermixed with each other in the LGN: the eye-specific layers are not present and individual retinogeniculate axons have only a sparse branching pattern consisting of a main axon with several side branches (7). By E59, eye-specific layers are well formed and retinogeniculate axons have adult-like terminal arbors: their height is equivalent to approximately the thickness of an eye-specific layer (one-third of the thickness of the LGN). In addition, by E59, the inner one-third of the LGN (layer A) is occupied solely by terminals of contralaterally projecting axons, whereas the middle one-third of the LGN (layer A1) is occupied by terminals of ipsilaterally projecting axons (6–8).

After the removal of one eye at E44, the axons of the remaining eye have formed one of two types of terminal arbor by E59. The first type is illustrated in Fig. 1*A* which shows, in the horizontal plane of section, four retinogeniculate axons projecting from the remaining eye to the contralateral LGN. These axons arise from the optic tract below the LGN, course through the LGN, and elaborate well-defined terminal arbors that are indistinguishable in size and shape from those of normal animals at the same age (7). As in normal axons, each

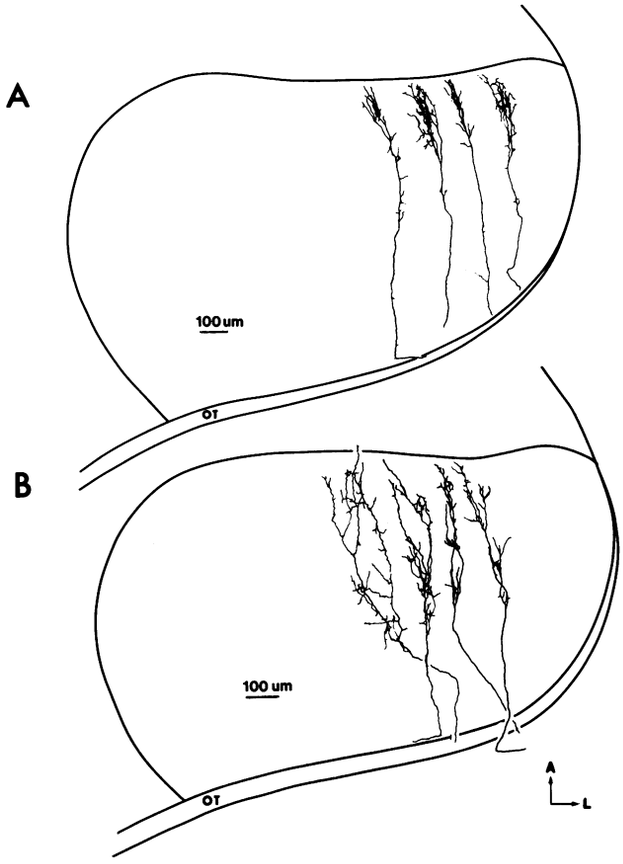


FIG. 1. Camera lucida drawings of retinogeniculate axons at E59 after monocular enucleation at E44. All axons arise from the optic tract (OT) and course through the LGN to give off a terminal arbor. (*A*) Horizontal section showing four axons projecting to the LGN contralateral to the remaining eye. These axons have normal-sized arbors spanning approximately one-third the thickness of the LGN. (*B*) Four contralaterally projecting axons with abnormally tall terminal arbors that span about two-thirds the thickness of the LGN or the equivalent of two eye-specific layers. A, anterior; L, lateral.

arbor is restricted to approximately one-third of the LGN (i.e., the thickness of a normal eye-specific layer). Furthermore, these axons terminate in the inner one-third of the nucleus (a region that normally would have been lamina A), which is the appropriate target for contralaterally projecting axons. The second type of terminal arbor is shown in Fig. 1*B*, which illustrates four additional axons; the axons are notable because their terminal arbors are abnormally tall and extend into the middle one-third of the nucleus. These axons arise from the optic tract in the usual fashion but give rise to terminal arbors that span the inner and middle thirds of the nucleus (regions that would have been layers A and A1).

Axons from the remaining eye that projected to the ipsilateral LGN were also found to be of two types. Some had normal-sized terminal arbors restricted to the middle one-third of the LGN (i.e., lamina A1, the appropriate target for ipsilaterally projecting axons), whereas others had enlarged arbors that inappropriately spanned the inner and middle thirds of the nucleus. Table 1 summarizes the data from all experiments in E59 fetuses after monocular enucleation at E44.

**Experiments Performed in Adult Cats.** The LGN in 6-month old cats following monocular enucleation at E44 is of approximately the normal adult size and consist of two subdivisions: a larger, dorsal magnocellular region and a smaller, ventral parvocellular region (18, 19). We have provided evidence elsewhere (19) that the magnocellular region in-

Table 1. Retinogeniculate axons at E59 after monocular enucleation at E44

| LGN | Axon arbor | |
|---|---|---|
| | Normal-sized | Expanded |
| Ipsilateral | 3 | 4 |
| Contralateral | 5 | 4 |

Summary of retinogeniculate axon arbor size in the ipsilateral and the contralateral LGNs of E59 fetuses after monocular enucleation at E44.

cludes not only the A layers but also the dorsal portion of layer C, whereas the parvocellular region includes the ventral portion of layer C and the remaining layers of the C complex.

Physiological recordings from the optic tract of these animals indicated that X and Y axons from the remaining eye could be recorded and had essentially identical responses to those in normal animals. The results obtained by using intracellular recording and HRP injection into physiologically identified optic tract axons after monocular enucleation at E44 were similar to those found by using the *in vitro* bulk-filling technique at E59. Again, two types of axons were found: the arbors of some axons were of normal size and shape, whereas others had abnormally tall arbors.

Physiologically identified X axons were normal with respect to gross arbor morphology and arbor location within the LGN. All X axons (three contralateral, three ipsilateral) had normally proportioned terminal arbors cylindrical in shape with the long axis of the arbor spanning about one-third the thickness of the LGN (i.e., the equivalent of one eye-specific layer), as in normal animals. Moreover, the location of X axon arbors was always within appropriate regions of the LGN with respect to their eye of origin. Fig. 2*A* shows, in a parasagittal plane of section, a camera lucida drawing of an X axon projecting to the LGN contralateral to the remaining eye. The basic framework of the terminal arbor resembles that of normal adults (3–5). In addition, the arbor is located within an area of the LGN appropriate for its eye of origin—i.e., the inner one-third of the nucleus where layer A would have formed under normal circumstances. X axons projecting to the ipsilateral LGN likewise elaborated arbors resembling those of normal adults in their morphology and in their location within the middle third of the nucleus, an area corresponding to layer A1 (Table 2).

In contrast to the X axons, all physiologically identified Y axons (six contralateral, three ipsilateral) were abnormal. Fig. 2*B* shows a Y axon projecting to the LGN contralateral to the remaining eye. This arbor spans almost the entire thickness of the LGN and occupies regions of the nucleus normally receiving inputs from axons of the ipsilateral eye. Five of the six contralaterally projecting Y axons had arbors like this one. Two of the three Y axons projecting to the ipsilateral LGN also formed abnormally tall arbors, extending into regions normally occupied by axons of the contralateral eye. However, not all Y axons formed abnormally tall arbors (Table 2). Fig. 2*C* shows an example of the less commonly observed type of Y axon. It terminates in a relatively normal-sized arbor that spans only about one-third the thickness of the nucleus. Nevertheless, this arbor is abnormal because, despite its contralateral origin, it is situated in the middle one-third of the nucleus, a region corresponding to layer A1, which is normally innervated by axons from the ipsilateral eye. The remaining normal-sized Y axon in our sample was from the ipsilateral eye, yet it terminated in the inner one-third of the nucleus where contralateral axons would normally project. It should be noted that we have not recovered any Y axon of normal size and location; however, our sample size is small. Nevertheless, monocular enucleation at E44 results in at least two forms of Y axon abnormalities in the adult: the terminal arbors either are abnormally tall or are of normal size and shape but abnormal in *location*.

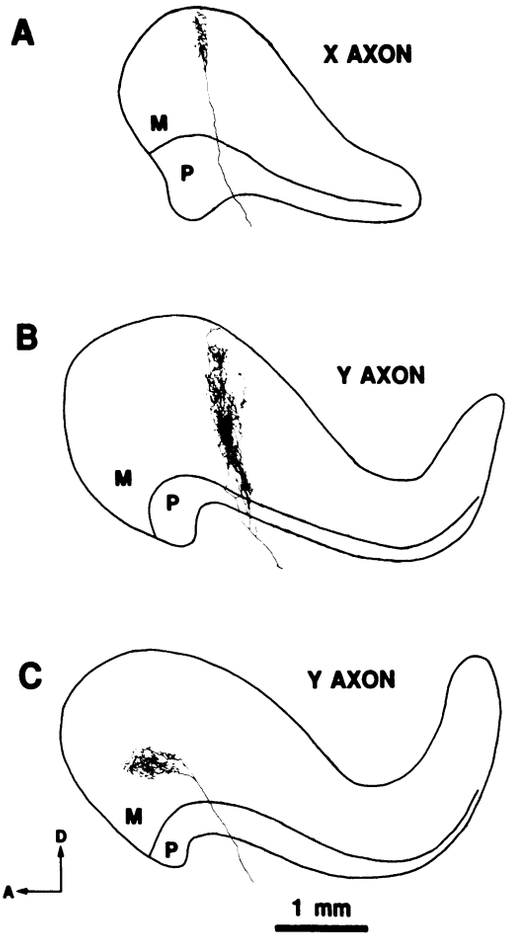


FIG. 2. Pattern of terminal arborization of physiologically identified retinogeniculate axons at 6 months postnatally following monocular enucleation at E44. These are three examples of axons that terminate in the LGN contralateral to the remaining eye. Each LGN contains two subdivisions: a larger, dorsal magnocellular region (M) and a smaller, ventral parvocellular region (P). (*A*) Parasagittal section showing the terminal arbor of an X axon that had an on-center/off-surround receptive field, with linear spatial summation, located at an azimuth of 9.0° and an elevation of −6.0°. It had a receptive field diameter of 0.9° and a latency of 0.85 msec to optic chiasm stimulation. This axon, like all X axons recovered in this study, had a normally proportioned arbor located in a region of the LGN appropriate for the eye of origin. (*B*) A Y axon that had a receptive field with an on-center but no appreciable surround, showed nonlinear spatial summation, and was located at an azimuth of 5.0° and an elevation of −6.0°. It had an optic chiasm latency of 0.5 msec and a receptive field diameter of 0.7°. Like seven of the nine Y axons recovered in the present study, the terminal arbor of this axon was abnormally tall, spanning those regions of the LGN appropriate to the eye of origin and also regions of the nucleus normally reserved for terminal arbors from the missing eye. (*C*) A Y axon with a small arbor located abnormally in the middle third of the nucleus (presumptive layer A1), a region where afferents from the missing eye would normally terminate. This particular axon had an on-center/off-surround receptive field with nonlinear spatial summation and was located at an azimuth of 3.5° and an elevation of −11.5°. It had a receptive field center diameter of 1.6° and an optic chiasm latency of 0.5 msec. A, anterior; D, dorsal.

## DISCUSSION

Results of this study demonstrate that prenatal monocular enucleation, performed when axons from the two eyes are

Table 2. Retinogeniculate axons at 6 months of age after monocular enucleation at E44

| LGN | X | Y |
|---|---|---|
| Ipsilateral | | |
| Normally proportioned and appropriately located | 3 | 0 |
| Normally proportioned and inappropriately located | 0 | 1 |
| Abnormally proportioned (expanded) | 0 | 2 |
| Contralateral | | |
| Normally proportioned and appropriately located | 3 | 0 |
| Normally proportioned and inappropriately located | 0 | 1 |
| Abnormally proportioned (expanded) | 0 | 5 |

Summary of the size and location of X and Y terminal arbors in the ipsilateral and the contralateral LGN of 6-month-old cats after monocular enucleation at E44.

intermixed in the LGN, does not affect all axons in the same manner. X axon arbors are relatively unaffected; they appear normally proportioned in their basic arbor framework and are located in appropriate regions of the LGN. In contrast, Y axons form abnormal arbors in two respects. Either they are abnormally tall and therefore not restricted appropriately within the LGN or they are of roughly normal proportions but are inappropriately located within the LGN with respect to eye of origin. These findings are summarized in Tables 1 and 2 and in Fig. 3. The fact that Y axons can form arbors that extend into regions normally occupied by axons from the removed eye provides a morphological basis, at the level of individual axons, for the previous observations in cats and in

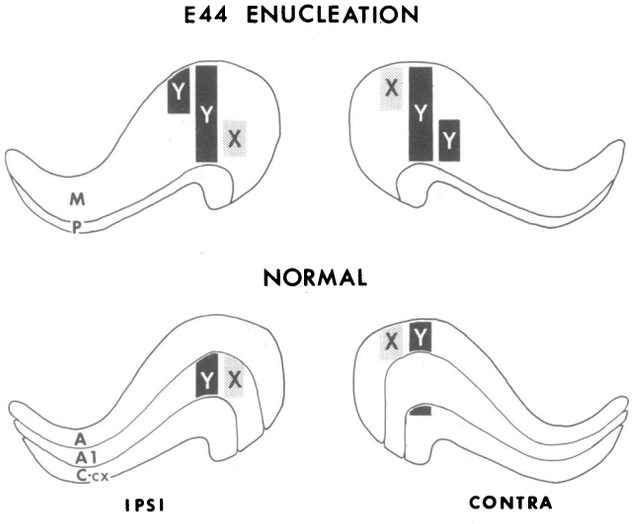


FIG. 3. Summary diagram showing the appearance and location of adult X and Y axons following enucleation of the right eye at E44. The termination patterns of X and Y axons from the remaining (left) eye in the ipsilateral and contralateral LGN are represented schematically. Y axons either elaborate terminal arbors that are abnormally tall or form qualitatively normal arbors but in inappropriate regions of the LGN with respect to eye of origin. X axons all form terminal arbors that are qualitatively of the normal size and shape and that are all located in regions of the LGN appropriate to the eye of origin. The normal adult pattern of termination of X and Y axons from the left eye in the contralateral and ipsilateral LGN is shown below for comparison (modified from refs. 2–5). Laminae A, A1, and the C complex (C-cx) in the normal LGN are indicated as are the magnocellular (M) and parvocellular (P) layers in the LGN after enucleation at E44.

other species that following monocular enucleation early in development the retinogeniculate projection from the remaining eye is no longer restricted exclusively to its normal eye-specific layers within the LGN (9, 10, 13, 18, 20, 21). It seems reasonable to conclude that of the axons studied at E59, those with expanded terminal arbors are likely to be Y axons, whereas most axons with appropriately located and restricted arbors are likely to be X axons. It is clear that since many of the axons studied either at E59 or at 6 postnatal months of age do form arbors that resemble those in normal animals of the same age in morphology and location, ongoing binocular interactions after E44 are not needed by these axons to elaborate their normal terminal arbor framework or to achieve their stereotypical adult locations within the LGN.

Since axons arising from X or Y retinal ganglion cells respond differently to prenatal enucleation at E44, class identity may be an important factor in the development of axon arbors. There are two ways in which class identity might contribute to the different responses of X and Y axons: (*i*) X and Y ganglion cells could have intrinsically different developmental programs with respect to differentiation of their terminal arbors; (*ii*) X and Y ganglion cells could have the same developmental program that differs in its timing. With regard to the first alternative, it may be that the basic arbor framework and position of X, but not Y, axons are intrinsically predetermined and not susceptible to extrinsic influences such as the removal of one eye. Therefore binocular interactions might not be required by X axons, but they would be required by Y axons to form arbors of the normal size and shape in the appropriate location.

The second alternative is that both X and Y axons may be susceptible to external influences, and X axons have the same developmental program as Y axons but implemented at an earlier time. Thus, X and Y axons might have different periods of susceptibility to the effects of removing binocular interactions. At the time of monocular enucleation in this study (E44), the majority of retinogeniculate axons are very immature and have not yet even begun to elaborate a clear terminal arbor (7, 8). Nevertheless, it may be that X axon arbors are already committed with regard to shape and location because those binocular interactions important for X arbors have already occurred, whereas those for Y axons are still ongoing. A difference in developmental schedule is consistent with studies of retinal neurogenesis showing that medium-sized ganglion cells (X cells) are born slightly before large-sized ganglion cells (Y cells) (22). It should be noted that eye removal at E44 not only disrupts binocular interactions but may also produce degeneration of retinal axons and denervation of postsynaptic neurons within the LGN (23). Denervation and degeneration products could perturb arbor morphology by stimulating the growth of axons from the remaining eye. Thus the two axon classes could differ in their ability to respond to these extrinsic cues.

To differentiate between these two alternatives requires further experiments, possibly monocular enucleations performed even earlier than E44. In fact, Sretavan and Shatz (13) have studied HRP-filled axons in E59 fetuses in which monocular enucleation was performed on E23, a time when retinal afferents have not yet reached the optic chiasm and hence before binocular interactions are possible (6, 24). Surprisingly, in these animals, *all* axons are restricted in extent, arborizing either in the middle or inner one-third of the nucleus. Since physiological classification was not possible in these experiments, it could not be determined whether the appropriately located axons were X or Y or a combination of both. However, because we have seen here that normal-sized Y axons can terminate in inappropriate regions of the LGN after enucleation at E44, it is possible that all of the inappropriately located axons found after E23 enucleation are from Y cells. If the *location* of X axons is

determined by intrinsic factors, X axons should always be appropriately located: in the inner one-third of the contralateral LGN or in the middle one-third of the ipsilateral LGN, just as after monocular enucleation on E44 or prenatal day 0 (P0). Y axons should then terminate in the middle one-third of the contralateral LGN or inner one-third of the ipsilateral LGN. In contrast, if the location of X (or Y) axons is determined by time of arrival, and if the first axons to grow into the LGN selectively target the inner one-third of the nucleus (6, 8), a reasonable alternative hypothesis is that X axons would terminate in the inner one-third and Y axons would terminate in the middle one-third of the LGN on both sides. These hypotheses could be tested by intracellularly staining physiologically characterized axons in adult cats after E23 enucleation.

The results presented here indicate that X axons can develop arbors of essentially normal size, shape, and location in the absence of ongoing binocular interactions after E44. The results discussed above imply that X axons can also develop normal morphology even in the absence of all binocular influences (e.g., following enucleation at E23). Studies of the consequences of enucleation at P0 similarly show no effect on X axon terminal arbor shape (12). Thus the shape, but not necessarily the location, of X axon arbors must depend upon factors intrinsic to each eye rather than upon binocular interactions. Y axons, on the other hand, sprout into denervated territory when enucleation is performed at P0 and retain and elaborate branches within denervated territory when enucleation is performed at E44. However, enucleation performed at E23 does not perturb retinogeniculate axon morphology. Y axons, therefore, appear to react to the elimination of ongoing binocular interactions quite differently depending upon when in development the elimination is imposed (see also refs. 25 and 26). Regardless of underlying mechanism, the results after prenatal monocular enucleation underscore the fact that axons originating from the same source and projecting to the same target in the mammalian central nervous system can be under very different developmental control.

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