THE JOURNAL OF COMPARATIVE NEUROLOGY 288:208-242 (1989)

Terminal Arbors of Single ON-Center and OFF-Center X and Y Retinal Ganglion Cell Axons Within the Ferret's Lateral Geniculate Nucleus

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ABSTRACT

The lateral geniculate nucleus of the ferret contains not only eye-specific layers, but a further subdivision of layers A and A1 into inner and outer sublaminae that contain, respectively, ON-center and OFF-center cells (Stryker and Zahs, '83). To study how the arbors of single retinal ganglion cell axons correlate with these cellular divisions, we have examined the morphology of physiologically classified retinal axons in the ferret's lateral geniculate nucleus.

As in cats, we could classify retinal axons as X or Y on the basis of a number of physiological criteria. X and Y axons have distinct patterns of termination in the lateral geniculate nucleus. Contralateral X axons innervate lamina A and ipsilateral axons lamina A1. X axons are further segregated in these laminae so that ON-center axons terminate in the inner sublamina, and OFF-center axons in the outer sublamina. We did not observe any branches of X axons innervating the medial interlaminar nucleus or the midbrain. Y axons have much larger terminal arbors and exhibit greater variation in their terminations. Generally, within layers A and A1, ON-center Y axons innervate the inner sublamina and OFF-center Y axons innervate the outer sublamina. However, they often innervate both sublaminae, and occasionally have a few boutons in the inappropriate lamina as well. Y axons also terminate in the dorsal C laminae, the interlaminar zones, and the medial interlaminar nucleus; branches of these axons course toward the midbrain, presumably to innervate the superior colliculus. Thus, whereas the Y pathway in the ferret is one of high divergence, the X pathway appears to be the substrate for segregated ON and OFF channels through the lateral geniculate nucleus.

Key words: intracellular labeling, retinogeniculate axons

The visual system of the ferret (*Mustelidae putorius furo*) bears marked similarities to the cat visual system, which has been extensively studied (see Sherman, '85 for review). The ferret's retina contains each of the morphological cell classes found in the cat (Vitek et al., '85). The lateral geniculate nucleus (LGN) is composed of laminae A, A1, and C; lamina A and two subdivisions of the C laminae—layers C and C2—receive projections from the contralateral retina, whereas laminae A1 and C1 receive ipsilateral retinal projections (Guillery and Oberdorfer, '77; Linden et al., '81; Zahs and Stryker, '84). However, in ferrets, unlike cats, lamina A and A1 each can be further subdivided into an inner sublamina containing primarily ON-center cells and an outer sublamina containing OFF-center cells (Stryker and Zahs, '83). These ON and OFF channels remain segregated up to the level of the visual cortex (Stryker and Zahs, '83; Zahs and Stryker, '88).

Accepted May 19, 1989.

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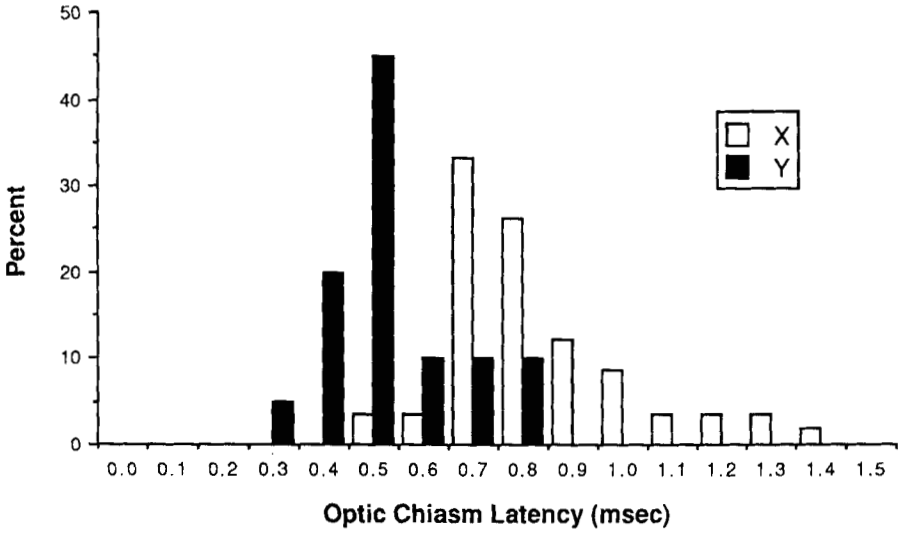

Fig. 1. Distribution of spike latencies to optic chiasm stimulation recorded for X axons and Y axons. The mean latency for X axons (n = 57) is 0.8 msec and the mean for Y axons (n = 20) is 0.5 msec.

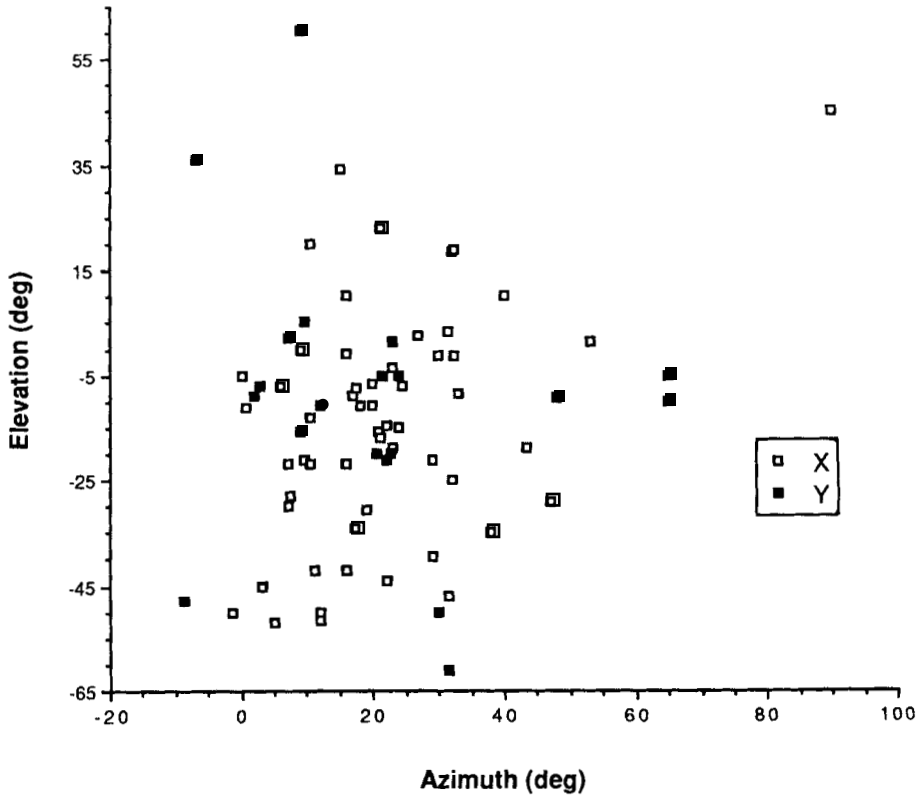

Fig. 2. Receptive field locations for all X and Y axons recorded in this study. X axon azimuths range from −1.5° to 90.0° and elevations from −52.0° to 45.0°. Y axon azimuths range from −8.7° to 65.0° and elevations from −61.0° to 60.5°.

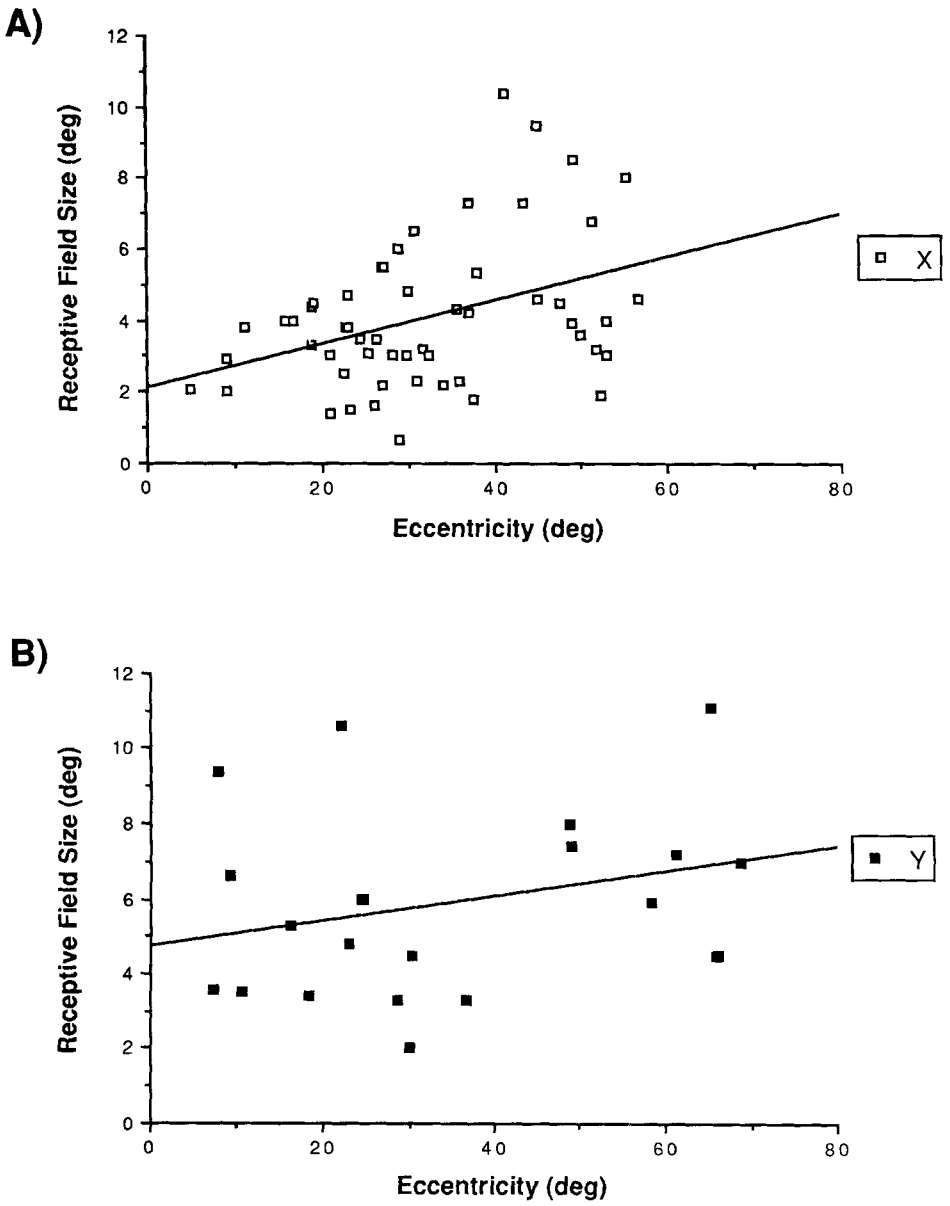

Fig. 3. Plot of receptive field center size versus eccentricity for X axons and Y axons. Receptive field center size is calculated as the average of horizontal and vertical receptive field center diameters.

Previously, the cat's retinogeniculate pathway has been shown to consist of functionally distinct X, Y, and W cells that differ structurally as well, both in terms of retinal dendritic morphologies (Fukuda et al., '84; Stanford and Sherman, '84; Stanford, '87a) and geniculate terminal arbors (Mason and Robson, '79; Bowling and Michael, '80, '84; Sur and Sherman, '82; Sur et al., '87). In this study, we first sought to determine whether or not ferret retinal ganglion cells (specifically, their axons) can be classified physiologically by the same criteria as those used in cats. Second, by filling single physiologically identified retinogeniculate axons with horseradish peroxidase (HRP) and examining their

TABLE 1. Number of Axons Recorded and Recovered

Recorded	X		Y	
	ON	OFF	ON	OFF
Contralateral	24	13	6	13
Ipsilateral	16	4	0	1
Total	40	17	6	14
Recovered	**X**		**Y**	
	ON	OFF	ON	OFF
Contralateral	7	4	1	5
Ipsilateral	7	0	0	1
Total	14	4	1	6

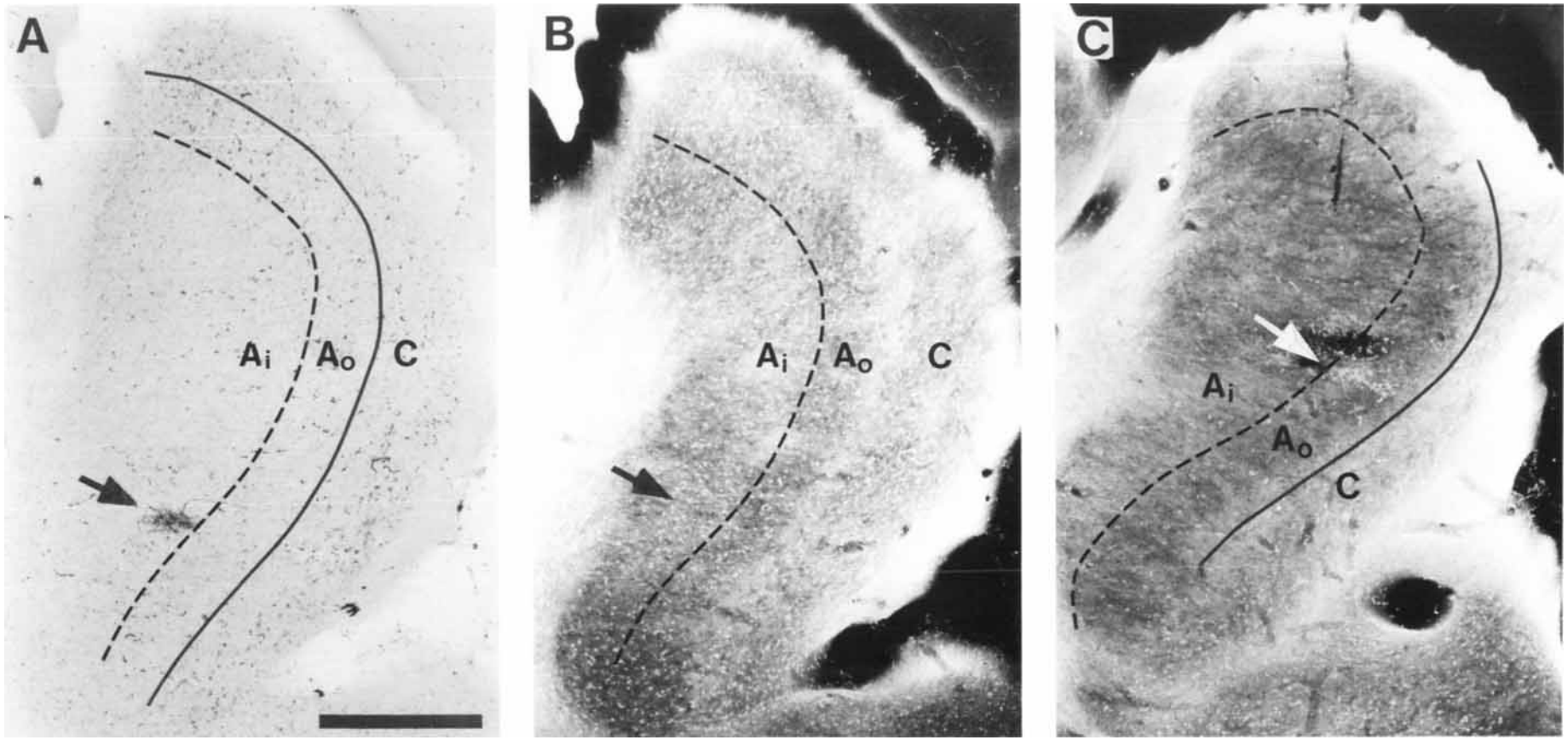

Fig. 4. Sublaminar locations of typical contralaterally projecting X axons. In all micrographs, dorsal is toward the top, anterior toward the left. In each micrograph, the arrow points to an HRP-filled axon. Solid lines indicate laminar borders and dotted lines sublaminar borders. (**A**) Lightfield micrograph of the LGN in parasagittal section. This is a contralaterally projecting ON-center X axon terminating in inner lamina A (A_i). As this is the monocular segment, lamina A1 is absent. Arrow indicates position of axon. (**B**) Darkfield micrograph of the same section shown in A. Laminar and sublaminar boundaries are clearer in darkfield. (**C**) A contralaterally projecting OFF-center X axon (white arrow) in darkfield. It is situated in outer lamina A (A_o). C, C laminae. Scale bar in A: 500 μm, and applies as well to B and C.

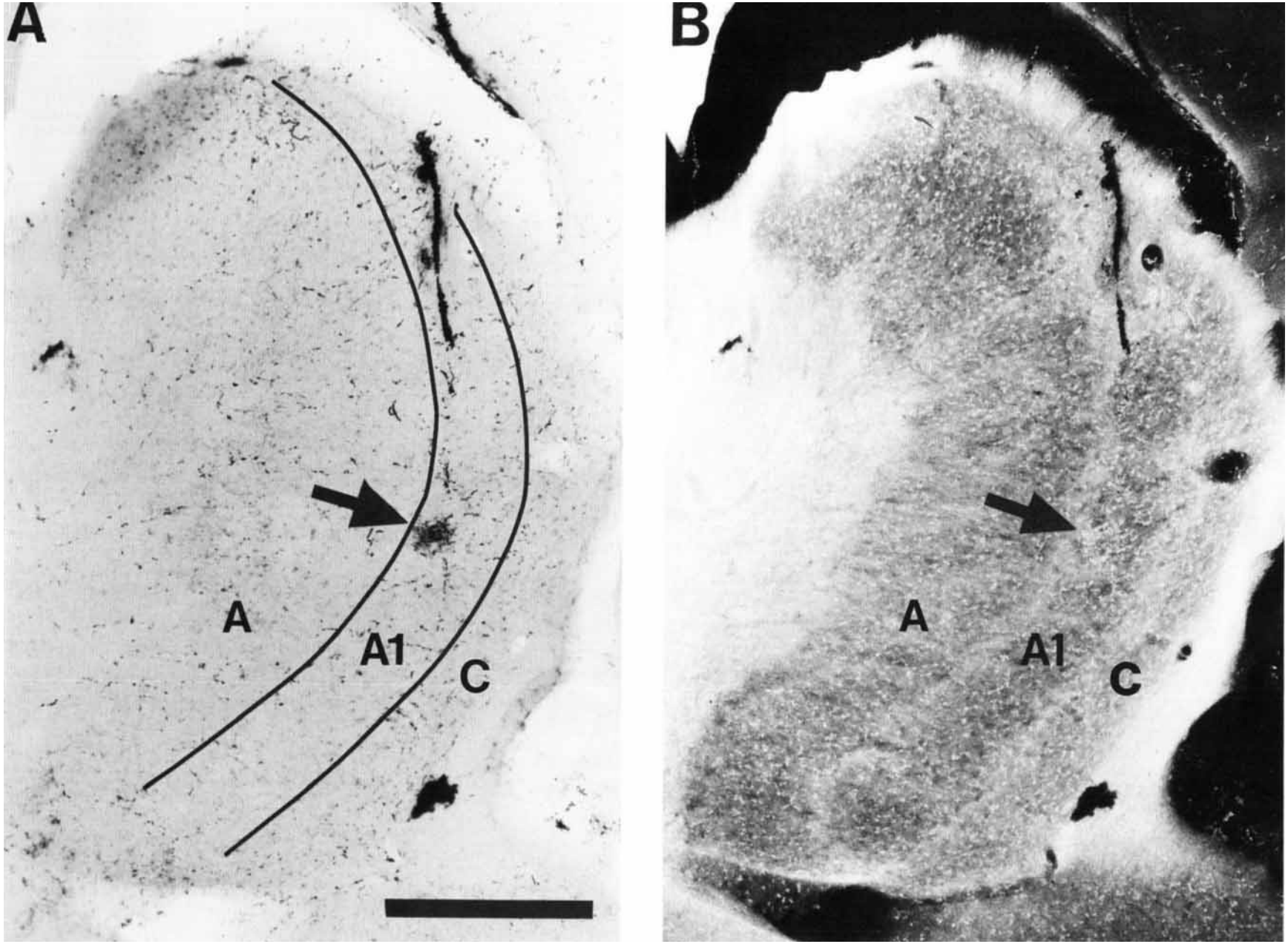

Figure 5

TABLE 2. Recovered Axons

Eye	Center	Latency (msec)	Azimuth (°)	Elevation (°)	Receptive Field Size (°)	Bouton Number	Arbor Volume ($\times 10^6$ μm^3)	Figures
A. X Axons								
contra	ON	0.8	38.0	−35.0	3.2	485	2.80	4ab,8,11,13bc
contra	ON	0.7	−1.5	−50.0	3.6	485	2.16	6a
contra	ON	0.8	24.5	−7.0	3.1	302	1.55	6b
contra	ON	0.7	30.0	−1.5	4.8	544	2.40	6c
contra	ON	0.7	23.0	−3.5	1.5	522	3.86	6d
contra	ON	0.5	17.3	−34.0	5.3	326	3.30	6e
contra	ON	0.9	12.0	−51.5	4.0	417	3.00	6f
contra	OFF	0.8	40.0	10.0	10.4	537	3.79	4c,9
contra	OFF	0.9	20.0	−6.5	1.4	413	1.79	6g
contra	OFF	1.3	20.0	−11.0	3.8	475	1.65	6h
contra	OFF	0.7	21.0	−17.0	2.2	366	1.62	6i
ipsi	ON	0.8	20.8	−16.0	1.6	368	1.24	5ab,7b
ipsi	ON	0.7	16.0	−22.0	5.5	308	1.97	7a
ipsi	ON	0.8	29.0	−39.5	3.9	614	2.40	7c
ipsi	ON	0.7	16.0	−42.0	4.6	286	1.84	7d
ipsi	ON	0.8	33.0	−8.5	2.2	548	2.29	7e
ipsi	ON	0.7	23.0	−19.0	3.0	555	3.27	7f,12ab
ipsi	ON	0.6	7.0	−22.0	3.8	635	5.10	10
B. Y Axons								
contra	ON	0.5	7.0	2.0	3.6	1542	19.23	19
contra	OFF	0.5	9.5	5.0	3.5	923	12.30	15
contra	OFF	0.4	30.0	−50.0	5.9	1424	12.29	16,22bc
contra	OFF	0.4	21.5	−5.2	10.6	1256	5.40	7ab,18,21ab
contra	OFF	0.8	22.5	−20.0	2.0	1002	7.66	20a
contra	OFF	0.4	48.0	−9.5	7.4	1036	6.24	20b
ipsi	OFF	0.5	−8.7	−48.0	8.0	320	3.94	14.22a

terminations in the LGN, we examined the structural correlates of these functional axon classes in the LGN. Third, we examined whether and to what degree single ON- and OFF-center retinogeniculate axons in each class exhibit *sublaminar* specificity.

We find that ferret retinal ganglion cells can be physiologically classed as X or Y (cf. Price and Morgan, '87; W axons are rarely encountered by our electrodes.) X and Y axons have distinct terminal morphologies in the LGN; whereas X axon arbors have relatively uniform morphologies, Y axon terminations are very heterogeneous. Because X axons exhibit a high degree of laminar and sublaminar specificity, it is mainly the X axons that contribute to the sublaminar segregation of ON and OFF channels in the LGN. A preliminary report has been presented elsewhere (Roe et al., '86).

MATERIALS AND METHODS

Our experimental methods were similar in general to those used previously for cats in this laboratory (Garraghty et al., '86b; Sur et al., '87) and are described only briefly here.

Fifteen normal adult ferrets were anesthetized, paralyzed, and artificially ventilated. All wound margins and pressure points were infiltrated with lidocaine. Vital signs such as expired carbon dioxide, body temperature, and heart rate were carefully monitored. End-tidal carbon dioxide was maintained at 4.0% and rectal temperature at 37.5°C; heart rate normally ranged from 280–320 beats per minute. Phenylephrine hydrochloride (Mydfrin) was applied to the eyes to retract the nictitating membranes, atropine sulfate to dilate the pupils, and neosporin eyedrops to prevent infection. The eyes were then fitted with appropriate contact lens so that they focused on a tangent screen located 114 cm in front of the animal. The locations of the optic disks (33° azimuth, 3° elevation with respect to area centralis) were plotted by reflection onto the tangent screen. This enabled subsequent determination of receptive field locations of recorded units (Zahs and Stryker, '84).

After resecting the skin overlying the skull, craniotomies and durectomies were made over the position of each LGN (centered at A-1.0, L6.0). Cylindrical plexiglas recording chambers were cemented to the skull around the craniotomies. Two small holes were drilled over the optic chiasm (A5.5, L1.5). Stimulating electrodes straddling the optic chiasm were then lowered through these holes until a visually evoked electric potential of at least 3–4 mV driven through each eye was obtained. These electrodes were fixed in place with dental cement.

To locate the LGN, an initial recording pass was made with a 3–5 MΩ parylene-coated tungsten microelectrode. All subsequent recording was conducted with glass micropipettes filled with 10% horseradish peroxidase (HRP) in a solution of 0.05 M KCl-Tris. Recording pipettes were pulled to an initial impedance of 150–170 MΩ and then bevelled at an angle of 22° to an impedance of around 100 MΩ. After a recording pipette was lowered into the brain, the recording chamber was filled with 3% agar in saline and sealed with dental wax.

Units recorded in the LGN or the optic tract were easily distinguished as either retinogeniculate axons or geniculate neurons (Sur et al., '87). Briefly, retinogeniculate axons (1) have shorter latencies to optic chiasm stimulation than do LGN cells, (2) can follow high (>100 Hz) rates of optic chiasm stimulation without failure, (3) have long monophasic action potentials, (4) do not exhibit slow waves or epsp's, and (5) typically have much higher background activity than do LGN cells. Each retinogeniculate axon was

Fig. 5. Sublaminar location of an ipsilaterally projecting X axon. (**A**) Lightfield micrograph of ON-center X axon terminating in inner lamina A1. Arrow points to HRP-filled axon. (**B**) Darkfield micrograph of the same section. The arbor is situated in the inner half of lamina A1. Solid lines indicate laminar borders. Scale bar in A: 500 μm, and applies as well to B. Conventions as in Figure 4.

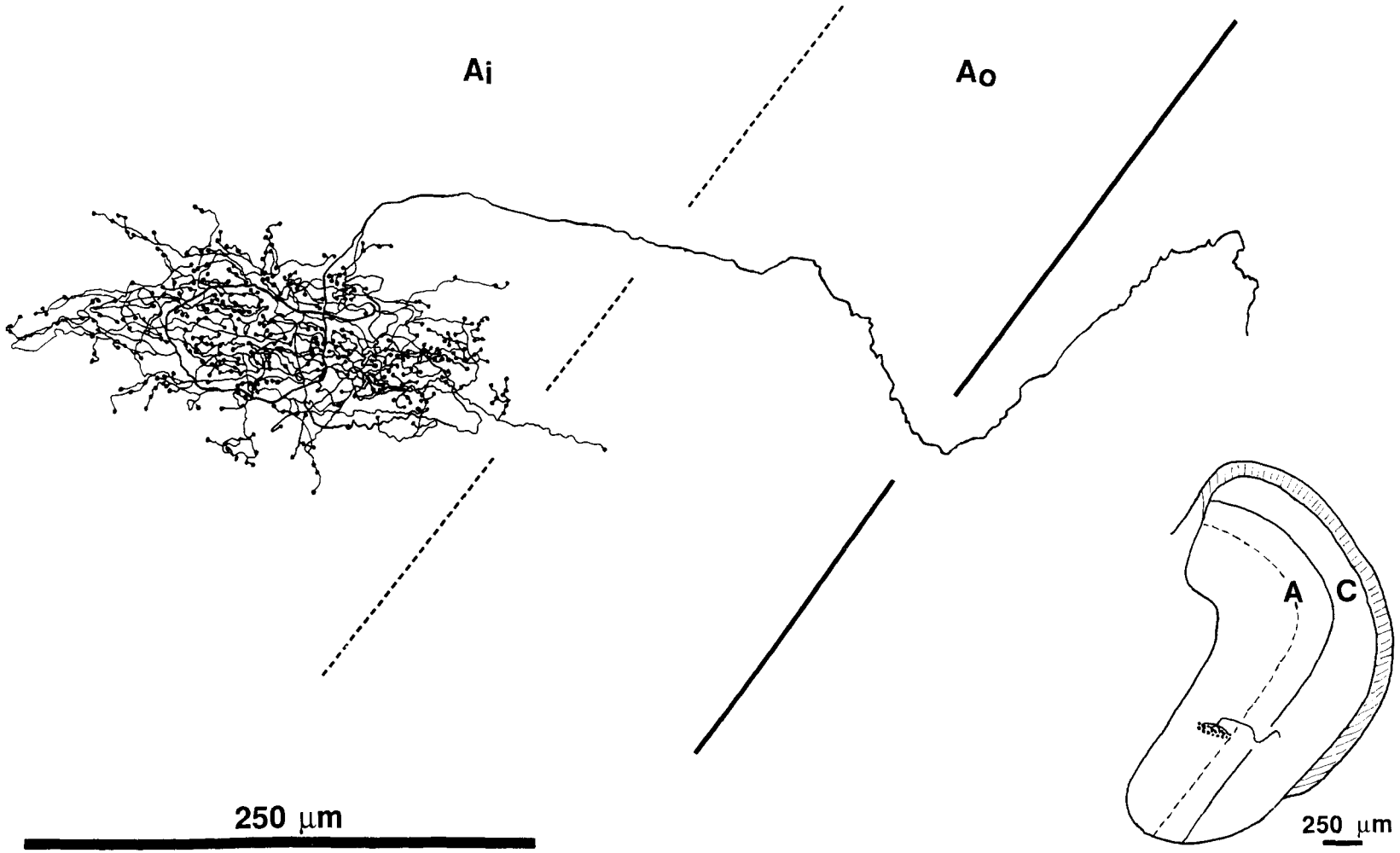

Figure 6

then subjected to a battery of physiological tests. Hand-held stimuli were used to determine the eye of origin, receptive field location and size, tonicity, ON/OFF center-surround preference, and response to large fast-moving, center-inhibiting stimuli. The axon was then classified as linear or nonlinear on the basis of its response to counterphasing square wave or sine wave gratings. These tests were used to classify each axon as X or Y (Enroth-Cugell and Robson, '66; Hoffmann et al., '72; So and Shapley, '79; Lehmkuhle et al., '80). After completion of these tests, an attempt was made to impale the axon by advancing the electrode and/or by application of brief depolarizing current pulses. Upon impalement (as indicated by a sudden 20–60 mV drop in the tip potential), the axon's physiological responses were rapidly verified and HRP was iontophoresed into it by passing depolarizing current pulses up to 20 nA for 20–60 seconds. HRP injections were attempted only in axons with receptive field locations spaced sufficiently far apart so that histologically recovered axons could be unambiguously identified. Typically, we attempted to fill 5–10 axons in each hemisphere.

After a survival time of at least 6 hours after the last injected axon, the animal was euthanized by an overdose of sodium pentobarbital and then perfused through the heart with, in order, 0.9% saline, 1% paraformaldehyde-2% glutaraldehyde fixative, and 10% and 20% phosphate-buffered sucrose solutions. After storage in 30% phosphate-buffered sucrose overnight, each LGN was sectioned parasagittally at 100 μm and processed for HRP histochemistry with 3,3-diaminobenzidine intensified by cobalt chloride (Adams, '77). The reacted sections were then mounted onto slides, dried, dehydrated through a series of alcohols, cleared in xylene, and coverslipped.

With the aid of maps of the visual field representation in the LGN constructed by Zahs and Stryker ('84), recovered axons in the LGN were then matched to the recorded units according to the position of their receptive fields. Well-filled axons were reconstructed under a 50 X oil immersion objective and a camera lucida drawing tube attachment. Laminar and sublaminar boundaries in the LGN were determined in darkfield illumination.

In addition to qualitative observations of axon arbor and terminal bouton appearances, several quantitative measurements were made for each axon. Arbor volumes were estimated by using a computer-assisted digitizing pad to determine the area enclosing the terminal boutons in each section and then multiplying that area by the thickness of the section(s). The number of boutons per arbor were counted from bouton distribution patterns drawn under camera lucida. Bouton density estimates were then calculated by taking the ratio of the bouton number and arbor volume. For bouton size measurements, at least 100 boutons for each axon were drawn under a 100X oil objective; all the boutons within each field of view were drawn for as many fields of view as necessary to reach the minimum of 100 boutons. The diameter of each bouton was measured along its longest axis; bouton size distributions and means were then calculated. Axon diameter was obtained by taking the average of measurements made at 50-μm intervals along the entire length of the well-filled parent axon trunk in the optic tract (the number of these measurements ranged from 3 to 20). Unless otherwise indicated, all statistical analyses were conducted with the Mann-Whitney U test.

Fig. 6. Camera lucida reconstruction of the contralaterally projecting ON-center X axon shown in Figure 4A. It terminates almost completely in the inner sublamina of A; there is a single bouton in the outer sublamina of A. The inset indicates its location in the LGN; as this is the monocular segment, lamina A1 is absent. Conventions as in Figure 4.

RESULTS

Physiological classification of X and Y retinogeniculate axons

We used a battery of tests to characterize retinogeniculate axons in ferrets and found that the major physiological properties used to classify cat retinal ganglion cells as X or Y (Enroth-Cugell and Robson, '66; Cleland et al., '71; Hochstein and Shapley, '76; Bullier and Norton, '79a,b) also distinguish ferret retinal ganglion cells. Since physiological differences between retinal X and Y cells have been described extensively in cats, and since the responses of these retinal cell classes in ferrets are very similar to those in cats, we describe only briefly their major response features.

Both X and Y units respond briskly to visual stimulation and have roughly circular receptive fields. A major determinant of X/Y classification in cats is the linearity of response to counterphasing square wave gratings; we first separated ferret axons as "X-like" or "Y-like" on this basis (see also below). Axons classified as X-like exhibit linear summation with their responses modulated at the fundamental temporal frequency of the stimulus. Furthermore, they exhibit well-defined "null positions" as grating phase is varied over the receptive field (Hochstein and Shapley, '76; Sur and Sherman, '82b). Axons classified as Y-like also exhibit linear responses, but only at low spatial frequencies; at higher spatial frequencies, these axons do not exhibit "null positions" and respond nonlinearly with their responses modulated at higher harmonics (generally the second harmonic) of the fundamental temporal frequency of the counterphasing grating. Virtually all axons classified on the basis of linearity of spatial and temporal summation also fall into distinct groups based on two other tests: the latency to optic chiasm stimulation and the size of the receptive field center.[1]

Y axons have significantly shorter latencies to electrical stimulation of the optic chiasm compared to X axons (Fig. 1; $p < 0.00003$ for all axons; $p < 0.05$ for each animal as an independent measure). X axon latencies range from 0.5–1.4 msec with a mean of 0.8 msec, whereas Y axon latencies range from 0.3–0.8 msec with a mean of 0.5 msec.

Receptive field center sizes of X and Y axons also differ. The receptive fields of our recorded axons were located throughout the visual field (Fig. 2); whereas there is significant overlap in the range of X and Y receptive field sizes, at comparable eccentricities, receptive field center diameters of X axons are smaller than those of Y axons (Fig. 3; $p < 0.004$ for a pooled comparison of X and Y axon receptive fields at all eccentricities; for comparisons in 0–10°, 10–33°,

[1]We used primarily the linearity of spatial and temporal summation to classify retinal axons as X or Y. Latency to optic chiasm stimulation and size of receptive field center were also used in conjunction. For one axon, when the three tests together did not yield an unequivocal classification, two tests that were consistent were used to classify the axon. This axon showed linear summation (generally an X cell property) but an optic chiasm latency of 0.4 msec (generally a Y cell property) and a large receptive field center size of 10.6°. This axon was thus classified as Y; no nonlinear axon was classified as X.

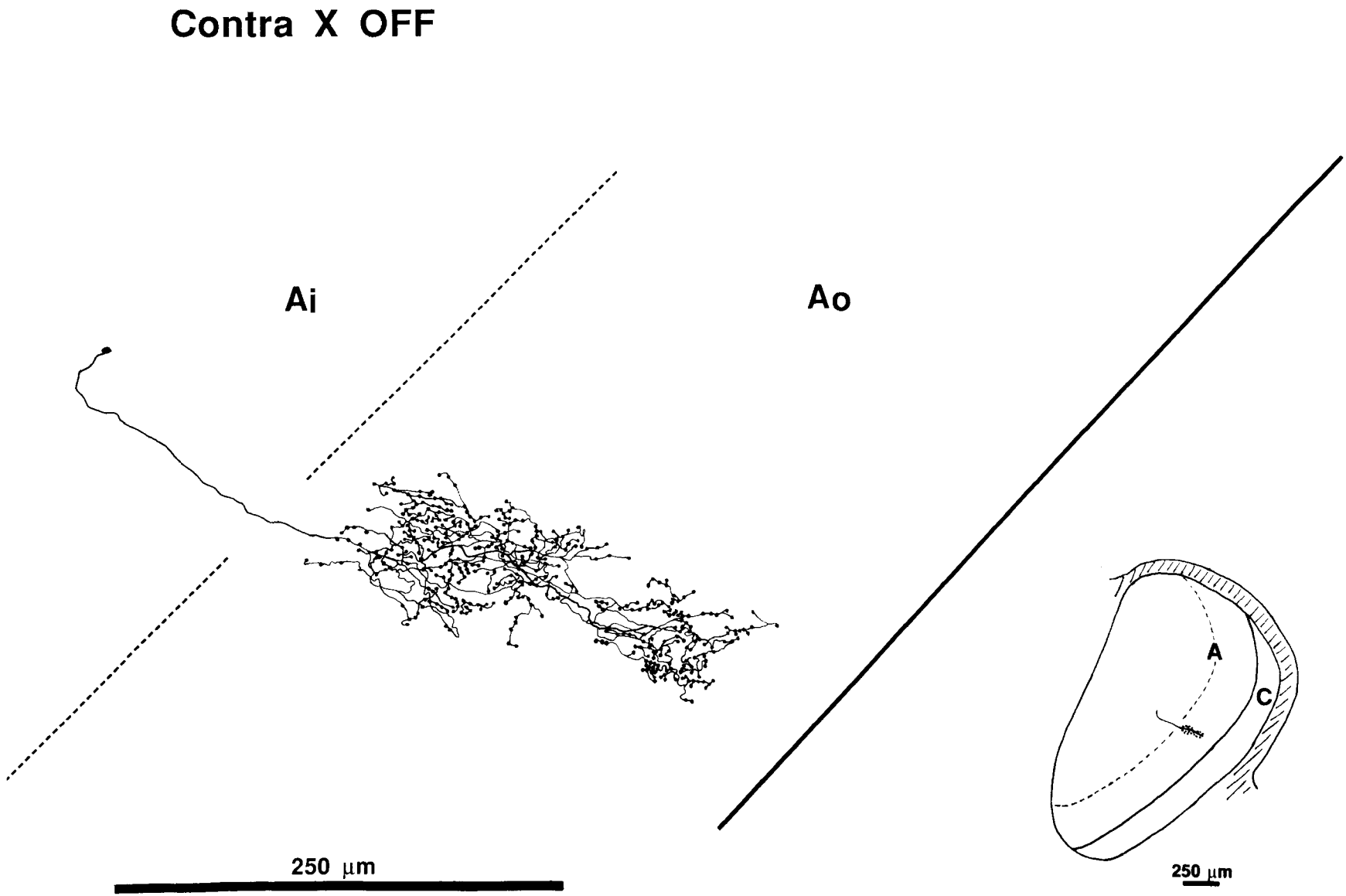

Fig. 7. Camera lucida reconstruction of a contralaterally projecting OFF-center X axon, terminating in the outer A sublamina. Conventions are as in Figure 4.

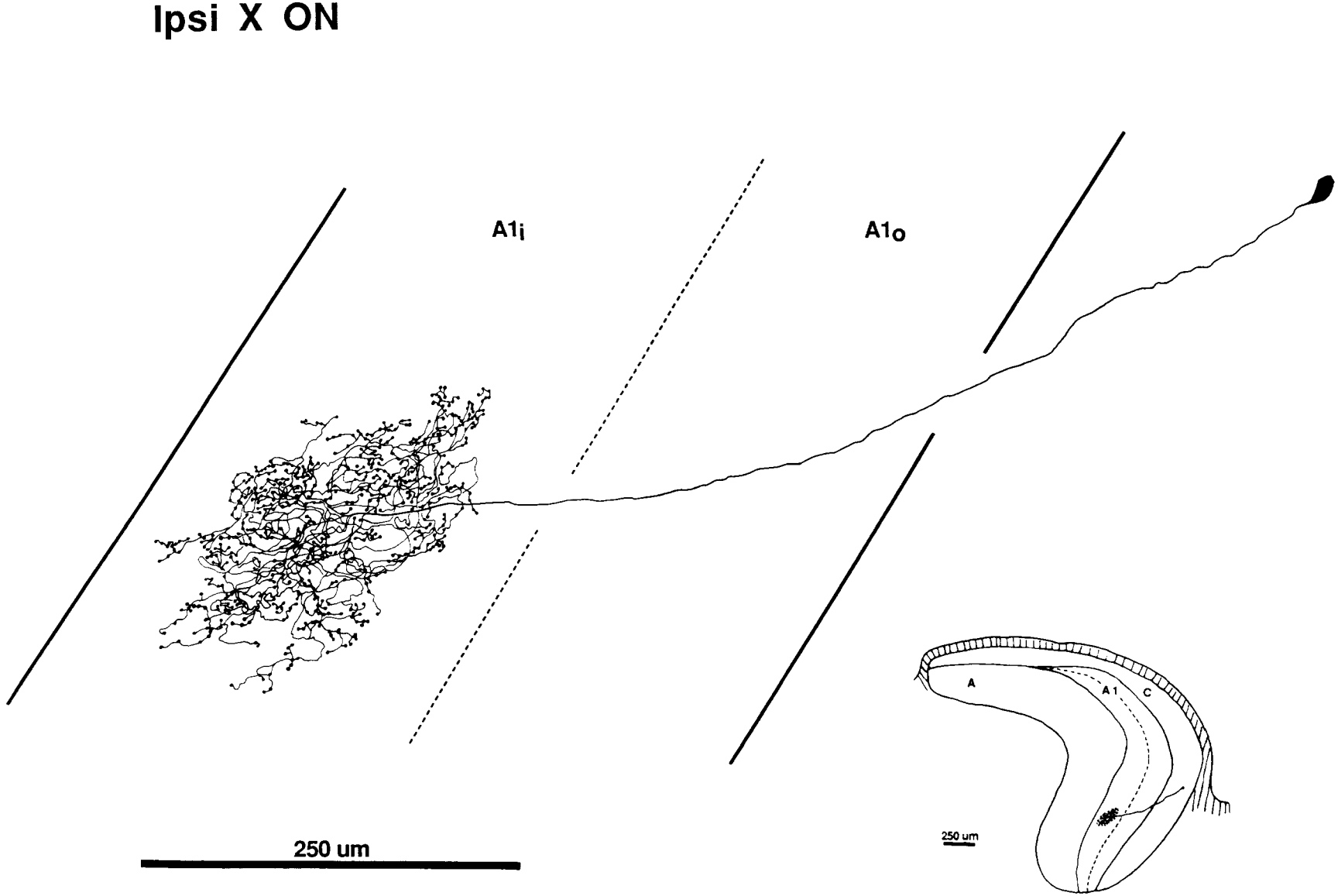

Fig. 8. Camera lucida reconstruction of an ipsilaterally projecting ON-center X axon, terminating in the inner A1 sublamina. Conventions as in Figure 4.

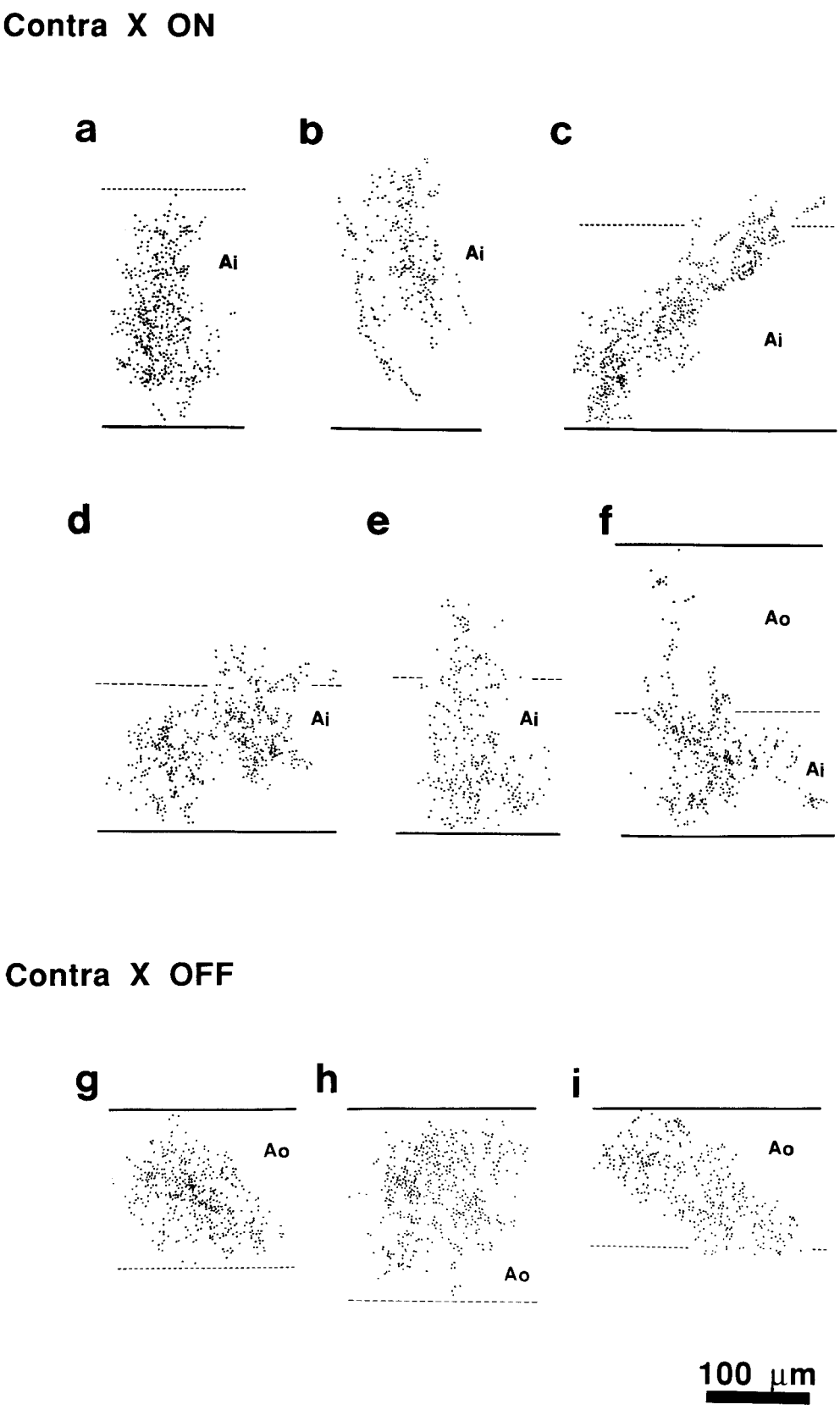

Fig. 9. Bouton distributions of 6 contralateral ON-center (**a–f**) and 3 contralateral OFF-center (**g–i**) axons. Solid lines indicate laminar borders and dotted lines sublaminar borders. The outer A sublamina (A_o) lies dorsal and inner A sublamina (A_i) lies ventral to the dotted line in each figure, as shown in part f. The majority of boutons are confined to the inner A (A_i) and outer A (A_o) sublaminae for ON-center and OFF-center axons, respectively.

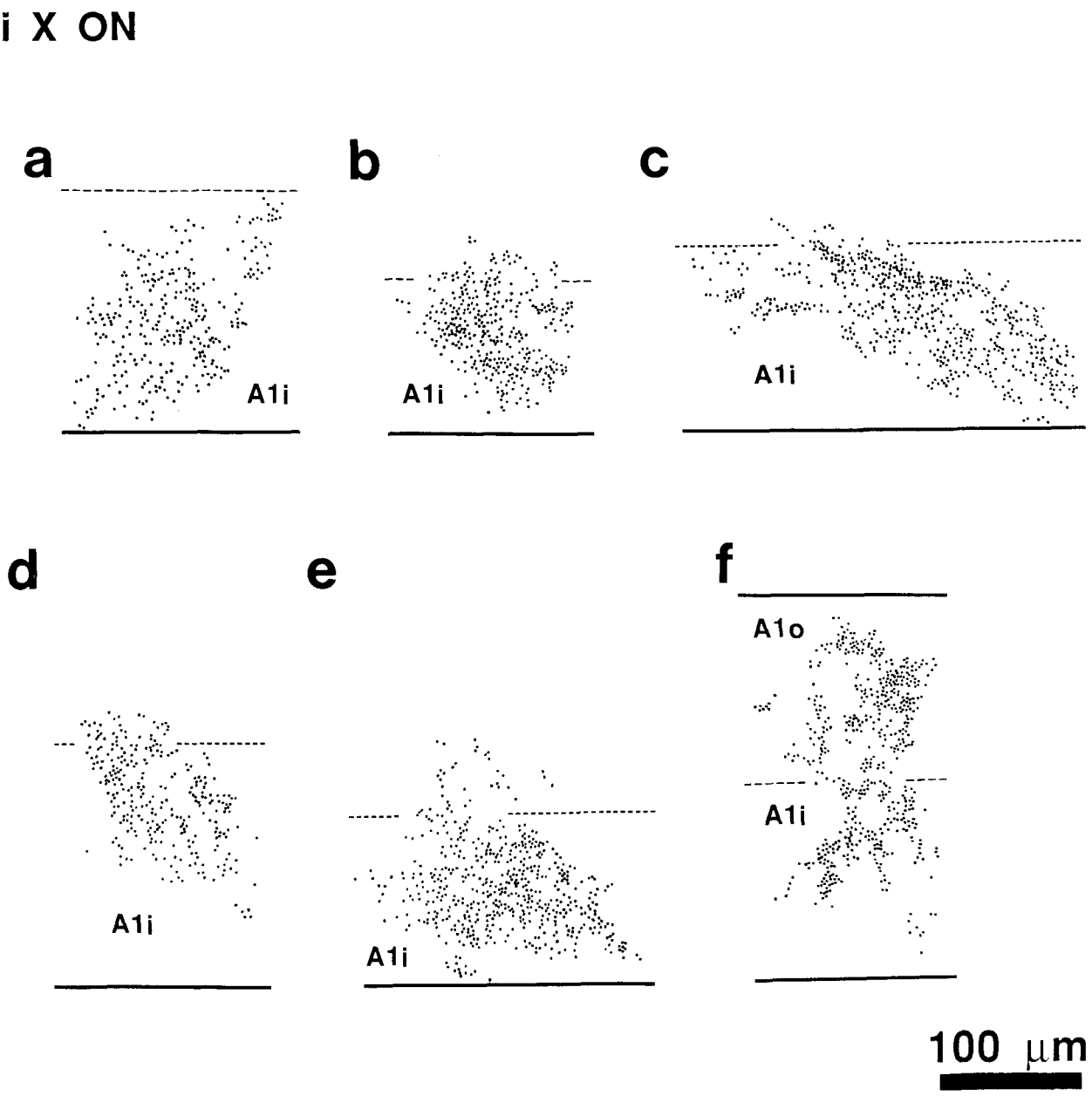

Fig. 10. Bouton distributions of 6 ipsilateral ON-center X axons. Conventions as in Figure 6. Except for the axon shown in **f**, almost all boutons are confined to the inner A1 sublamina ($A1_i$). The outer A sublamina ($A1_o$) lies dorsal and inner A sublamina ($A1_i$) lies ventral to the dotted line in each figure, as shown in part f.

and >33° eccentricity groups, $p < 0.065$ for each comparison). Our sample of X axon receptive field center diameters range from 0.7° to 10.4° with a mean of 4.1°; those of Y axons range from 2.0° to 11.1° with a mean of 5.9°. We found no significant difference between the receptive field center sizes of ON- and OFF-center axons, or between those of contralaterally and ipsilaterally projecting axons.

Three physiological tests that usually distinguish X and Y axons in cats turn out to be less selective in ferrets. First, tonicity of center response (Bullier and Norton, '79a,b) often fails to discriminate between X and Y axons. Whereas X axons always respond tonically under our recording conditions (mesopic light levels), a majority (60%) of the Y axons we have recorded also respond tonically. Second,

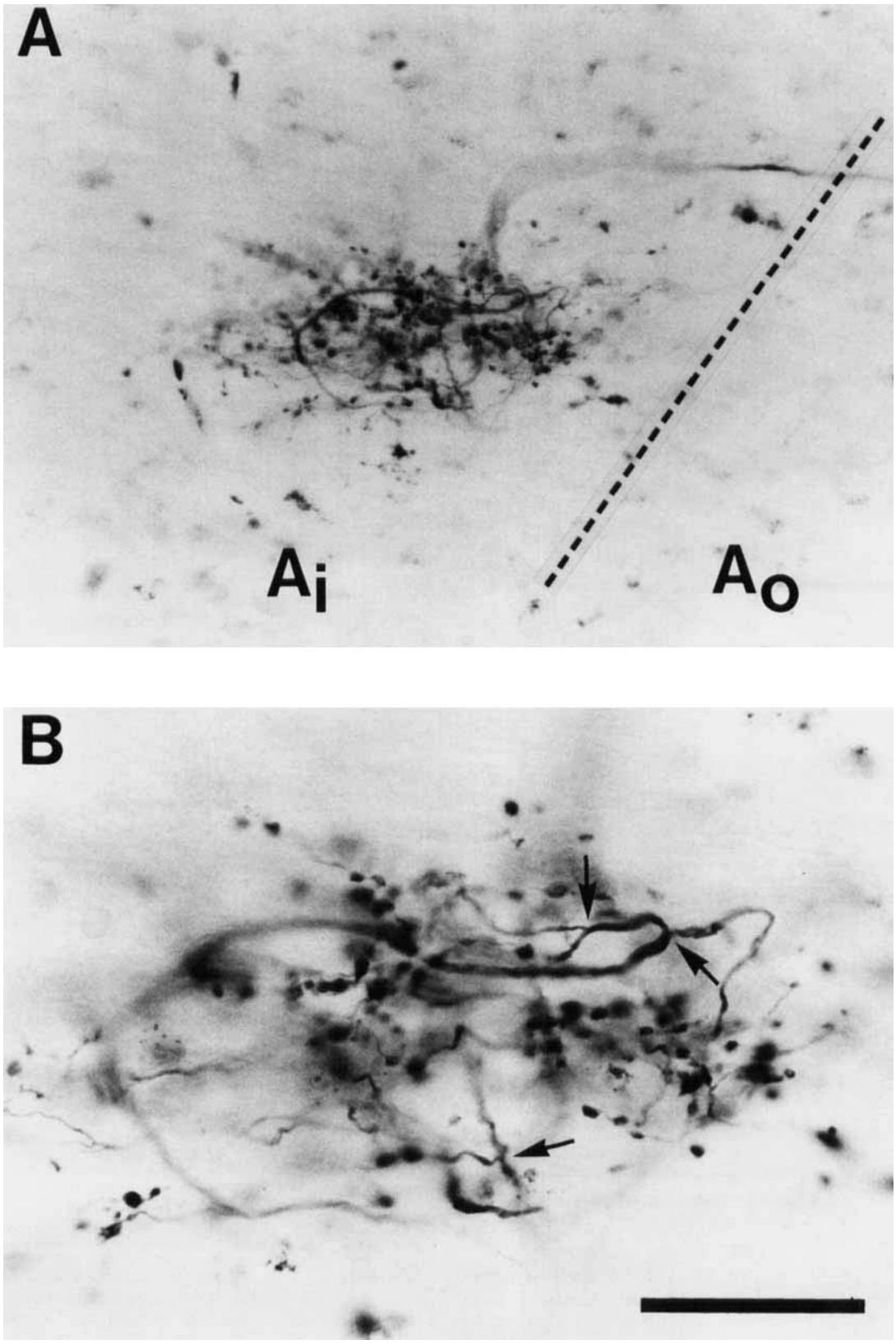

Fig. 11. High power micrographs of X axon preterminal branches: (**A**) The high density of boutons typical of X axons is illustrated by this contralateral ON-center X axon arbor (also shown in Figures 4A and 6). (**B**) The same axon at higher power. The preterminal branchlets can be seen taking contorted paths in the terminal zone. Several bifurcations are indicated by arrows. Scale bar A: 100 μm, B: 40 μm.

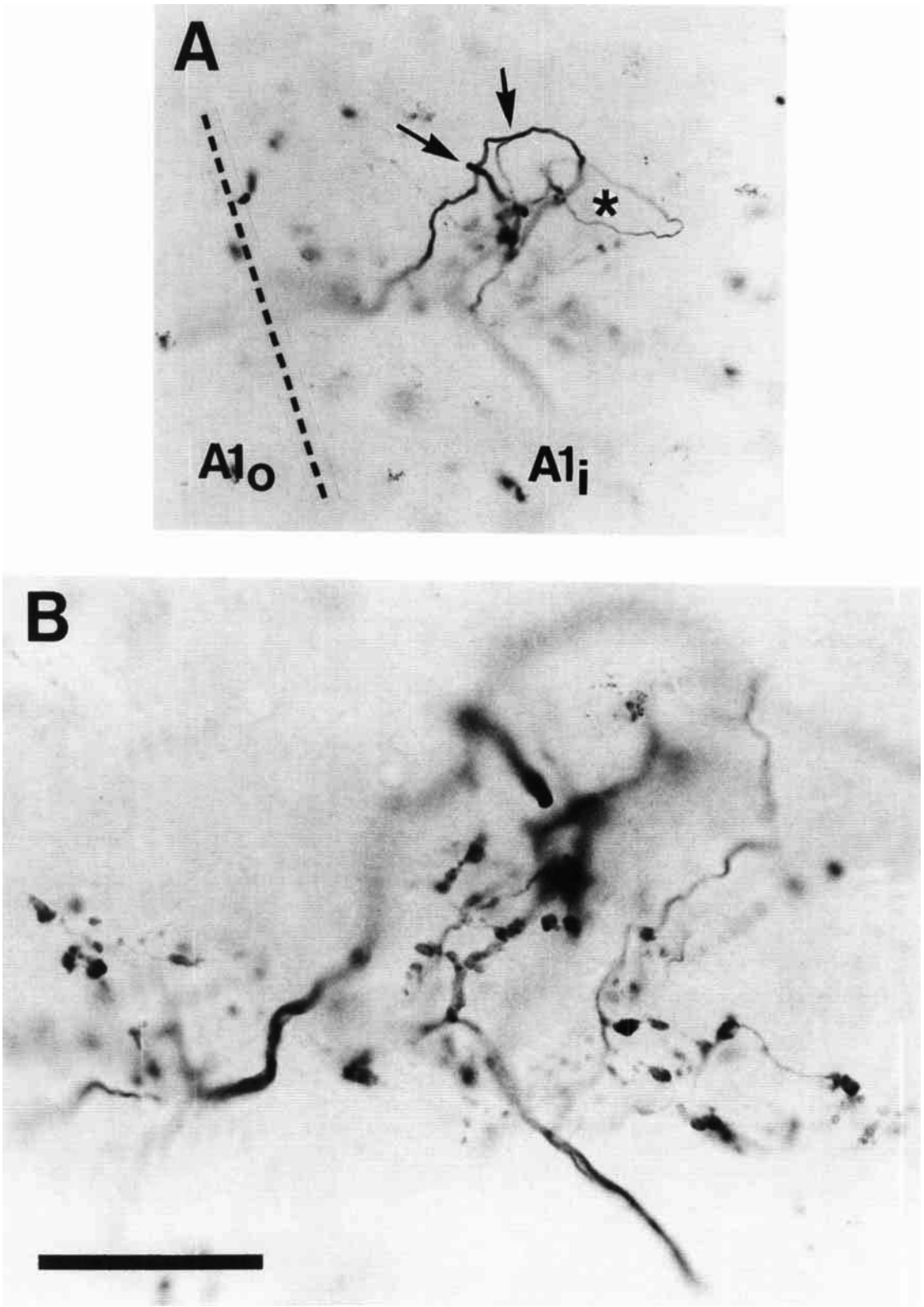

Fig. 12. (A) Ipsilateral ON-center X axon arbor taking U-shaped and even a looped (asterisk) path. Arrows indicate bifurcations. (B) Same axon shown in A. Higher power view of terminal boutons, indicating their range of sizes. Scale bar A: 100 μm, B: 40 μm.

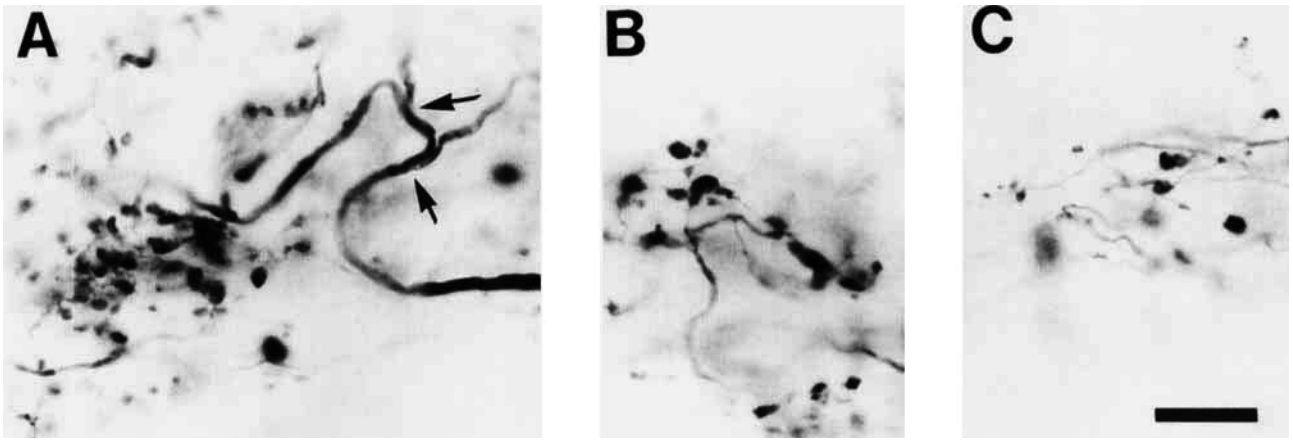

Fig. 13. High power micrographs of typical X axon boutons. (**A**) Arrows indicate bifurcations. Note contorted course of axon and high density of boutons. (**B**) Boutons of different sizes are often seen adjacent to each other. (**C**) Boutons often arise from very fine terminal fibers. Scale bar A, B, C: 25 μm.

many of the axons we recorded (41 out of 57 X axons, and 17 out of 20 Y axons) lack marked inhibitory surrounds. Thus the relative degree of center-surround antagonism (Bullier and Norton, '79a,b) could not be used to distinguish X from Y axons. Finally, both X and Y axons respond in variable fashion to rapidly moving, center-inhibiting stimuli larger than their receptive field centers. Thus the presence or absence of a response to such stimulation (Bullier and Norton, '79a,b) cannot be used to reliably discriminate between X and Y axons.

Our sample of extracellularly recorded retinogeniculate axons, all recorded either in the LGN or the adjacent optic tract, consists of 20 Y axons and 57 X axons. Receptive field eccentricities for X axons range from 5.0° to 100.6° and for Y axons from 7.3° to 68.7° (Fig. 2). There is a tendency for receptive field center sizes to be larger in peripheral than in central visual areas (Fig. 3), though the correlation is not high for either X axons (R = 0.39) or Y axons (R = 0.28).

Morphology of identified X and Y axons

Qualitative observations. After completion of extracellular physiological characterization of each axon, we attempted to impale the axon and inject it with HRP. Of the total pool of recorded axons, 18 X axons and 7 Y axons were sufficiently well filled to permit qualitative and quantitative analyses of the anatomical features of the recovered arbors. The anatomical descriptions and analyses in this study are based on this sample of 25 well-filled axons.

Of the 57 X axons we recorded, there were approximately twice as many contralateral as ipsilateral axons, and about twice as many ON-center units as OFF-center units (Table 1). Of the 20 recorded Y axons, there were 19 contralateral axons and 1 ipsilateral axon, suggesting a marked asymmetry in the retinogeniculate projections of Y axons (cf. Vitek et al., '85; see Discussion). Out of the 18 X axons recovered after intracellular labelling with HRP, there were 7 contralateral ON-center, 4 contralateral OFF-center, and 7 ipsilateral ON-center axons. The paucity of ipsilaterally projecting Y axons is reflected as well in our sample of axons recovered after intracellular filling: only 1 of 7 recovered axons was from the ipsilateral retina. This axon was OFF-center. The contralateral Y axons included 1 ON-center and 5 OFF-center axons.

Our subpopulation of X and Y axons with well-labelled terminal arbors were physiologically representative of our total population of recorded axons. This subpopulation of axons exhibited: (1) latencies to optic chiasm stimulation for X axons in the range 0.5–1.3 msec (mean 0.8 msec), for Y axons in the range 0.4–0.8 msec (mean 0.5 msec), (2) receptive field eccentricities for X axons ranging from 21.0° to 52.9°, for Y axons from 7.3° to 58.3°, and (3) receptive field sizes for X axons in the range 1.4°–10.4° (mean 3.8°), for Y axons in the range 2.0°–10.6° (mean 5.9°). The correlations described above for the entire population of recorded axons also hold for this subpopulation of well-filled axons. Table 2 lists the general physiological parameters of recovered axons and indicates the figures in which they appear.

X Axons. *Laminar and sublaminar distribution in the LGN.* Laminar boundaries in the ferret LGN can be clearly distinguished in unstained sections when viewed under low power in darkfield illumination. Sublaminar borders within laminae A and A1 cannot always be consistently discerned in unstained or even Nissl-stained material, being more distinct in some cases and in some parts of the nucleus than in others. The only way to unequivocally identify sublaminae is to inject one eye with an anterograde tracer (see also Linden et al., '81). This causes the sublaminae to stand out, for the interlaminar plexus has lighter label than the sublaminae themselves. In our experiments, however, intraocular injections (at least of HRP or WGA-HRP) would obscure our injected axons and probably compromise the optics. Thus in cases in which sublaminar borders are clear, we have drawn them accordingly; in cases in which sublaminar borders are not obvious we have simply used a division midway between the inner and outer borders of that lamina ("inner" denotes away from the optic tract and "outer"

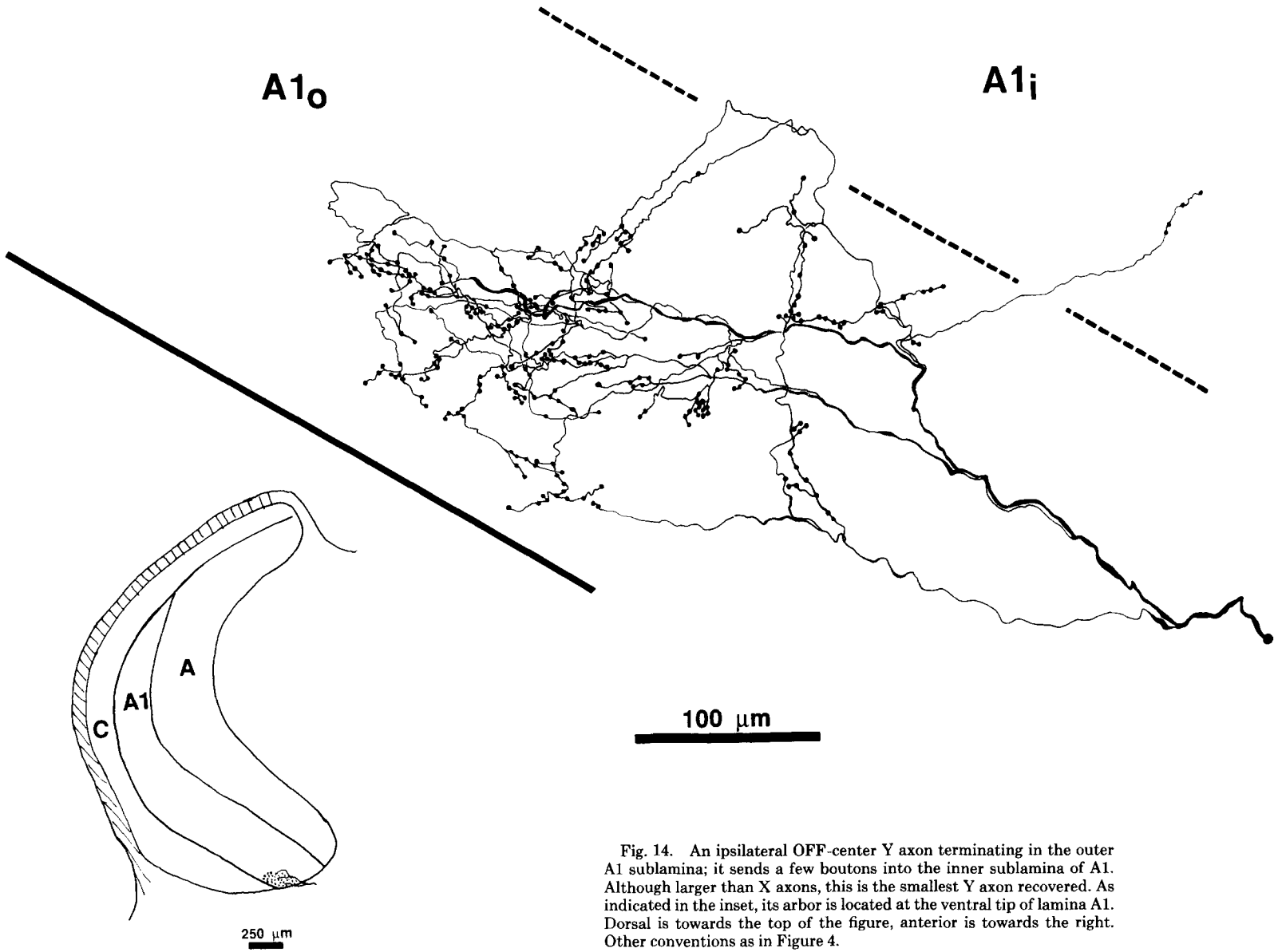

Fig. 14. An ipsilateral OFF-center Y axon terminating in the outer A1 sublamina; it sends a few boutons into the inner sublamina of A1. Although larger than X axons, this is the smallest Y axon recovered. As indicated in the inset, its arbor is located at the ventral tip of lamina A1. Dorsal is towards the top of the figure, anterior is towards the right. Other conventions as in Figure 4.

Figure 15

denotes toward the optic tract). All axon reconstructions are in the parasagittal plane, unless otherwise stated.

All retinogeniculate X axons in our sample have only a single termination either in lamina A, if contralaterally projecting, or in lamina A1, if ipsilaterally projecting; none has a termination within the C laminae. Furthermore, in addition to eye-specific laminar segregation, retinogeniculate X axons in ferrets segregate by ON-center/OFF-center sublaminar divisions as well. Figures 4 and 5 show the locations of typical X axon terminations in the LGN.

Figure 4 displays contralateral X axons terminating in sagittal sections of the LGN. Figure 4a contains a contralateral ON-center X axon terminating in the inner sublamina of A; the laminar and sublaminar borders are seen more clearly in the darkfield photomicrograph of the same section in Figure 4b. Figure 4c shows a contralateral OFF-center axon terminating in the outer sublamina of A. An ipsilateral ON-center axon is shown in Figure 5a,b. Whereas a sublaminar border is not evident in this case, this axon clearly terminates in the inner half of lamina A1. Although our sample does not include ipsilateral OFF-center X axons, it is likely that these axons follow a complementary pattern of termination and innervate the outer sublamina of A1. Camera lucida reconstructions of three X axons further illustrate these sublaminar termination patterns (Figs. 6–8).

All ON- and OFF-center X axons we recovered have exhibited these patterns of termination in the LGN. Bouton distributions of the 15 remaining X axons in our sample are illustrated in Figures 9 and 10. As shown in Figure 9, contralateral ON-center axons terminate with the vast majority of their boutons in the inner A sublamina (A_i), whereas contralateral OFF-center axons terminate in the outer A sublamina (A_o). Ipsilateral ON-center axons (Fig. 10) terminate similarly (with the exception of one axon shown in Fig. 10f) in the inner A1 sublamina ($A1_i$). From these many examples, it is clear that ON-center X axons innervate the inner and OFF-center X axons innervate the outer sublamina of their respective eye-specific laminae. This ON/OFF segregation of retinogeniculate X axons is therefore a key anatomical substrate for sublaminar organization of ON- and OFF-center cells in the ferret LGN.

Morphology of axon trunks, branches, and arbors. X axons have small and compact terminal arbors with a high density of boutons and their arbors show a relatively small range of variation. Retinogeniculate X axons have one primary axon that branches only at the site of termination; we have not seen branching collaterals elsewhere, either in the optic tract or in the preterminal part of the axon within the LGN. X axon parent trunks enter the LGN from the optic tract and take a direct course to the zone of termination where they terminate in narrow fields about 100–150 μm wide that are oriented perpendicular to the laminar borders. Figures 6–8 illustrate some of these features of X axons.

Figure 6 is a reconstruction of the contralateral ON-center axon pictured in Figure 4a. Its field is approximately 110 μm in width and 250 μm in height. Its preterminal branches all emerge from a single point of the parent trunk in a "burstlike" fashion. Figures 7 and 8 further exemplify these patterns of termination of X axons. Figure 7 is a reconstruction of a contralateral OFF-center X axon. Its entire arbor, located in the monocular segment of the LGN, is located well within the outer sublamina of A. Oriented perpendicular to laminar borders, the arbor is 95 μm in width and 220 μm in height. Figure 8 illustrates a large (width 250 μm, height 200 μm) ipsilateral ON-center X axon located in the inner sublamina of A1, with a dense terminal plexus. The X axons in Figure 9 and 10 also illustrate similar dense terminations. Their boutons all lie in small arbors, encompassing up to 250 μm in height and 150 μm in width.

The parent trunks of retinogeniculate X axons often emerge from the optic tract at a sharp angle and head straight for the destination. Within the arbor, however, they branch repeatedly. These branches course in tortuous fashion, often reversing direction across the terminal field, and many branch several times before giving rise to a dense field of terminal boutons. Figures 11 and 12 depict such branching at high magnification. In Figure 11b, a large branchlet is seen taking a U-turn and bifurcating several times before giving rise to its terminal boutons. Figure 12a shows another X axon making similar contorted U-turns and loops. Two bifurcations can be clearly seen here (arrows).

X axon boutons tend to be round and plump and variable in size; medium-size boutons (3–5 μm) are often seen adjacent to small boutons (1–2 μm) on the same branchlet (see Figures 12b, 13). Boutons do not appear to form clusters, as often seen for X axons in cats (Sur et al., '87).

Y Axons

Laminar and sublaminar distribution in the LGN. The laminar and sublaminar distribution of Y axons in the LGN is much more extensive and variable than that of X axons. As each Y axon terminates in multiple loci and spans up to 800 μm in width, it is impossible to display a significant portion of the arbor in a photomicrograph of any single 100 μm section. Thus we present only camera lucida drawings of our Y axons (Figs. 14–19).

Figures 14 and 15 illustrate the simplest Y axons we have recovered in terms of regions of termination and laminar specificity. Figure 14 illustrates an OFF-center Y axon from the ipsilateral retina terminating with a single arbor in the outer sublamina of A1. As in cats, this ipsilaterally projecting Y axon does not have terminations in the C laminae (Sur et al., '87; but see one axon in Bowling and Michael, '84). However, as this axon was injected fairly close to its field of arborization and we were unable to trace its parent trunk very far into the optic tract, the possibility of other terminations cannot be absolutely ruled out. This axon is the only ipsilaterally projecting Y axon in our sample.

Figure 15 illustrates a contralateral OFF-center Y axon with a major termination in the outer sublamina of A and a smaller termination in the dorsal C laminae. Note the relatively complete confinement of the lamina A terminations to the outer sublamina. Aside from their restriction to single sublaminar locations, these laminar termination patterns are reminiscent of Y retinogeniculate axons found in cats.

The other Y axons we recovered have more complex patterns of termination. Two Y axons recovered in the monocular segment of the LGN have a major termination that crosses from the outer sublamina of A, through the interlaminar zone between laminae A and C, and into the dorsal C laminae. One of these axons is shown in Figure 16. This contralateral OFF-center Y axon has a major terminal arbor that spans a wide expanse from outer lamina A to the C laminae, although its innervation is heaviest in the interlaminar

Fig. 15. OFF-center Y axon from the contralateral eye. This axon has terminations in the outer A sublamina and in the dorsal C laminae. Both arbors, which are oriented parallel to laminar borders, are well restricted to within laminar and sublaminar borders. Note also the collateral branch heading towards the midbrain (arrow). Dorsal to the top, anterior to left. Conventions as in Figure 4.

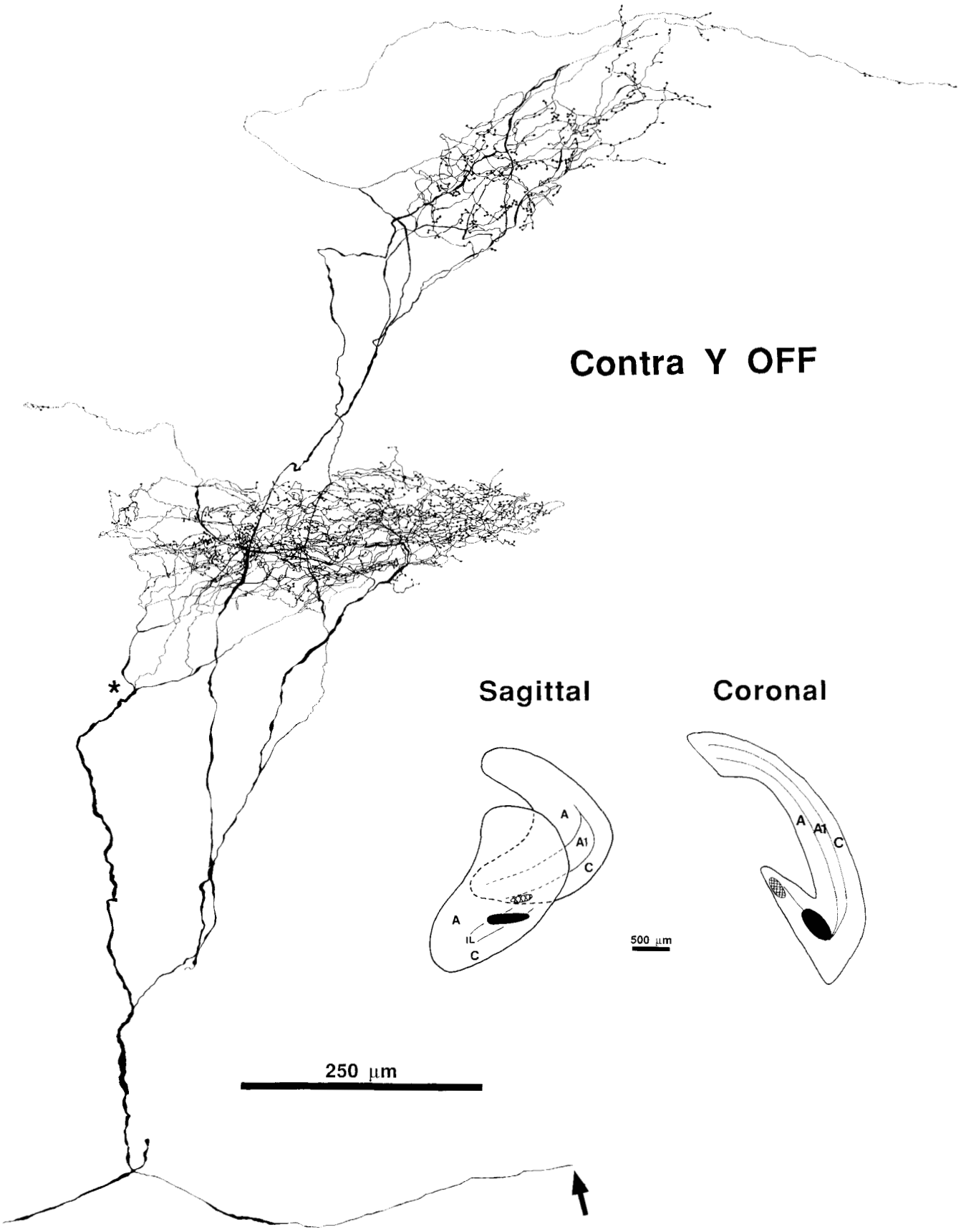

Figure 16

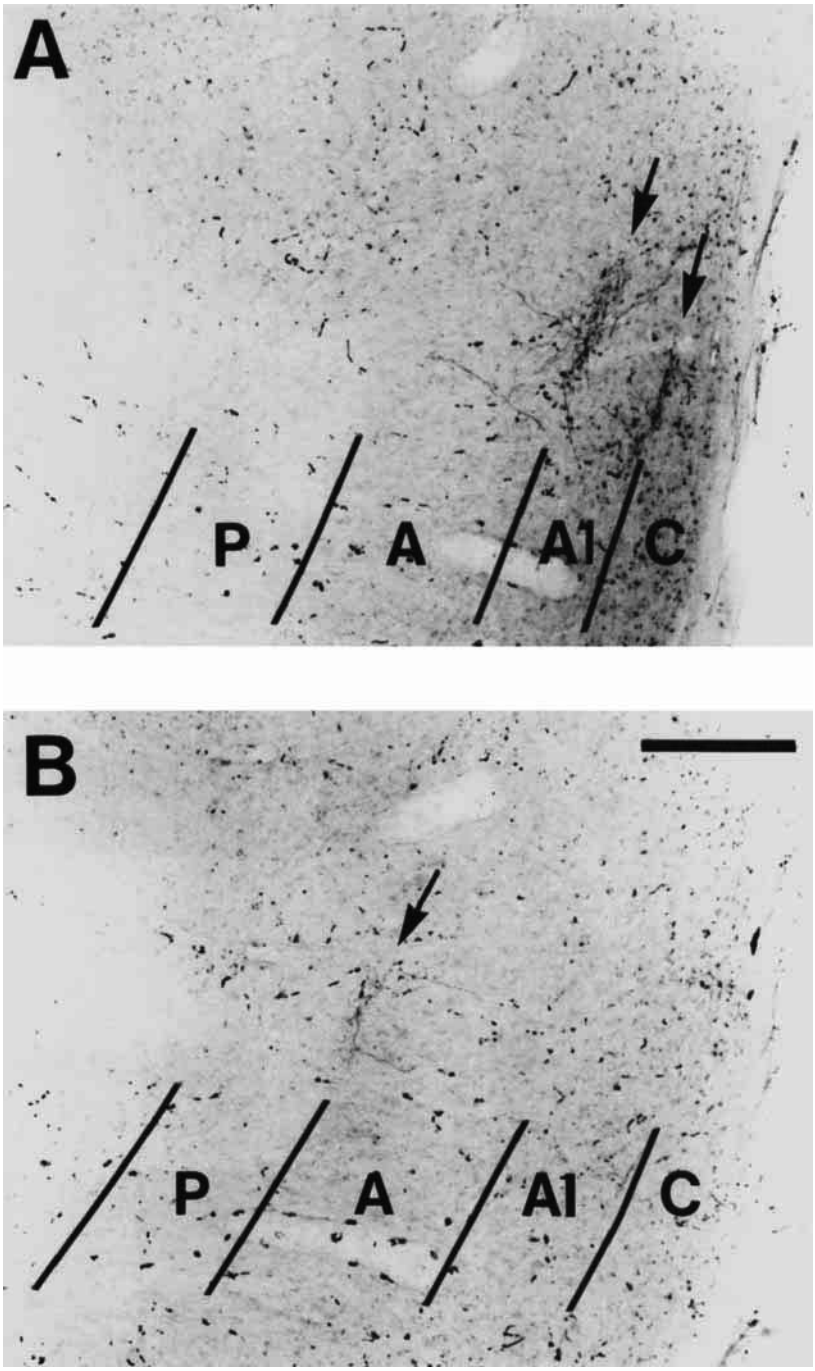

Fig. 17. Contralateral OFF-center Y axon. (**A**) Two terminal zones of this axon (arrows) are located in the A1/C and the A/A1 interlaminar zones. (**B**) The third termination (arrow) is located in the intranuclear zone between the perigeniculate nucleus (P) and the A lamina. Dorsal is to the top, anterior to left. Scale bar A: 500 μm, and applies as well to B.

Fig. 16. Contralateral OFF-center Y axon. This axon has two terminations. Its larger termination crosses from the outer A sublamina, through the A/C interlaminar zone, and into the dorsal C laminae (indicated by blackened ellipse in insets); the majority of its boutons are actually located in the A/C interlaminar zone. The second termination is located entirely in the C laminae (indicated by the cross-hatched area in the insets) and is quite distant from the larger termination. The two termination zones are separated mediolaterally from each other, as indicated in the insets by the two sections in the sagittal plane, and as indicated schematically on a coronal section reconstructed from sagittal sections that contained this axon arbor. Arrow points to branch heading towards midbrain. Asterisk indicates a prominent trifurcation point outside the zones of termination.

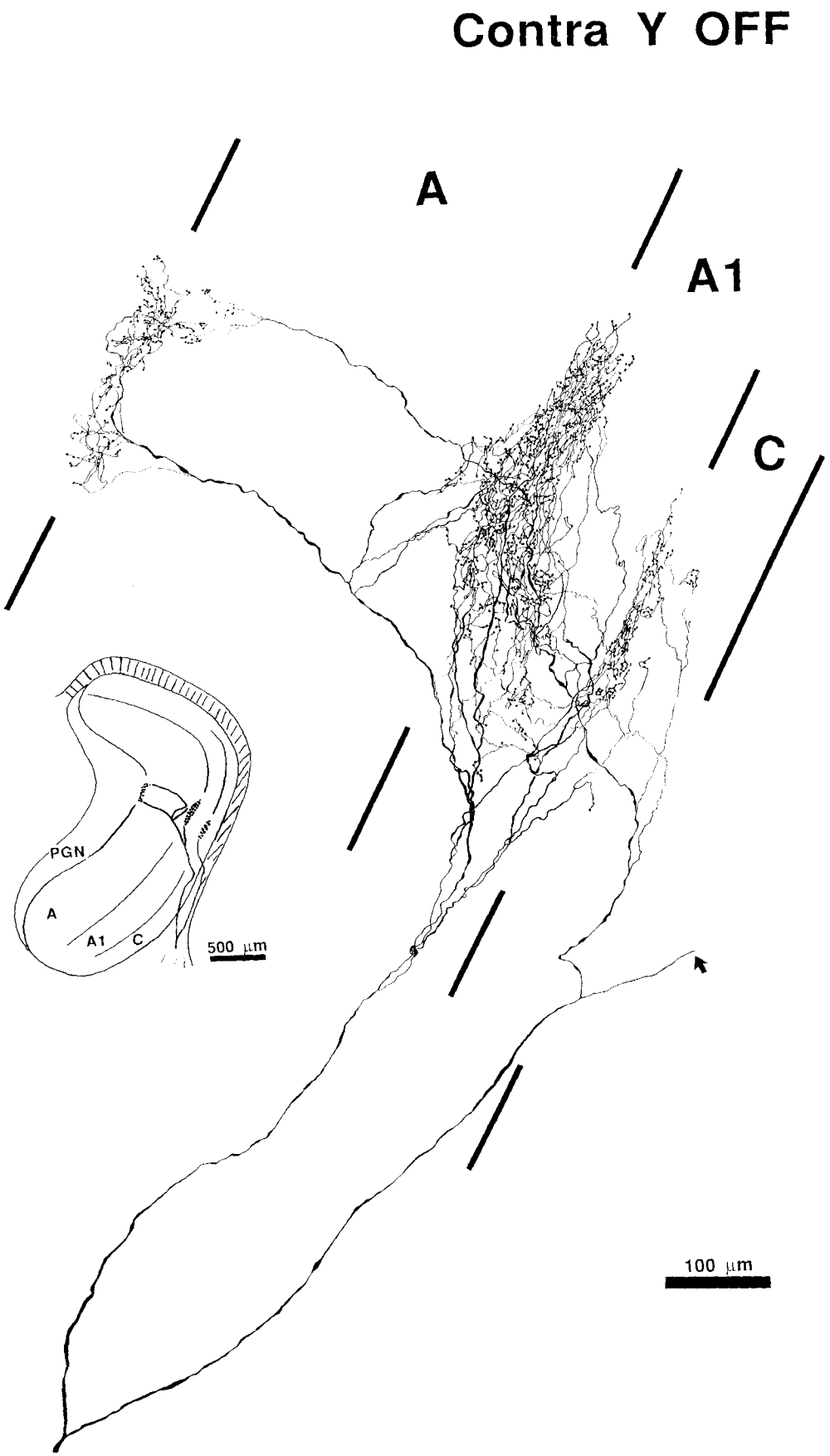

Figure 18

zone between laminae A and C. A smaller termination zone, located in the dorsal C laminae, is displaced medially from its large termination in the interlaminar zone, as shown by the cross-hatched area in the inset of Figure 16. Since the arbor in the interlaminar zone enters the dorsal C laminae as well, this axon actually has two zones of termination within the C laminae that are quite distinct and indeed somewhat distant from each other.

Interlaminar zones appear to be a major target of retinogeniculate Y axons in ferrets. Heavy innervation of the interlaminar zones is illustrated dramatically by the axon in Figure 17. This contralateral OFF-center Y axon has three terminal fields, two terminating in interlaminar zones—one between laminae C and A1 and a second between laminae A1 and A (Fig. 17a)—and a third terminal field between lamina A and the perigeniculate nucleus (Fig. 17b). This axon is fully reconstructed in Figure 18. Whereas boutons do encroach on adjacent A, A1, and C laminae, about 80% of the total number of boutons are located within interlaminar zones (see Table 3). This axon is the most extreme example of interlaminar zone innervation by a retinogeniculate axon in our sample.

Whereas the Y axon in Figure 18 exhibits a remarkable degree of specificity, albeit for interlaminar and internuclear zones, the Y axon shown in Figure 19 displays a less confined pattern of termination. This large sprawling contralateral ON-center Y axon primarily innervates the inner sublamina of A, the interlaminar zone between laminae A and A1, and the medial interlaminar nucleus (MIN). Its termination in the C laminae was rather faintly filled, and we cannot be certain that it has been fully reconstructed. This axon also has the most extensive termination in the MIN of any axon we have recovered (cf. Price and Morgan, '87). It gives off boutons in every lamina (Table 3); there are a small number of boutons in outer lamina A, as well as in both inner and outer lamina A1. Bouton distributions of two remaining Y axons (contralateral OFF-center) are shown in Figure 20. One axon has its terminals restricted to the C laminae and outer lamina A (Fig. 20a), whereas the other displays significant innervation of the lamina of the inappropriate eye (Fig. 20b, Table 3).

As can be seen from the above descriptions, ferret Y axons have extensive arbors with multiple regions of termination, many of which are quite variable. Whereas some Y axons are similar in laminar locations to that of cats, others display novel, unexpected patterns such as heavy innervation of interlaminar zones and terminal boutons in laminae dominated by the other eye. In contrast to X axons, ON- and OFF-center Y axons often do not respect sublaminar divisions, and most axons have boutons in both inner and outer sublaminae.

Morphology of axon trunks, branches, and arbors. Preterminal branches of Y axons arise from more than one point along the parent trunk distant from the terminal zone. Figure 16 shows an example of a Y axon that branches repeatedly at points outside the zone of termination. Branch points in the optic tract or in the LGN are most commonly bifurcations or trifurcations; Figure 21 shows a rare pentafurcation. Preterminal branches often meander in unpredictable directions across the nucleus before finally converging upon one of their terminal zones. Figure 18 illustrates an example where the two primary branches of a Y axon can take diverging paths, but each eventually gives rise to parts of all three terminations of the axon. Figure 19, for example, shows several looping branchlets that seem to stray and then find their way back to a termination zone. In addition, branching collaterals are often seen coursing toward the midbrain, presumably to innervate the superior colliculus or pretectum (arrows in Figs. 15, 16, 18). The multiplicity and complexity of Y axon branching patterns contrasts sharply with the direct, unbranched axon trajectories taken by X axons.

Y axon arbors, perhaps because of their large size, are often oriented parallel to laminar borders. Thus the C laminae terminations of Y axons in Figures 15, 16, and 19 extend in length parallel to the laminar borders as does the A lamina termination in Figure 15. In contrast, A lamina terminations in Figures 16 and 19 extend largely perpendicular to laminar boundaries.

Unlike X axons, Y arbors tend to be large and at times diffuse, often expressing at least a few boutons in areas through which they pass. Y axon terminations typically occupy widths (perpendicular to the lines of projection) of 350–400 μm in the A laminae and 300–350 μm in the C laminae. Bouton densities of Y axons are on average about two-thirds that of X axons (see also below). In the reconstructions shown in Figures 14–16, 18, and 19, arbors often appear denser than they are because several (up to 8) sections are collapsed onto a single plane. Whereas most Y axons have low bouton density, the axon in Figure 18 has an extremely high density of boutons (more than double that of most other Y axons). It is as if the axon attempted to cram its boutons into the limited space available in the interlaminar or internuclear zones.

Boutons of Y axons characteristically occur en passant, with single thin terminal branchlets composed of a series of widely, but fairly constantly spaced boutons extending for great distances. Examples are shown in Figure 22. Though most boutons are small (1–2 μm) or medium size (3–5 μm), some boutons on Y axons can be quite large (6–10 μm).

Quantitative analyses. The previous section describes the structure of single retinogeniculate axons that underlies functional organization in the LGN at the laminar and sublaminar level. We have strengthened some of these qualitative observations with further quantitative analyses. For each well-filled axon, we measured axon diameter in the optic tract; we also determined terminal arbor volume and numbers of boutons as described in Methods; from these, we calculated the mean bouton density in each arbor. We also determined, for each arbor, the mean size of its boutons along with the standard deviation.

Sublaminar segregation. ON- and OFF-center X axon terminations typically span the entire width of their respective sublaminae and are particularly well restricted within laminar and sublaminar boundaries. Whereas ON-center Y axons do have terminations in the inner sublaminae and OFF-center Y axons in the outer sublaminae, only two of the 7 Y axons displayed sublaminar segregation to the degree typical of X axons (Figs. 14, 15).

The segregation of X and Y axons into sublaminae is depicted more quantitatively in Figure 23. A "segregation index" (range 0–100) was calculated for each axon; it is simply the ratio of boutons located in the appropriate sub-

Fig. 18. Camera lucida reconstruction of the contralateral OFF-center Y axon shown in Figure 17. Its major regions of termination are in the interlaminar zones between laminae A and A1, and between A1 and C, as well as the border region between lamina A and the perigeniculate nucleus (PGN). The axon also has a collateral heading towards the midbrain (arrow).

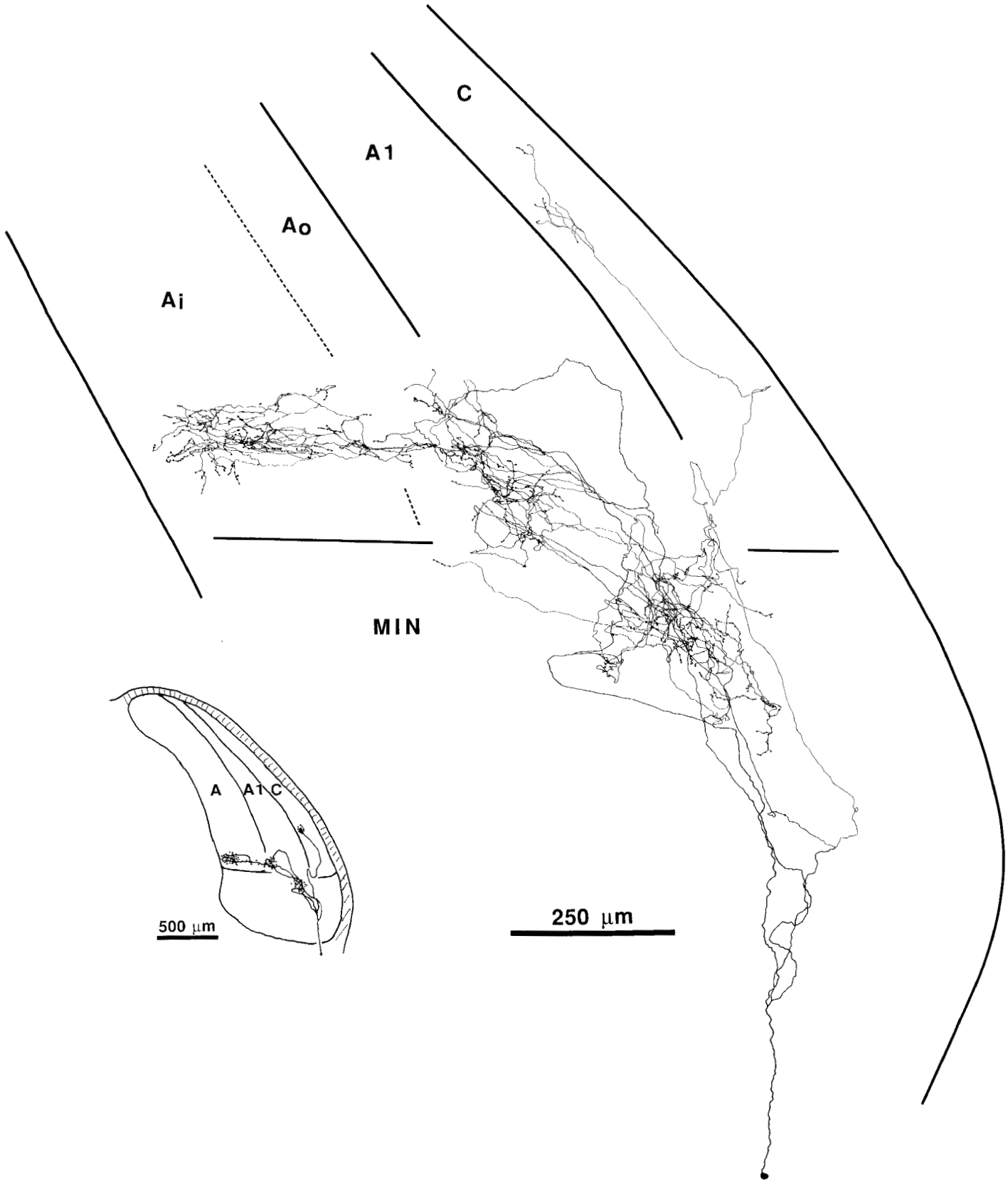

Figure 19

TABLE 3. Bouton Distribution of Y Axons in the LGN (%)

Axon	Ai	Ao	Ali	Alo	IL	C	MIN	Total # Btns	Figures
Contra Y ON	8.9	0.8	1.4	1.7	49.2	2.1	35.9	1542	19
Contra Y OFF		48.0				40.8	11.5	923	15
Contra Y OFF		9.5			49.4	41.1		1424	16,22bc
Contra Y OFF (linear)	3.8	9.1	8.3	0.2	77.0	0.7		1256	16ab,18,21ab
Contra Y OFF		14.0	0.7	13.7		71.9		1002	20a
Contra Y OFF		77.4			12.6	10.0		1036	20b
Ipsi Y OFF		11.6		65.3	23.1			277	14,22a

lamina of termination (i.e., sublamina corresponding to the axon's center type) to the total number of boutons in the A laminae. For example, for contralateral ON-center X axons, the index equals the percentage of total boutons in the inner A sublamina; similarly, for contralateral OFF-center X axons, the index denotes the percent of boutons in the outer A sublamina. The segregation index for Y axons reflects the percent of boutons in the appropriate sublamina of termination out of their total bouton number less their C laminae and MIN terminations.

Since the sublaminar borders are at times indistinct, for several axons the proportion of boutons in the appropriate sublamina was determined by arbitrarily dividing each lamina in half parallel to the laminar borders; the inner half was designated the inner sublamina and the outer half, the outer sublamina.[2] This method of sublaminar division results in lower estimates of the segregation index for ON-center axons, since the inner sublamina is often wider than the outer (see, e.g., Fig. 4; cf. Linden et al., '81; Stryker and Zahs, '83; Kageyama and Wong-Riley, '84; Henderson, '87).

As shown in Figure 23, X axons, both ON-center (open squares) and OFF-center (open circles) have very high segregation indices, most (17 of 18 axons) of them being above 70. Most Y axons (5 of 7), on the other hand, have low indices (less than 70), as exhibited by both ON-center axons (closed squares) and OFF-center axons (closed circles).[3]

Axon diameter. We measured the diameters of axonal parent trunks in the optic tract (see Methods). Since axon diameters within the LGN are often different from those in the tract (Sur et al., '87; our unpublished observations), only axons that were traced into the tract were included for analysis. X axon diameters are smaller than Y axon diameters ($p < 0.006$). X axon diameters range from 1.4–2.0 μm with a mean of 1.6 μm, and Y axons range from 2.0–3.7 μm with a mean of 2.9 μm (Fig. 24). This is consistent with our finding that X axons have slower conduction velocities than Y axons (see Fig. 1). Furthermore, within each physiological class, axons with shorter latencies to optic chiasm stimulation exhibit larger diameters (Fig. 24).

Interestingly, for Y axons, larger receptive field sizes correlate well with shorter latency to optic chiasm stimulation (Fig. 25a) and somewhat with larger axon diameter (Fig. 25b); X axons do not exhibit such correlations (Fig. 25c,d). This relationship for Y axons might follow from the fact that Y cells with larger dendritic arbors give rise to larger diameter axons. Dendritic arbor size may indeed correlate with receptive field size for Y retinal ganglion cells in cats (Peichl and Wassle, '81). The dendritic arbor size of retinal X cells, however, is a poor predictor of receptive field size (Stanford, '87b), and this might account for the poor correlations for X axons in Fig. 25c,d.

Terminal volume, bouton number, and bouton density. Terminal arbor volumes, bouton numbers, and bouton densities differ dramatically between X and Y axons. Consistent with the morphological descriptions above, Y axon arbors occupy much greater volume within the LGN (including the A and C laminae) than do X axons ($p < 0.001$). X axon volumes range from 1.24 to 5.10 $\times 10^6$ μm^3 (mean = 2.56×10^6 μm^3), whereas Y axon volumes range from 3.94 to 19.23 $\times 10^6$ μm^3 (mean = 9.58×10^6 μm^3). This difference in arbor volume follows from the fact that Y axons have arbors at multiple locations, and often larger extents of arbors at each location. Comparison of only the lamina A or A1 termination of Y axons and X axons provides a similar result: for 3 Y axons with significant terminations in the A-laminae, arbor volumes in the A laminae range from 2.80 to 8.92 $\times 10^6$ μm^3 (mean = 5.45×10^6 μm^3); this is still larger ($p < 0.05$) than arbors of X axons (which are, of course, confined totally to the A laminae).

Along with the difference in arbor volume between X and Y axons is a similar difference in bouton number within the LGN. X axon arbors contain from 286–635 boutons (mean = 455); Y axon arbors, from 320–1542 (mean = 1,072). Y axons thus have significantly larger numbers of boutons than X axons ($p < 0.001$). However, the bouton numbers for Y axons in lamina A or A1 (range 231–1,092, mean = 591) are not statistically different from those of X axons.

Figure 26a graphically illustrates the relationship of total bouton number to arbor volume for X and Y axons. Not only do Y axons have larger volumes and bouton numbers than X axons, this plot also demonstrates that greater bouton number correlates well with larger arbor volume within each axon class. X axons have higher bouton densities than Y axons (Fig. 26b) ($p < 0.009$). In fact, bouton densities of the A-lamina arbors of Y axons (range 75.0–232.6, mean 126.0 boutons per 10^6 μm^3) are on average approximately two-

[2]The rationale for the arbitrary division of lamina A or A1 into halves is not to assign rigid boundaries for retinogeniculate arbors but to compare the degree of segregation of X and Y arbors into tiers within the A laminae.

[3]We note that if Y axon terminations in the interlaminar zones are excluded from analysis, along with the C laminae and MIN terminations, the proportions of boutons Y axons have in the appropriate A sublamina will be higher. The actual proportions of boutons each Y axon has in each of its regions of termination is shown in Table 3.

Fig. 19. Large diffusely terminating ON-center Y axon from the contralateral eye. This axon terminates in the inner A sublamina, the C laminae, the A/A1 interlaminar zone, and the medial interlaminar nucleus (MIN); it also has a few boutons in the outer A sublamina and in both inner and outer lamina A1. Because this axon spans 800 μm in mediolateral extent, a drawing of a single sagittal section does not accurately depict the laminar boundaries over this distance.

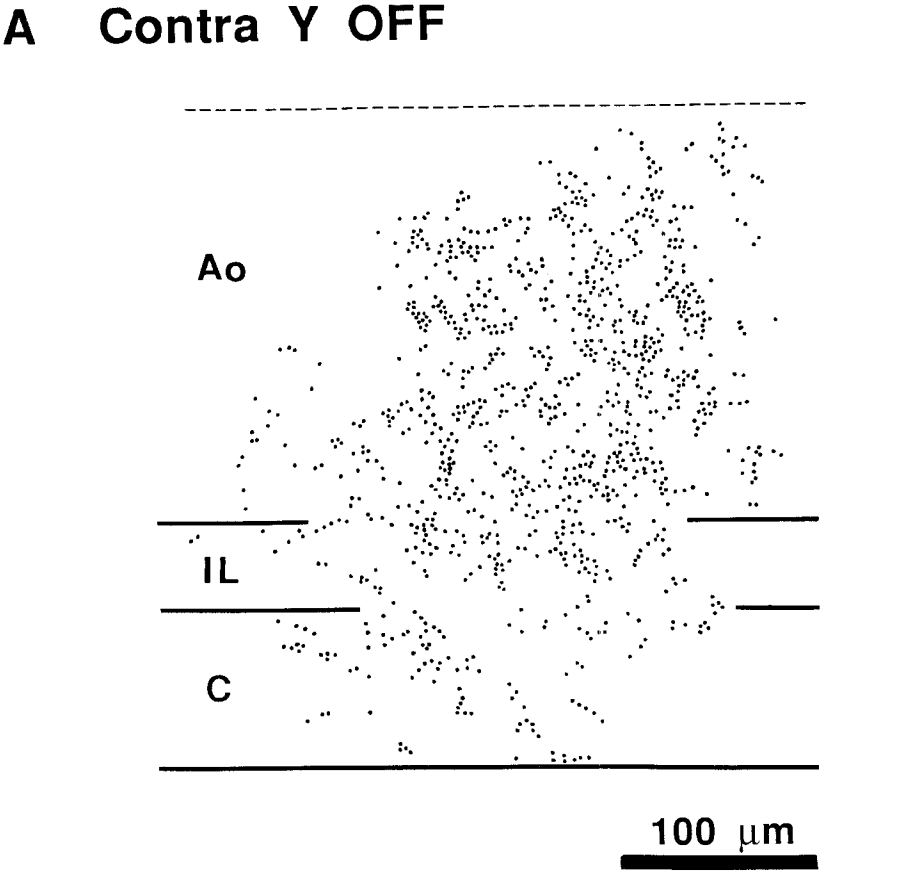

Figure 20

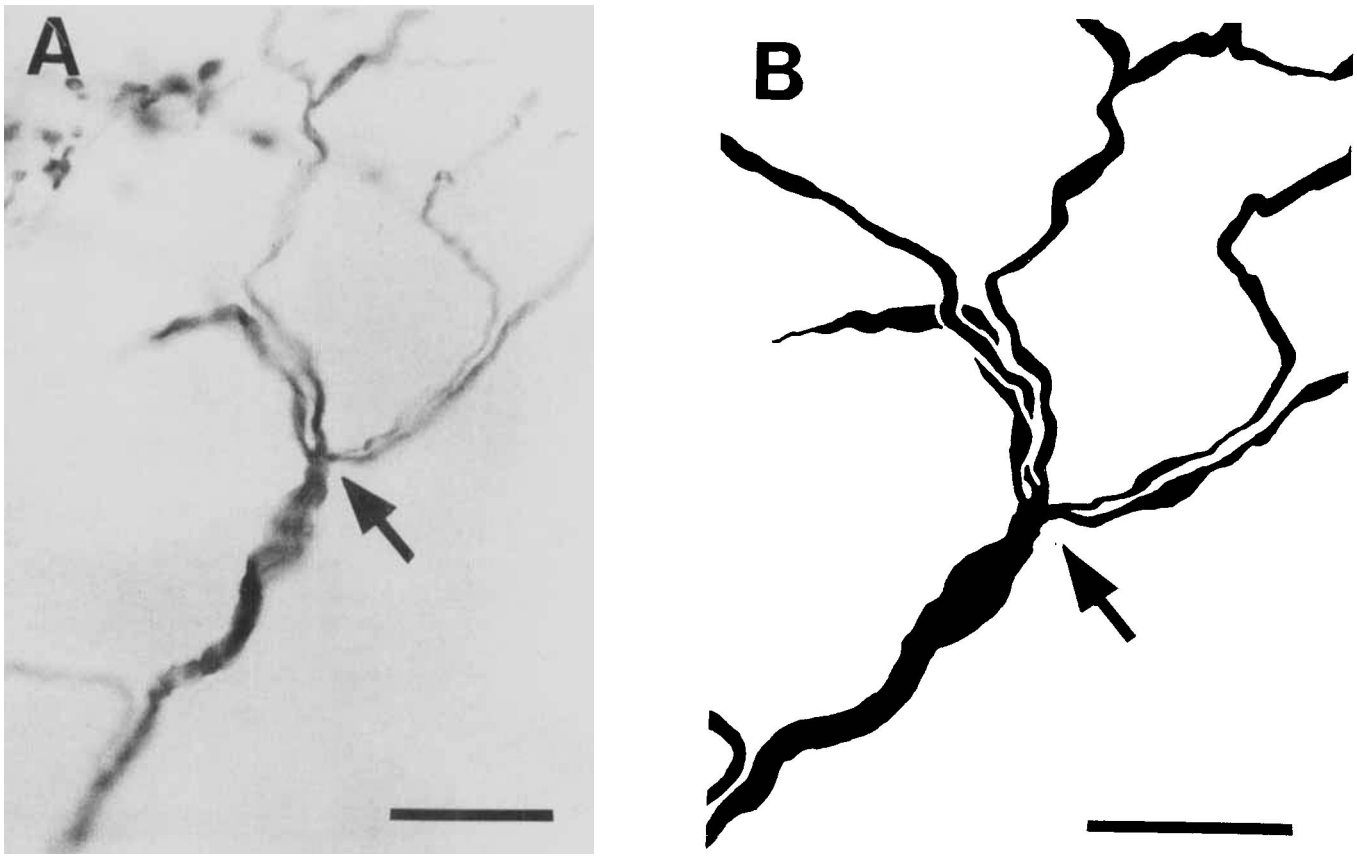

Fig. 21. A rare point of pentafurcation arising in the Y axon shown in Figure 16. (**A**) At this plane of focus, four of the five branches are seen emanating from a single branch point in this high power photomicrograph. Scale bar: 20 μm. (**B**) The camera lucida reconstruction indicates the fifth branch as well. Multiple branchings such as this are only seen in axon trunks of very large diameter. Scale bar: 25 μm.

thirds that of X axons (range 98.8–296.8, mean 193.1 boutons per 10^6 μm^3). Overall bouton density, however, actually falls with increase in volume (Fig. 26b); thus increases in arbor size are not accompanied by an equivalent increase in bouton number for either class of axon.

The relationship of terminal arbor size to receptive field eccentricity is shown in Figure 27. Whereas X axon arbor sizes are relatively constant with respect to receptive field location, Y axon arbor volumes tend to decrease with eccentricity. That is, Y axons in central visual field locations have larger volumes, whereas those in peripheral locations have smaller volumes. Qualitative inspection of these Y axons reveals that those in extreme ventral (e.g., Fig. 14) and lateral (e.g., Fig. 20b) portions of the LGN (which contain peripheral representations of the visual field) have a compressed appearance compared to those in the thick central regions of the LGN representing more central fields (e.g., Fig. 19). At the functional level, the larger volume of retinogeniculate Y axons in portions of the LGN representing central vision might serve to compensate, at least in part, for the difference in X to Y cell ratios between central and peripheral vision that exists in the retina.

Bouton sizes. Bouton size measurements were taken from each retinogeniculate terminal arbor (see Methods). Figure 28a shows the distribution of boutons sizes for X and Y axons, pooled for all axons. Bouton sizes of Y axons are larger than those of X axons ($p < 0.001$). X axon bouton sizes range from 2.1 to 2.9 μm with a mean of 2.5 μm; Y axon bouton sizes range from 2.7 to 3.4 μm with a mean of 3.0 μm. Each axon's mean bouton size is computed and graphed in Figure 28b. Treating each axon as a datum, bouton sizes of Y axons are larger than those of X axons ($p < 0.0003$ treating each axon as a datum; $p < 0.003$ treating each ferret as a datum).

Fig. 20. Bouton distributions of the remaining two Y axons recovered. (**A**) Contralateral OFF-center Y axon terminating in outer lamina A, the C laminae, and the A/C interlaminar zone. (**B**) Contralateral OFF-center Y axon terminating in outer lamina A, outer lamina A1, dorsal C laminae, and A1/C interlaminar zone.

DISCUSSION

Physiological characteristics of X and Y axons

We have recorded retinogeniculate axons in the optic tract of ferrets and have classified them as either X or Y.

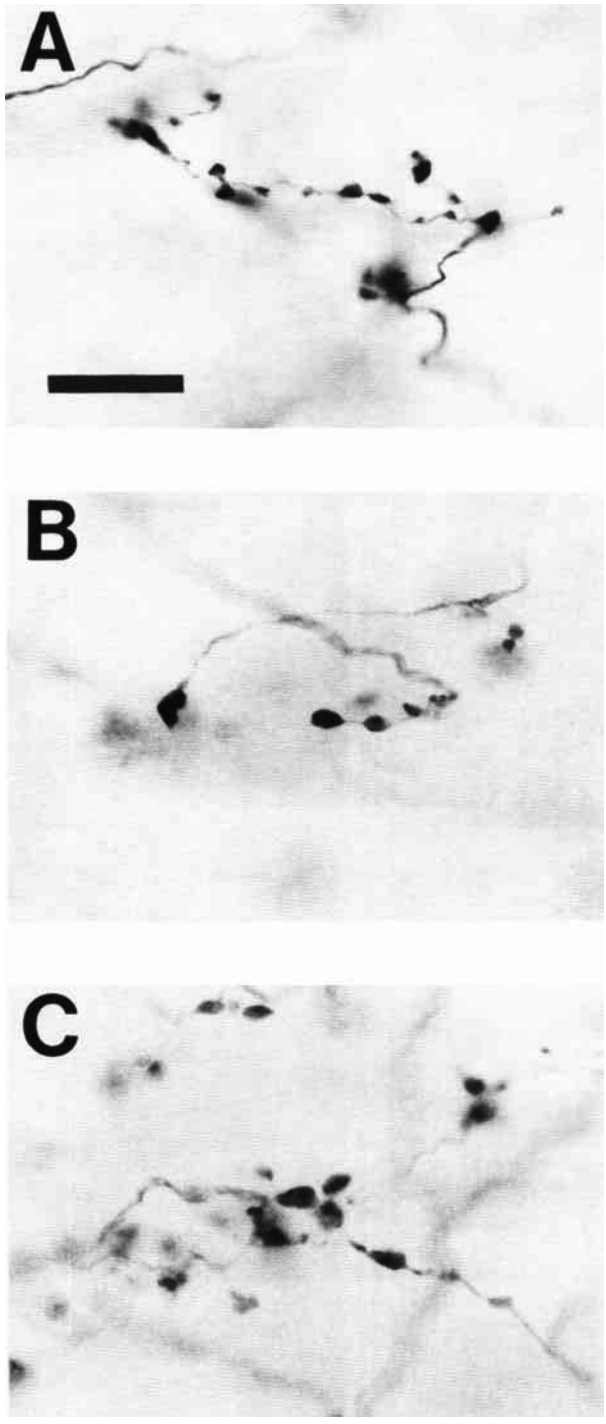

Fig. 22. Examples of boutons en passant commonly seen in Y axons. Scale bar: 25 μm.

The three major characteristics that distinguish X from Y axons are linearity of spatial (and temporal) summation, conduction velocity, and receptive field size. X axons exhibit linear summation, conduct slowly and have small receptive fields; Y axons exhibit nonlinear summation, conduct rapidly, and have larger receptive fields. These differences parallel those found for X and Y retinal ganglion cells in cats (Enroth-Cugell and Robson, '66; Stone and Fukuda, '74; Hochstein and Shapley, '76; Kratz et al., '78). Along with other studies of X and Y cells in the ferret LGN (Esguerra et al., '86; Price and Morgan, '87), these findings establish the presence of parallel X and Y pathways in ferrets.

Some physiological characteristics of cat retinal ganglion cells are less developed in ferrets or otherwise simply not useful for distinguishing X from Y cells. Thus both X and Y retinogeniculate axons in ferrets have either weak inhibitory or antagonistic surrounds, or sometimes lack surrounds altogether. Tonicity of response to a standing stimulus does not effectively discriminate between X and Y cells. Finally, ferret retinogeniculate axons give rather variable responses to fast moving stimuli of contrast appropriate for stimulating the surround, though this may stem from the poor surrounds that many retinal ganglion cells seem to have.

Morphological differences between X and Y axons

By labeling individual retinal X and Y axons with HRP, we have identified both the regions of termination of single fibers in the thalamus as well as the detailed morphology of arbors within eye-specific laminae and ON and OFF sublaminae in the LGN (Fig. 29). Our results point to a number of important differences between the terminations of X and Y retinal ganglion cells axons. These include differences in the major zones of termination and in the size, shape, and specificity of arbors within the LGN (these differences are discussed separately below). In addition, Y axons have larger diameters than X axons and often multiple and complex branching patterns before giving rise to arbors. Y axon arbors within the LGN are much larger in volume than arbors of X axons and contain more boutons, though the density of boutons is lower for Y axon arbors. Terminal boutons on Y axons often occur en passant, and tend to be larger on average than boutons on X axons.

Regions of termination of retinogeniculate axons

X axons always have a single zone of termination within lamina A or A1 (including the adjacent interlaminar zone) of the LGN. No terminations of X axons are seen outside of the A laminae, either in the C laminae or in the MIN. In cats, while X axons have not been observed to terminate in the MIN, occasional terminations in the C laminae have been described (Bowling and Michael, '84; Sur et al., '87). Similarly, whereas some X axons in cats have branches that head towards the midbrain (Sur and Sherman, '82a), ostensibly to terminate in the pretectum or in the superior colliculus, inspection of X axon trunks in ferrets as far into the optic tract as possible has so far revealed no branching collaterals. Thus X axons in ferrets have highly focal arbors and may be more restricted in their regions of termination than X axons in cats.

In contrast to X axons, Y axons have multiple and variable termination sites. Within the LGN, their targets include lamina A or A1, the C laminae, interlaminar zones, as well as the MIN. Y axons also branch in the optic tract adjacent to the LGN; axon branches are seen coursing medially and posteriorly toward the midbrain, presumably to terminate in the pretectum and/or superior colliculus. Not only do single Y axons in ferrets innervate more targets than do X axons, the total volume of terminal arbor of Y

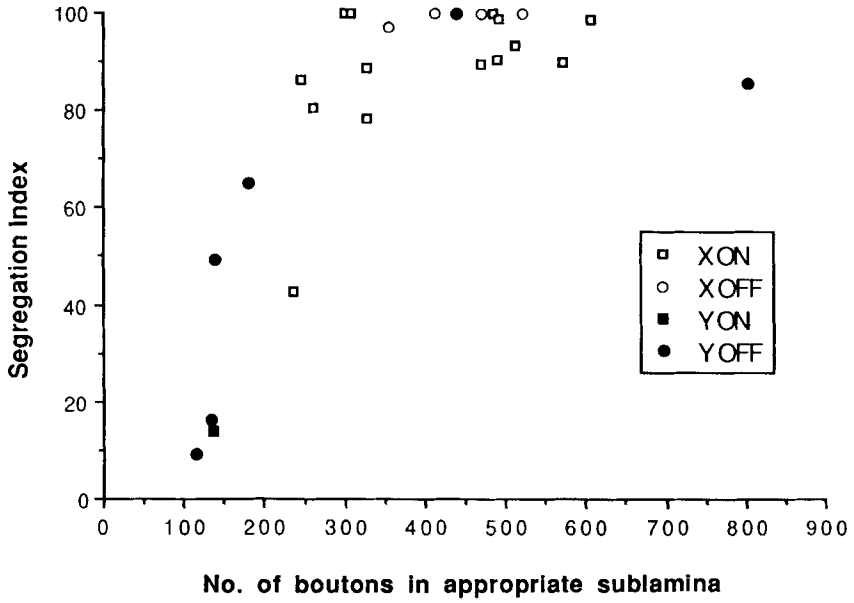

Fig. 23. The degree of segregation of ON- and OFF-center retinogeniculate axons into individual sublaminae of the LGN. The segregation index for each axon is the ratio of boutons located in the appropriate sublamina of termination to the total number of boutons in the A layers, expressed as percent. X axons (n = 18) are more segregated into their respective inner (ON-center) and outer (OFF-center) sublaminae than Y axons (n = 7).

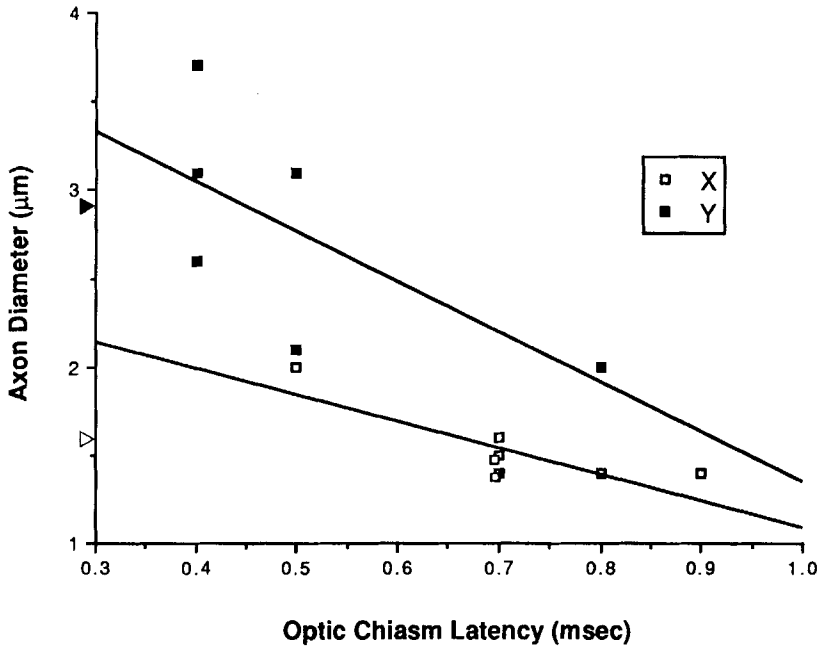

Fig. 24. The relationship of axon diameter to the latency to optic chiasm stimulation for X axons (n = 8) and Y axons (n = 6). Larger diameter parent trunks predict faster conduction velocities for both X axons (R = 0.82) and Y axons (R = 0.67). Open and closed triangles on ordinate axis indicate mean axon diameters for X and Y axons, respectively. Axon diameter measurements were taken only from axons whose parent trunks could be traced into the optic tract.

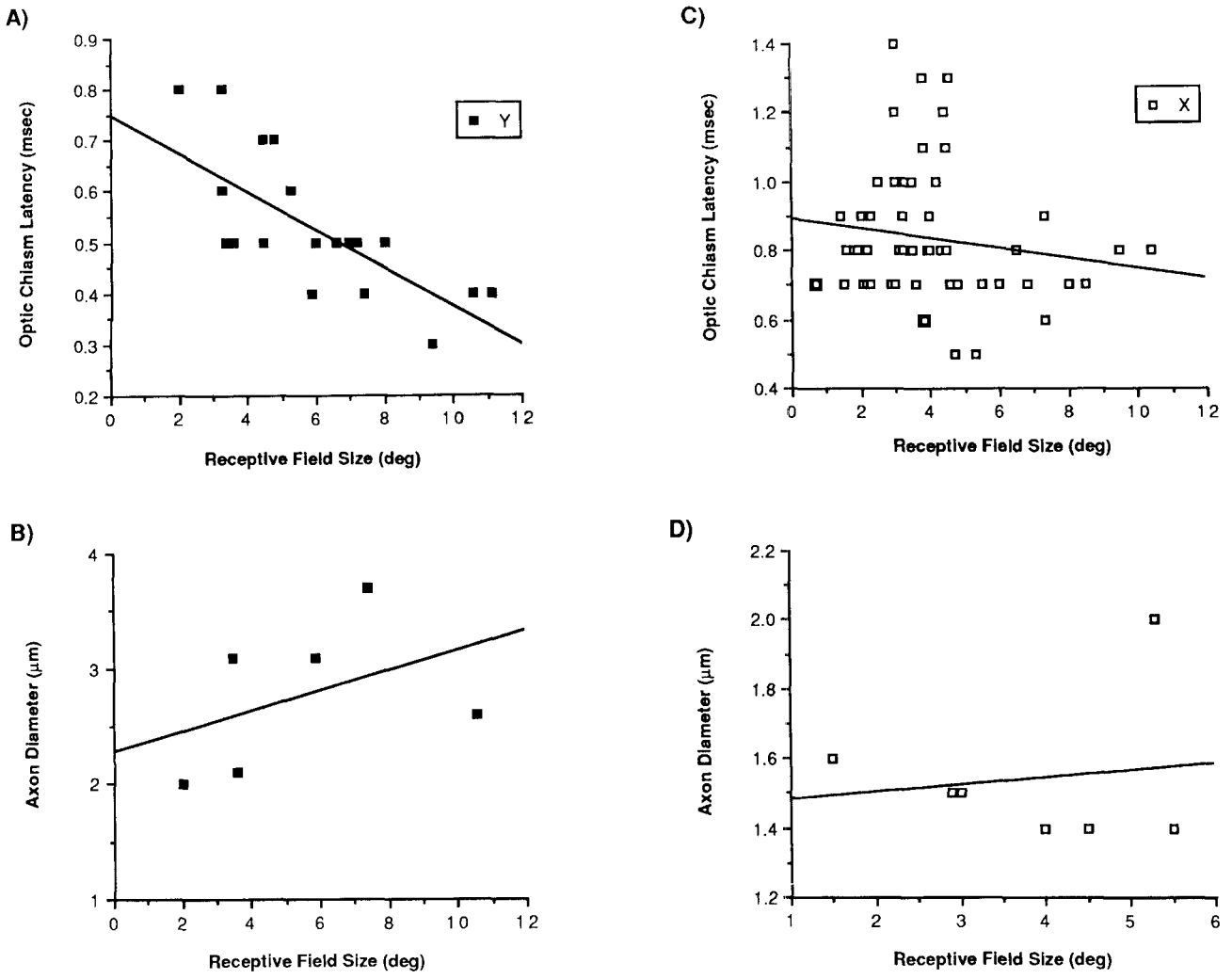

Fig. 25. Relationship of receptive field size to latency (**A, C**) and to axon diameter (**B, D**). Y axon receptive field sizes have (A) an inverse correlation with latency (n = 20, R = 0.71) and (B) positive correlation with axon diameter (n = 6, R = 0.42). X axon receptive field sizes do not show clear correlations with either (C) latency (n = 54, R = 0.16) or (D) axon diameter (n = 7, R = 0.14).

axons is up to an order of magnitude larger than that of X axons. The size of arbor at each Y axon termination site within the A laminae also usually exceeds the size of an individual X axon arbor.

While the overall regions of termination of the Y pathway in ferrets resemble those in cats, individual Y axons in ferrets exhibit a higher degree of variation, both in terms of termination sites and the morphology of their arbors within the LGN. Unlike Y axons in cats, not all contralaterally projecting Y axons in ferrets have heavy terminations in lamina A and the C laminae. Furthermore, some Y axons display a dense innervation of the interlaminar zones that is rarely seen in cats; such terminations could conceivably lead to increased interactions between retinal and cortical afferents on postsynaptic cells in the LGN (cf. Sanderson and Kaas, '74). Individual Y axon terminations in the LGN can be extensive, at times covering up to 10° of visual field (e.g., Fig. 15), and Y axons can display two terminations at distinct loci in the C laminae of the LGN (Fig. 16). In general, then, single axons in the Y pathway exhibit a high degree of divergence compared to X axons, exhibiting both multiple terminal zones and larger arbors at each zone.

Laminar and sublaminar specificity of arbors

Apart from differences between X and Y axons in their regions of termination, X and Y axons differ importantly in the specificity they exhibit for individual eye-specific laminae and for ON and OFF sublaminae within the LGN. X axon terminals are always strictly confined to their

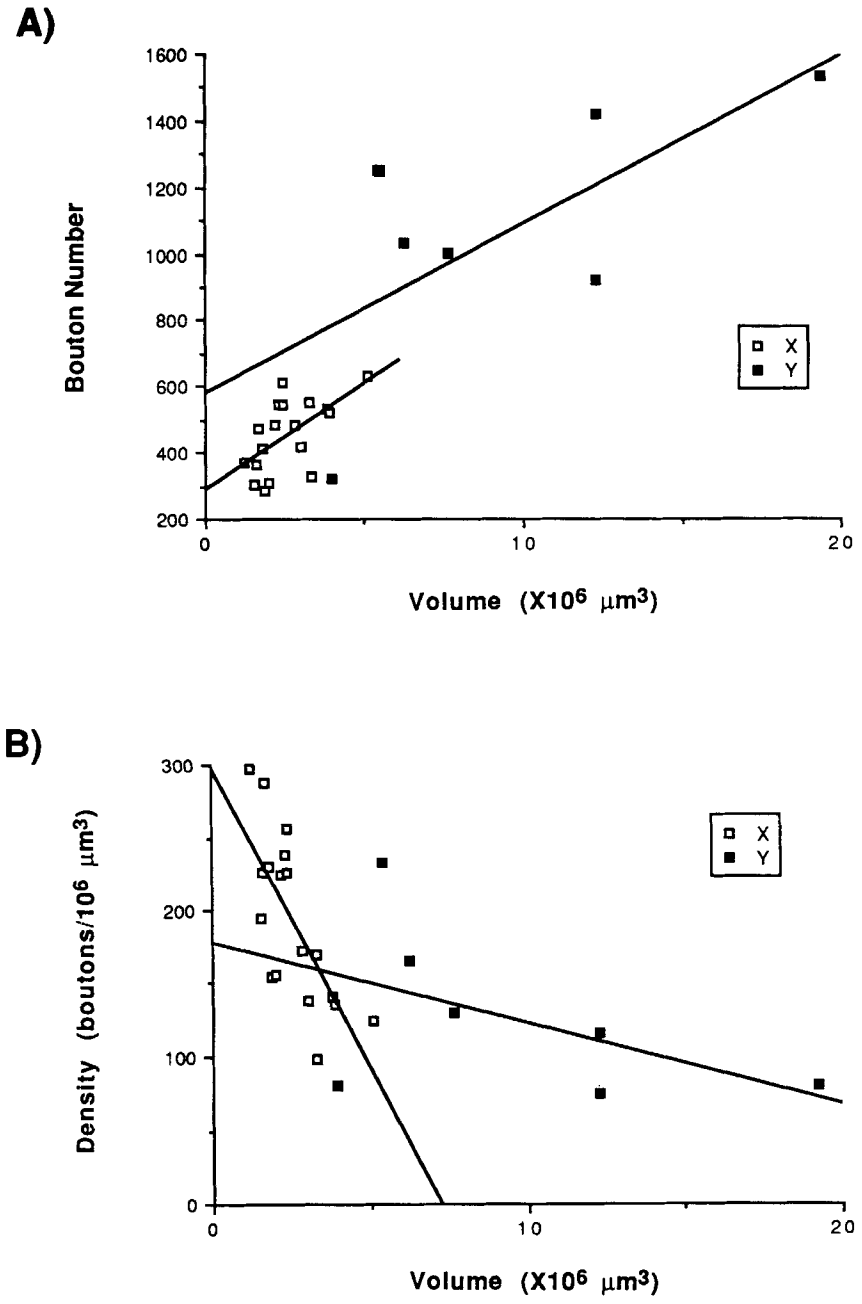

Fig. 26. (A) Plot of the total bouton number of each X and each Y axon vs. its total arbor volume. X axons have smaller terminal arbor volumes and fewer boutons than do Y axons. Furthermore, increased bouton number predicts larger arbor volume for both X axons (n = 18, R = 0.59) and Y axons (n = 7, R = 0.68). (B) Plot of volume vs. bouton density. Bouton density varies inversely with arbor volume for both X (n = 18, R = 0.71) and Y (n = 7, R = 0.51) axons.

appropriate eye-specific layer in the LGN: lamina A if contralateral and lamina A1 if ipsilateral. In contrast, Y axon terminals are sometimes not confined to their appropriate eye-specific laminae. Thus two of six contralaterally projecting Y axons have terminal boutons in lamina A1, a pattern that is never seen for X axons (Fig. 29).

A major result of our study is the difference between X and Y axons in the degree of segregation they exhibit for ON and OFF sublaminae within the A laminae of the LGN. X axon arbors are segregated rather strictly by center preference into their appropriate sublamina. Thus ON-center X axons have their arbors in the inner sublamina of lamina A

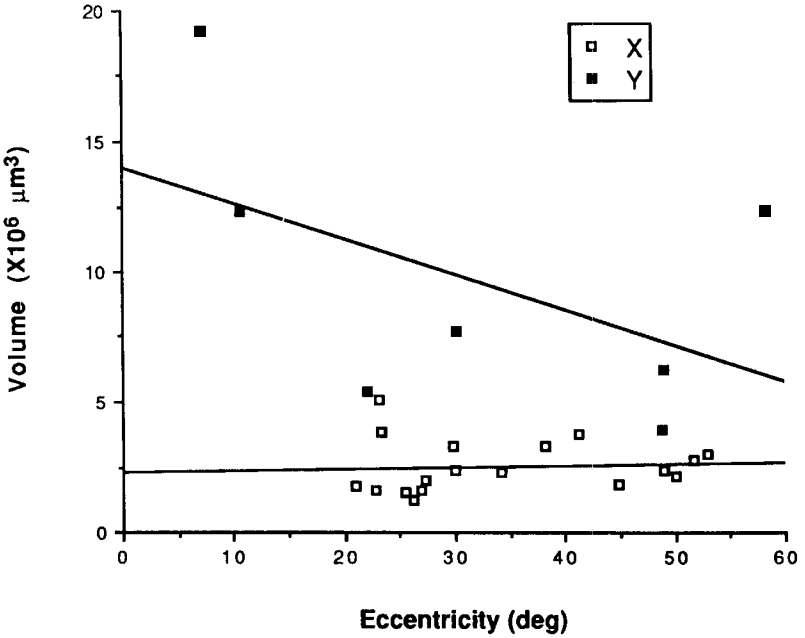

Fig. 27. Arbor volumes of X and Y axons as a function of visual field eccentricity. Whereas X arbor volumes remain relatively constant across the receptive field (n = 18, R = 0.07), Y axon arbor volumes decrease with eccentricity (n = 7, R = 0.51).

or A1, whereas OFF-center axons terminate in the outer sublamina. Y axons, on the other hand, show much less specificity for their appropriate sublamina. A few Y axons have their terminations entirely within their center-specific sublamina. Some Y axon arbors, however, freely disregard sublaminar boundaries (Fig. 29). We could find no evidence for a segregation of ON- and OFF-center Y axon terminations within the dorsal C layer, to where contralateral Y axons project in addition to lamina A.

These results provide the morphological basis for the physiological segregation of cells by eye within LGN laminae and by center type within sublaminae. Since all X axons and most Y axons respect laminar borders within the LGN, both kinds of axons contribute to maintaining eye dominance within eye-specific layers in the LGN. The terminals in layer A1 arising from several contralaterally projecting Y axons in our sample could relate to the "bridges" observed within layer A1 following injections of the contralateral eye (Zahs and Stryker, '85; our own unpublished observations). That is, even in normally pigmented ferrets, injection of anterograde tracers into one eye leads to label not only in laminae A, C, and C2 of the contralateral LGN but also to occasional "bridges" in lamina A1 between laminae A and C. Zahs and Stryker ('84) showed, by using a different anterograde tracer for each eye, that the "bridges" in layer A1 are regions that contain only contralateral afferents and no ipsilateral afferents.

It is possible that Y axon terminations in the "inappropriate" layer could lead to cells within the A layers receiving input from the "wrong" eye (cf. Sanderson et al., '71; Robson, '87). If so, our observations suggest that cells driven by the inappropriate eye are likely to receive retinal Y input. Alternatively, it is known that the dendrites of LGN cells that lie close to laminar borders often cross these borders (Friedlander et al., '81; Humphrey and Weller, '87a,b). Eye-specific segregation within the LGN could then still be maintained if the Y axon terminals in the inappropriate lamina selectively contact translaminar dendrites of cells with somata in the appropriate layer.

Our results on sublaminar segregation of X and Y arbors suggest that the segregation of ON and OFF input to the LGN (Stryker and Zahs, '83), and hence to striate cortex (Zahs and Stryker, '88), is maintained primarily by the X cell pathway. Whereas every X axon in our sample has terminals that are either confined to or are very close to sublaminar borders, many retinogeniculate Y axons have terminals in the A layers that simply ignore sublaminar borders. Such inappropriate terminations could lead to an occasional cell of the "wrong" center type within a given sublamina (Stryker and Zahs, '83). We would predict that such cells are likely to receive input from retinal Y cells. Again, it is possible that cells with dendrites that cross sublaminar borders could have, in highly specific fashion, connections with Y axon terminals in the inappropriate sublamina. Such connections could restore, at the level of postsynaptic cells, the specificity that appears to be lost at the level of retinogeniculate projections for Y axons.

Widespread retinal Y axon terminations within the A layers of the LGN might also lead to more convergence of ON and OFF inputs to single LGN neurons for the Y pathway compared to the X pathway. More generally, our results suggest that the retinogeniculate pathway in ferrets bears a striking resemblance to the retinogeniculate pathway in monkeys, in which the parvocellular (X-like?) but not the

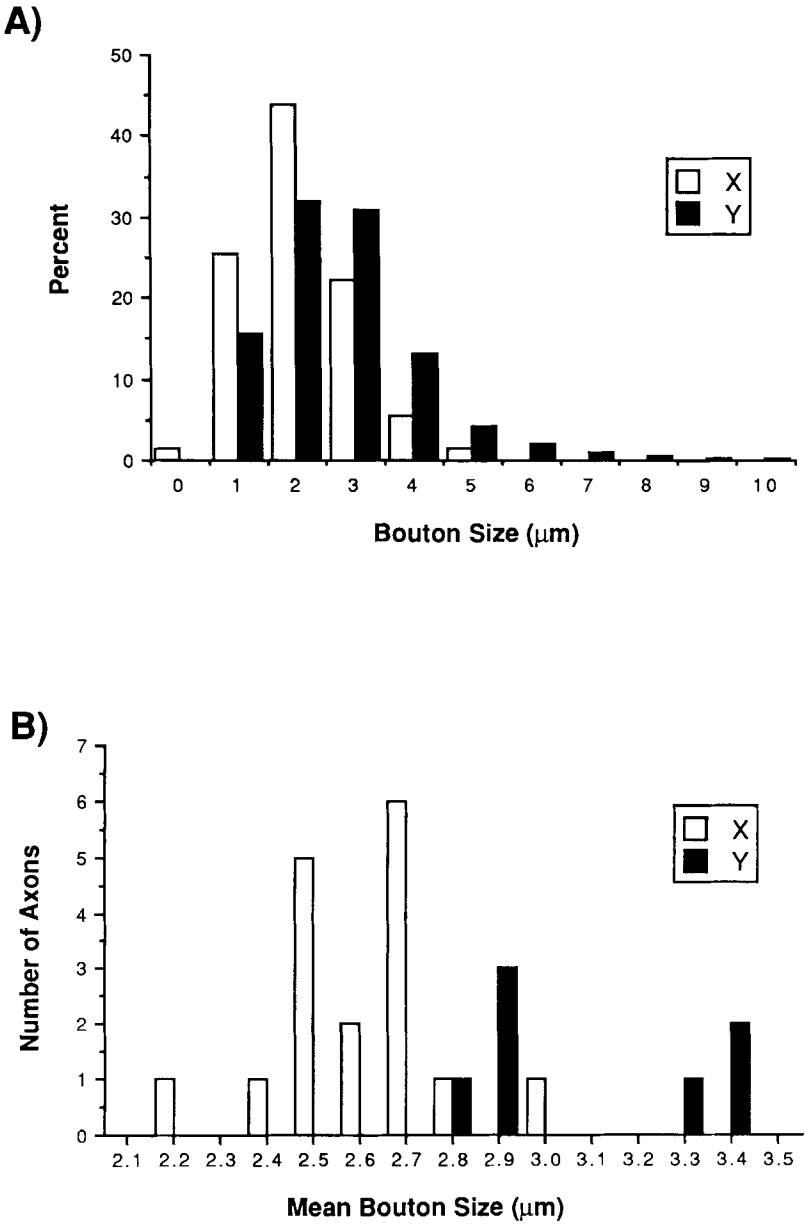

Fig. 28. (**A**) Size distribution of X and Y axon boutons expressed as a percentage of total X boutons (N = 1940) and total Y boutons (N = 940) measured. Bouton size range for X axons, 2.1–2.9 μm, mean 2.5 μm; bouton size range for Y axons, 2.7–3.4 μm, mean 3.0 μm. (**B**) Histogram of mean bouton sizes for each X axon (n = 17) and each Y axon (n = 7) recovered.

magnocellular (Y-like?) pathway maintains a laminar segregation of ON and OFF channels within the LGN (Schiller and Malpeli, '78; Schiller, '82; but see Derrington and Lennie, '84). Consistent with this finding, ON- and OFF-center afferents to the parvocellular layers in monkeys appear to be strictly segregated by center type (Michael, '88).

On the variability in retinogeniculate Y axon arbors

One of the unexpected results of our study is the wide range of variations exhibited by Y axon arbors within the LGN. Y axons in cats, although larger in terminal volume compared to X axon arbors in the LGN, are fairly consistent in size, shape, and location within the A and C laminae. The variability in Y axon arbors in the ferret LGN thus points to an important difference in retinogeniculate organization between cats and ferrets.

We can suggest two reasons that, individually or in concert, might underlie the variations in retinal Y axon arbors in the LGN. First, it is possible that there are multiple subclasses of Y cells in the ferret retina. Whereas a fairly homogeneous population of retinal alpha (presumably Y) cells has been defined anatomically in ferrets by retrograde

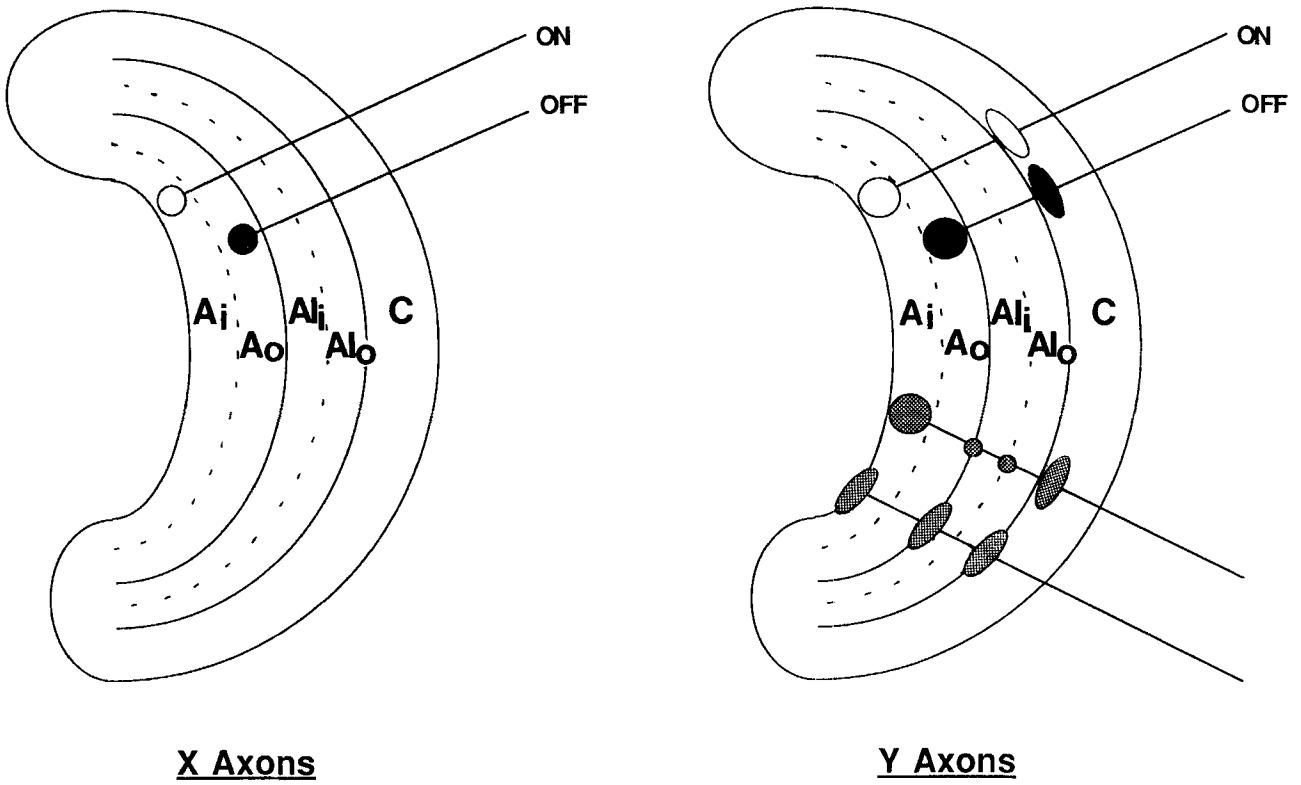

Fig. 29. Schematic illustration of patterns of retinal X and Y axon terminations in the ferret LGN. Only contralaterally projecting axons are illustrated. Left: ON-center X axons innervate inner sublaminae and OFF-center X axons innervate outer sublaminae of the A layers. Right: Y axons have much more variable termination patterns. They vary from having two zones of termination (illustrated at the top of the figure), one in lamina A and another in the dorsal C laminae, to having multiple terminations (illustrated at the bottom) including laminae A and C, interlaminar zones, the MIN, and even lamina A1.

labelling from the LGN (Vitek et al., '85), there might exist different physiological subclasses of retinal Y cells (cf. Frascella and Lehmkuhle, '84; Mastronarde, '88) with corresponding subtle differences in retinal dendritic morphology as well as differences in terminal arbor morphology within the LGN.

Second, developmental factors may play a major role in the morphological diversity of Y axon arbors. In cats, there is considerable evidence now that Y axon arbors in the LGN are highly susceptible to variations in the visual environment or to alterations in the conditions of development (reviewed in Garraghty and Sur, '88; Sur, '88). Thus rearing cats with monocular lid suture (Sur et al., '82; Garraghty et al., '86a), binocular lid suture (Uhlrich et al., '86), or convergent strabismus (Garraghty et al., '88a) all lead to profound alterations in the size, shape, and even location of retinogeniculate Y arbors. Specifically, in these cats, Y arbors from the deprived or affected eye(s) have significantly smaller arbors in the A laminae; some contralaterally projecting Y axons have terminations only in the C lamina and lack lamina A terminations altogether. X axons are relatively unaffected. In cats reared with retinal impulse blockade (Sur et al., '85) or with prenatal or postnatal monocular enucleation (Garraghty et al., '86a,b; Garraghty et al., '88b), Y axons (but not X axons) again show pronounced plasticity in their arbors by sprouting into adjacent denervated or blocked laminae. We have hypothesized elsewhere (Garraghty and Sur, '88; Sur, '88) that a possible reason why Y axon arbors can be influenced by even subtle abnormalities in the postnatal visual environment is that Y cells in the retina are born later than X cells, hence the "critical period" for development of Y axon arbors extends later than that for X axons (though in cats the period of susceptibility of Y axons to environmental changes includes at least the early postnatal weeks). Alternatively, Y axons may be intrinsically different from X axons in their susceptibility to the rearing environment or to developmental conditions (Garraghty et al., '88a).

Ferrets are born after 41 days of gestation, whereas cats are born after 64 days; retinogeniculate development in ferrets matches that in cats almost on a day-by-day basis, so that the developmental status of the retinogeniculate pathway in newborn ferrets is similar to that in cats at around embryonic day 42 (Linden et al., '81; Shatz, '83). Whatever the reason for external influences on Y axon arbors, the early parturition in ferrets compared to cats suggests that

even small environmental imbalances may have a major impact on the structure of Y axon arbors in ferrets. Thus, whereas some Y axons in ferrets have relatively "normal" morphology similar to those seen in normal adult cats, other Y axons have arbors that resemble to various extents some of the "abnormal" features associated with rearing cats with different developmental manipulations.

It is unlikely that the variations in Y axon arbors reflect traits associated with albinism. The major abnormality in the retinogeniculate pathway in albinos is an abnormal crossed pathway from temporal retina to islands within lamina A1 (Cucchiaro and Guillery, '84). This leads to an abnormal representation of the ipsilateral visual field through the contralateral eye within each LGN (Guillery and Kaas, '71). Such a projection would imply that axons from the contralateral eye terminate within layer A1; indeed, Leventhal ('82) has suggested that these projections in albino cats arise largely if not exclusively from retinal alpha cells. However, the cells of origin of such axons must lie in the temporal retina, whereas the contralaterally projecting Y axons in our sample with boutons extending into lamina A1 all had receptive fields in the contralateral visual field and hence had their somata located in nasal retina (see Table 2B). The one axon that did have its receptive field within the ipsilateral hemifield arose from the ipsilateral retina and projected to lamina A1 (Table 2B, Fig. 14; this axon's receptive field location thus suggests that its soma might be located in nasal retina). Furthermore, the map of the ipsilateral visual field in the LGN of albinos (Guillery and Kaas, '71) indicates that individual retinogeniculate axons projecting abnormally to lamina A1 from the contralateral eye would have their arbors confined to lamina A1. This was never the case in our material; contralaterally projecting Y axons had the major portion of their terminations in the appropriate laminae (A and C), and only a minority of their boutons in lamina A1 (Table 3).

Finally, Vitek et al. ('85) have pointed out an interesting variation in the distribution of alpha retinal ganglion cells in ferrets: the temporal retina has markedly few ganglion cells with alphalike morphology. In our study, there was only one ipsilaterally projecting retinogeniculate Y axon that we recorded and recovered after HRP injection (Table 1). Yet large ganglion cells are present in the temporal retina of ferrets (Henderson, '85; Morgan et al., '87; Peichl et al., '87). These cells may project mainly or even exclusively to the superior colliculus (Roe et al., unpublished observations). Such features of the distribution and central projections of Y cells in ferrets again stand in sharp contrast to the distribution and projections of retinal Y cells in cats, where ipsilaterally projecting retinal Y axons are commonly found in the LGN and every Y axon studied to date innervates both the LGN and the superior colliculus (Bowling and Michael, '84; Sur et al., '87).

ACKNOWLEDGMENTS

We thank Manuel Esguerra for helping with some experiments and Martha MacAvoy and Teresa Sullivan for excellent technical assistance. This work was supported by NIH grant EY 07023 and NIGMS training grant #5 T32 GM-07484.

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