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Organization of the Feedback Pathway from Striate Cortex (V1) to the Lateral Geniculate Nucleus (LGN) in the Owl Monkey (*Aotus trivirgatus*)

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ABSTRACT

The function of the corticogeniculate feedback pathway from the striate cortex (V1) to the lateral geniculate nucleus (LGN) in primates is not well understood. Insight into possible function can be gained by studying the morphology and projection patterns of corticogeniculate axons in the LGN. The goal of this research was to examine how corticogeniculate axons innervate the functionally specific (e.g., parvocellular [P], magnocellular [M], and koniocellular [K]) and eye-specific layers of the LGN. Pressure injections of biotinylated dextran were made into owl monkey V1, and the resulting labeled axons were reconstructed through serial sections of the LGN. All of the corticogeniculate axons, regardless of termination pattern, were thin with boutons en passant or at the ends of small stalks, as described in cats. Axons were found in all layers of the LGN, and two main patterns of innervation were observed. In the first pattern, axons terminated in individual M or P LGN layers. In the second pattern of innervation, axons terminated in pairs of functionally matched layers. Examples of this type were seen within pairs of M, P, or K layers. In most cases, both classes of axons contain arbors focused within the P or M layers but also had collateral side branches in neighboring K layers. Unlike corticogeniculate axons seen in the cat, corticogeniculate axons in the owl monkey maintained topographic innervation in the LGN layers that was consistent with receptive field sizes represented in V1. The patterns of layer projections along with the retinotopic match of corticogeniculate axons within the LGN suggest that in primates V1 can modulate activity in the LGN through functionally specific projections in a more tightly tuned retinotopic fashion than previously believed. J. Comp. Neurol. 454:272–283, 2002.

Indexing terms: corticogeniculate; parallel pathways; koniocellular; parvocellular; magnocellular

Feedback pathways are one of the most universal yet least well understood aspects of sensory system organization. This is understandable, given that feedback pathways are likely to be functionally diverse and do not provide the main sensory drive to neurons. Within the visual system, one of the major feedback pathways is the corticogeniculate pathway (Swadlow, 1983; Sherman and Guillery, 1996). The synaptic bouton density of this pathway in all examined species is anatomically enormous relative to the size of the retinal input to the lateral geniculate nucleus (LGN). Although retinal activation is the primary driving input to the LGN, this input accounts for less than 30% of the synapses in the LGN (Guillery, 1969; Wilson, 1989; Montero, 1991; Van Horn et al., 2000).

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Attempts to define the function of the corticogeniculate pathway have led to a variety of often conflicting conclusions. One problem has been that many details of the anatomy and physiology of this pathway remain to be elucidated. Within the LGN of primates, retinal signals are segregated into three parallel pathways, the magnocellular (M), parvocellular (P), and koniocellular (K) channels. At the level of the LGN, these three pathways can be distinguished based on a number of criteria including morphology, physiology, and neurochemistry (Casagrande and Norton, 1991; Casagrande, 1994; Hendry and Reid, 2000). These distinctions, as well as others that concern the cortical processing streams engaged by these pathways, have led to the hypothesis that M, P, and K pathways play different roles in vision (Merigan and Maunsel, 1993; Casagrande, 1994).

Despite what is known about the corticogeniculate pathway in cats, this visual feedback pathway is not well studied in primates. Although there are similarities between cats and primates, the organization of the visual system also shows a number of important differences between these species. Both cats and primates have well-laminated LGNs, but the primate LGN shows greater functional segregation than the cat, with the different classes of cells (M, P, K) found in separate and specific layers. In the cat, X and Y cells are found mixed in the A and A1 laminae, with Y cells found in the C lamina and also in a separate LGN subdivision called the medial interlaminar nucleus (MIN) that does not exist in primates. The cat LGN also receives major projections from several cortical areas including areas 17, 18, and 19 (Updyke, 1975). In primates, there is evidence of only very minor projections to the LGN from a few extrastriate areas (Lin and Kaas, 1977; Hendrickson et al., 1978), with the vast majority of feedback to the LGN coming from V1. Also, in cats the LGN projects strongly to several extrastriate areas, whereas the primate LGN sends only minor projections outside V1 (Rodman et al., 2001).

The main objective of the present study was to provide more detailed information on the organization of the corticogeniculate pathway in primates, beginning with an analysis of the topography, morphology, and branching patterns of individual axons. First, we wanted to know whether more than one morphological class of corticogeniculate axon innervates the LGN in primates. Recent data in cats (Murphy and Sillito, 1996) predict that we should see only one type of corticogeniculate axon, although there is some evidence that there are other types (Robson, 1984, 1983). Second, we were interested in whether the parallel output pathways (M, P, K) are regulated via separate corticogeniculate feedback pathways. There are four basic patterns of projections that might be seen in the primate LGN with reference to functionally specific layers and eye-specific layers. Axons could project to all the layers indiscriminately (binocular and functionally promiscuous), to layers that are innervated by only one eye (monocular and functionally promiscuous), to functionally matched layers (binocular and functionally specific), or to individual layers (monocular and functionally specific). Each of these possible patterns suggests a different way that feedback from the cortex could modulate or gate visual information and allows us to hypothesize about the ultimate role(s) of the corticogeniculate pathway in processing visual information. Finally, we wanted to determine the relative topographic specificity of the corticogeniculate pathway in primates. Current data suggest that these projections are topographically organized, although there also is evidence that feedback axons may have a wider range of influence than originally believed (Murphy and Sillito, 1996).

MATERIALS AND METHODS

Surgical procedures

Eight adult owl monkeys (*Aotus trivirgatus*) were used in this study. All surgical procedures were carried out under aseptic conditions. Animals were given atropine (0.06 mg/kg) prior to surgery and were then intubated and anesthetized with 3–4% isofluorane in oxygen. Anesthesia was maintained during surgery with the gas mixture at 1–2%. Heart rate, body temperature, and respiration rate were monitored throughout the procedure, and depth of anesthesia was additionally monitored by lack of reaction to toe pinch. Following stabilization, animals were secured in a stereotaxic apparatus, the skull was exposed, and a unilateral craniotomy was performed over V1. The dura was cut and retracted to expose the pial surface. Two to four pressure injections of 5–10% biotinylated dextran (BDA; 3,000 kD or 10,000 kD; Molecular Probes, Eugene, OR) were made on the dorsal surface of V1. Injections were placed in positions representing 0–20° eccentricity within the lower visual quadrant at depths ranging from 1 to 1.5 mm. The skin was then sutured, and fluid (~30–50 ml lactated Ringer's solution) was administered subcutaneously.

Following surgery, all animals were given 1 mg/kg Banamine (Schering-Plough, Kenilworth, NJ) every 8 hours as an analgesic, as well as 2.0 mg/kg gentamicin (Boehringer Ingelheim, Ingelheim, Germany) and 1.0 mg/kg dexamethasone (Phoenix Scientific, Inc., St. Joseph, MO). During recovery, the animals were carefully monitored until awake and observed eating and drinking. The animals were then returned to their home cages. All of the animals were cared for according to the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and the guidelines of the Vanderbilt University Animal Care and Use Committee.

Histological procedures

After 14–25 days of survival, the animals were sacrificed with a lethal dose of sodium pentobarbital (0.7–1.0 ml) and perfused transcardially with a saline rinse followed by a fixative containing 2–4% paraformaldehyde (EMS, Ft. Washington, PA), 0.2% glutaraldehyde (Marival, Halifax, Nova Scotia) and 0.2% saturated picric acid (VWR, Atlanta, GA) in 0.1 M phosphate buffer (pH 7.4) and then the same fixative containing 10% sucrose. The brain was then removed, blocked, and cryoprotected by allowing it to sink overnight in 30% sucrose in 0.1 M phosphate buffer (pH 7.4) at room temperature. The tissue was then frozen on dry ice and stored until use at −70°C. Sections through V1 and the thalamus were cut parasagitally or coronally at 40–50 μm on a sliding microtome.

To visualize BDA, sections were first treated with 10% methanol plus 0.3% H_2O_2 in 0.1 M Tris-buffered saline (TBS, pH 7.4) for 30 minutes at room temperature. Following three rinses in TBS, sections were then placed in TBS plus 0.01% Triton-X 100 with avidin biotin complex (Vector Elite; Vector, Burlingame, CA) for 24–48 hours at 4°C. The tissue was then rinsed three times in TBS and placed into a solution containing 50 mM TBS, 50 mM imidazole (Sigma, St. Louis, MO), 25 mM nickel ammonium sulfate (Fisher, Pittsburgh,

PA), 0.25 mM diaminobenzidene (DAB; Sigma, St. Louis, MO), and 0.0003% H_2O_2 (Sigma, St. Louis, MO). Sections remained in this solution until the reaction product became visible (20–30 minutes). The sections were then rinsed twice in TBS, mounted, air-dried overnight, and coverslipped. To aid in analysis, some sections were also counterstained with Giemsa to reveal the cell layers in the LGN. Giemsa counterstaining was carried out according to the protocol of Singleton and Casagrande (1996).

Reconstruction and analysis

Anterogradely filled corticogeniculate axons in the LGN were reconstructed from serial sections using a microscope with a camera lucida drawing tube. Only those cases in which the filling appeared to be complete (based on examination of fine structure at high magnification) were used for reconstruction and analysis. Cases in which the filling was patchy, granular, or very faint were not used. Axons were selected for reconstruction based on how certain we were that the filling of the axon was complete and our ability to distinguish all parts of that axon from parts of neighboring axons. These criteria allowed us to be more confident that our reconstructions did not include parts of other axons. Low-magnification drawings were used to orient and align adjacent sections using matching blood vessels and section artifacts. Lamination boundaries were also included in the low-magnification drawings. Axons were then examined and traced at higher magnification (100× oil immersion objective), and these drawings were then compiled to provide a complete reconstruction of the axon. Occasionally we were not able to find pieces of an axon that connected segments as they traveled from one section to another. Unconnected segments were included in the final reconstruction only if there were no other segments in the immediate area or neighboring sections that could possibly have given rise to the unconnected segment via a separate axon.

Measurements of the anterior/posterior spread were made to determine the relative amount of visual field that was covered by individual axons and the entire column of axonal label. Measurements of individual axons were made after reconstruction at high resolution, and the spread was measured across the most distal branches that had boutons along a plane parallel to the layer(s) in which the axon terminated. The anterior/posterior spread of the anterograde column of labeling was made with the camera lucida at the lowest resolution at which the axons could be easily distinguished and the whole column of label was visible in the field. Measurements were taken at the widest point of spread parallel to the layer where the majority of terminations were located; the boundary of axonal labeling was placed at the ends of the most robustly labeled axons. All sections containing a patch of anterograde labeling were reconstructed so that the label could be tracked as the position changed from section to section. This allowed us to compare the spread of label in different layers.

The area of visual space that axons covered was estimated by converting the measurements of anterior/posterior spread into degrees. The map of the visual field in the owl monkey LGN is such that central vision lies posterior, peripheral anterior, upperfield lateral, and lowerfield medial; the optic disc lies at 20° eccentricity (Kaas et al., 1978). In LGN sections that have been Giemsa-stained, the optic disc representation appears as a cell-free gap in the contralaterally innervated K, M and P layers (see Fig. 1A). This gap served as a useful landmark from which we were able to estimate the visual field map in the portion of the LGN that lies posterior to the optic disc. This estimation was based on previously published maps of the owl monkey LGN (Kaas et al., 1978). We divided the portion of the LGN posterior to the optic disc representation into three equal portions representing 0–5°, 5–10°, and 10–20°. Thus, using the optic disc representation as a landmark, measurements in the anterior/posterior domain allowed us to estimate the relative amount of the visual field that was covered by either an individual axon or the column of axonal label.

Photomicrographs were taken with a Spot digital camera attached to an Olympus microscope. Digital images were compiled in Adobe Illustrator version 6.

RESULTS

Examination of the injection sites in cortex revealed that the injections were located within V1 and that many of the injections included layers 4, 5, and 6. Labeled axons were seen in the LGN, as well as the thalamic reticular nucleus (TRN) and the pulvinar. Cortical injections resulted in distinct patches of label in the LGN, with continuous patches of label found in 10–20 adjacent LGN sections, depending on the size and number of cortical injections. In most cases, patches of label included anterogradely labeled axons as well as retrogradely labeled cells, indicating that the injections included parts of cortical layer 4.

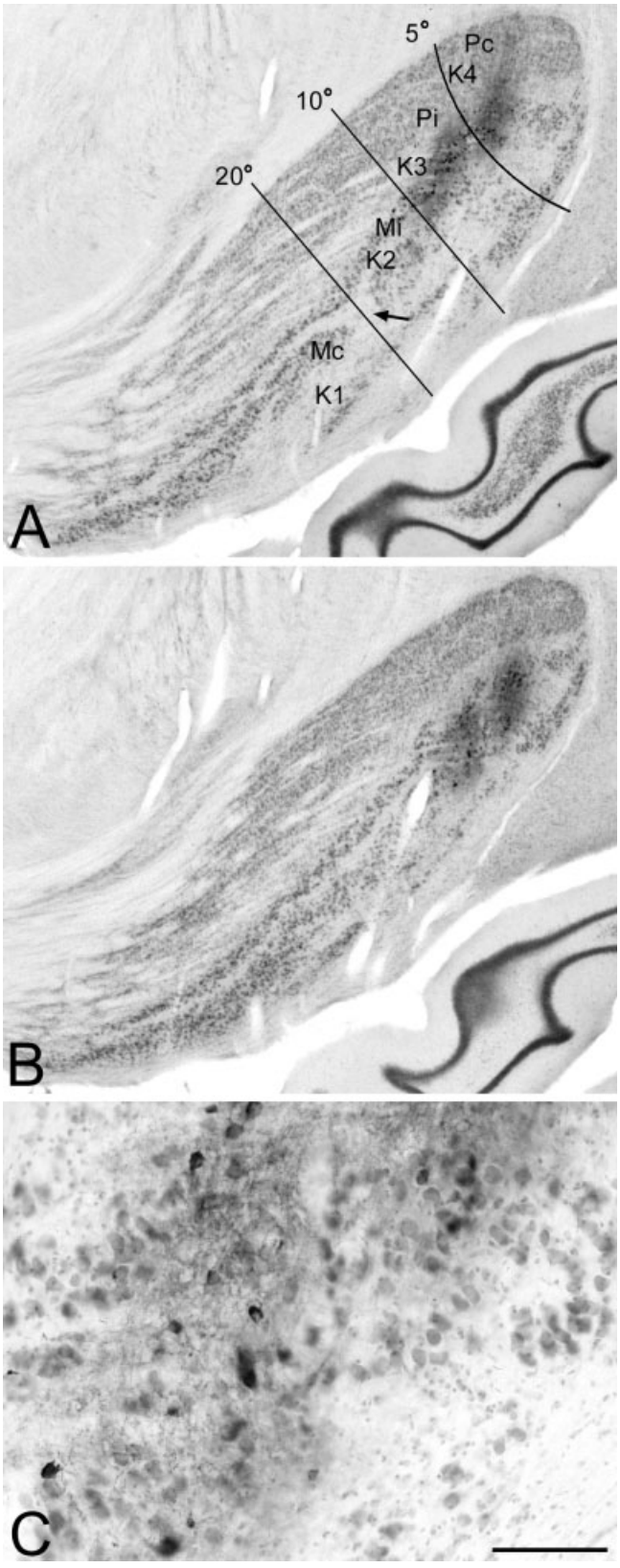
Figure 1 shows low- and medium-power photomicrographs of the LGN with representative patches of labeling. A total of 12 corticogeniculate axons were fully reconstructed through serial sections, and 24 additional segments of axons were examined and reconstructed in individual sections. The quality of labeling for individual axons was quite good, resulting in dark filling of these very fine-caliber axons and boutons (Fig. 2), which is the typical morphology of corticogeniculate axons described in cats (Guillery, 1966). As in cats, corticogeniculate axons in owl monkeys had boutons at the end of short stalks as well as en passant. These types of terminations were observed in all LGN layers, as well as in the TRN (Fig. 3) where they may all be collaterals from corticogeniculate axons (Guillery, 1995; Murphy and Sillito, 1996). Although many of the boutons in the TRN were qualitatively similar to those seen in the LGN, there was a subset of boutons that appeared much larger than any observed in the LGN (compare Fig. 3A and B). Terminations observed in the LGN were distinct from those seen in the pulvinar, where cortical axons commonly terminate in very large boutons (Fig. 3C).

Axon size

All the corticogeniculate axons examined had a similar morphology, and although there were variations in the size of collaterals, no consistent variations based on layer terminations were observed (Fig. 4). In general M, P, and K layers were innervated by axons of similar caliber. The size variations that were observed did not correlate with any specific layers.

Layer projections

Examination of reconstructed individual axons as well as axon segments in all LGN layers revealed a somewhat



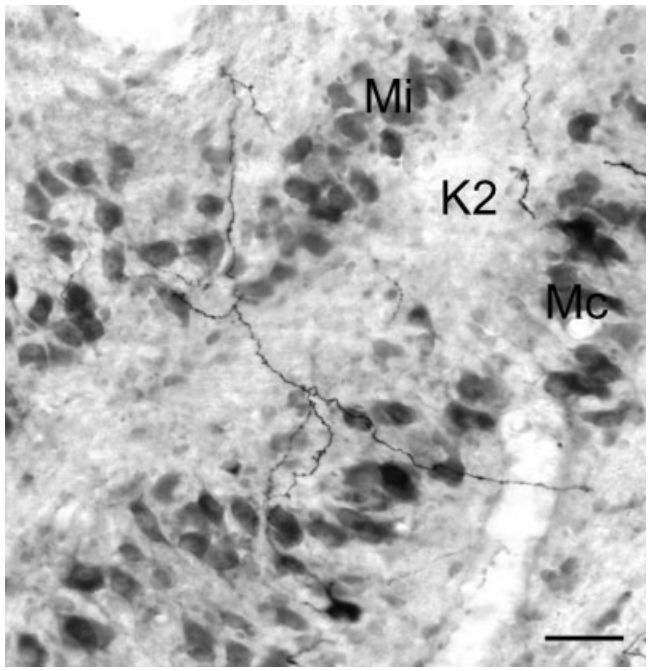


Fig. 2. Photomicrograph of an individual corticogeniculate axon with branches and terminals in both M layers of the LGN. c, contralateral; i, ipsilateral. Scale bar = 50 μm.

segregated pattern of innervation with respect to the M, P, and K layers. We never observed any axons or axon segments with obvious branches in both M and P layers, but we almost always observed axons that branched in M and K layers or P and K layers; no axons were found that innervated only K layers. Boutons were generally concentrated along segments of the axon branches within the innervated layer, but there were occasional boutons along the main trunk of the axons. For example, the axon shown in Figure 5A has a few boutons en passant along the main trunk at the layer boundary between the ipsilateral P and K3 layers. To classify better the patterns that we observed, we grouped our axons into two patterns of innervation: 1) axons with terminations in individual M or P layers; and 2) axons with terminations in both M layers or both P layers (functionally matched layers) (Table 1).

In the first pattern of innervation, corticogeniculate axons terminated and branched in individual M or P layers (Fig. 5).

Fig. 1. **A:** Photomicrograph of a parasagittal section through the LGN showing patches of label in the M layers that correspond to the injections in V1. Both retrogradely labeled cells and anterogradely labeled axons retain topographic specificity. The arrow indicates the position of the optic disc representation in the contralateral M layer. Solid lines represent the lines of projection associated with the topographic map of the visual field present in each layer. The optic disc representation and map of the LGN (Kaas et al., 1978) are used to estimate these lines (see text for details). **B:** Photomicrograph of a nearby section to that shown in A. In this section the patches of label shown become two discrete patches that continue into neighboring sections. **C:** Higher power photomicrograph showing details of patches of label shown in B. Dorsal is to the top and anterior to the left. c, contralateral; i, ipsilateral. Scale bar = 1 mm for A and B; 100 μm for C.

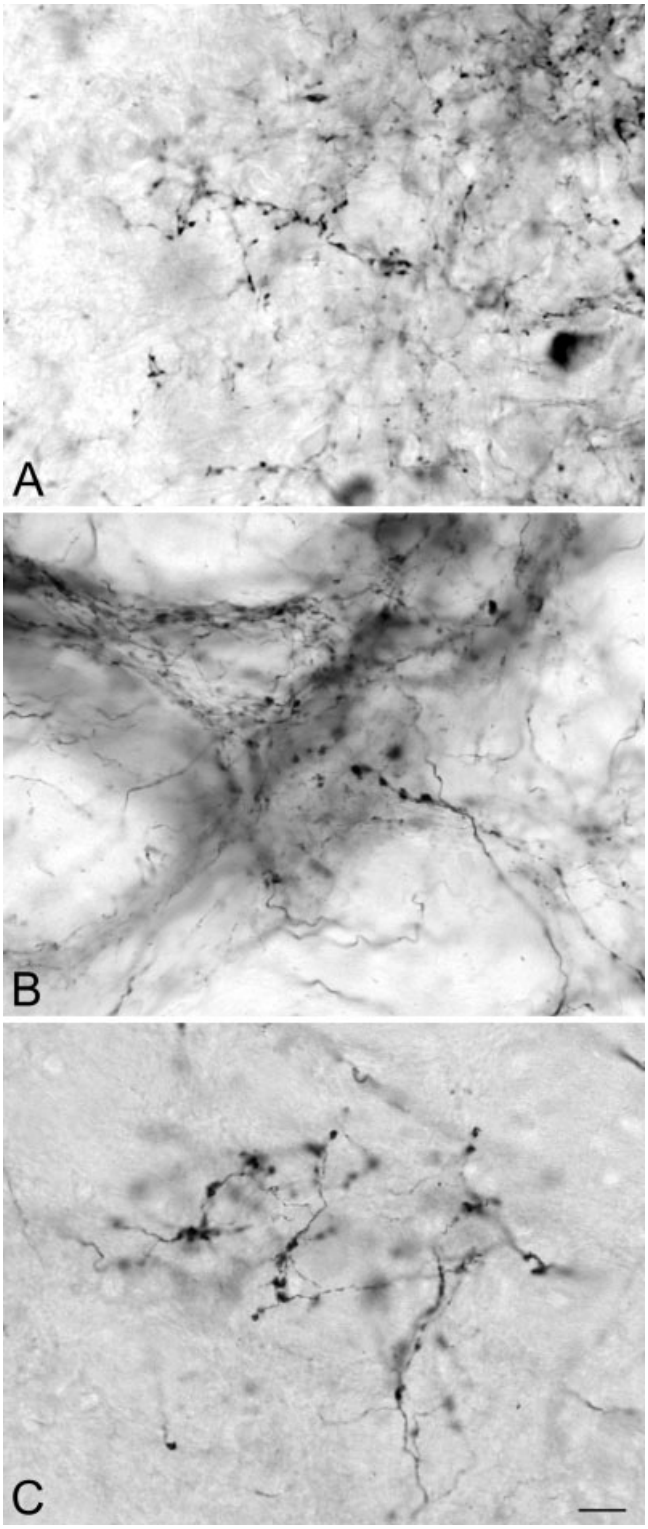


Fig. 3. High-power photomicrographs of boutons in the LGN (**A**), TRN (**B**), and pulvinar (**C**) labeled after injections into V1. Boutons in the LGN are small and arise from very fine-caliber axons. Boutons in the TRN vary in size from small (similar to those seen in the LGN) to much larger. Terminations in the TRN are presumably collaterals of axons that terminate in the LGN (see text for details). Scale bar = 10 μm.

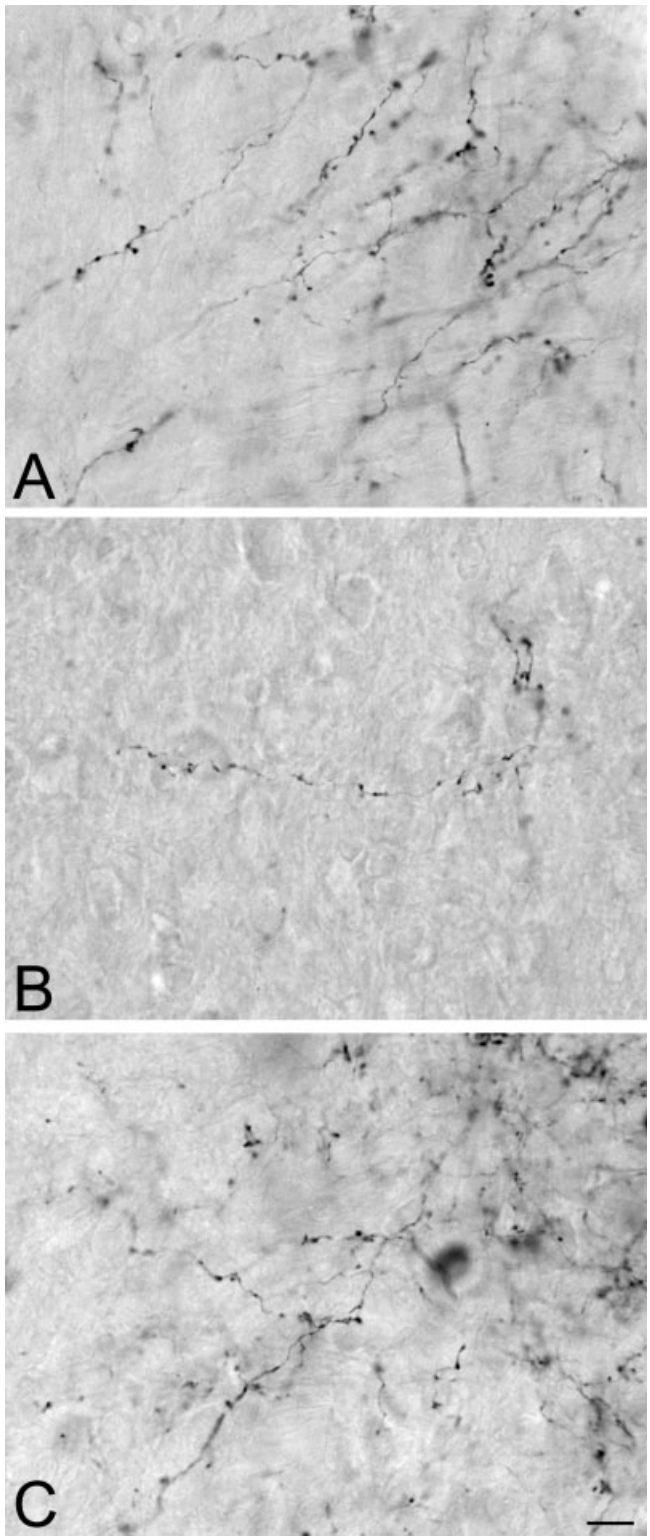


Fig. 4. High-power photomicrographs of axons within M (**A**), P (**B**), and K (**C**) layers of the LGN. There is no qualitative difference in axon morphology or the size of boutons. Some size variations are present, but these variations are not consistent with layer termination (i.e., axons of varying sizes are observed in all layers). Scale bar = 10 μm.

A total of five completely reconstructed axons displayed this innervation pattern. Axons following this pattern typically entered the LGN and traveled through nontarget layers along a course perpendicular to the layers (Fig. 5A). Occasionally, axons with branches in an M layer entered the LGN and traveled along the target layer before branching. Axons that branched in a given M or P layer often extended branches into a neighboring K layer (3 of 5 axons; Fig. 5), however, most of the total axonal branches were within an M or P layer. The axon shown in Figure 5B traveled along the dorsal edge of the LGN, before turning to innervate the contralateral P layer. Boutons were located primarily within the P layer, but there were a few along the trunk of the axon before it entered the P layer.

In the second pattern of innervation, corticogeniculate axons branched within pairs of functionally matched layers. Five of the reconstructed axons terminated in dual-layer projections. Like axons that branched in only one layer, these axons followed a perpendicular path through the LGN, giving off branches in either both M or both P layers (Fig. 6). We did not observe any axons that innervated M and P layers together. Again, similar to axons with individual layer projections, axons with terminations in pairs of M or P layers also frequently had collaterals in neighboring K layers. Only one reconstructed axon had no obvious branches in a neighboring K layer.

TABLE 1. Summary of Terminations for All Reconstructed Axons

Layer(s)	A/P width (μm)	Position relative to optic disc	Degrees
M	900	Anterior	—
M + K	400	Posterior	3.5
M + K	420	Posterior	3.6
P	320	Posterior	2.2
P + K	—[1]	—[1]	—
2 M + K	290	Posterior	5
2 M + K	460	Posterior	3.2
2 M + K	—[1]	—[1]	—
2P	500	Posterior	3.5
2 P + K	140	Anterior	—
2 K	340	Anterior	—
2 K	430	Posterior	3.8

[1]This axon was reconstructed through coronal sections, and accurate measures of anterior/posterior (A/P) length were not possible. Only axons located posterior to the optic disc representation (20° eccentricity) were included in degree measurements (see Materials and Methods for details).

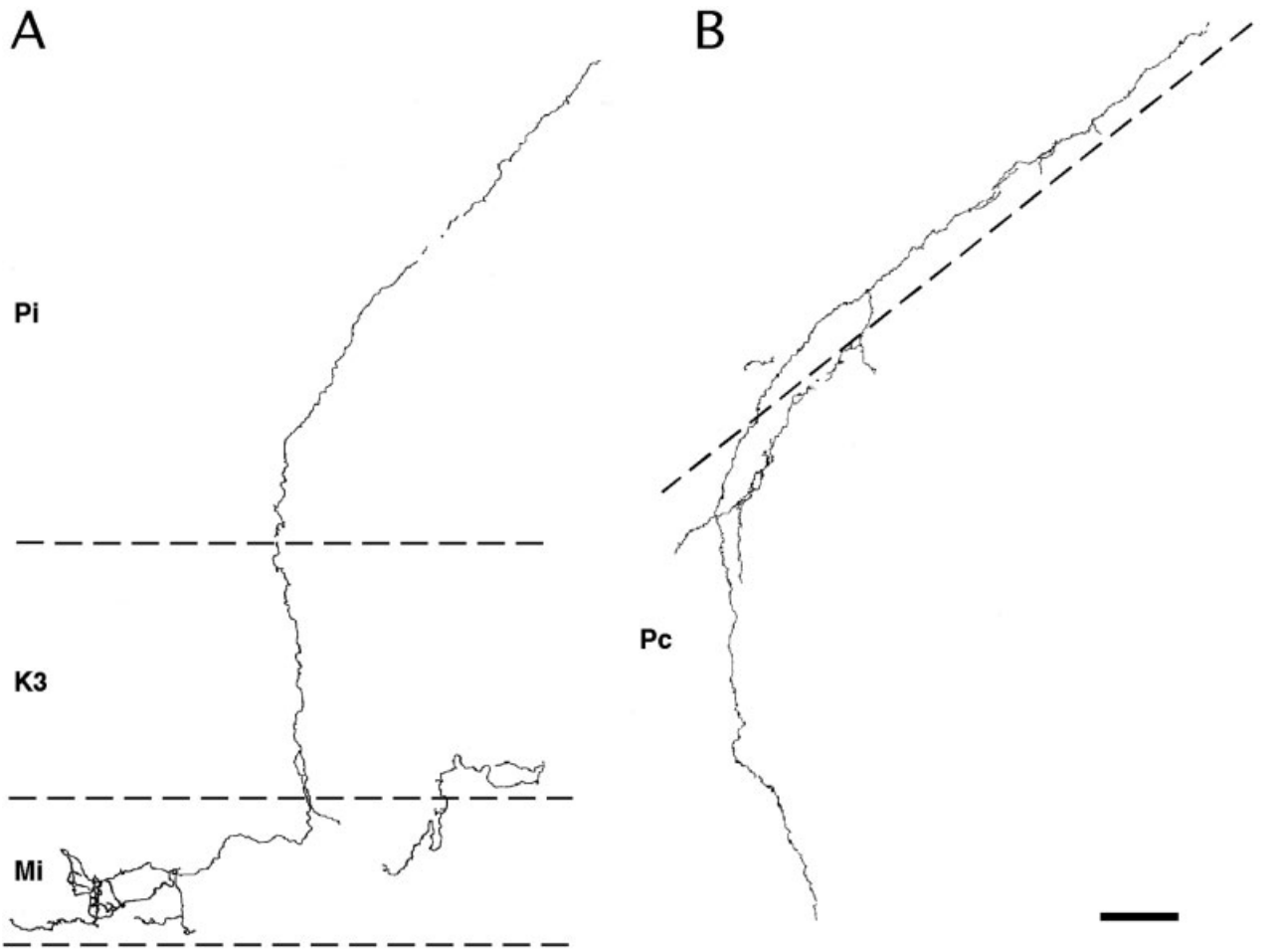


Fig. 5. Reconstructions showing corticogeniculate axon branching patterns in individual P and M layers. **A:** An axon that innervates the ipsilateral M layer. **B:** Reconstruction of an axon that innervates the contralateral P layer. Unconnected axons segments are included as part of the axon based on examination of neighboring sections for possible other axonal sources (see text for details). c, contralateral; i, ipsilateral. Scale bar = 50 μm.

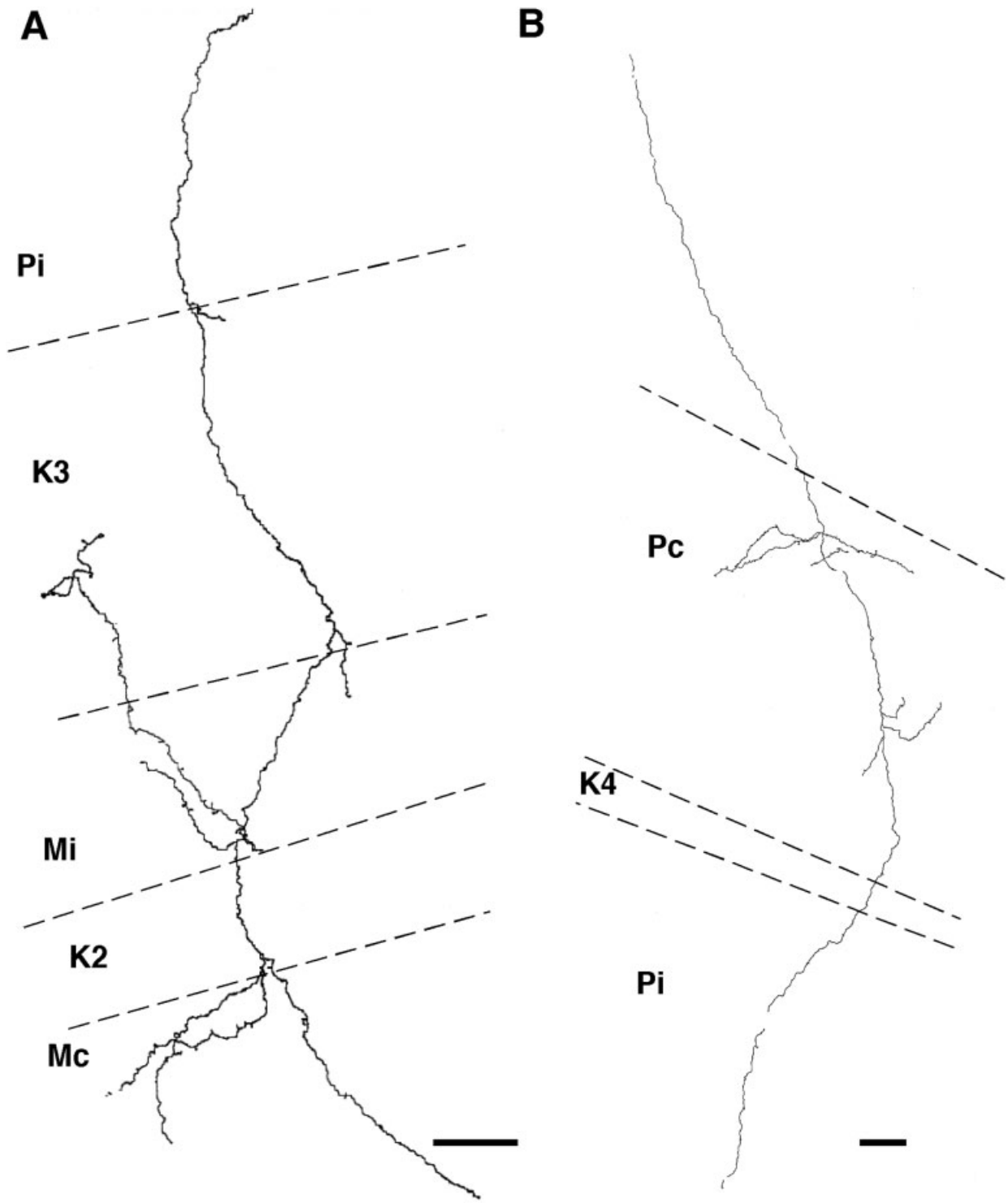


Fig. 6. Reconstructions showing corticogeniculate axon branching patterns in pairs of functionally matched M or P layers. **A:** Axon that innervates the ipsilateral and contralateral M layers, with a collateral in the K3 layer. **B:** Axon that innervates the contralateral and ipsilateral P layers. Other conventions as in Figure 5. Scale bars = 50 μm.

As mentioned, individual K layers did not appear to receive specific innervation from corticogeniculate axons; however, pairs of K layers did receive innervation from V1, and two of the reconstructed axons displayed dual K layer projections. As shown in Figure 7, the K layers that received innervation could lie adjacent to functionally

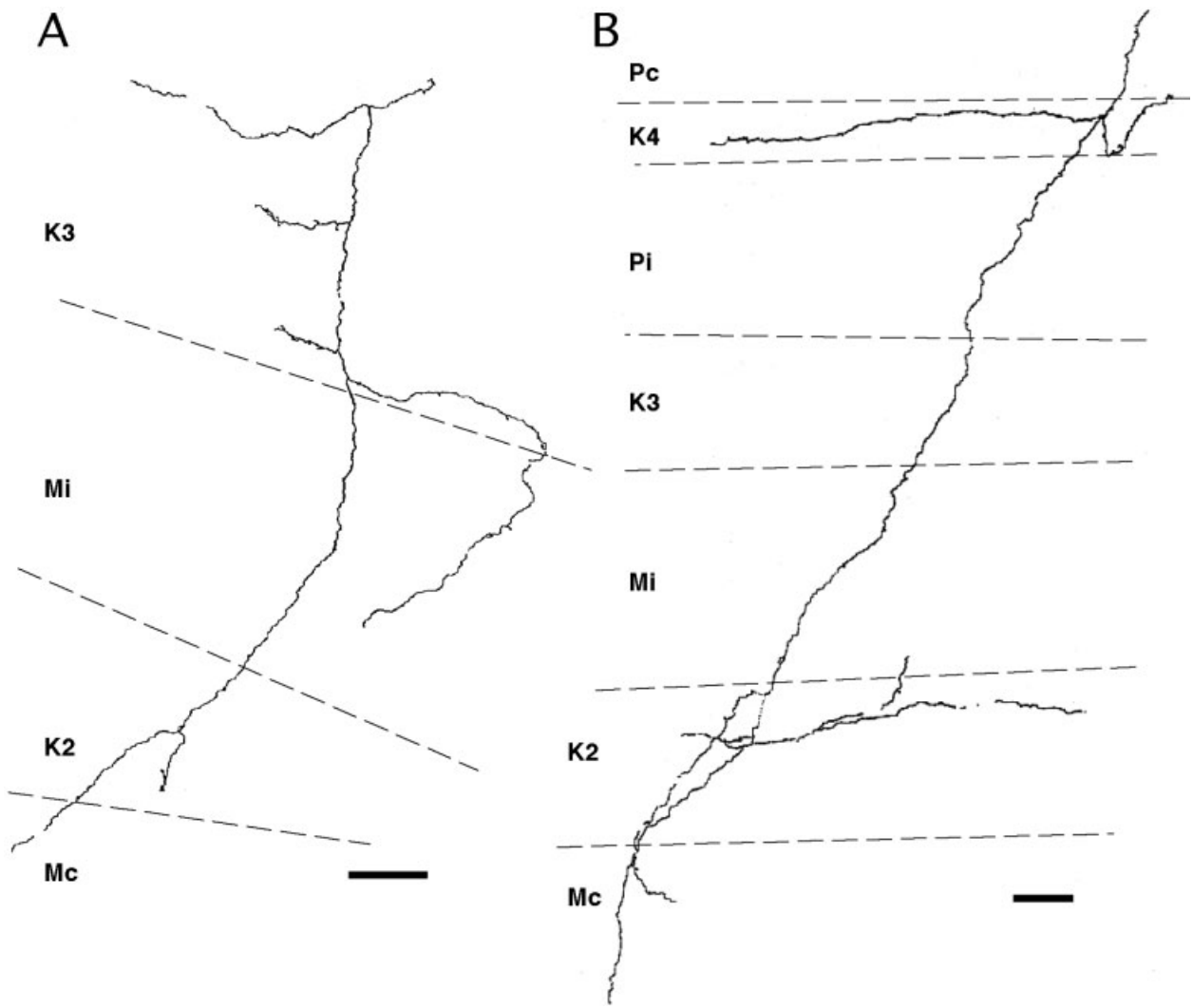


Fig. 7. Reconstructions showing corticogeniculate axon branching patterns in the K layers. **A:** Axon that innervates K layers that lie adjacent to the ipsilateral M layer, with a collateral that extends into the ipsilateral M layer. **B:** Axon that innervates K layers that lie adjacent to P and M layers with a collateral that extends into the contralateral M layer. Other conventions as in Figure 5. Scale bars = 50 μm.

matched layers (K2 and K3; Fig. 7A), or they could lie adjacent to nonmatched layers (K2 and K4; Fig. 7B). Although the axon shown in Figure 7B did have occasional boutons along the length of its trunk as it passed through the ipsilateral P and M layers, there were no indications of branches in those layers. We did not observe any axons that innervated K layers with obvious collaterals in both M and P layers.

Spread of axons

Measurements across the most distal branches that included boutons yielded terminal spreads of individual axons that covered 140–460 μm, with one that covered 900 μm. This axon innervated one M layer, entered the LGN near the posterior pole, and traveled through the ipsilateral M layer for 800 μm, with only a few boutons, before branching. Individual axons located posterior to the OD representation (n = 7) had terminal boutons that covered 2.2–5° of visual space (Table 1).

In three LGNs in which the patch of axonal label was distinct, relatively free of retrogradely labeled cells, and posterior to the OD representation, we measured the anterior-posterior spread of the whole column of label. Overall, the anterior-posterior spread in all three LGNs ranged from 200 to 833 μm, representing, on average, 4.2 ± 0.3° of visual space. The three cases differed significantly in the extent of the axonal spread ($P \leq 0.05$, ANOVA), but this difference was due to one case in which the label was confined to the most posterior end of the LGN (representing 0–3° of visual space) with an average spread of 2.6 ± 0.1°. The two cases that did not differ significantly in the extent of axonal spread ($P > 0.05$, t-test) had patches of label located between 5 and 20°, with average spreads of 4.4 ± 0.3° and 5.4 ± 0.3°, respectively.

The spread in different layers (M/K vs. P/K) did not differ ($P > 0.05$, t test).

DISCUSSION

Our chief finding is that corticogeniculate feedback in owl monkeys is in a position to modify signals from the parallel input pathways in distinct ways based on laminar specificity. The axons providing feedback, however, are morphologically very similar, suggesting that, although they can potentially regulate LGN layers independently, the type of signals that are sent may be similar. Importantly, we find no evidence that the cortical feedback in these primates is more retinotopically diffuse than would be expected based on the size of receptive fields of cells in V1. In the discussion that follows we consider the implications of these findings in light of what has been published by others.

Axon size and timing

The corticogeniculate axon morphology in all LGN layers in the owl monkey matches that described in cats by Guillery (1966) as type I: thin axons with boutons located along the axon (en passant) or at the ends of short stalks. We observed some variations in the thickness of individual axons, but these variations did not correlate with location or layer of termination within the LGN. Variations in corticogeniculate axon size were reported by Murphy and Sillito (1996) in cats; however, Murphy and Sillito still concluded that despite such variations the corticogeniculate axons that they reconstructed following labeling in the cortex all conformed to the original type I morphology described by Guillery.

A second corticogeniculate axon class, however, was described in the cat (Robson, 1983, 1984). These axons were reported to be slightly larger in caliber, with a distinctly beaded morphology. Because Robson (1983, 1984) labeled axons by horseradish peroxidase injections into the optic radiations just above the LGN, and because the beaded axons described were reported to make symmetric synapses indicative of an inhibitory pathway, it is likely that this second axon class actually originates from the perigeniculate nucleus or the TRN rather than from the visual cortex. Both the perigeniculate nucleus and TRN are known to contain only γ-aminobutyric acid (GABA)ergic neurons. Nevertheless, at least two distinct classes of layer 6 cells with identified corticogeniculate axons have been identified in the cat (Katz, 1987), suggesting that there may be more morphological types within this feedback pathway. Our visual cortical injections did not reveal any axons with a beaded morphology. The only variation in axon morphology that we did notice was a qualitative difference in the distribution of bouton sizes between the axons within the LGN and those within the TRN (Fig. 3). Whether some axons terminate only within the TRN and not within the LGN remains to be determined. It is known that many corticogeniculate axons in cats send a collateral branch into the perigeniculate nucleus (Murphy and Sillito, 1996).

Axons in the retinogeniculocortical pathway of owl monkeys and other primates are organized in parallel according to size where M axons are larger than P axons, which are larger than K axons (Ding and Casagrande, 1997). This same organization, as mentioned, is not reflected in the corticogeniculate pathway of owl monkeys where axons innervating the LGN do not vary in size based on layer terminations. Within the feedforward pathway, therefore, signals arriving from M, P, and K pathways reach the LGN at different times. Because M, P, and K axons also synapse on large, medium, and small cells within the LGN in which axon caliber matches cell body size, the conduction latency to the cortex from the LGN (as measured by antidromic stimulation) is also distinct between the three feedforward pathways, with the large M axons conducting the most rapidly and the small K axons the least rapidly (Casagrande and Norton, 1991).

Qualitative examination revealed that corticogeniculate axons that innervated different layers are all of small caliber. These fine-caliber axons approach the resolution power of the light microscope, so quantification of this feature was not possible with the available tissue. The relatively uniform size of corticogeniculate axons, however, indicates that these axons all have similar conduction speeds, a suggestion confirmed by examination of latencies within the LGN following orthodromic stimulation. What this means for the function of corticogeniculate input is unclear, especially given the high degree of processing that could take place before information is fed back to the LGN. Similar conduction speeds could help to synchronize feedback to the LGN within the different cell classes. Alternatively, the timing difference imposed by the feedforward input arriving from the retina could be maintained in the LGN, particularly given the fact that M and P axons send collaterals into cortical layer 6, where they are in a position to terminate directly on cells in different strata that feed information back to the LGN (Lund et al., 1975; Conley and Rackowski, 1990; Fitzpatrick et al., 1994).

Although the size of the axon is central in predicting its conduction speed, size alone certainly does not determine the effect of input on the postsynaptic cell (Maunsell et al., 1999). The number of inputs to the postsynaptic cell, the size and location of those inputs, and the types of receptors and their response times are some of the many factors that can determine the response characteristics of the LGN cell. Although retinal and cortical inputs to LGN relay cells both arrive from axons that contain glutamate, they also differ in a number of respects that could affect response timing. Retinal axons terminate as large boutons close to the cell body, whereas cortical axons terminate as small boutons on the distal dendrites of these same cells, at least in cats, bush babies, and macaque monkeys (Guillery, 1969; Wilson, 1989; Feig and Harting, 1994); electron microscopic data are not available for owl monkey LGN. In cats the receptor types associated with each pathway also differ. Retinal input to the LGN primarily accesses ionotropic glutamate receptors (Scharfman et al., 1990; McCormick and Von Krosigk, 1992). Corticogeniculate input mainly accesses a specific metabotropic glutamate type 1 receptor (mGlur1α; Godwin et al., 1996a). When activated, mGlur1α receptors have been shown to change the response properties of LGN cells from a burst to a tonic mode of firing (Godwin et al., 1996b). If the same pattern occurs in primates, then synchronized timing of the feedback pathway may aid in coordinating the transmission of information about sensory quality because tonic firing creates a more faithful representation of retinal input (Sherman, 2001).

Layer-specific terminations: binocularity and functional specificity

The fact that some corticogeniculate axons in owl monkeys are confined to individual LGN layers suggests that the cortex can influence the activity of left and right eye layers independently. We were somewhat surprised by this finding on two counts. First, ocular dominance columns within V1 of owl monkeys are weak or absent (Kaas et al., 1976; Rowe et al., 1978; Diamond et al., 1985). This means there is very little ocular segregation of LGN axons within the cortex from the first synapse onward. Physiological investigation of V1 in owl monkey also suggests that there are fewer monocular cells (Felleman, 1981; O'Keefe et al., 1998) than in primates with clear ocular dominance columns. Second, no corticogeniculate axons reconstructed in cats or ferrets are restricted to one LGN layer, although a bias is seen in cats, in which there are a greater number of boutons in the layer that matches eye dominance of the cell of origin (Claps and Casagrande, 1990; Murphy and Sillito, 1996). Ocular dominance columns in cats, although not as distinct as in macaque monkeys, are still clear (Löwel and Singer, 1987; Anderson et al., 1988). It may be the case, however, that cells sending axons back to the LGN in owl monkeys are monocularly driven. Regardless, it is evident that in owl monkeys feedback projections are in a position to influence both monocular LGN layers independently and functionally matched layers together.

What advantage could such an arrangement have? It has been suggested that the monocular laminar pattern of the LGN combined with feedback from cortex could provide a mechanism to explain the alternations in visual perception seen when nonmatching stimuli are presented to each eye, a phenomenon known as binocular rivalry (for reviews, see Alais et al., 2000; Blake and Logothetis, 2002). In fact, inhibitory interactions between the dominant and nondominant eye have been widely reported to occur in the LGN of cats and monkeys based on single cell recording (Singer, 1970; Sanderson et al., 1971; Rodieck and Dreher, 1979). The only demonstration to support the idea that feedback to the LGN might be important in binocular rivarly, however, comes from work by Varela and Singer (1987). They found that as two grating stimuli designed to drive cortical cells became more rivalrous, the inhibition of dominant eye responses in the LGN increased. Unfortunately, using a similar anesthetized cat preparation, Sengpiel et al. (1995) were not able to confirm these results. Additionally, no evidence for changes in the LGN were found under conditions designed to produce rivalrous percepts in awake behaving monkeys (Lehky and Maunsell, 1996).

Many reports of binocular interactions within the LGN certainly suggest, however, that feedback from the cortex may be involved in some way in binocularity. One theory, proposed by McIlwain (1995), suggests that binocular fusion occurs in the LGN to aid in stereopsis. McIlwain describes how changes in vergence cause changes in the retinal location of images. If disparity is important for stereopsis, as is commonly thought, these changes ought to cause problems in stereopsis unless the receptive fields of LGN neurons are not fixed on the retina (i.e., changes in vergence ought to cause slight shearing in the receptive field map in the LGN). McIlwain proposes that the function of feedback is to "match up" the slightly displaced maps in each layer of the LGN for the benefit of disparity sensitive cells in cortex. If this is the case, then the cross-layer projections of corticogeniculate axons put them in position to mediate several receptive fields and possibly serve to align receptive fields in separate layers. This theory remains to be tested.

Although some segregation is maintained in the corticogeniculate pathway, axons almost always terminate in combinations of M and K or P and K layers. This pattern is not seen in either the retinogeniculate or geniculocortical projections, where all three pathways maintain a strict segregation. There is evidence in primates that the cells in layer 6 of V1 that give rise to the corticogeniculate feedback are somewhat segregated according to which functional LGN layer they project. In macaque monkeys, cells projecting to the P layers are primarily located in the upper part of layer 6, whereas the M-projecting cells are seen in the lower part of layer 6 (Lund et al., 1975; Fitzpatrick et al., 1994). A similar pattern has been observed in bush babies, although in this species the upper part of layer 6 appears to be further subdivided into P- and M-specific cells, with P-projecting cells found in the topmost subdivision, near the bottom of layer 5, and M-projecting cells located immediately beneath them (Conley and Raczkowski, 1990). As shown by our data, the K layers do not appear to receive input that is segregated from M and P input, so the location of cells in layer 6 that project primarily to the K layers is difficult to determine; however, it appears likely from data in bush babies that this population is intermixed with the populations that project to M and P layers (Conley and Raczkowski, 1990).

This intermingling of input suggests that there may be some functional overlap between P or M and neighboring K layers. In fact, there is both anatomical and physiological evidence that different K layers that lie adjacent to P layers differ functionally from those that lie near M layers. Using anatomical tracer methods similar to ours, Ding and Casagrande (1997) showed that in owl monkeys, cells in the K layers lying below and between the M layers (K1 and K2) mainly project to cortical layer 1, whereas cells in the K layer that lies between the M and P layers (K3) primarily project to the cytochrome oxidase (CO) blobs in cortical layer 3. Extracellular recordings in the owl monkey LGN also revealed that K cells in K1 and K2 were more M-like, whereas the cells in K3 had properties that were intermediate to M and P cells (Xu et al., 2001). With these data in mind, it seems clear that K cells represent a heterogenous population of relay cells that are, for whatever reason, treated differently by cortical feedback. Feedback to the M and P layers also differs from that to the K layers in that M and P geniculocortical axons give off sparse collaterals within cortical layer 6 (Hendrickson et al., 1978; Blasdel and Lund, 1983; Florence and Casagrande, 1987; Ding and Casagrande, 1997). There is little evidence that geniculocortical K axons have collaterals in layer 6. Blasdel and Lund (1983) found one axon in macaque monkey V1 that had branches in layer 1 and layer 6, but there is no evidence of K axon collaterals in layer 6 in the owl monkey (Ding and Casagrande, 1997). Collaterals in layer 6 could play a role in forming a direct loop between P and M relay cells in the LGN and corticogeniculate feedback cells in layer 6 of V1. Regardless of whether or not the M and P geniculate collaterals terminate directly onto feedback cells, this is a circuit in which

geniculocortical K axons in the owl monkey do not participate.

Scaling and feedback projections

The topographic specificity of owl monkey corticogeniculate axons indicates that V1 feedback restricts its influence to a retinotopic zone that matches the zone from which it receives input from the LGN. The anterior/posterior spread of individual axons, as well as the spread of the whole column of labeled axons, covers the same amount of the visual field representation as the receptive fields of cells of origin reported in V1. Our individual corticogeniculate axons covered an estimated 2.2–5°, with an average of 3.6°. The anterior/posterior spread of the whole column of labeled axons was not much larger than the individual axons, with a range of 2.1–7° and an average of 4.2°. Cells in V1 of the owl monkey have receptive field sizes that range between 1 and 7°, with an average size of 2.7° (Felleman, 1981).

These receptive field sizes are based on recordings made primarily from the dorsal surface of V1 (Felleman, personal communication), which only includes the central 20° of the lower visual field (Allman and Kaas, 1971). This eccentricity matches the estimated eccentricity in which we measured the anterior/posterior spread of individually reconstructed axons and the column of axonal label. In the LGN, receptive field center sizes are smaller, averaging for all classes slightly under 1.0° (Xu et al., 2001). Regardless, there does not appear to be strong evidence for a retinotopic mismatch between the size of receptive fields in cortex and the projection back from cortex in the owl monkey. We should, however, add a note of caution to this conclusion. Because we do not know the exact receptive field sizes of the specific cortical cells from which our sample is drawn, it remains possible that the feedback pathway is broader than our averages can judge.

The corticogeniculate pathway in the cat displays a somewhat different pattern. Cortical terminations in the cat LGN have a core region that covers approximately the same topographic area as represented by the cell of origin in cortex, but this feedback projection also includes a peripheral region of more diffuse termination that covers, in some cases, more than twice the topographic zone estimated as a match (10° or more; Murphy and Sillito, 1996). The difference between our findings in owl monkeys and the findings in cats could have important implications for the function of this pathway in each species. In the cat the mismatch between feedback and feedforward pathways would allow feedback axons to influence visual processing over areas much greater than their own responses summate. At present it is unclear what impact this might have, although one might predict a form of lateral inhibition to occur in regions that did not match because in cats, feedback axons from the cortex tend to terminate more frequently on inhibitory interneurons than on relay cells (Weber et al., 1989).

Interestingly, research on the role of corticogeniculate feedback in cats has revealed some possible roles of the corticogeniculate pathway that might depend on the more topographically matched feedback connections. Work done by Sillito et al. (1994) has shown that cortical feedback produces synchronized firing of relay cells in the cat LGN. When stimulated with a drifting grating or a drifting bar, cells in the LGN were shown to fire together. Using a cross-correlational analysis, Sillito et al. (1994) were able to demonstrate that this synchronization is enhanced over that present in relay cells that are already firing due to retinal input alone. When the stimulus was changed, from a drifting grating or bar to a pair of flashing squares, the coordinated firing disappeared. These effects are proposed to be due to the nature of the stimuli: a drifting grating and a bar are both capable of driving layer 6 cortical cells, whereas flashing spots drive only retinal ganglion cells. Thus, the change in stimulus from a bar to a square effectively removes the cortical feedback, and when the cortical influence was removed in this way the synchronous firing disappeared as well. The function of this synchronization may be to enhance the firing related to a stimulus that drives a given cortical cell. In this scheme, only those LGN cells that are already firing due to retinal input will be further affected by matching cortical input (Sillito et al., 1994). The matching retinal feedforward and cortical feedback inputs found in owl monkey fit well with such a model.

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