Brain Research, 137 (1977) 233–252

THE VISUAL CORTEX OF THE OPOSSUM: THE RETROGRADE TRANSPORT OF HORSERADISH PEROXIDASE TO THE LATERAL GENICULATE AND LATERAL POSTERIOR NUCLEI

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(Accepted March 16th, 1977)

SUMMARY

The visual cortex of opossum was studied by injecting horseradish peroxidase into the cortex and identifying labeled neurons in the thalamus. The results show that the lateral geniculate nucleus projects to area 17 in a topographical manner: the rostral lateral geniculate is represented in caudal striate cortex, and the dorsal extremity of the lateral geniculate, which probably corresponds to the zero vertical meridian, is represented along the border of area 18. Small injections in area 17 produced restricted bands of labeled neurons across the medial-lateral extent of the lateral geniculate, suggesting a greater precision in the topography than previously shown by retrograde degeneration studies. Following injections into area 17, labeled cells were also found in the lateral posterior nucleus. Injections of peristriate cortex produced labeled cells in the lateral posterior nucleus, as well as the lateral intermediate, posterior and intralaminar nuclei. Since the lateral posterior nucleus receives visual projections from the superior colliculus, the results show two visual pathways: the geniculo-striate path projecting just to core area or area 17, and a more diffuse parallel path that projects to *both* the core and belt. Whether or not this overlap is characteristic of the mammalian prototype it seems to be present in widely separated species.

INTRODUCTION

The visual cortex of the opossum has been studied by the method of thalamic

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retrograde degeneration[6,8,15], and by the method of tracing terminal degeneration in the cortex following thalamic lesions[3,16]. The two approaches have reached the same conclusion about the topography of the projections of the lateral geniculate nucleus to area 17, and results from both methods suggest that the lateral posterior or pulvinar nucleus may project to area 17 as well as to extrastriate visual belt. In spite of this general agreement there are several questions still unsettled. The first question is: how precise is the topographic projection of the lateral geniculate nucleus upon area 17? The method of retrograde degeneration does not seem to be well suited to provide an answer because small lesions have very little effect on the thalamus[6,15].

A second question is closely related to the first: do cells in the lateral geniculate nucleus send sustaining collaterals to different sectors of area 17 and to the visual belt adjacent to 17? This question grows out of the relation between severity of retrograde degeneration in the lateral geniculate nucleus and lesion size[15].

The third question that remains unsettled concerns a projection from the lateral posterior nucleus to area 17. After large thalamic lesions, terminal degenerating axons, other than axons arising from the lateral geniculate nucleus, can be traced to area 17 (see ref. 3). Presumably the lateral posterior nucleus is their source, but small lesions confined to the lateral posterior nucleus have never been made. The retrograde evidence supports this idea since the lateral posterior nucleus is severely degenerated after large lesions of striate plus extrastriate cortex[15]. If the lateral posterior nucleus projects to area 17 at all, these projections can be removed without affecting the cell bodies; that is to say they are sustaining collaterals. Concerning thalamic nomenclature, we thought it would be less confusing to continue to use the term 'lateral posterior' nucleus rather than shift to the term pulvinar nucleus. However, there is no doubt that this nucleus in the opossum is homologous to the pulvinar nucleus of the tree shrew and other experimental mammals[1,26].

The answers to these questions bear on our understanding of parallel visual pathways, especially since the opossum is usually regarded as a generalized and lowly mammal. We felt that the method of retrograde transport of horseradish peroxidase was especially appropriate to answer them

METHOD

Horseradish peroxidase (HRP; Sigma Chemical Co., Type VI) was injected into the striate or extrastriate cortex in both hemispheres of 14 adult opossum of either sex *(Didelphis marsupialis virginiana)* except for one unilateral case. During the surgical procedure the animals were deeply anesthetized with sodium pentobarbital. The amount of HRP injected was varied from 0.05 to 0.1 μl, since one aim was to try to establish a correlation between the amount injected and the number and distribution of cells labeled in the thalamus. Toward the end of the study we shifted from using a 1 μl Hamilton syringe to a glass pipette. In every instance the HRP was diluted in saline to a concentration of 30% and gradually injected over a 15 min period.

Forty-eight hours after the injection the animals were deeply anesthetized with sodium pentobarbital and perfused through the heart. The perfusion began with a

small amount of physiological saline, followed by a solution of a 0.5 % paraformaldehyde and 2.5 % glutaraldehyde in sodium cacodylate buffer, warmed to body temperature. The pH of these and each of the incubating solutions was 7.2. After perfusion the head was placed in a stereotaxic machine and the brain blocked through the olfactory bulbs in the coronal plane. The brains were stored overnight at 4 °C in buffer. The next day the brain was frozen and sectioned at 60 μm; every section through the visual cortex and thalamus was prepared by the procedure of Graham and Karnovsky[18]. Each section was collected in cacodylate buffer and then incubated at room temperature in a solution of 3,3′-diaminobenzidine and H_2O_2. The sections were then mounted on gel-coated slides, dried overnight and then lightly counterstained with cresyl violet.

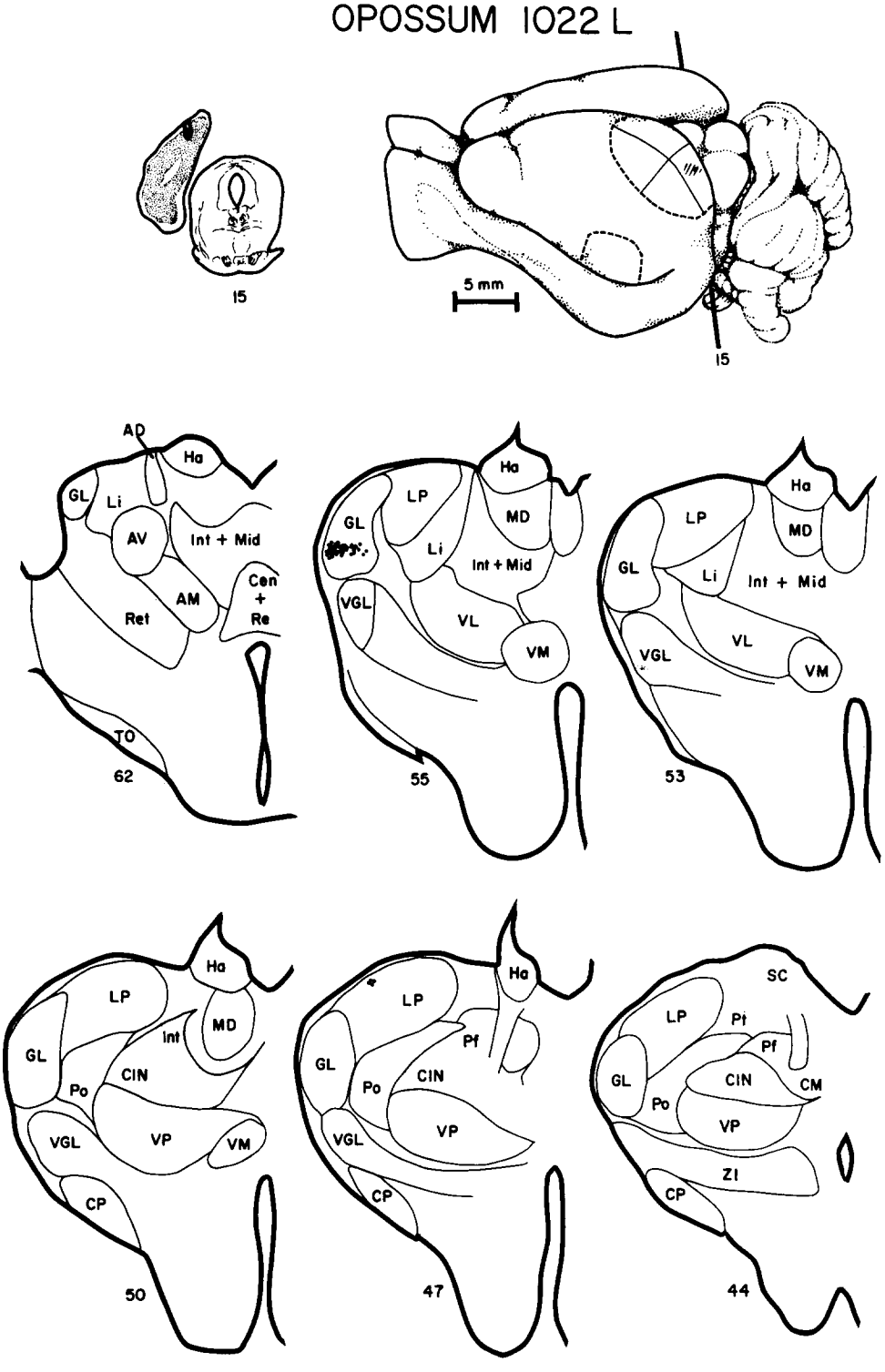
Both light and dark field condensers were used in the microscope to identify labeled cells. The distribution of HRP-positive cells was established in three steps. First, the position of these cells was marked on a scale drawing of the thalamus by and x–y plotter coupled to the microscope stage. Next, major cytoarchitectonic subdivisions of the visual thalamus were drawn with a microprojector and microscope. Finally, the charts of labeled cells and thalamic architecture were superimposed to yield a final picture which correlated the position of labeled cells with respect to thalamic boundaries.

To locate the injection site and the extent of the dark brown stain, a 45° view of the cortical surface was reconstructed. The injection site was then translated onto a standard view of the cerebral cortex. To help in this translation we measured the distances of the injections from the midline, from the caudal pole and from the borders of the striate cortex.

RESULTS

In order to present the main results which relate the locus of the cortical injection to the distribution of labeled cells in the thalamus, it is necessary to have some way of assessing the area of the cortex which incorporates HRP. In other words it is necessary to know how extensively HRP diffuses and whether or not HRP is taken up and transported by axons of passage as well as axon terminals. In earlier experiments with the cat cortex we varied the amount of HRP injected and noted the correspondence between amount injected, the extent of a dark brown stain and the number of labeled cells[32]. As a first approximation, the area of dark brown stain appeared to define the area of cortex in which HRP is incorporated and transported. We were less successful in determining whether diffusion of HRP into fibers of passage would result in HRP transport. However, it seems conservative to assume that the penetration of fibers by the syringe or pipette could result in the incorporation of HRP, and accordingly we attempted to restrict the HRP to cortex itself.

That the extent of dark brown stain does reflect the diffusion of HRP can be shown by a comparison of the two hemispheres in opossum 1022 (see Figs. 1 and 2). On both sides the same amount was injected (0.1 μl), but apparently the injections were not equally effective, and on the right side the brown stain in the striate cortex was many times more extensive than on the left. Correspondingly a large number of cells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were labeled in the lateral geniculate and lateral posterior nuclei on the right side and many fewer on the left. To further illustrate the density of labeled cells in the lateral geniculate we present a photomicrograph of a section in case 1022R (See Fig. 3A).

The extent of brown stain may reflect the diffusion of HRP and yet not define precisely the cortical area incorporating HRP for transport. To meet this objection we relied on our earlier experience, which seemed to show that cortex beyond the limits of the dark brown stain was not incorporating HRP[32]. In the present study we can offer evidence for this very point. In case 1039R (see Fig. 4), HRP was injected in the cortex of the visual belt and the brown stain reached the border of area 17 and just barely crossed the border. Correspondingly a few cells in the lateral geniculate body were labeled and, as could be expected, these were found along the border between the lateral geniculate and lateral posterior nuclei. This result supports the idea that the dark brown stain coincides with the cortical area incorporating HRP.

Results such as these made us reasonably secure in representing the cortical area transporting HRP by the borders of the dark brown stain. While there are some instances where the intensity of the stain diminishes gradually from some central locus, it is usually easy to draw a border, on one side of which the stain is dark brown and the other side of which there is little or no stain (see, for example, Fig. 8). The question of the effect of HRP on axons of passage cannot be answered with our material and we can only try to show in each case whether or not the brown stain entered the white matter.

The topographic projection of the lateral geniculate body upon area 17. Area 17 of the opossum has been described several times and we accept the consensus of these views in defining its borders[2,3,6,15,16,19].

Only in a few mammals, notably in primates, does area 17 have those distinctive features which give 'striate' cortex its name. In the opossum it is doubtful if area 17 has

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Fig. 1. The injection site and location of thalamic neurons labeled with HRP in hemisphere 1022L. This and subsequent figures show 6 representative frontal sections through the lateral geniculate and lateral posterior nuclei. The position of each labeled cell is depicted by a dot. The extent of the brown stain at the center of the injection is shown in black in a frontal section of the cortex, while the syringe or pipette track is shown in white. A standard view of the opossum cortex shows the boundary of striate cortex as indicated by dashed lines and the injection site projected to the cortical surface defined by hatched lines. The vertical lines above and below the site of injection represent the plane of section in each experiment. The striate cortex has been divided into quadrants to facilitate comparisons of the topography of the geniculo-cortical projection between cases. One of two 60 μm frontal sections is shown for each number which represents an interval of 120 μm. Abbreviations in this and the following figures: AD, anterior dorsal nucleus; AM, anterior medial nucleus; AV, anterior ventral nucleus; Cen, central nucleus; CG, central gray; CIN, central intralaminar nucleus; CM, centre médian; CP, cerebral peduncle; FF, fields of Forel; GL, dorsal nucleus of the lateral geniculate body; GM, medial geniculate body; Ha, habenula; Ha-IP, habenulo-interpeduncular tract; Int. intralaminar nuclei; Li, lateral intermediate nucleus; LP, lateral posterior nucleus; MD, medial dorsal nucleus; Mid, midline nuclei; PC, posterior commissure; Pf, parafascicular nucleus; Po, posterior group; Pt, pretectum; PV, paraventricular nucleus; Re, nucleus reuniens; Ret, reticular nucleus; SC, superior colliculus; TO, optic tract; VGL, ventral nucleus of the lateral geniculate body; VL, ventral lateral nucleus; VM, ventral medial nucleus; VP, ventral posterior nucleus; VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus; ZI, zona incerta.

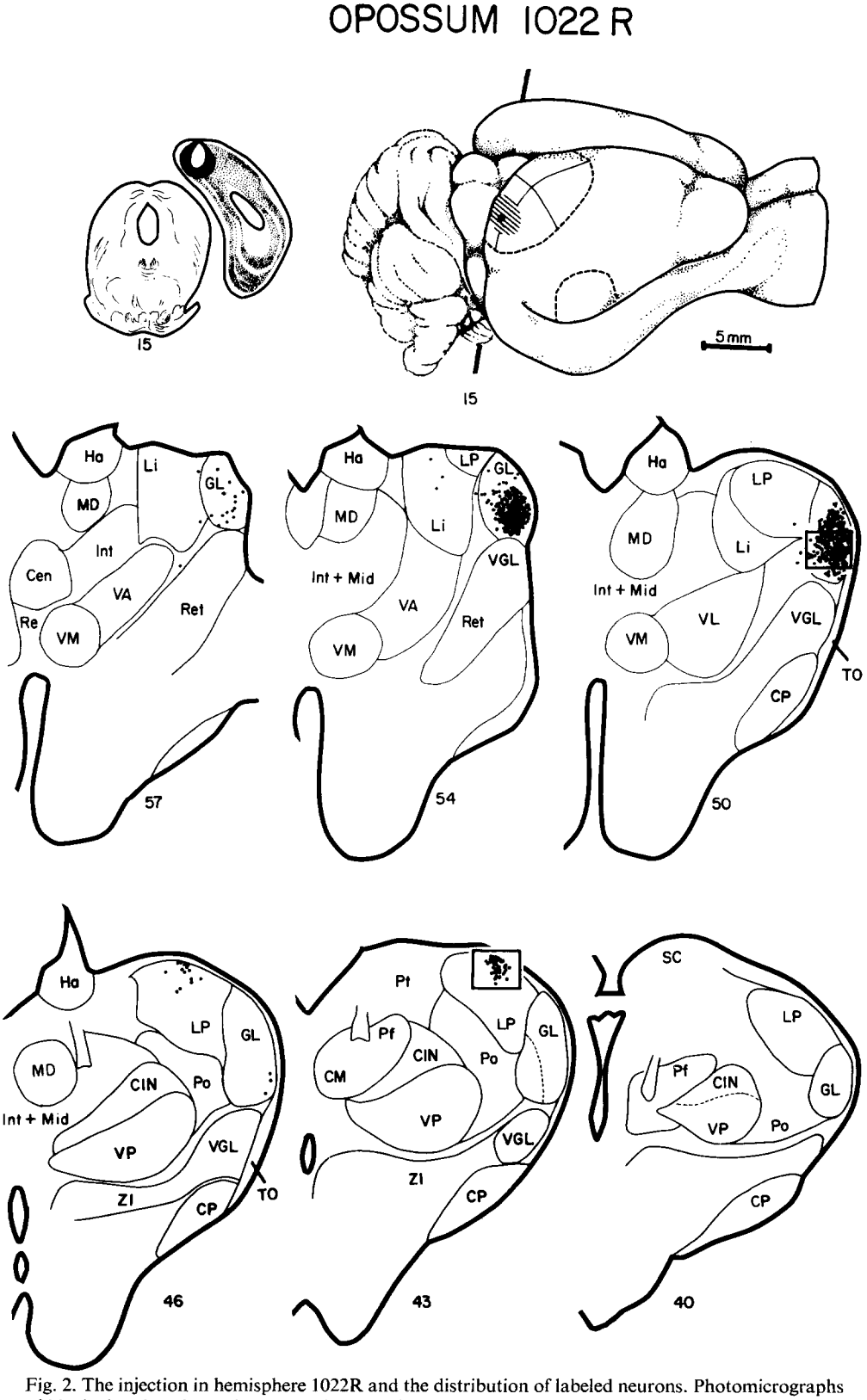

Fig. 2. The injection in hemisphere 1022R and the distribution of labeled neurons. Photomicrographs of blocked regions in sections 43 and 50 are shown in Fig. 3.

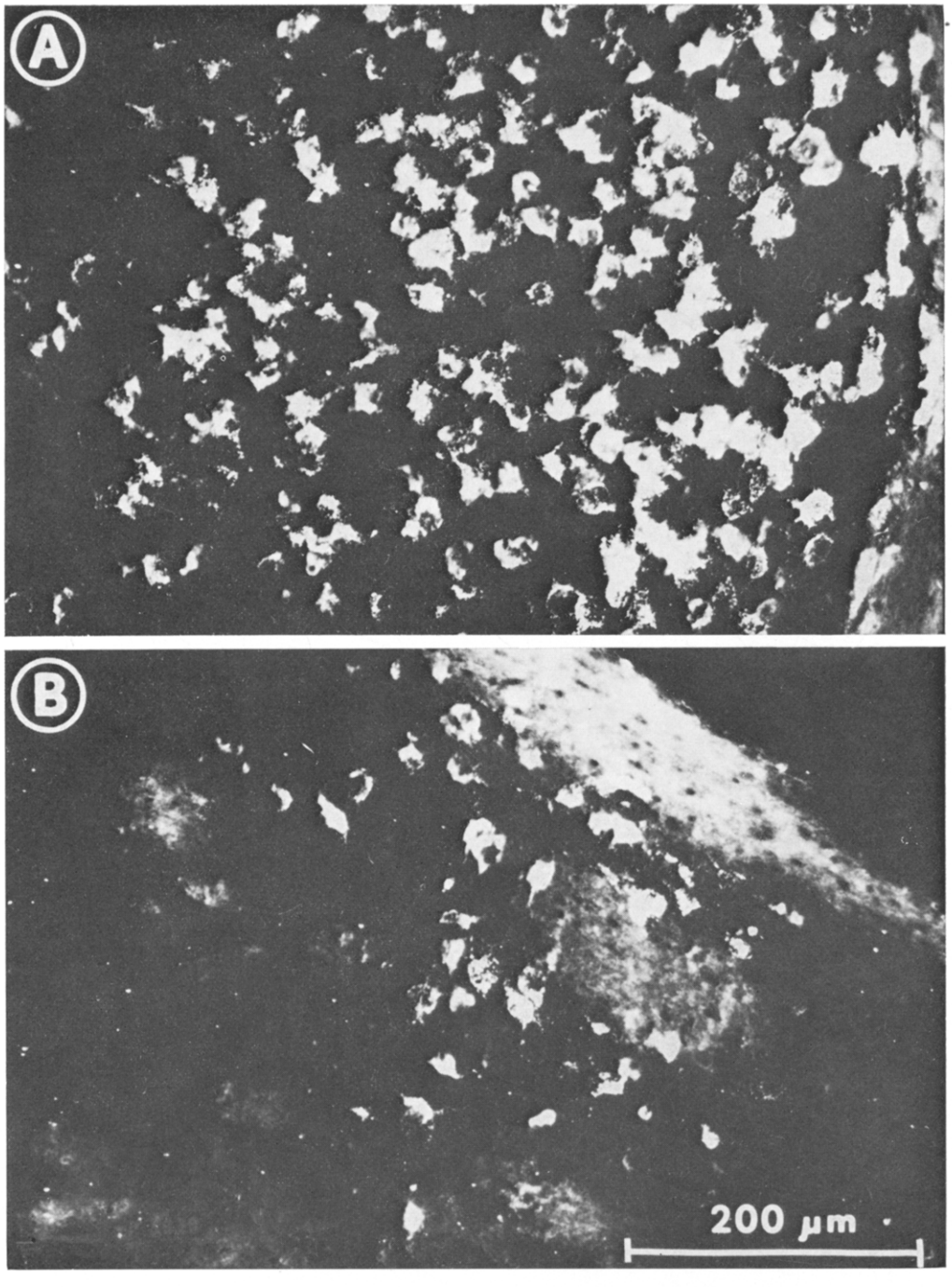

Fig. 3. Photomicrographs of labeled cells in (A) the dorsal lateral geniculate nucleus and (B) the lateral posterior nucleus following injection of striate cortex in hemisphere 1022R. Dark field condensor.

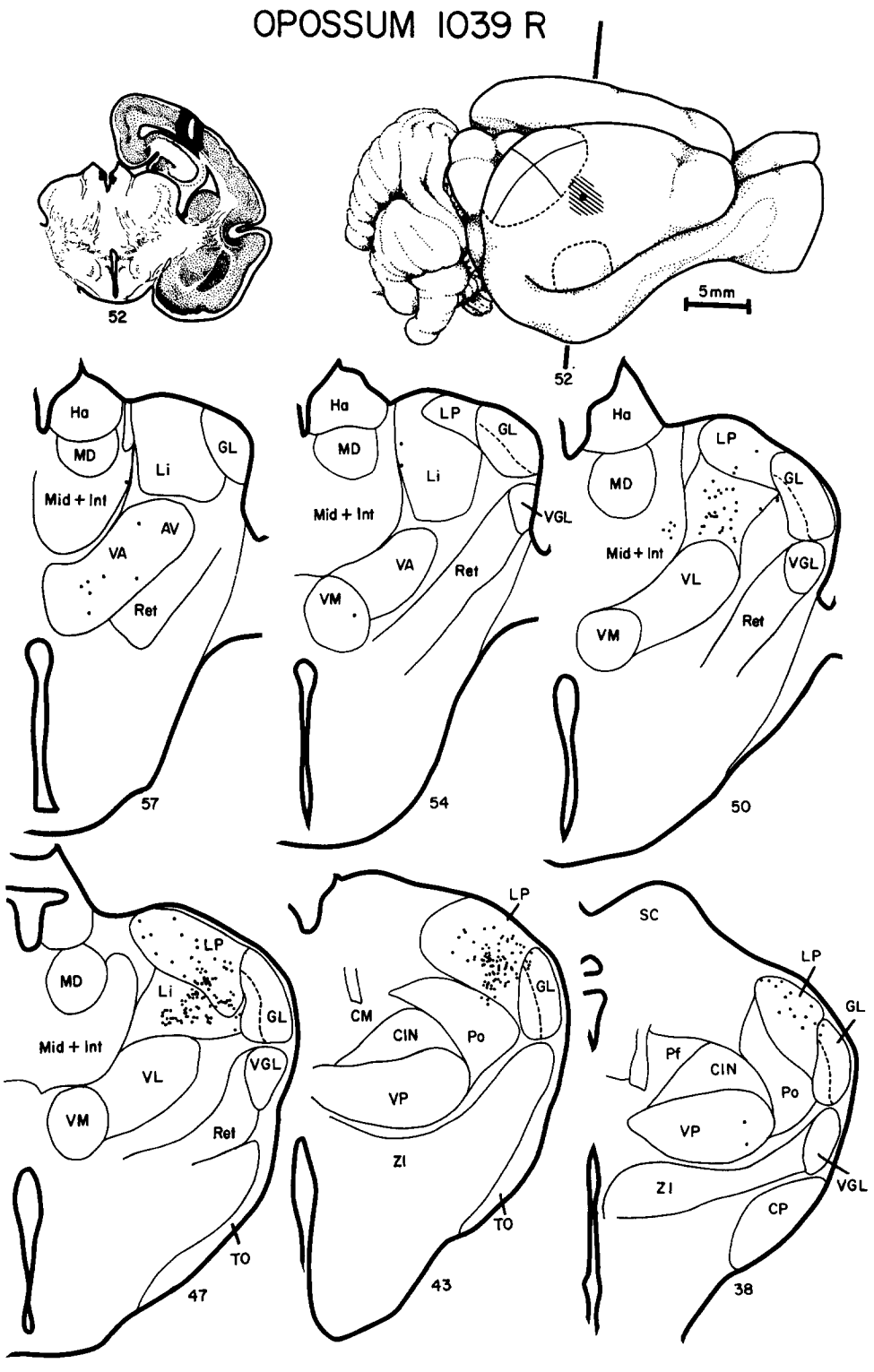

Fig. 4. The injection in hemisphere 1039R and the distribution of labeled neurons.

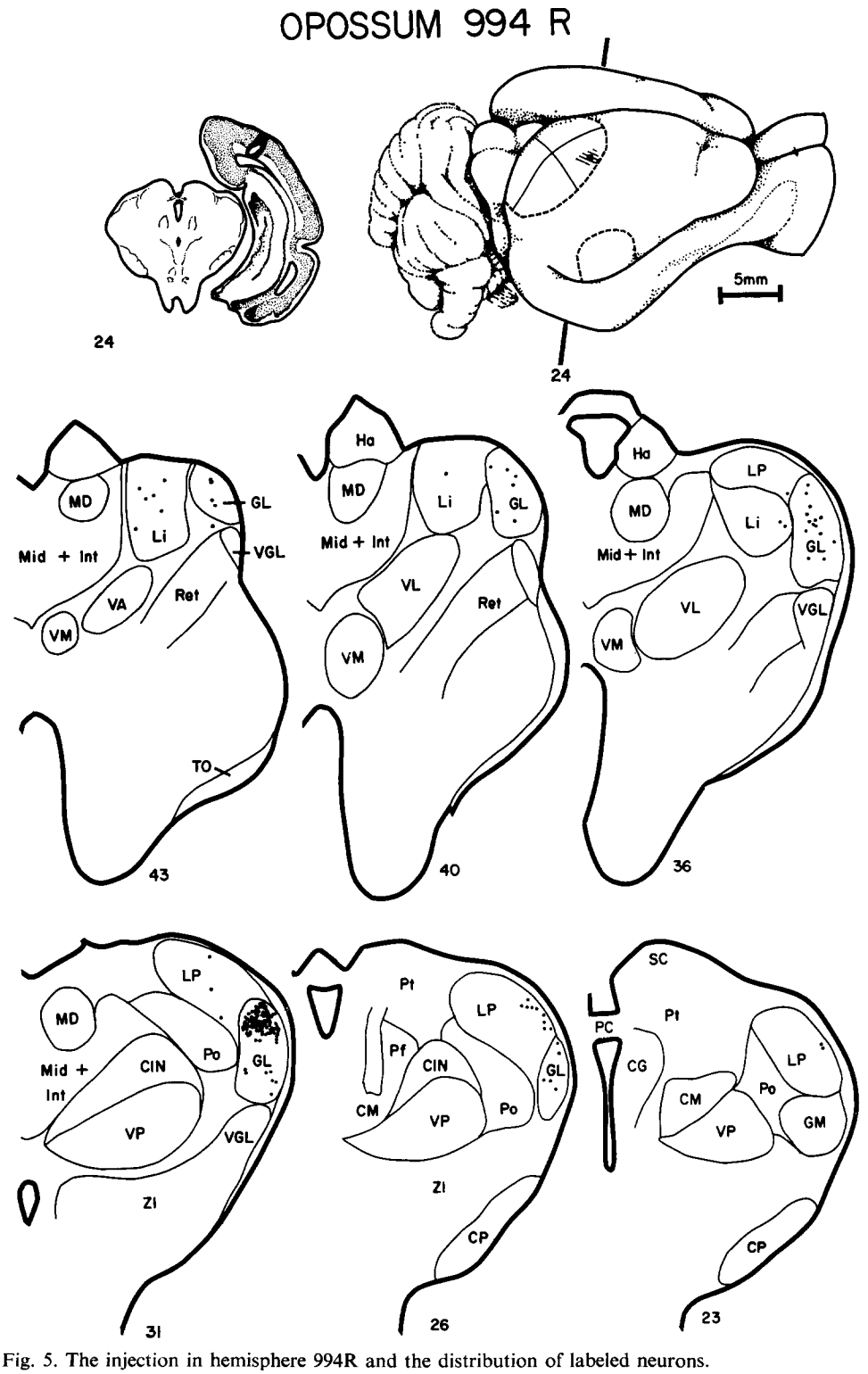

Fig. 5. The injection in hemisphere 994R and the distribution of labeled neurons.

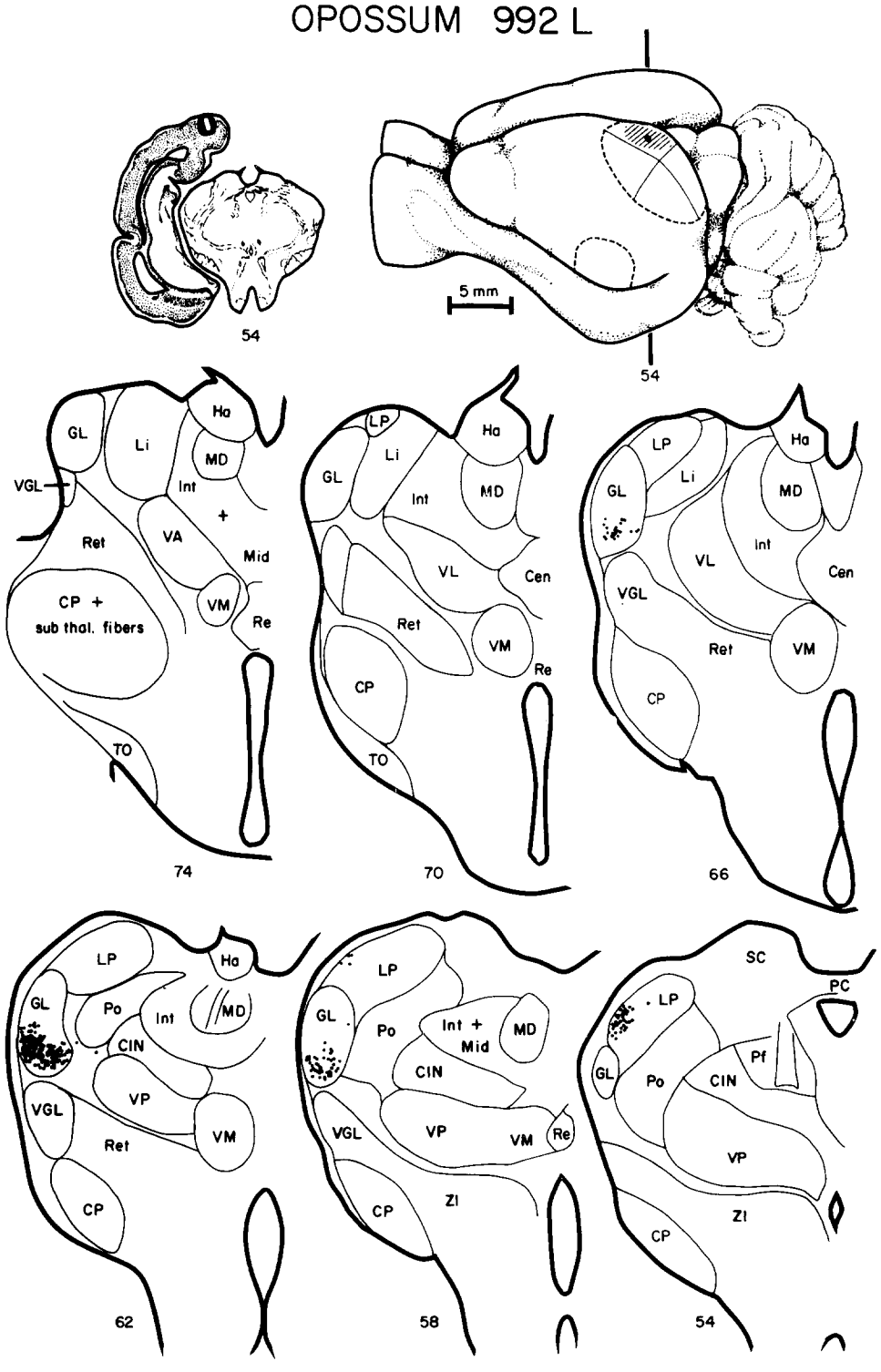

Fig. 6. The injection in hemisphere 992L and the distribution of labeled neurons.

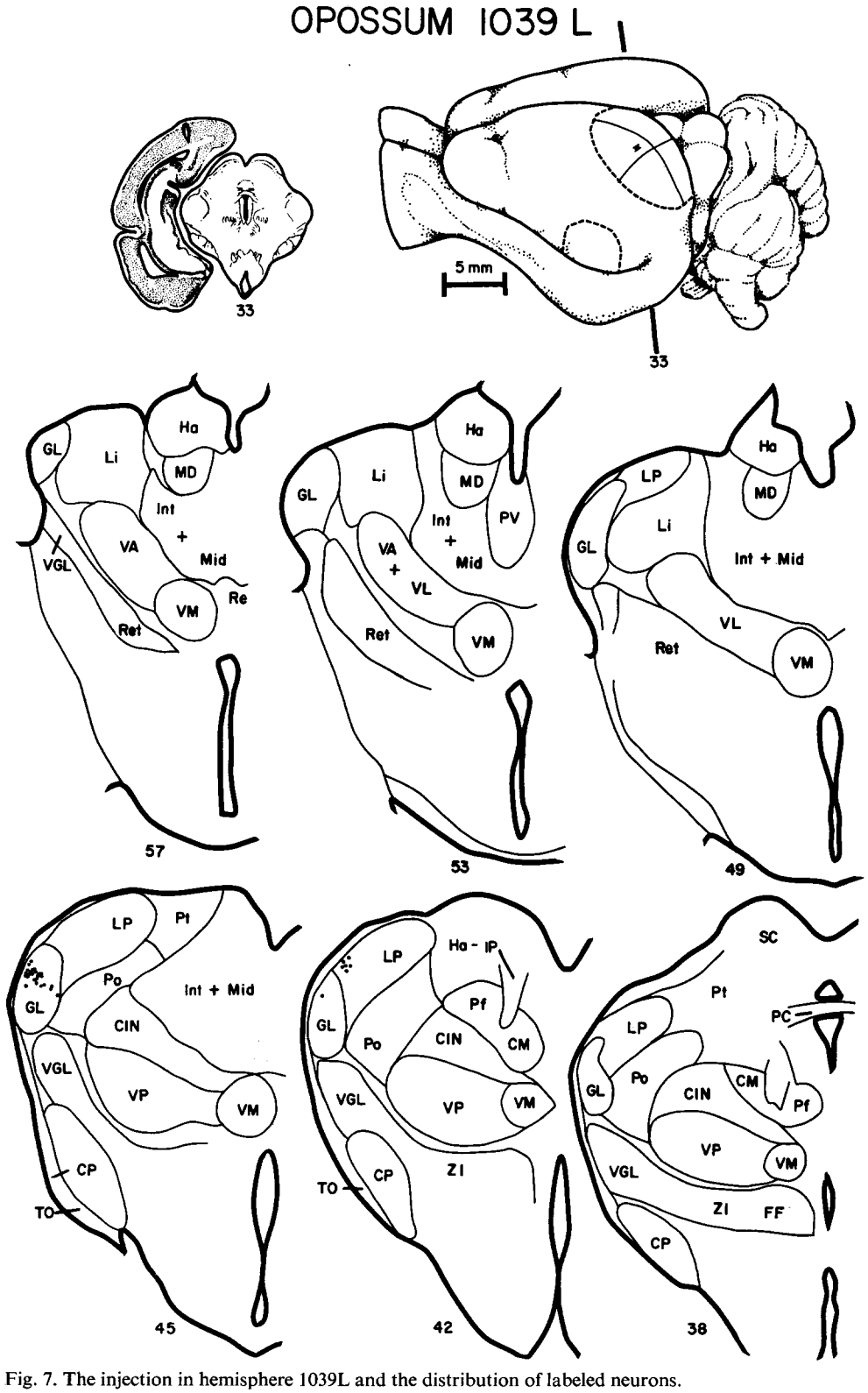

Fig. 7. The injection in hemisphere 1039L and the distribution of labeled neurons.

even achieved a level of development and differentiation that merits the term koniocortex as used by Sanides[34,35]. Layer IV is not very conspicuous and it is *not* highlighted by light bands in layers III and V above and below; there is no apparent stripe of Gennari. Still, area 17 is more like koniocortex than are the adjacent areas. Layer IV is thicker in area 17 than in the adjacent regions and its cells are smaller than the pyramidal cells in layers III and V.

The lateral geniculate has also been adequately described in opossum[7,8,15,30], and it should suffice here just to say that there is a densely populated lateral division and a medial division (the borders of which are indicated by dashed lines in Fig. 4) which is sparsely populated and merges without sharp borders with the posterior group. That this sparsely populated subdivision is indeed a part of the lateral geniculate body is shown by the results now to be presented.

Every injection of striate cortex led to a band in the lateral geniculate nucleus populated by labeled cells. For the sake of simplifying the picture of the topography of these projections we have divided the striate cortex in quadrants. If the injection was in the lateral half of area 17, the labeled cells were located in the dorsal half of the lateral

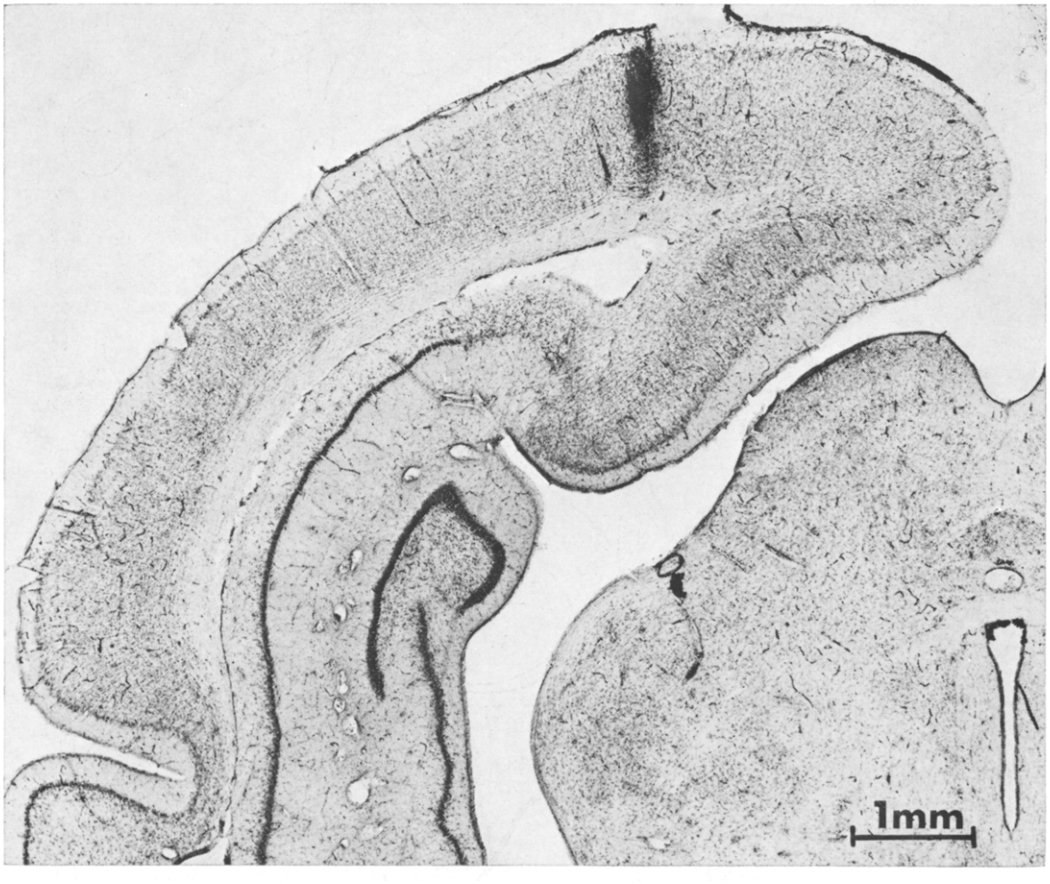

Fig. 8. Photomicrograph of the pipette injection site in hemisphere 1039L. Nissl stain.

geniculate body. In one case, 994R (see Fig. 5), where the brown stain reached the lateral border of area 17, and ended just short of area 18, the labeled cells in the lateral geniculate body reached its dorsal border with the lateral posterior nucleus. Very likely this border represents the zero vertical meridian as does the border between areas 17 and 18 (see ref. 10). When the injection site is remote from the lateral border of area 17, the labeled cells are remote from the dorsal border of the lateral geniculate body. Thus, in case 992L (see Fig. 6) where the injection was medial to 994R but still remained in the rostral half, the labeled cells were in the ventral half of the lateral geniculate; but like 994R they were concentrated in the caudal part of the lateral geniculate body. A very small injection located between the two preceding cases is represented by case 1039L (see Fig. 7). A photomicrograph of the injection site in this case is shown in Fig. 8.

The third dimension of the lateral geniculate body — medial to lateral — is not represented in the cortex. Instead a column of cells from lateral to medial border projects to a cortical 'point'. The form of these columns is apparent in very small injections such as 1022L (Fig. 1) and 1039L (Fig. 7).

Does the lateral geniculate send sustaining projections throughout the striate cortex? Because the evidence from retrograde degeneration experiments suggested the presence of widely spread collaterals we expected to find scattered labeled neurons in all sectors of the lateral geniculate nucleus after each injection of HRP. In fact, such a result was observed only in one experiment (see Fig. 5, case 994R) and in this instance we attributed the presence of labeled neurons scattered throughout the lateral geniculate to involvement of the underlying white matter; HRP could have been incorporated by axons of the visual radiations which are passing to the caudal portion of area 17. The failure to find such scattered neurons in any of the other four similar experiments is evidence against the existence of widely scattered sustaining collaterals from the axons of the lateral geniculate nucleus.

Projections from the lateral posterior nucleus to striate cortex. In every one of these five cases we also saw labeled cells in the lateral posterior nucleus. In interpreting this finding it is necessary to determine whether or not any injection resulted in diffusion of HRP beyond the borders of area 17 into the visual belt of area 18. If we use the brown stain as a sign of this diffusion it is relatively easy to rule out a spread of HRP into area 18. In none of the five cases did the brown stain spread across the 17–18 border on the lateral surface. It was more difficult to rule out another way in which the HRP could be transported by thalamo-cortical axons. If the syringe or pipette entered the white matter underlying striate cortex the HRP would be delivered in the vicinity of axons projecting to the medial wall. Some of this cortex is 'peristriate' according to Benevento and Ebner[2] and this area might well receive fibers from the lateral posterior nucleus. We cannot say from our material whether HRP entered and was transported by axons of passage, although there is evidence from other laboratories that HRP can be taken up by cut axons[9,25].

Results from several of the present experiments suggest that at least some of the labeled neurons in the lateral posterior nucleus cannot be attributed to HRP entering cortical areas outside area 17 by any means. In 1022L (Fig. 1), the injection lies caudal

to all neocortex except area 17; at the level of the injection the neocortex on the medial wall is restricted to striate itself. In this case where the spread of HRP was minimal and where only a thin band of cells were labeled in the lateral geniculate body, cells in the lateral posterior nucleus were also labeled.

Experiment 1039L (Fig. 7) is another case where the injection was apparently limited to striate cortex. Again only a single band of cells was labeled in the lateral geniculate nucleus and a conspicuous cluster of the labeled cells was apparent in the lateral posterior nucleus. Finally, in the case with the largest spread of HRP, 1022R (Figs. 2 and 3), there were a considerable number of labeled cells in the lateral posterior nucleus and it is hard to attribute this result to diffusion of HRP into other cortical subdivisions because of the caudal locus of the injection.

In conclusion, while the interpretation of the results is complicated by the presence of a visual belt along the medial wall and by the uncertainty of HRP transport by cut

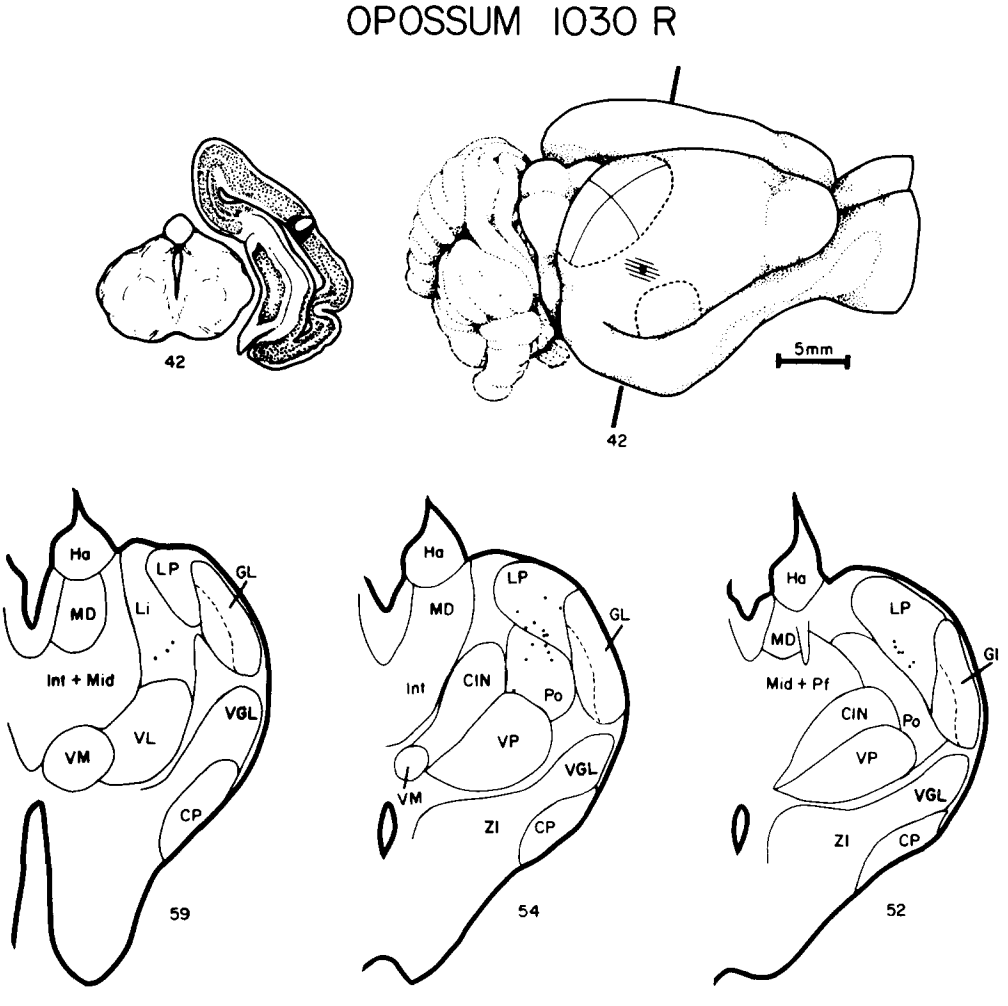

Fig. 9. The injection in hemisphere 1030R and the distribution of labeled neurons.

axons, the results suggest that cells in the lateral posterior nucleus are labeled after injections confined to area 17.

Results of injections of the visual belt cortex. The cortex lying between area 17 and auditory cortex consists of two or more visual strips, i.e. areas 18 and 19, as well as auditory belt[2]. The three injections in the present study (see Figs. 4, 9 and 10) were too large to take advantage of this parcellation of cortex, since each injection involved more than one of the visual belt strips and case 1030R (Fig. 9) encroaches on the auditory belt. In each case a number of cells were labeled in the lateral posterior nucleus. The distribution of these cells was more diffuse than seen in the lateral geniculate nucleus after area 17 injections. Further, the labeled cells were not restricted to the lateral posterior nucleus and a few scattered cells containing HRP were found in the nuclei adjacent to the lateral posterior nucleus: in the lateral group rostral to the lateral

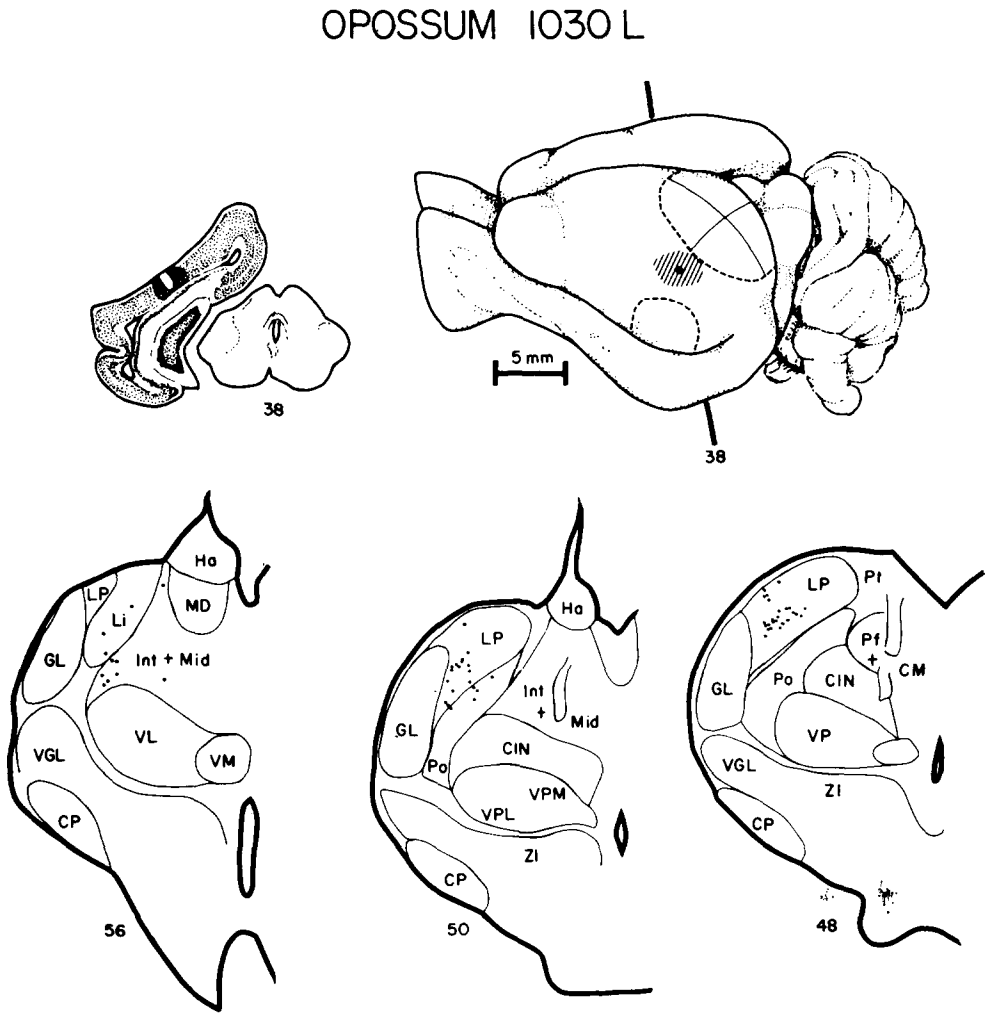

Fig. 10. The injection in hemisphere 1030L and the distribution of labeled neurons.

posterior nucleus, in the anterior part of the posterior group and in the intralaminar nuclei.

When the injections were restricted to the extrastriate belt labeled cells were not found in the lateral geniculate nucleus. Experiments 1030R and 1030L (Figs. 9 and 10) show that even when the brown stain in peristriate cortex approached the border of area 17, the lateral geniculate nucleus contained no labeled cells. These findings suggest that projections of the lateral geniculate body in opossum are confined within the borders of area 17. In the case of a peristriate cortex injection which *did* cross the border of 17, shown in Fig. 4, labeled cells were found in the lateral geniculate body on the dorsal-medial border.

DISCUSSION

The geniculo-cortical projections. The present experiments using the method of retrograde transport show a topographic organization of the projection of the lateral geniculate body that agrees with the organization found by the earlier studies using the established methods of retrograde and anterograde degeneration[3,6,15]. For example, the dorsal border of the lateral geniculate body projects to the lateral border of 17 and the rostral pole of the lateral geniculate body projects to the caudal pole of area 17. Such a congruence of results can be taken as support of the newer method as well as a confirmation of the earlier conclusions.

While there is good agreement about the gross topography, the precision of the organization is much more refined than would be expected from the retrograde degeneration evidence. We were surprised to find that after an injection of HRP restricted to a small sector of area 17, labeled cells were confined to a narrow band in the lateral geniculate; within the confines of the band, the population of labeled cells was high, while outside the band, there were no labeled cells. A review of the evidence from the study of retrograde degeneration will show why the present results are unexpected. First, small lesions of area 17 did not produce columns of severe retrograde degeneration in the lateral geniculate of opossum. To be sure, Bodian[6,8] detected some degenerative changes after small lesions, 1 sq.mm. But in our studies[14,15,23] we were more impressed by the difference between the opossum and those species in which small lesions in area 17 resulted in a column of severely degenerated neurons; for example, we reported that after a lesion of area 17 (apparently much larger than the extent of dark brown stain in the cortex of cases 1022L or 1039L), there was no column of cell loss and, within the degenerated zone, most of the neurons could be identified. Even when all of the striate cortex was removed and all parts of the lateral geniculate underwent retrograde degeneration, many cells still remained preserved. The percentage of preserved cells in any sector was further decreased when extrastriate cortex was removed in addition to area 17.

The failure to find a restricted column of degeneration in the lateral geniculate nucleus after small lesions of the striate cortex could be accounted for by the existence of widely distributed collaterals. These sustaining collaterals should be revealed by the transport of HRP. However, after very small injections, a column of labeled cells

was *not* accompanied by a few cells scattered around other sectors of the lateral geniculate, as might be expected if every cell sends collaterals to remote sectors of area 17. Further, there was no sign of lateral geniculate collaterals projecting outside of area 17. Injections of the extrastriate belt alone never led to labeled cells in the lateral geniculate body. The next section will argue that collaterals can transport HRP; still, the concentration of the HRP transported may be influenced by such factors as the size of the collateral and the number and size of the axon terminals.[22]

The cortical projections of the lateral posterior nucleus. The failure to find evidence for widespread sustaining collaterals in the projections of the lateral geniculate cannot be attributed to a general failure of collaterals to transport HRP. The labeled neurons in the lateral posterior nucleus after area 17 injections were likely the result of tranport of HRP by collaterals since lesions restricted to area 17 never produced degeneration in the lateral posterior nucleus. Of course we cannot rule out the possibility that the projections of the lateral posterior nucleus to area 17 are so diffuse that the scattered loss of cells after lesions would not be detected. To establish with certainty that the same cell of the lateral posterior nucleus sends one collateral to the extrastriate belt and one to the striate cortex, requires a method employing two tracers, for example, HRP conjugated with fluorescein and rhodamine[29].

Whether or not the projections of the lateral posterior nucleus are sustaining collaterals there is little doubt that these projections are relaying visual impulses in a parallel system. Martin[26] and Benevento and Ebner[1] have shown that the lateral posterior nucleus is the recipient of fibers from the superior colliculus.

In conclusion, the visual system of the opossum consists of a precisely organized geniculo-striate path and a second pathway, the tecto-pulvinar path, that has a widespread cortical target including the visual core area as well as the visual belt.

The concept of a sensory core and a sensory belt. In this section we wish to discuss the significance of the overlap in the projections of the lateral geniculate nucleus and the lateral posterior nucleus to area 17. In particular the question to be considered is: how does this overlap relate to the view that every sensory area of cortex is divisible into a core and a belt? The sensory core is defined as the cortical target of the primary or lemniscal path and it usually corresponds to koniocortex. The core is surrounded by a belt which is the target of one or more parallel pathways[11,12]. The core and belt together constitute a complex field unified by cortico-cortical connections and by descending pathways[13]. Thus the core visual area, area 17, projects to the superficial layers of the superior colliculus, which in turn projects to visual belt via the pulvinar or lateral posterior nucleus[1,27,31]. We have argued that the belt cortex may reflect an earlier stage of cortical evolution. This argument was based first on the fact that the belt cortex is intermediate between koniocortex and the more primitive proisocortex[34, 35], second, on the ancient origin of the tectal areas which project to the belt, and third, on the diffuse character of the projections to the belt.

The concept that precise topographic pathways consisting of large fibers evolved from, but do not replace, small fibers and diffuse pathways was postulated by Herrick and Bishop[5,21]. According to Bishop the belt cortex represents the persistence of the older sensory pathways. The widespread projection of the lateral posterior nucleus

in opossum supports just this idea. For example, it is easy to picture that the geniculate projection developed later than the more diffuse pathway and that the striate cortex was the result.

The discovery that there is a 'geniculo-striate' system in birds and reptiles[20,24] as well as a tecto-thalamic system raises doubts about our phylogenetic interpretation. Still the distinction between a core and belt is fruitful. First, it now appears established beyond any doubt that the belt cortex receives fibers from the secondary or non-lemniscal pathways. Whether or not these secondary pathways project more diffusely to the cortex is not so certain. But there is growing evidence that the secondary pathways are more diffuse in all three neocortical sensory systems and in all lines of descent. For example, in the cat, the ventral division of the medial geniculate projects only to the core auditory area, AI, while the posterior group and especially the magnocellular division of the medial geniculate project to AI as well as to several divisions of the belt surrounding AI[32]. A similar analysis of the visual system in the cat is complicated by the difficulty of comparing cats with other mammals. Only in cats is area 18 part of the core koniocortex. Further, the lateral geniculate is subdivided into several parts and homologous divisions are not readily identified in other species. It could be argued that the best candidate for the core relay is laminae A and A_1 of the lateral geniculate which project just to areas 17 and 18[33,36]. The projections to the cortex of other divisions of the lateral geniculate and the projections of the tecto-pulvinar system, overlap with each other as well as with the primary or core pathway[28,33,36]. It has even been claimed that the tecto-pulvinar system projects to area 17 in primates[4], although we have no evidence for such a projection in Galago[17] or in tree shrew (unpublished observation).

To summarize, two parallel visual pathways can be identified in the opossum and this organization certainly represents the mammalian plan. The secondary path from the superior colliculus to the lateral posterior or pulvinar nucleus projects both to the visual core and to the visual belt. Whether or not this organization also reflects the mammalian prototype, it is certainly characteristic of a number of widely diverse species.

ACKNOWLEDGEMENTS

We wish to thank Nada Staddon for her help with illustrations and photography and Pamela Madren for typing the manuscript.

This research was supported by USPHS Grant MH-4849 to I.T.D. and NIH/NEI postdoctoral fellowship (1 F22 EY01800-01) to J.A.W.

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