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Visual Projections Induced Into the Auditory Pathway of Ferrets: II. Corticocortical Connections of Primary Auditory Cortex

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ABSTRACT

Although the development of corticocortical projections has been well studied, less is known about the role of sensory inputs in the specification of these connections. As part of an ongoing series of studies in our laboratory, we have examined the role of thalamic input modality in the development of corticocortical connections. These studies involve making unilateral lesions and inducing retinal inputs into the auditory thalamus (MGN) during early development in ferrets, thereby conferring visual responsiveness on primary auditory cortex (AI). In this way we can examine the role of input identity in cortical specification in general, and connectivity patterns specifically.

A previous paper (Pallas et al. [1990] J. Comp. Neurol. 298:50–68) described the pattern of thalamocortical and corticothalamic connections of auditory cortex in normal and lesioned animals. This study compares the pattern of auditory corticocortical connections in normal and lesioned animals. We injected neuroanatomical tracers into AI and mapped out the distribution of retrogradely labelled cells in the cortex. We report that the cortical inputs to ferret AI resembled those in cats, and that the pattern of ipsi- and contralateral corticocortical connections of ferret AI with visual input was similar to the normal pattern. Auditory cortex with visual input did not make ectopic connections with visual cortex, but maintained its connections with other auditory cortical areas. These results suggest that the overall corticocortical connections of an area are not influenced by the modality or activity pattern of its inputs. In particular, altering the input activity to a cortical area does not seem to promote the formation of entirely new connections, although small changes in the strength of existing connections are possible (Sur et al. [1990] Trends Neurosci. 13:227–233).

Key words: cross-modal plasticity, synaptic specificity, visual topography, auditory topography, cortical development

The pattern of connectivity with subcortical and cortical structures is one of the major identifying characteristics of a cortical area, and determines to a large extent both the way in which that region of cortex processes information and what is subsequently done with that information. Although there is increasing understanding of the normal development of connectivity patterns, little is known about the factors that may influence it. In this and the previous study (Pallas et al., '90), we have addressed whether the modality of afferent activity plays a role in specifying the connectivity of a primary sensory cortical area.

We have shown that, following lesions in neonatal ferrets which divert retinal projections to the medial geniculate nucleus (MGN), primary auditory cortex (AI) exhibits features normally considered unique to visual cortex, such as a retinotopic map (Roe et al., '90) and selectivity for oriented bars of light (Roe et al., '92). These properties require a two-dimensional representation of visual space, whereas AI normally carries a one-dimensional representation of frequency. We were interested in finding out whether these marked functional changes were associated with anatomical changes, such as alterations in synaptic connections. We suspected that the change in inputs might disrupt the normal connectivity of AI or even cause new projections to visual areas. A previous study (Pallas et al., '90) reported

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on the subcortical connectivity of AI with visual inputs, which was quite similar to that in normal animals, with the exception of a minor reciprocal connection with the lateral posterior/pulvinar thalamic nuclei. We now report on the corticocortical connectivity patterns of this altered AI.

The pattern of retrograde label resulting from tracer injections in AI of neonatally lesioned adult ferrets was compared to that resulting from tracer injections in normal adult ferrets. We found that corticocortical connections of AI seemed to be unaffected by anomalous visual inputs from the day of birth. A preliminary report of these results has appeared previously (Pallas et al., '88).

MATERIALS AND METHODS

Methods are substantially similar to those described in Pallas et al. ('90), and thus will be described only briefly here.

Five normal and five lesioned ferrets (*Mustela putorius furo*) were used for this study (Table 1). Timed pregnant females (42 days gestation) or adult animals were obtained from Marshall Farms (North Rose, NY).

Ferret kits were deeply anesthetized by hypothermia on the day of birth. After the brain was exposed, the superior colliculus and the visual cortex were ablated directly. The brachium of the inferior colliculus was sectioned with a scalpel blade. The visual cortical lesion causes retrograde degeneration of much of the dorsal lateral geniculate nucleus (dLGN). These surgical manipulations remove or reduce the major targets of the retina and deafferent the MGN, allowing retinal axons to innervate the MGN. After suturing the incision, the kits were rewarmed and returned to their mother until weaning. All subsequent experiments were done after the ferrets reached adulthood (15 weeks or more).

To determine its cortical connections, various neuroanatomical tracer substances were injected into AI (Table 1), and retrograde label (Fig. 1) was mapped in coronal reconstructions. Anterograde terminal label was often visible, but was not mapped. For these tracer injections, adult ferrets were anesthetized to a surgical level with ketamine (30–40 mg/kg) and xylazine (1–3 mg/kg). Supplemental half-doses of ketamine were given as indicated by monitoring of heart and respiration pattern, and withdrawal reflexes. After exposure of AI, located in the middle ectosylvian gyrus (Kelly et al., '86; Phillips et al., '88), one or more of four tracers were injected separately by microliter syringe: 50–100 nl 20% horseradish peroxidase (HRP)/2% wheat germ agglutinin conjugated to HRP (WGA-HRP) (HRP), 500 nl 25% rhodamine-labelled beads (RLB), 50–100 nl 4% Fluoro-Gold (FG), and 50–100 nl 5% Fast Blue (FB). After survival periods of 5–7 days, animals were overdosed with sodium pentobarbital and perfused with 1% paraformaldehyde/2% glutaraldehyde or, if fluorescent tracers were used, with 4% paraformaldehyde. Frozen sections were cut coronally at 50 μm. Nissl stains were done on alternate sections. Horseradish peroxidase histochemistry employed tetramethylbenzidine as a chromogen (Mesulam, '78).

In 4 of 5 lesioned animals, we recorded visual units and mapped visually responsive auditory cortex with standard electrophysiological methods (the fifth animal was prepared for physiological recording but the experiment was terminated prematurely). The results of these physiology experiments have been reported previously (Roe et al., '90, '92).

TABLE 1. Summary of Corticocortical Projections

Animal no.	Condition	Injection site	Tracer	Ipsilateral label	Contralateral label
F88-5	Normal	AI	HRP	AI, A, AII, VP	AI, AII
F88-33	Normal	AI	HRP	AI, AII, VP	AI
		AI	RLB	AI, A, AII, VP, M, SSG	AI, AII
		AI	FG	AI, AII, VP	AI
F88-39	Normal	AI	HRP	AI, AII	AI
		AI	RLB	AI	none
		AII	FB	AI, AII, VP	AI, AII
F88-40	Normal	AI	HRP	AI, AII	AI, AII
		A	FB	A, M	A
F88-53	Normal	AI	HRP	AI, AII	AI
		A	FB	AI, A, AII, M, LS	A, M
		AII	RLB	AI, AII, VP	AII, VP
F88-16	Lesioned	AI	HRP	AI, AII, VP, M	AI, AII, M
F88-24	Lesioned	AI	HRP	AI, A, M	AI
		AI	FG	AI, AII, VP, LS	none
F88-34	Lesioned	AI	HRP	AI	none
		AI	RLB	AI, AII, VP, M, SSG	AI, AII, VP, M, LS
		AI/LS border	FG	AI, AII, VP, LS, SSG, 19	AI, A, LS, 18
F88-61	Lesioned	AI	HRP	AI, VP	none
			RLB	AI, AII, VP, M	CB
			FG	AI, AII	none
			FB	AI, AII, VP, M	none
F88-76	Lesioned	AI	RLB	AI, AII, VP, M	none
			FG	AI, AII, VP	none
			FB	AI, A, AII, VP, M, SSG	none

Abbreviations

A	anterior auditory cortical field
AI	primary auditory cortex
AII	secondary auditory cortex
aes	anterior ectosylvian sulcus
dLGN	dorsal division of the lateral geniculate nucleus
DP	dorsoposterior auditory belt area
EVA	ectosylvian visual area
FB	Fast Blue
FG	Fluoro-Gold
HRP	horseradish peroxidase
LP	lateral posterior nucleus of the thalamus
ls	lateral sulcus
LS	lateral suprasylvian cortex
M	medial cortical area labelled by AI injection
MGN	medial geniculate nucleus
P	posterior auditory cortical area
pes	posterior ectosylvian sulcus
pss	pseudosylvian sulcus
RLB	rhodamine labelled beads
SSG	suprasylvian gyrus
SSS	suprasylvian sulcus
V	ventral auditory cortical area
VP	ventroposterior auditory cortical area
WGA-HRP	wheat germ-agglutinated HRP

RESULTS

Identification of brain areas

We used a combination of cytoarchitectural, connectional, and surface (sulcal) features to identify the different cortical areas described in this paper. Identifications based on sulcal patterns alone might not be reliable, especially in the lesioned animals, whose sulcal pattern is somewhat altered by the lesions.

All injections intended to be within AI were made within the boundaries of the middle suprasylvian sulcus and the anterior and posterior ectosylvian sulcus, which in the ferret are considered to delineate AI (Kelly et al., '86; Phillips et al., '88). A photomicrograph of an injection site from one of the animals used in this study is shown in a previous paper (Fig. 1, Pallas et al., '90). The location of the

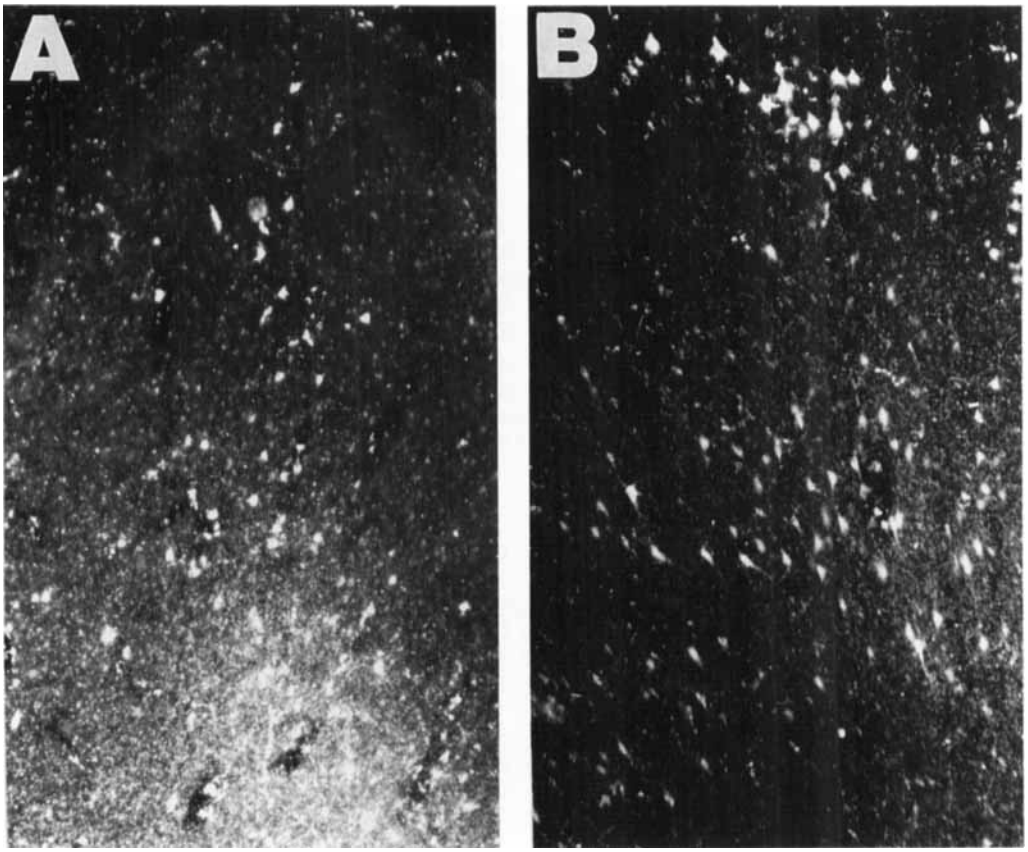


Fig. 1. Photomicrographs of labelled cells and terminals in (**A**) ipsilateral AII and (**B**) contralateral AI following an injection of HRP in AI of a normal ferret (F88-40). In both figures, the pial surface is just above the top of the micrograph. Scale bar: 250 μm.

injection site was confirmed physiologically in 4 of the 5 lesioned animals. In these cases, it was determined that the injection sites lay inside the edges of the retinotopic map established by the lesioning procedure (Roe et al., '90). In all cases, the injection location was confirmed cytoarchitecturally. Our cytoarchitectural criteria are shown photographically in a previous paper (Fig. 3, Pallas et al., '90). AI has a distinctive cytoarchitecture (Rose, '49; Otsuka and Hassler, '62; Sanides and Hoffmann, '69); the most notable features are the cell-sparse layer V and the blending of layer IV into layers II–III. In addition, injections in AI produce heavy label in the medial geniculate nucleus in both normal and lesioned animals (Pallas et al., '90), and this was another criterion for the location of our injection sites. The subcortical connectivity of all except one (F88-40) of the animals described here is shown in Pallas et al. ('90). The identities of secondary auditory cortical areas were established by relation to the location of AI, by their connectivity, and by their cytoarchitecture.

Ipsilateral cortical connections of AI in normal ferrets

The corticocortical connectivity of the normal ferret AI had not been described at the time our studies were begun and so in order to understand how visual inputs affect the connectivity of AI in the lesioned animals, we first had to describe the normal pattern of connectivity. Subsequently, there have been several other studies of ferret auditory cortical connectivity (Wallace and Roeda, '92; Wallace and Bajwa, '92; Angelucci et al., '93), and our results are basically in agreement.

As expected, in all of the animals studied, there were a large number of labelled cells surrounding the injection site in AI. Labelled cells were also found in three other areas in the ipsilateral cortex in the normal animals (Table 1, cf. Fig. 11), an area lateral to AI within the ectosylvian gyrus/posterior sylvian gyrus, a ventral area caudal to the sylvian sulcus and near the posterior rhinal sulcus, and an anterior area extending medially from the lateral bank of the suprasylvian sulcus onto the suprasylvian gyrus. Cells were often located in both superficial and deep layers in all the areas (Fig. 1; cf. Winguth and Winer, '86). The lateral area is just lateral to AI, and probably corresponds to the second auditory area, or AII, in the cat. The transition from AI to AII in the cat is marked mainly by a change in the appearance of layer V (Rose, '49), and we also noted this in the transition from AI to the lateral area in our ferrets. We will refer to this area as AII for convenience. It was always less extensively labelled than the ipsilateral AI, but contained labelled cells in all the normal animals. An even less extensively labelled area seen in 4 of the 5 normal ferrets was ventrally located, in the lateral convexity of the cortical

hemisphere. This is similar in location to the ventroposterior area, termed VP in cats (Reale and Imig, '80; Imig et al., '82, '86), although it could also be the area called V in the cat. We will refer to it as VP because of its connectivity (see below). There were also cells labelled in a more anterior location in all but one of the normal animals. In the cat, the area immediately anterior to AI is the anterior auditory field, termed Field A by Imig and Reale ('80) or AAF by Merzenich et al. ('84). We will refer to it as A. By giving these areas names associated with areas identified in the cat, we are not implying a definitive identification, which would require a more extensive physiological mapping study. We do this simply to make our descriptions more convenient for the reader and to suggest one possible interpretation of our data.

The ipsilateral pattern of labelling from injections of tracers in AI in two of the normal animals is shown in Figures 2 and 3, and is similar to what we saw in all the animals. The figures represent the overall pattern of labelling; the label was too extensive to represent every labelled cell with a dot. Rather, each dot represents 2–4 labelled cells. In some cases, due to swelling of the brain through the craniotomy, the injected AI protrudes somewhat from its normal outline.

The animal in Figure 2 (F88-5) received two closely spaced injections of HRP (cf. Fig. 10). The two injection sites are depicted as dots in the lateral view of the brain. This animal was the first in the study and our aim was to make a large injection site. As seen in the inset, almost the entire AI is filled with labelled cells. There is also a large patch of label in AII, and much smaller patches in the ventral (VP) and the anterior (A) sites.

Figure 3 is drawn from an animal (F88-33) that received injections of three tracers (see Fig. 10). Only the RLB label is depicted in the figure for clarity, and can be seen in AI, A, AII, and VP. HRP was injected in the medial part of AI, and the label in AI is centered around that site. There were a few HRP-labelled cells in both AII and VP. An injection of FG in AI also labelled cells in AI, AII, and VP.

We also observed a small amount of label in the lateral bank of the lateral sulcus (Fig. 3, fourth and fifth sections) and far medially along the medial wall of the cortex (second and third sections in Fig. 3) in this animal. These may represent small projections not normally seen except with large injections, or they may result from labelling fibers of passage in this particular animal. The label along the medial wall (M in Abbreviations list; cf. Fig. 11) appears to correspond in location to Area 7 in the cat (Diamond et al., '68), although it may also be Area 19 (see Discussion). Definitive identification of these areas in the ferret must await a detailed physiological and connectional study. Because our interest was in the potential changes to the connectivity pattern of AI resulting from our neonatal lesions, we concentrated our efforts on a comparison of normal and lesioned animals.

Injections in AI were made in three other animals which are not shown in detail. In F88-39, we made injections of HRP, RLB, and FB in AI. The RLB did not transport well and was seen only in cells surrounding the injection site. The HRP and FB injections both resulted in labelled cells in AI and AII, and the FB injection also labelled cells in VP. An injection of HRP in AI of both ferrets F88-40 and F88-53 also resulted in label within AI and AII. Thus, the connection between AI and AII was quite strong in normal ferrets.

In two animals (see Table 1, Fig. 10), in addition to tracer injections in AI, we made an injection of FB in the anterior area (A) on the suprasylvian gyrus labelled by the AI injections. In one animal (F88-40), the injection did not provide good ipsilateral transport, and we saw label only in the surrounding area A and area M. We also saw label in the corresponding anterior location (A) on the contralateral side (see below). In the other animal (F88-53), a FB injection in the anterior area labelled a few cells in ipsilateral AI, in the posterior ectosylvian/medial suprasylvian sulcus (corresponding in location to the lateral suprasylvian [LS] areas; Rosenquist, '85), sometimes referred to as Clare-Bishop area (Clare and Bishop, '54; Sherk, '86), in AII, and in M. In this animal, an injection of RLB was made in AII, labelling cells ipsilaterally in AI, the surrounding AII, and VP. The results of the injections in all animals are summarized in Table 1.

Callosal projections in normal ferrets

Contralateral label was much less extensive than ipsilateral label. With injections in AI, there was always heavy label in the contralateral AI (Table 1, Figs. 4, 5) except in one case where the tracer was not transported. As in the ipsilateral projections, cells were labelled in both superficial and deep layers of the cortex. In addition to the AI label, we found retrogradely labelled cells in AII (Figs. 4, 5).

The animal shown in Figure 4 (F88-5) received 2 injections of HRP in AI. Retrograde label was located in the contralateral AI and in AII in this animal. The animal illustrated in Figure 5 (F88-33) had three tracers injected in AI, and the labelling from the RLB injection is shown in the figure. The RLB label was located in both AI and AII. The HRP and FG injections also labelled cells in the contralateral AI but not in AII. The absence of label outside AI from the other tracers probably reflects less vigorous transport of these tracers. Cells labelled with each tracer were found to be concentrated in AI at the location corresponding to that tracer's injection site in the other hemisphere. Interhemispheric connections between the left and right AI were thus topographically organized.

In two other animals (F88-40 and F88-53, not shown, but see Table 1) which received injections anterior to AI in the suprasylvian gyrus (presumably area A), there was callosal label in the corresponding contralateral area A in both, and a small amount of label in area M in F88-53. Injections lateral to AI (in area AII) produced callosal label in the contralateral AII and in VP, but not in AI in one animal (F88-53), and in AI and AII in another (F88-39).

We did not notice any patchiness in the callosal projections with the methods used in the present study, although in the normal cat it has been shown that only certain binaural response types of cells project contralaterally (Imig and Brugge, '78; Imig et al., '86). Ferrets also have different types of binaural cells (Judge and Kelly, '88), but the binaural specificity of callosal projections has not been reported. This issue is now being investigated in flattened cortices using larger injections, and in this case, extensive patchiness in the callosal projection is observed (Pallas and Wright, '93).

Ipsilateral cortical projections in lesioned ferrets

The pattern of retrograde label in the neonatally lesioned ferrets following injections in AI was very similar to that seen in normal animals. Retrogradely labelled cells were

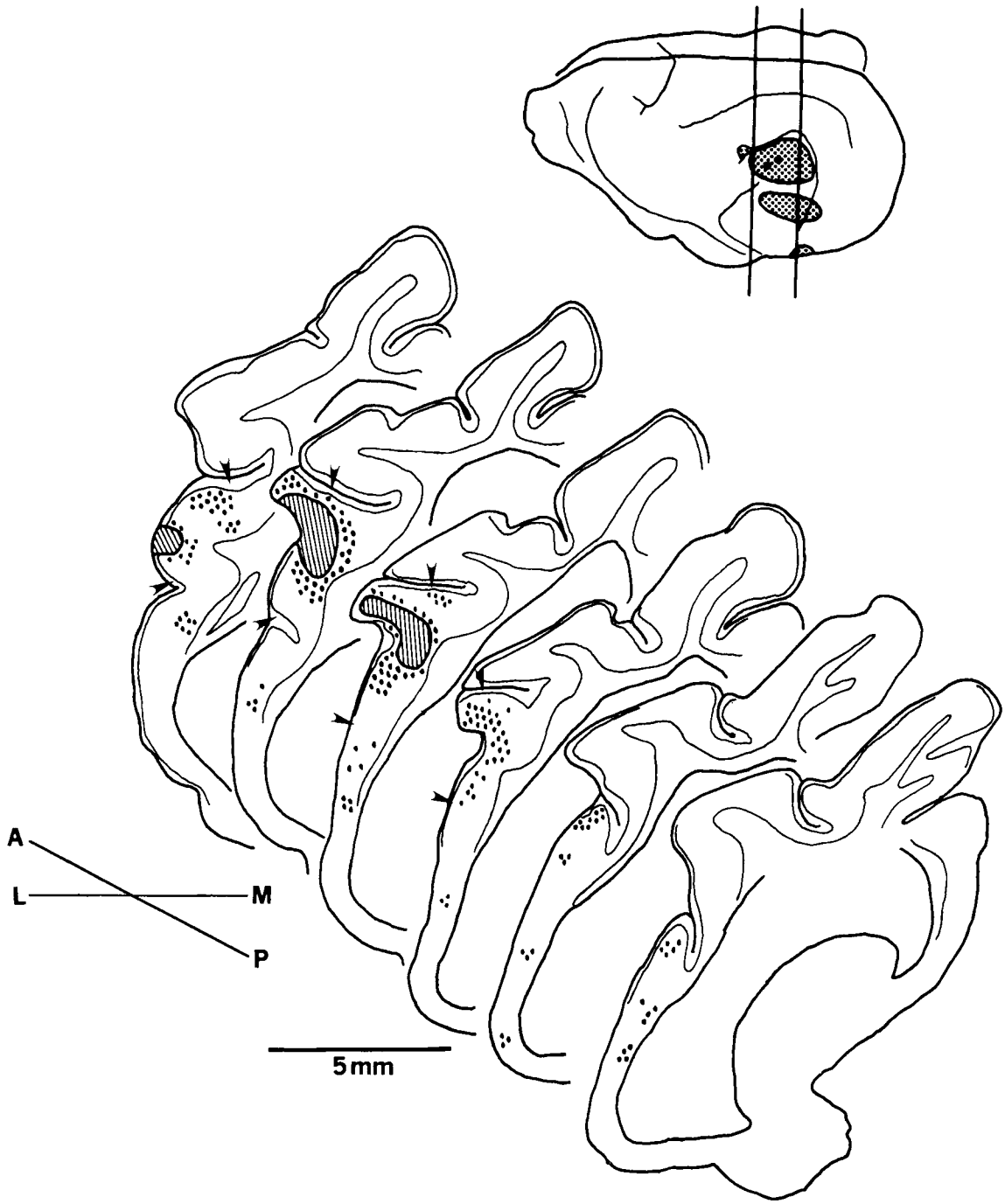


Fig. 2. Normal ipsilateral corticocortical projections. Ipsilateral pattern of retrogradely filled cells following injections of HRP in two locations in AI of a normal ferret (F88-5). Coronal sections are presented in a caudal to rostral sequence (right to left), and the limits of these sections are shown on the lateral view of the left hemisphere above. The most caudal two sections are 800 μm apart; the others are 400 μm apart. Each filled circle in the coronal sections represents 2–4 labelled cells. The halo surrounding the injection site is shown by the hatched areas. The arrowheads show the medial and lateral limits of AI as determined cytoarchitectonically (cf. Fig. 11). The **inset** shows a lateral view of the left hemisphere, with the rostral and caudal limits of the sections presented below indicated by the vertical lines. The shading on the inset shows the approximate location of cells retrogradely filled from the tracer injections in AI. The compass shows the lateral-medial (L–M) and anterior-posterior (A–P) axes of the sections.

found in the AI surrounding the injection site, in A, AII, VP, and M, and in a few cells on the suprasylvian gyrus. The differences we did see had to do with the quantity rather than with the location of filled cells. In general, transport was less robust in lesioned animals compared to the normal animals in our study.

In Figure 6 (F88-61), the label from a FB injection is shown. In addition to the label in AI, there is a small

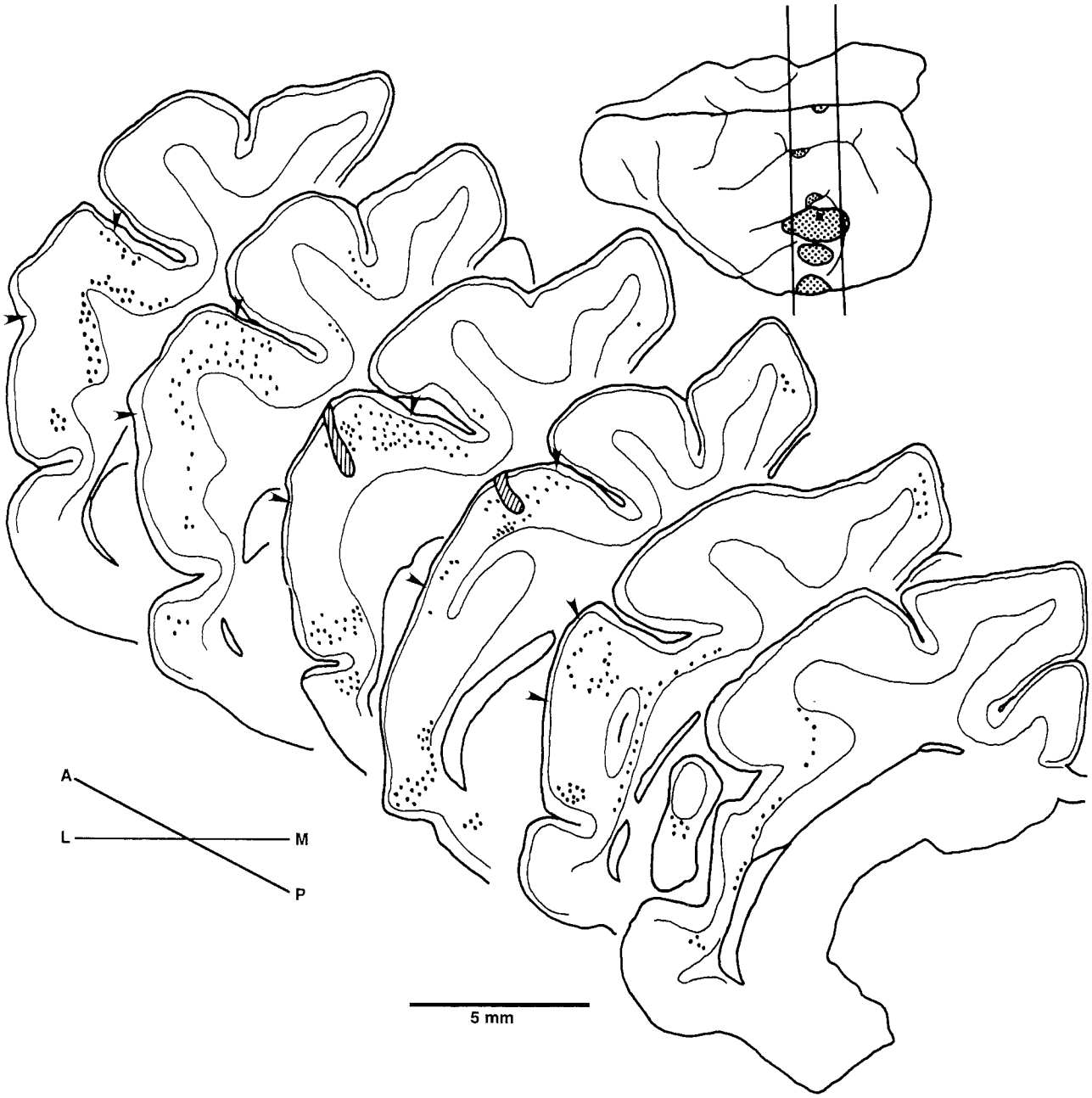


Fig. 3. Ipsilateral pattern of label in another normal ferret (F88-33) following injection of RLB in AI. Sections in this and all other figures are separated by 400 μm. Conventions as in Figure 2.

amount of label in VP, and a few labelled cells in AII. Interestingly, the label in AI looks somewhat patchy in the most caudal section, but not in the others. There is also a substantial amount of label in area M, especially as compared to the normal animals, where label in this area was only occasionally seen and then only sparsely.

The animal shown in Figure 6 had injections of 3 other tracers in AI (HRP, FG, and RLB). The FG injection resulted in labelled cells surrounding the injection site in AI and also in AII. The RLB injection labelled cells in M as well as in AI, VP, and AII. The HRP resulted in labelled cells within AI and VP only. None of the tracers labelled cells in the anterior area A.

The animal shown in Figure 7 (F88-76) received injections of 3 tracers in AI. The results of the FB injection are shown in the figure. The pattern of connections was similar to that shown in Figure 6. The sulcal pattern was disturbed as a result of the neonatal lesions, but the cortical areas could be determined by comparing the sulcal pattern with the cytoarchitecture. The FB injection backfilled cells in the surrounding AI and extending into A, with a second lobe of label extending into AII. Area VP, a few cells located in the suprasylvian gyrus, and a few cells in M were also labelled. The other tracers (RLB and FG) both produced labelled cells in AI, AII, and VP, and area M was labelled only by the RLB injection.

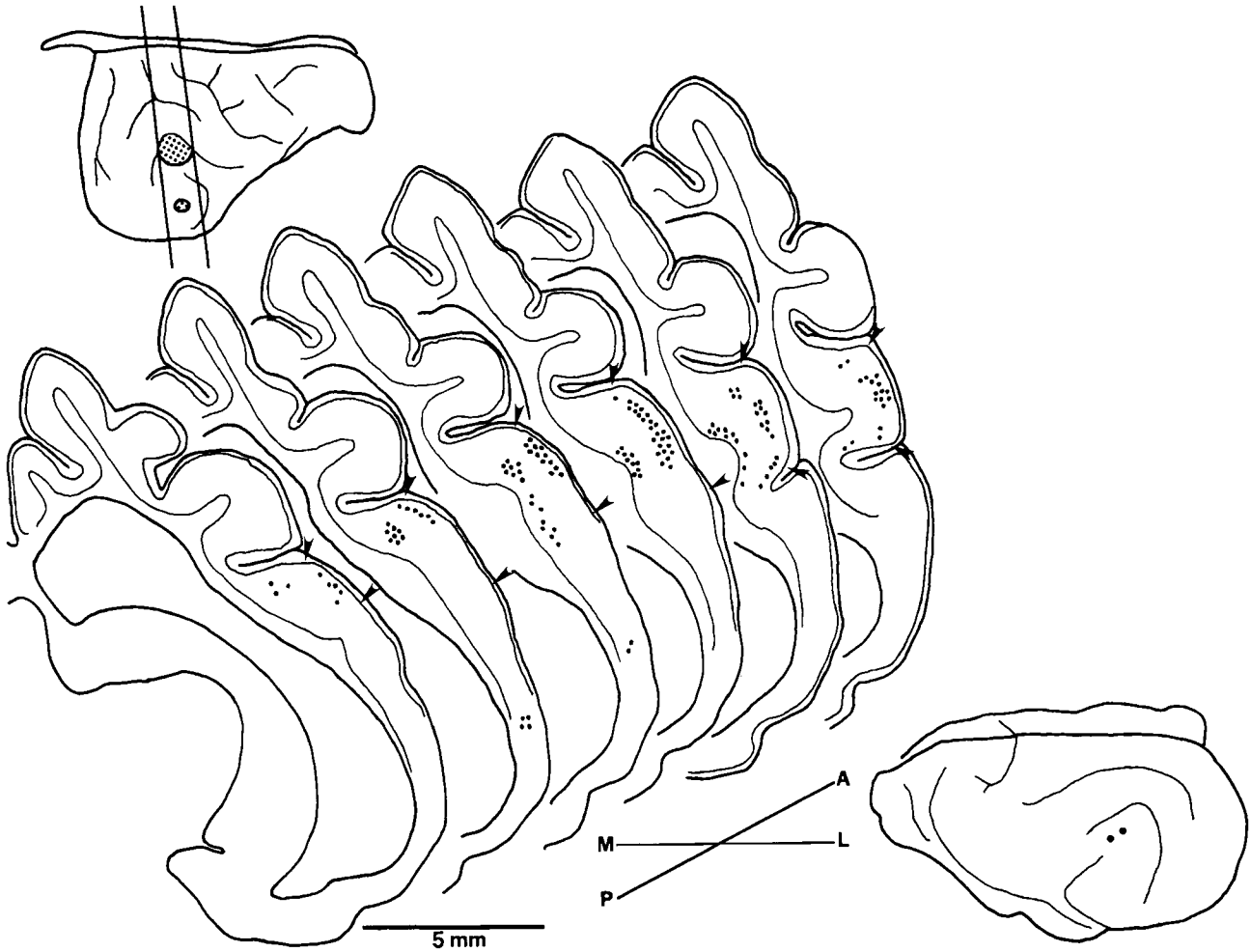


Fig. 4. Normal callosal projections. Pattern of label contralateral to the injection sites in AI in a normal ferret (F88-5). The **lower inset** shows the location of the injection sites in a lateral view of the left hemisphere, while the **upper inset** shows the pattern of callosal label. This is the same animal as in Figure 2. The coronal sections are presented from caudal to rostral (left to right). Conventions as in Figure 2.

In addition to the two animals represented in Figures 6 and 7, there were 3 other lesioned animals in the study (Table 1). All three of these animals had retrogradely labelled cells in M; two had label in AII, and one contained labelled cells in area A. Labelled cells were also found in VP of two animals, and in lateral suprasylvian cortex (LS) of one animal. In addition, in one of the animals (F88-34), FG was injected on the border of AI and the posterior ectosylvian sulcus (pes). In this case, a different pattern of label resulted, with backfilled cells in the suprasylvian gyrus (SSG) and area 19, as well as in the contralateral LS and visual area 18 (Law et al., '88) (the ipsilateral areas 17, 18 and most of 19 were removed by the neonatal lesions). Perhaps due to the fact that the injection was on the very edge of AI, there were a few cells labelled in the surrounding AI, AII, and VP.

Callosal projections in lesioned ferrets

Callosal connections in the lesioned ferrets also differed little from those in normal ferrets. We had difficulty in getting callosal label, probably due to problems with transport of the tracers. The two animals which yielded good callosal transport are shown in Figures 8 (F88-34) and 9 (F88-16). In Figure 8, the results from an RLB injection (in F88-34) in AI are shown. There was label in the contralateral AI with additional label spreading to the cortex beyond the pes into LS. In addition, there were small patches of callosal label in AII, VP, and M. In the same animal, an injection of FG on the border between AI and LS resulted in labelled cells in contralateral LS, area 18, AI and A. As shown in Figure 9, the pattern of callosal label from an HRP injection in AI (in F88-16) was less extensive than in Figure 8, and extended directly into AII from AI. There were also labelled cells in M along the central sulcus.

In two other animals (not shown, Table 1), there was some weak callosal transport. In F88-24, labelled cells were seen in the contralateral AI following AI injection. In F88-61, a RLB injection in posterolateral AI close to the pes labelled a few cells in LS.

DISCUSSION

Comparison of the auditory pathways of normal ferrets and cats

In the course of our study on the effects of visual inputs on AI connectivity, we have obtained substantial informa-

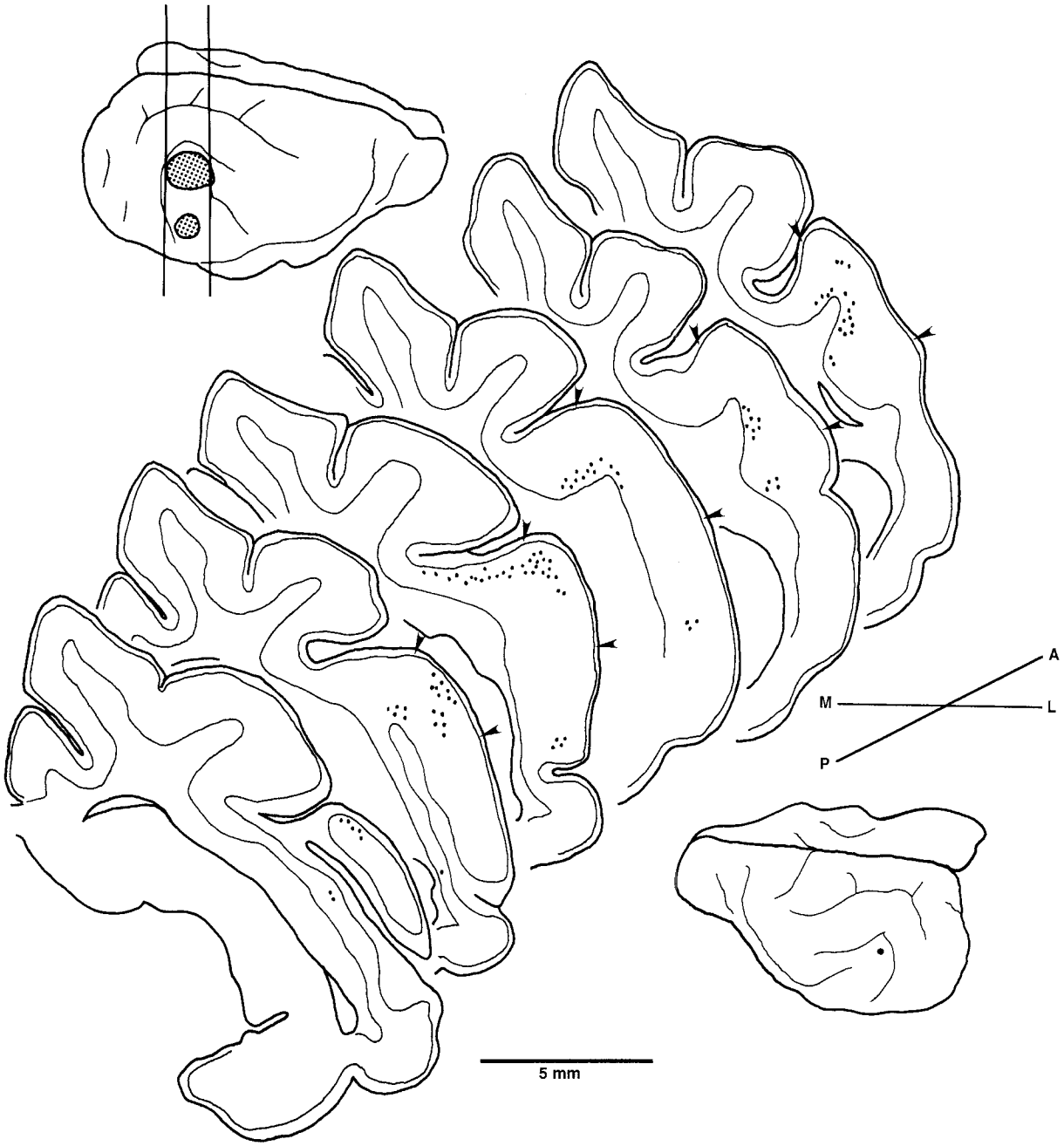


Fig. 5. Callosal label in another normal ferret (F88-33) after injection of RLB in AI. Conventions are as described in Figure 4. This figure is drawn from the same animal as in Figure 3.

tion on the normal connectivity of AI in the ferret. There are some interesting differences and similarities with respect to the well-studied auditory pathway of the cat, which, like the ferret, is a member of the mammalian order Carnivora. We offer our interpretations below as a preliminary attempt at subdividing nonprimary auditory cortex in the ferret. Final identification must await physiological mapping of frequency representations in the nonprimary auditory areas.

Primary auditory cortex in cats lies immediately lateral to the suprasylvian sulcus, between the arms of the anterior and posterior ectosylvian sulci. Imig et al. ('82) have identified four different tonotopically organized auditory fields in cats; AI, A, P, and VP. Each of these areas is reciprocally connected with the others (Imig and Reale, '80). In addition, they define several belt areas which are responsive to auditory stimulation; the secondary area (AII), the dorsoposterior area (DP), the ventral area (V), and the temporal area (T). The tonotopic organization in these belt fields has not been described in as much detail, and there is evidence both for and against tonotopy in AII (Woolsey, '61; Andersen et al., '80; Imig and Reale, '80; Rouiller et al., '91). AII is connected with all of the tonotopically organized fields as well as with T and DP.

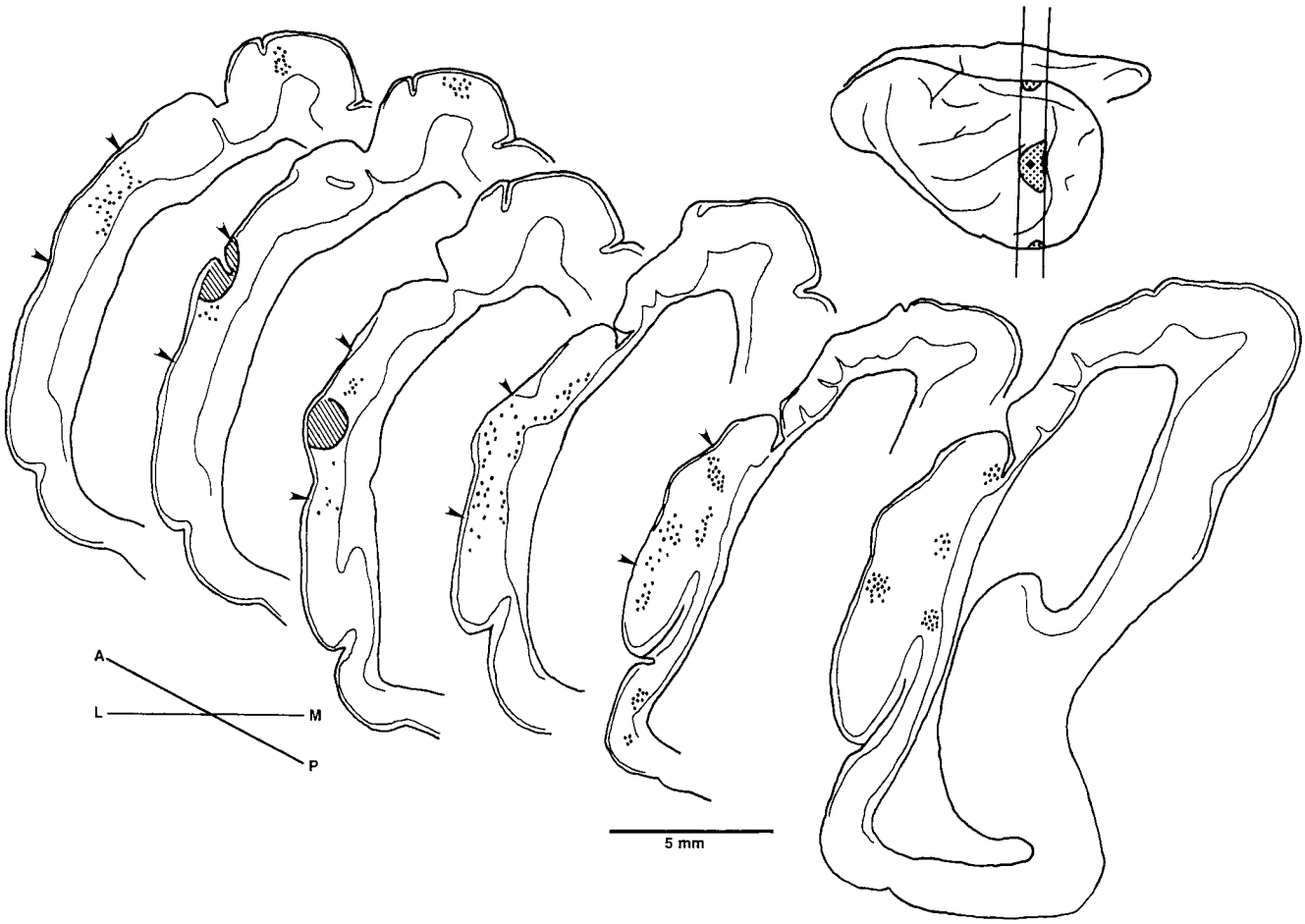


Fig. 6. Ipsilateral corticocortical connections in a lesioned ferret. Ipsilateral pattern of retrogradely filled cells following injection of FB in AI of a ferret (F88-61) with visual input to AI. Conventions as in Figure 2.

In ferrets (Fig. 11), the two ectosylvian and the suprasylvian sulci are fused, such that the position of AI in ferrets is the same as in cats with respect to the sulci, but the suprasylvian sulcus is more medial in the cat (Kelly et al., '86; Phillips et al., '88). Interestingly, the axis of orientation of the tonotopic map in the ferret is rotated 90 degrees with respect to the map in the cat, although the orientation of the map in the MGN is apparently the same (Pallas et al., '90; Roe, '91). The connectivity pattern of ferret AI seems quite similar to that in cats. Injections in ferret AI resulted in labelled cells in several areas surrounding AI both ipsi- and contralaterally. Although we do not report it here, we noted that connections seem to be reciprocal in that terminal label was generally located in the same places as labelled cells. We consistently saw label in an area lateral to AI in ferrets following AI injection, and we assume that this is ferret AII, given its location relative to cat AII, its cytoarchitecture and its consistent connectivity with AI. In addition, in the two normal ferrets in which we made an injection into this region, the equivalent contralateral area was heavily labelled, as was AI and VP both ipsi- and contralaterally. Anterior to AI in cats is field A (Imig and Reale, '80), also referred to as AAF (Merzenich et al., '82). We saw labelled cells in an area anterior to AI along the banks of the anterior ectosylvian sulcus (aes), which we refer to as A in our ferrets, in 2 of the 5 normal ferrets with AI injections. Conversely, we noted a reciprocal connection with AI in one animal when tracer was injected in A. We would thus suggest that this area corresponds to field A in the cat. In addition, we identified a more ventral area which may correspond to field V or VP in the cat. It seems more likely, given its strong connectivity with AI (Table 1), that this area is VP, and we refer to it as such. We made injections only in AI, A and AII, so are unable to comment on the inputs to P and VP. It would be of great interest to determine how these various connections of ferret AI relate to functional compartments within each field.

In addition to the consistent labelling in the putative auditory areas defined above, we sometimes found sparse label in other cortical areas in one animal. These included the medial area (M), and the suprasylvian gyrus. There is some evidence in cats for connections between AI and the suprasylvian gyrus (Diamond et al., '68; Kawamura, '73; Paula-Barbosa et al., '75). The medial area is difficult to identify because of the scarcity of connectional data on this region in cats and ferrets. Based on a comparison with the cat, we have tentatively identified this region as the medial portion of area 7. As defined cytoarchitectonically, area 7 in cats is located on both the anterior lateral gyrus and the middle suprasylvian gyrus, just rostral and lateral to visual area 19 and caudal to area 5 (Robertson and Cunningham, '81; Reinoso-Suarez, '84). Sparse connections between AI

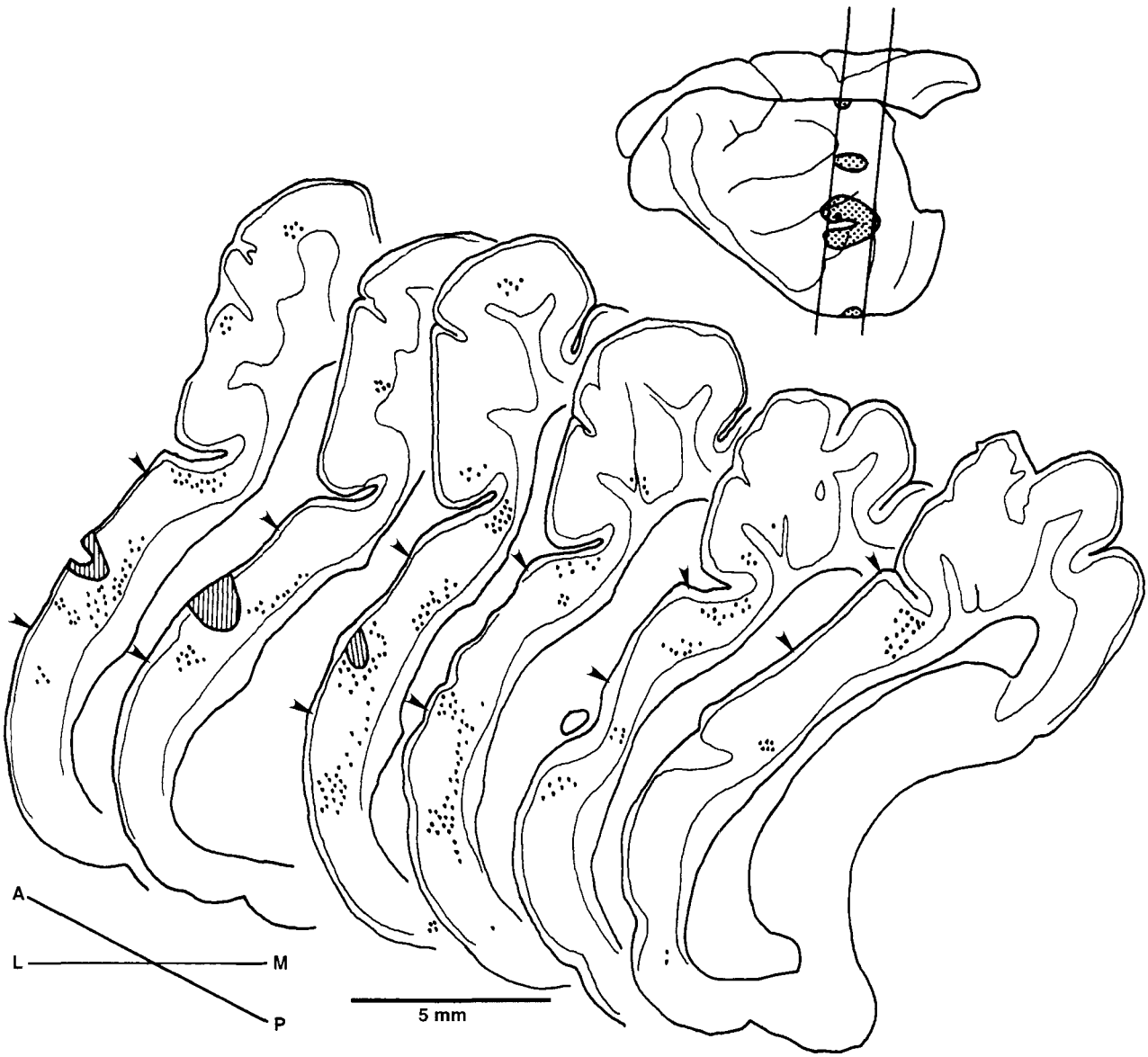


Fig. 7. Results from another lesioned animal (F88-76) in which AI received induced visual input, showing the pattern of retrogradely labelled cells following an injection of FB in AI. Conventions as in Figure 2.

and medial area 7 in cats have been reported in studies using anterograde degeneration (Diamond et al., '68; Paula-Barbosa et al., '75; Imig and Reale, '80). Imig and Reale ('80) also report connections between area A and this medial region in cats (see also Kawamura, '73). In the ferret, the visual cortices are located more caudally (Rockland, '85; Law et al., '88; Grigonis et al., '92), and thus M would likely be just anterior to the ferret area 19 and correspond to the portion of the cat area 7 located on the anterior lateral gyrus.

An alternative interpretation of the labelling in what we refer to as area A is that it corresponds to the anterior ectosylvian visual area (EVA, or AEV), an area within the aes in cats which responds to visual stimulation and has connections with LS cortex (Mucke et al., '82; Olson and Graybiel, '87). It is possible that some of our injections in AI may have encroached on the fringes of LS, and LS is reciprocally connected with EVA. Under this scenario, our area M would more likely correspond to visual area 19, which is connected to LS (Mucke et al., '82; Norita et al., '86; Olson and Graybiel, '87). This interpretation seems less likely, given the fact that injections spreading into anterior LS should have labelled surrounding LS areas and possibly areas 17, 18 and 19 as well (see Rosenquist, '85, for review). Our results show that label in A was not necessarily associated with label in M or LS in either the normal or lesioned ferrets. Also, one injection which definitely encroached on LS (F88-34, FG injection) resulted in a very different pattern of labelling compared to our other injections. Ferret LS has not been explored in detail, and a study of this sort would be quite interesting.

Although the overall pattern of corticocortical connections of AI in the ferret seems similar to cats, we noted some differences in the robustness of the projections. Imig and Reale ('80), using anterograde tracers injected into cat AI or A, consistently found projections between these two areas,

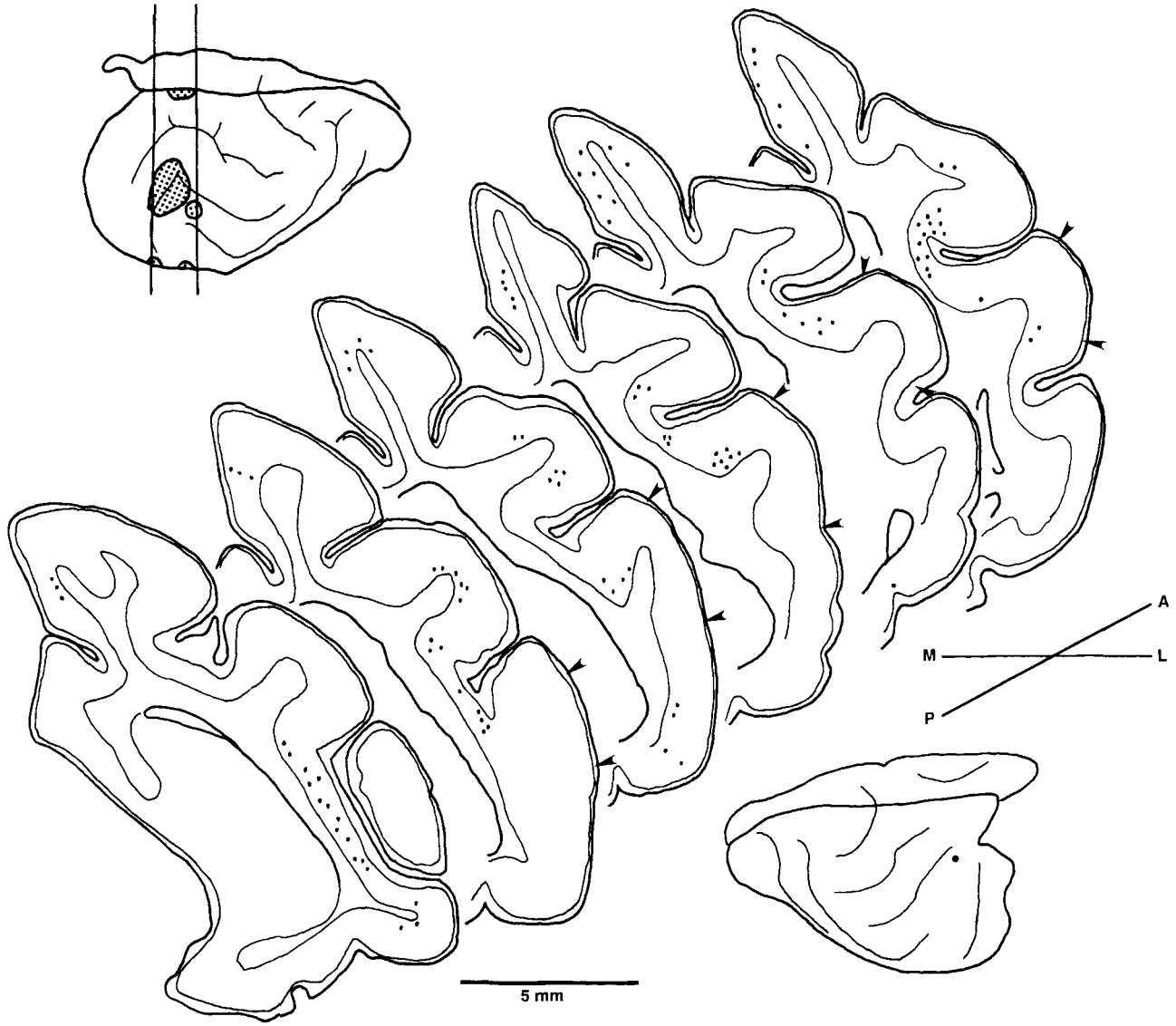


Fig. 8. Contralateral corticocortical connections in an animal (F88-34) with visual inputs to AI. The pattern of callosal label following injection of RLB in AI is shown. Conventions as in Figure 4.

but connections between AI and AII appeared less extensive from their data. We find in ferrets that the connections between AI and AII are more extensive that those between AI and A. If this is indeed a consistent anatomical difference between ferrets and cats, it might be reflective of an interesting functional difference.

Potential visual inputs to AI in lesioned ferrets

One of our aims in this study was to determine whether there might be any visual inputs to AI in the lesioned ferrets other than the one induced through the MGN from the retina. It is important to note here that visual responses cannot normally be obtained from AI in the ferret (Sur et al., '88). Previously, we found a small, novel, reciprocal projection from the lateral posterior nucleus of the thalamus to AI (Pallas et al., '90). We had considered the possibility that the early visual inputs from the MGN might cause AI to become interconnected with other visual cortical areas. O'Leary and Stanfield have shown that presumptive visual cortex transplanted into sensorimotor cortex in the rat forms output connections characteristic of its host tissue (Stanfield and O'Leary, '85; O'Leary and Stanfield, '89), raising the possibility that the inputs which cortical tissue receives determine its final pattern of connectivity. However, we find that visual inputs cannot influence auditory cortex to make connections typical of visual cortex. Auditory cortex with visual inputs remains connected primarily to other auditory cortical areas (Fig. 11). There was an apparent expansion of a projection from the medial wall of cortex (M) to AI in the lesioned animals that we saw in one normal animal. We suspect that this area may correspond to association area 7 in the cat (see above), which could possibly provide visual input to both the normal and lesioned AI, but at this point we lack the appropriate physiological or connectional data to demonstrate this definitively. Another possible visual input to AI in both normal and lesioned ferrets comes from the suprasylvian gyrus (SSG). We saw label in this region in one

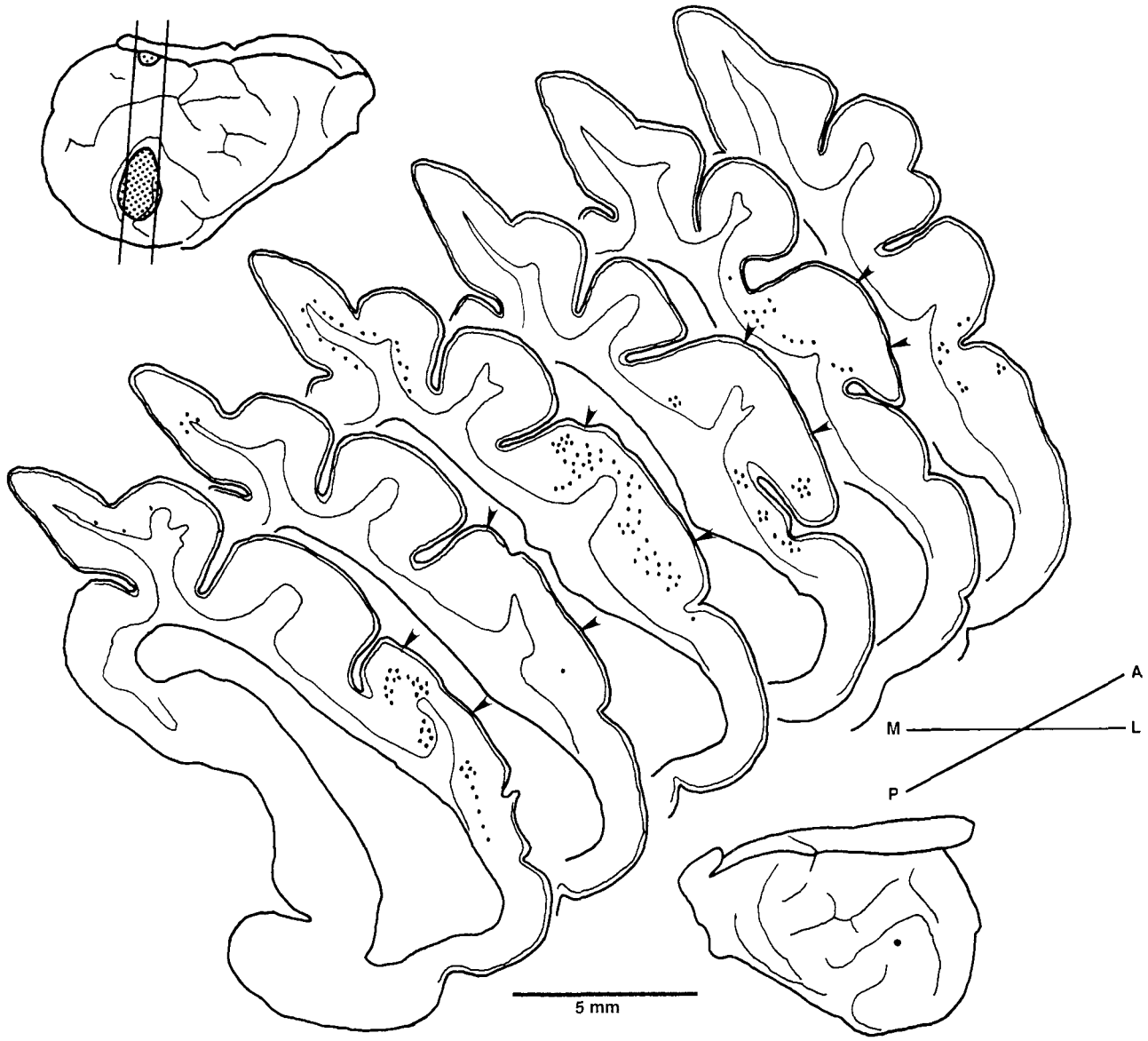


Fig. 9. The results from another lesioned ferret (F88-16) injected with HRP in AI, and showing the pattern of callosal label. Conventions as in Figure 4.

normal and two lesioned ferrets. Without further information on what is represented in this area, it is difficult to speculate about what its role in visual function might be. In addition, in two lesioned animals we saw sparse connections between AI and the posterior ectosylvian sulcus (pes). This area has not been defined in the ferret, but corresponds in location to the LS area in the cat (Clare and Bishop, '54; Rosenquist, '85; Sherk, '86). It is possible that this area may provide visual input to AI, but it is equally possible that some of our tracer injections intended to be in AI spread slightly into the pes. This is more likely to occur in the lesioned animals, given the difficulty of locating AI in vivo as a result of the disturbed sulcal pattern. However, these projections are quite minor in comparison to connections with secondary auditory cortical areas. Aside from the expansion of this projection, the corticocortical connections of AI in the lesioned animals appeared surprisingly normal.

We note that there is some variability in the amount of retinal innervation of the MGN in lesioned ferrets, probably due to variations in the extent of the early lesions (Roe et al., '93; Rocha et al., '93). However, visual responses were recorded in AI in 4 of the 5 lesioned ferrets used in this study, and AI in three of these was mapped fairly extensively in response to visual stimuli.

Representation of visual information in auditory cortex

Our previous physiological results (Sur et al., '88; Roe et al., '90, '92) have shown that AI in the lesioned ferrets can be responsive to visual stimulation and can have many of the characteristics of primary visual cortex. For example, AI can contain a two-dimensional representation of visual space (Roe et al., '90), and single cells in AI can code for the

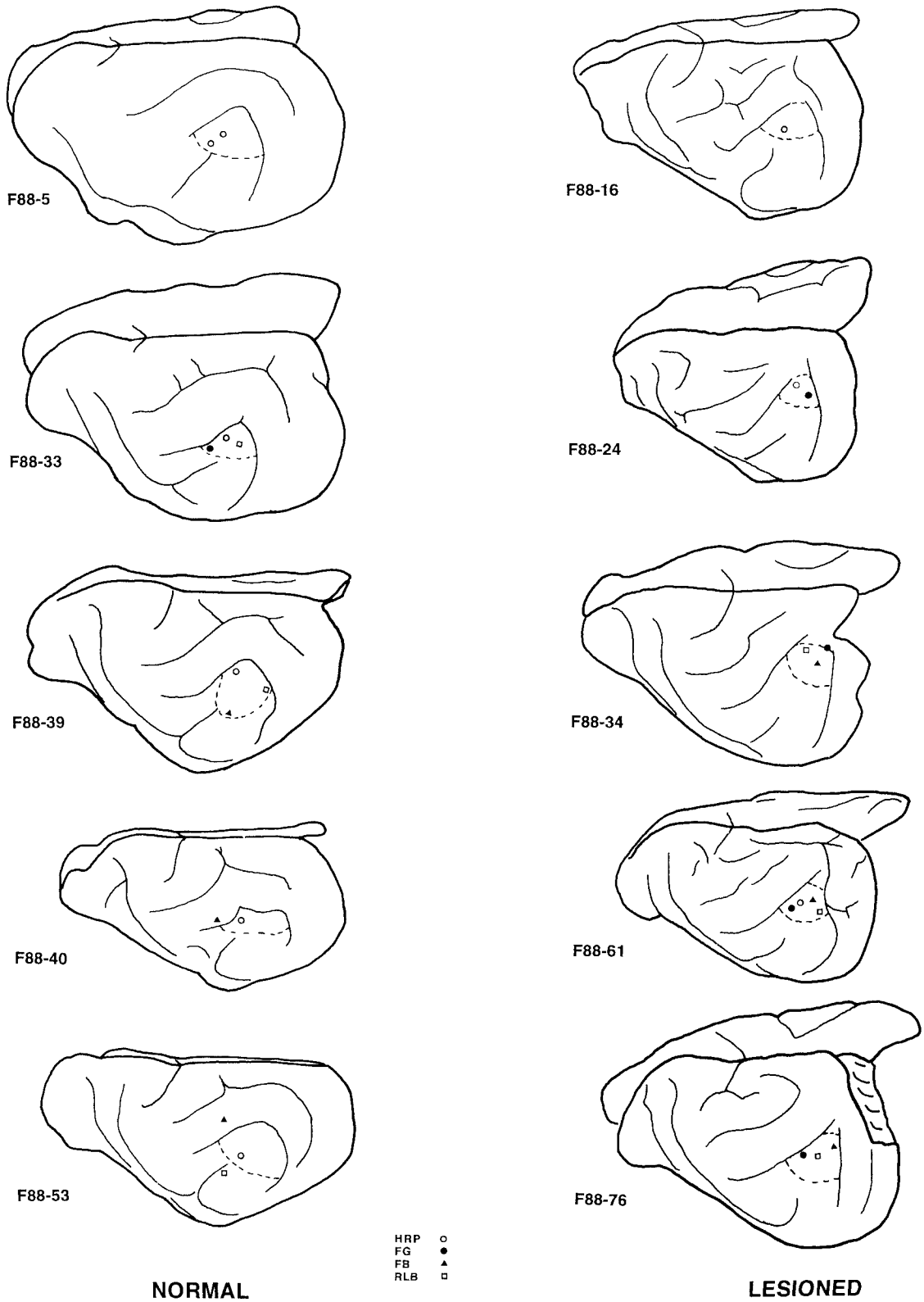
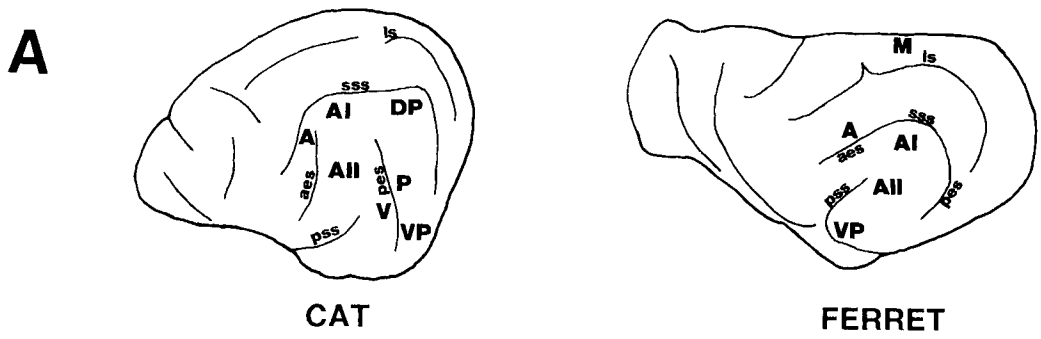
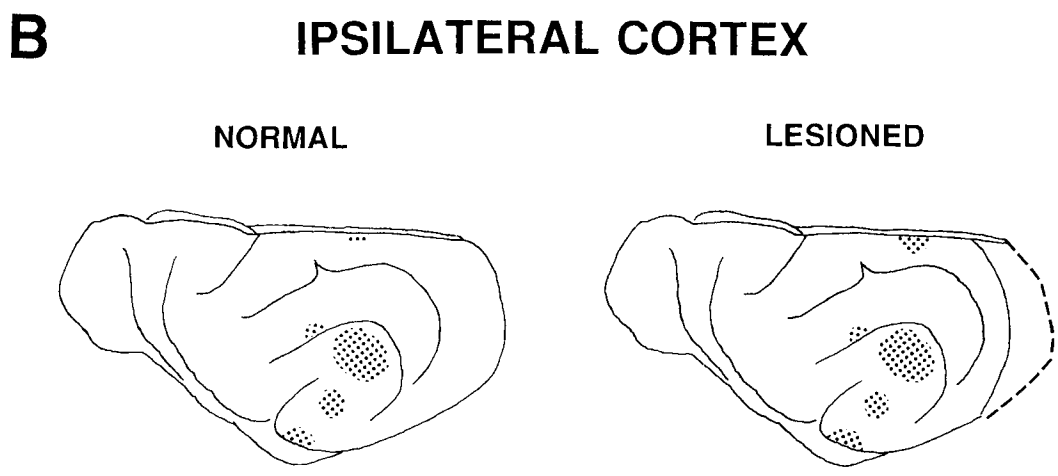


Fig. 10. The locations of the tracer injections for all the experiments are shown here. Normal animals are shown in the column on the **left,** and lesioned animals are on the **right.** The key for the 4 types of tracers is shown. The dashed line on each brain shows the approximate borders of AI as determined cytoarchitectonically. The ectosylvian/suprasylvian sulcus forms the medial boundary of AI.





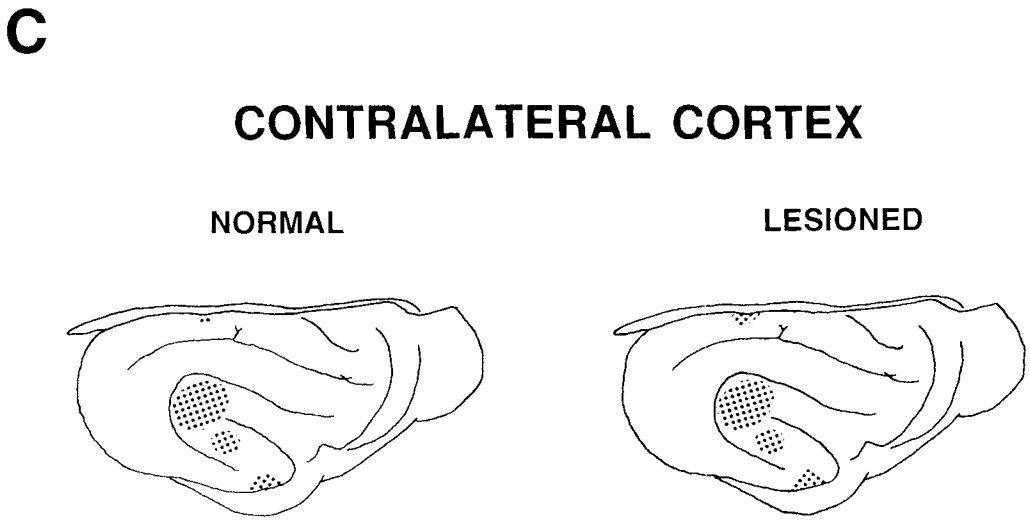


Fig. 11. Summary of results. **A:** On the left is shown the location of various auditory cortical areas in relation to the sulcal pattern as described in cats by Imig et al. ('82). To the right is shown our proposed identification of secondary auditory areas projecting to ferret primary auditory cortex as determined by injections of tracers in AI, A and AII. **B:** Drawing of the expected patterns of ipsilateral retrograde label (shown by dots) which would result from tracer injection into the center of AI in normal (left) and lesioned (right) ferrets. The dashed line on the right indicates the cortical lesion. **C:** Expected pattern of label in the contralateral hemisphere following tracer injection in the center of AI in normal (left) and lesioned (right) ferrets.

direction, velocity, length, and orientation of a visual stimulus (Roe et al., '92). These cells can also exhibit binocular responses and simple or complex types of receptive field arrangements (Roe et al., '92).

Because AI in the lesioned ferrets remains connected bilaterally to other auditory cortical areas, and because these animals can apparently hear well at least using the lesioned hemisphere (Carman et al., '92), it is somewhat surprising that the visual inputs have such a strong influence on the cellular receptive field properties. Auditory responses can be obtained from only a few cells in the lesioned AI (Sur et al., '88), despite the heavy callosal input from the "normal" AI. This suggests that the visual inputs are somehow suppressing the auditory responses. However, the role of the callosal input is poorly understood even in normal animals.

Our conclusions on topographical relationships between interconnected cortical areas are limited due to the size of our injections and limited information on functional maps. However, we did note that callosal connections were homotopic for the most part. We also noted a tendency for topographic restriction ipsilaterally along both the rostrocaudal and mediolateral dimensions. While it is true that the isofrequency axis is oriented roughly rostrocaudally in ferrets (Kelly et al., '86; Phillips et al., '88), and that we would expect connections to be elongated along the isofrequency axis, without accurate data on the correspondence of visual field location or frequency tuning and tracer transport, we cannot draw any conclusions about anisotropies in connections along one axis or the other. It would be of great interest to pursue topographic relationships further in the lesioned animals, because the presence of a two-dimensional visual map in at least some of these animals (Roe et al., '90) suggests the induction of topography along what would be the isofrequency axis in normal animals.

Implications for cortical development

The pattern of corticocortical connections is one of the identifying characteristics of different cortical areas, and an important step in their specification. How do these specific connections come about during development? Is the pattern programmed, or is it subject to outside influences, such as afferent input? Corticocortical projections, including callosal connections, show a high degree of exuberance early in development. For example, Innocenti and his colleagues have shown that the callosal projections of cat visual cortex are restricted to a small portion of area 17 and 18, but in the kitten they are distributed over a wide tangential extent (Innocenti et al., '77; Innocenti and Caminiti, '80). The exuberant connections are lost through collateral elimination (Innocenti, '81; Koppel and Innocenti, '83). A similar scenario takes place in the parietal cortex of rats (Ivy and Killackey, '81; Stanfield et al., '82; Olavarria and Van Sluyters, '85; O'Leary and Stanfield, '86) and in the auditory cortex of cats (Feng and Brugge, '83). Especially pertinent to this study are the observations of Innocenti and Clarke ('84, '88, '90) and Dehay et al. ('88) on transient cross-modal projections from the auditory cortex to the visual cortex (but not the reciprocal) in kittens. It is not known whether these connections exist in ferrets. This high degree of exuberance in corticocortical connectivity suggested to us that visual input to auditory cortex might stabilize any transitory connections between visual and auditory cortex. However, we find no connections between visual and auditory cortex, either in the normal adult ferret or in ferrets with developmentally induced visual input to AI.

One explanation for our results is that there is a critical period for plasticity which is terminated by the time we do our manipulations. Ferret cortex develops along a similar timetable as cat cortex (Luskin and Shatz, '85b; Jackson et al., '89), except that ferrets have a 42 day gestation compared to 63 days in the cat. Although by making our lesions in the ferret we are accessing early stages of cortical development, before geniculocortical cells reach the cortical plate, it is possible that specification of corticocortical connections has already occurred. In fact, Shatz and colleagues (McConnell et al., '89; Ghosh et al., '90) have provided evidence that subplate cells in the early developing cortex pioneer its efferent pathways. At the time we make our lesions, the subplate pathways are already in place (Luskin and Shatz, '85a,b; Jackson et al., '89). It would be of interest to make the lesions at an earlier stage to try and influence the connectivity patterns. However, because the subplate cells in both the cat and the ferret project to their targets before any contact with inputs from the thalamus occurs (McConnell et al., '89), the formation of the callosal and ipsilateral corticocortical projections may be independent of influences from the sensory periphery. In fact, these connections may be preprogrammed entirely. Support for this interpretation includes the finding by Innocenti et al. ('88) that binocular enucleation at birth does not cause retention of normally transient auditory to visual cortex projections. Thus, the elimination of these transient axons appears programmed, and not dependent on activity-based or environmental cues. It has also been shown that adult callosal projections are relatively normal in congenitally anophthalmic mice and rats, although visual experience during a critical period is required for some fine tuning of the connectivity pattern (Olavarria and Van Sluyters, '84; Olavarria et al., '87, '88). In some situations, however, transient callosal connections in the visual cortex can be stabilized by experience-dependent factors (Lund et al., '78; Innocenti and Frost, '79, '80), and manipulations of visual experience can also cause a decrease in the number of callosal axons (Innocenti and Frost, '80; Innocenti et al., '85; Frost and Moy, '89).

In conclusion, our results would support the hypothesis that both transient and permanent corticocortical connections are initially made independent of visual experience. However, as mentioned above, visual experience can perhaps either stabilize or eliminate these connections. More generally, the pattern of afferent activity apparently cannot promote the formation of entirely novel corticocortical connections, though afferent activity does influence cortical microcircuitry and the weights of thalamocortical and intracortical synapses (Sur et al., '90; Gilbert and Wiesel, '92; Recanzone et al., '92a,b).

Behavioral implications

Our behavioral results indicate that lesioned ferrets interpret activation of AI via visual inputs as a visual stimulation (Carman et al., '92). The behavioral paradigm involves sensory activation plus motor output, and the behavioral results argue that there must be at least subtle changes in the output connectivity of AI at some point downstream if not directly. The present anatomical results demonstrate little change in the major input projections of AI, and projections between auditory cortical areas are generally reciprocal (Andersen et al., '80; Imig and Reale,

'80). Thus, either the kinds of changes necessary for AI to provide a motor report of visual activation are below the resolution of the present methods, or the changes occur at sites more removed from AI.

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