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Cingulate Cortex of the Rhesus Monkey: II. Cortical Afferents

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ABSTRACT

Cortical projections to subdivisions of the cingulate cortex in the rhesus monkey were analyzed with horseradish peroxidase and tritiated amino acid tracers. These projections were evaluated in terms of an expanded cytoarchitectural scheme in which areas 24 and 23 were divided into three ventrodorsal parts, i.e., areas 24a–c and 23a–c.

Most cortical input to area 25 originated in the frontal lobe in lateral areas 46 and 9 and orbitofrontal areas 11 and 14. Area 25 also received afferents from cingulate areas 24b, 24c, and 23b, from rostral auditory association areas TS2 and TS3, from the subiculum and CA1 sector of the hippocampus, and from the lateral and accessory basal nuclei of the amygdala (LB and AB, respectively).

Areas 24a and 24b received afferents from areas 25 and 23b of cingulate cortex, but most were from frontal and temporal cortices. These included the following areas: frontal areas 9, 11, 12, 13, and 46; temporal polar area TG as well as LB and AB; superior temporal sulcus area TPO; agranular insular cortex; posterior parahippocampal cortex including areas TF, TL, and TH and the subiculum. Autoradiographic cases indicated that area 24c received input from the insula, parietal areas PG and PGm, area TG of the temporal pole, and frontal areas 12 and 46. Additionally, caudal area 24 was the recipient of area PG input but not amygdalar afferents. It was also the primary site of areas TF, TL, and TH projections.

The following projections were observed both to and within posterior cingulate cortex. Area 29a–c received inputs from area 46 of the frontal lobe and the subiculum and in turn it projected to area 30. Area 30 had afferents from the posterior parietal cortex (area Opt) and temporal area TF. Areas 23a and 23b received inputs mainly from frontal areas 46, 9, 11, and 14, parietal areas Opt and PGm, area TPO of superior temporal cortex, and areas TH, TL, and TF. Anterior cingulate areas 24a and 24b and posterior areas 29d and 30 projected to area 23. Finally, a rostromedial part of visual association area 19 also projected to area 23.

The origin and termination of these connections were expressed in a number of different laminar patterns. Most corticocortical connections arose in layer III and to a lesser extent layer V, while others, e.g., those from the cortex of the superior temporal sulcus, had an equal density of cells in both layers III and V. In one instance projections to area 24 arose almost entirely from layer V of areas TH, TL, and TF. Furthermore, although most projections terminated in layers I–III of cingulate cortex, those of the amygdala to rostral area 24 terminated in deep layer I and layer II while area Opt projections to area 23 terminated mainly in layers I, II, and IV.

Four classes of cortical connections have been characterized and each may play a role in the sensorimotor functions of cingulate cortex. These

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include connections with sensory association and multimodal areas, projections to and from premotor area 24c, subicular termination in areas 25, 24, and 29, and intracingulate connections that may transmit sensory input to areas 24 and 23 into area 24c.

Key words: corticocortical connections, prefrontal cortex, parietal cortex, intracingulate connections, parahippocampal cortex, primate

Cingulate cortex is involved in active avoidance learning in the rabbit, cat, and monkey (McCleary, '61; Moore, '64; Haller et al., '76; Gabriel et al., '80). This task requires association of a visual or auditory stimulus with an unconditioned stimulus (e.g., footshock) followed by a motor response on subsequent trials (e.g., hopping) to avoid the unconditioned stimulus. Although the specific role of cingulate cortex in this and other behaviors is not known, it has been implicated in a number of sensory and motor functions that are required for performance of the active avoidance task. Thus, visually evoked responses have been recorded in cingulate cortex (Cuénod et al., '65; MacLean et al., '68). Also electrical stimulation of cingulate cortex in the monkey produces somatic and autonomic motor responses (Kaada, '51), while in humans simple behavioral patterns involving the fingers, tongue, and eyes are evoked as well (Talairach et al., '73). Likewise, in humans, vascular damage to the cingulate cortex has been implicated in a condition termed akinetic mutism (Nielson and Jacobs, '51).

It is possible that a series of corticocortical connections contribute to sensorimotor and behavioral functions of the primate cingulate cortex. Previous connectional studies suggested that afferents from sensory cortices arrive in the posterior cingulate cortex via sequential connections through association areas in frontal and parietal cortices (Adey and Meyer, '52; Nauta, '64, '71; Pandya and Kuypers, '69; Jones and Powell, '70; Petras, '71; Pandya et al., '71; Van Hoesen et al., '72; Künzle, '78). In regard to projections into the motor system, anterior cingulate area 24 projects to motor and premotor cortices (Muakkassa and Strick, '79; Barbas and Pandya, '81) and spinal cord (Biber et al., '78). In addition, cingulate cortex projects directly to the striatal (Yeterian and Van Hoesen, '78; Royce, '82) and pontine (Vilensky and Van Hoesen, '81; Albus et al., '81; Glickstein et al., '85) nuclei.

The above-noted observations suggest that motor and sensory functions might be segregated in anterior and posterior cingulate cortex, respectively. If this were true, intracingulate connection pathways would be pivotal to integrating sensorimotor activities. Little is known about intracingulate connections other than that rostral and caudal cortices are reciprocally connected (Vogt et al., '79; Baleydier and Mauguiere, '80; Pandya et al., '81). Following precise cytoarchitectural parcellation and restricted injections of tracers, more refined information can be resolved regarding connections among the subdivisions of cingulate cortex (i.e., among areas 25, 24a–c, 23a–c, 30, and 29). In the present study a comprehensive analysis is made of the corticocortical connections of various longitudinal subdivisions of the cingulate gyrus by using both retrograde and anterograde tracers.

MATERIALS AND METHODS

Surgical procedures

In all instances in which injections were made into cingulate cortex the monkey was anesthetized with sodium pentobarbital and mounted in a stereotaxic instrument. A midline craniotomy was made and mannitol (Osmitrol, 25%) was injected intravenously to obtain shrinkage of the cerebral cortex. Then the dura was opened and retracted to one side and bridging veins between the cortex and falx cerebri were cauterized so that the hemispheres could be gently retracted. Tracer substances including horseradish peroxidase (HRP) and radioactively labeled amino acids were injected into the cortex with a 5-μl Hamilton syringe with a 32-gauge needle.

HRP histochemistry

Two series of animals were prepared for retrograde tracer analysis. First, ten animals received large 0.2–0.3-μl injections of 20% HRP in the cingulate cortex and were allowed to survive 2 days. The animals were then anesthetized and killed by perfusion-fixation according to the protocol of Rosene and Mesulam ('77). Thus, they were perfused through the heart with physiological saline followed by 2 liters of quarter-strength Karnovsky fixative (Karnovsky, '65) and finally 1 liter of phosphate buffer containing 10% sucrose. The brains were stored for one night in sucrose phosphate buffer and then frozen and sectioned into 40-μm-thick sections. An interrupted series of one-in-eight sections was processed with tetramethyl benzidine, mounted on subbed slides, dried, and then counterstained with neutral red. In a second series of five animals, very limited HRP injections were made with 0.015 μl of 5% HRP conjugated to wheat germ agglutinin (Sigma), and the brains were prepared according to the above protocol. The full rationale behind the use of HRP–wheat germ agglutinin in studies of cingulate cortex connections has been presented elsewhere (Vogt and Miller, '83; Miller and Vogt, '84). The locations of HRP-labeled neurons were plotted with an X-Y recorder coupled to the mechanical stage of a microscope by linear potentiometers. In a few cases the sections were drawn with the aid of a drawing tube attachment to the microscope or an Aus Jena Documentor projector onto which labeled neurons were plotted.

Autoradiography

For anterograde transport studies 22 animals were injected with 0.4–1.0 μl of ^{3}H-amino acids with a total specific activity of 40–80 μCi. Following a postoperative survival period of 5–7 days the animals were perfused with a saline wash and 1 liter of 10% formalin. After 1–3 weeks postfixation in 10% formalin, the brains were embedded in paraffin, cut into 10-μm-thick sections, mounted on slides dipped in NTB-2 Kodak emulsion, exposed in desiccated, light-tight boxes at 0°C for 3 months, and then developed in Kodak D-19 developer and fixed with Kodak Rapid Fixer. Thionin was used to counterstain autoradiographic preparations.

Cytoarchitecture

The cytoarchitectural schemata of Brodmann ('09) and von Bonin and Bailey ('47) are used throughout this study.

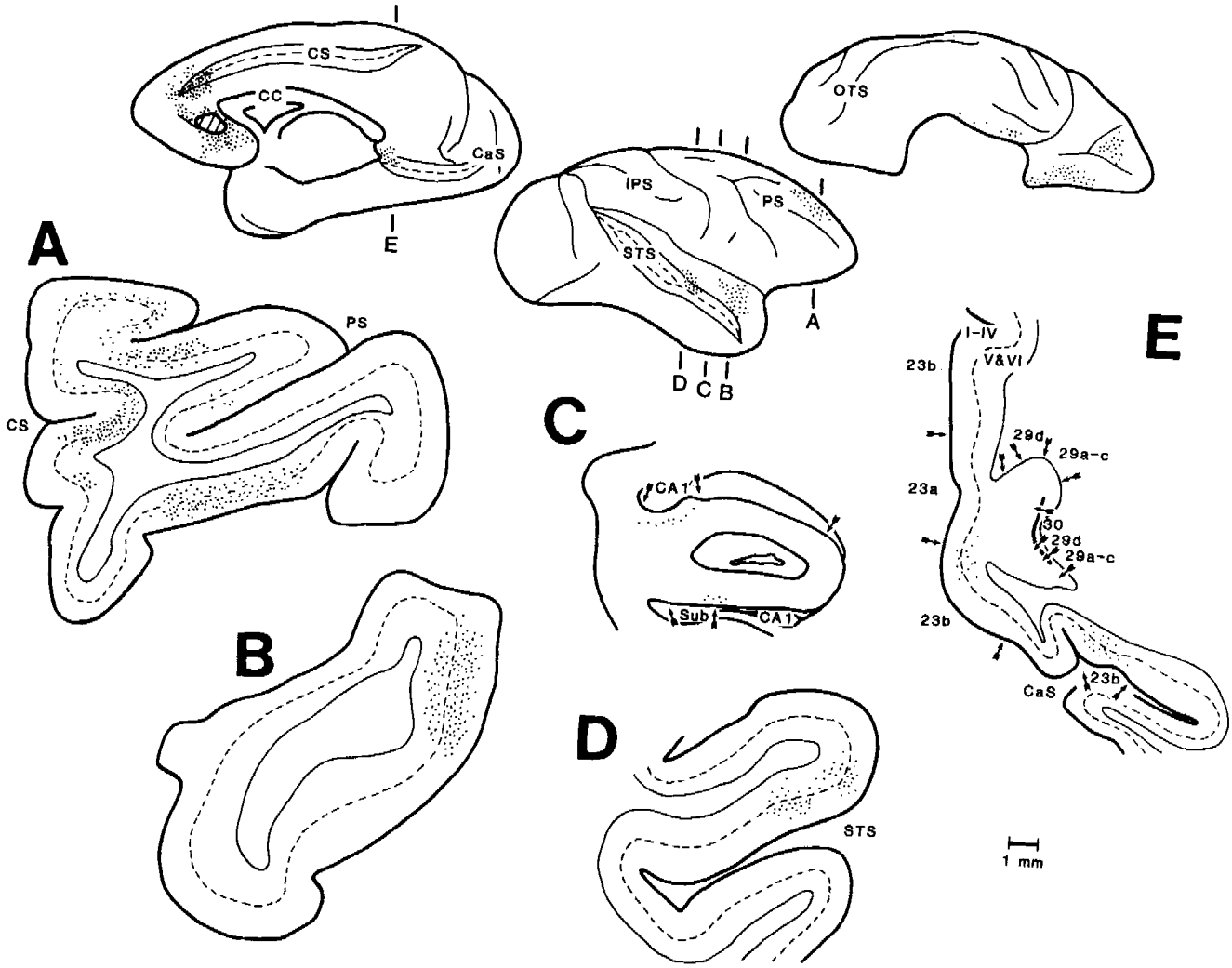

Fig. 1. Distribution of HRP-positive neurons (dots) throughout the cerebral cortex following an injection into area 25. CS, cingulate sulcus; CC, corpus callosum; CaS, calcarine sulcus; IPS, intraparietal sulcus; PS, principal sulcus; STS, superior temporal sulcus; OTS, occipito-temporal sulcus; Sub, subiculum.

These schemes have been substantially amplified in recent years, however, in accordance with experimental neuroanatomical observations. The companion article to this one describes cingulate cortex cytoarchitecture. Additionally, some of the more recently published architectonic parcellations of specific cortical regions will also be used, including those for frontal (Barbas and Pandya, '81; Petrides and Pandya, '84) and parietal (Pandya and Seltzer, '82) cortices, the superior temporal gyrus (Pandya and Sanides, '73), and cortex of the superior temporal sulcus (Seltzer and Pandya, '78).

RESULTS

Large HRP injections

The distribution of labeled neurons will be described in detail in six cases in which the HRP injections involved progressively more caudal regions of cingulate cortex.

Area 25. In the first case the injection involved area 25 below and rostral to the genu of the corpus callosum (Fig. 1). On the medial surface HRP-positive neurons were in areas 9 and 24b above the injection site and in area 14 below it. Some labeled neurons were also observed in area 32 rostral to the injection site. In posterior cingulate cortex there were labeled neurons in ventral area 23b in the caudomedial lobule and in the depths of the calcarine sulcus (Fig. 1E). On the lateral surface of the frontal lobe HRP-positive neurons were in area 9 above the principal sulcus, while on the orbitofrontal surface, clusters of labeled neurons were observed in areas 11 and 14.

In the temporal lobe labeled cells were in a number of foci. In the amygdala most cells were in the lateral basal nucleus, while fewer were in the accessory basal nucleus. A group of labeled neurons appeared in an extension of the CA1 sector of the hippocampus in the uncus (Fig. 1C, CA1'; see also Ekstein and Rosene, '86), and others were at the subicular/CA1 border. More caudally, cells were labeled in the subiculum only. Finally, labeled neurons were in cortex of the superior temporal gyrus including areas TS2 and TS3 and the adjacent bank of the superior temporal sulcus.

The laminar distribution of labeled neurons was not the same for all areas. In frontal lobe areas 9 and 11 as well as

cingulate area 23b most labeled neurons were located in layer III and less were in layer V. In contrast, in area 24b and in the superior temporal gyrus more neurons were labeled in layer V in addition to those in layer III.

Area 24. Figure 2 presents a second cingulate case in which the HRP injection was mainly in areas 24a and 24b with slight infringement on areas 24c and 32. On the medial surface labeled neurons were in areas 14 and 25 below the injection site and in area 9 above it. In posterior cingulate cortex labeled neurons were mainly in areas 23a and 23b and a few also in area 30 (Fig. 2A). In the frontal lobe most labeled neurons were in areas 9 and 46 above the principal sulcus, while fewer were in area 6 above the arcuate sulcus. On the orbital surface labeled cells were in areas 12, 13, and 10.

In the temporal lobe some neurons were located in regions that were similar to the previous case. Thus, the lateral and accessory basal nuclei of the amygdala contained labeled neurons with a small additional component in the medial basal nucleus (Fig. 2D). Although no neurons were seen in the CA1 sector of the hippocampus, there were a number of labeled cells in subicular cortex. There were also cells in temporal pole areas Pro and TS1 and cortex on the dorsal bank of the superior temporal sulcus. This case had additional neuronal labeling in rostral agranular insular cortex and extensive labeling throughout parahippocampal areas TH and TL and some in area TF (Fig. 2E). Finally, although more caudal injections of area 24 produced neuronal labeling in parietal cortex, no parietal neurons were labeled in this case.

There were three different laminar patterns for the projection cells in this case. First, in cingulate and frontal cortices, most labeled neurons were in layer III and there were a few in layer V. Second, in lateral and rostral temporal cortices, including the insula, the distribution of labeled cells was equal in layers III and V. Third, in parahippocampal cortex (i.e., areas TH, TL, and TF) almost all labeled neurons were in layer V.

In a third cingulate case the injection involved much of area 24, including parts of each subdivision (Fig. 3A). On the medial surface labeled neurons were more dense and there was a greater topographic dispersion than in the previous cases. In particular, posterior area 24a had labeled neurons, as did rostral parts of areas 23a, 23b, and 23c. In addition, more caudal parts of areas 23a and 23b had labeled neurons. The distribution of labeled cells in frontal and temporal cortices was similar to those in previous cases. However, in this case no cells were labeled in area 10 and additional labeled neurons were observed in and just below the principal sulcus (area 46). A few neurons were also observed in the depths of the superior temporal sulcus, temporal pole, and parahippocampal gyrus. Finally, the labeled neurons in the amygdala were in the same nuclei as in the previous case.

In the fourth case the injection was placed in the central part of the cingulate gyrus and involved all three divisions of areas 24 and 23 (Fig. 3B). Although many labeled neurons were located in places similar to those in previous cases, there was a lack of labeled neurons in caudal orbitofrontal cortex, temporal pole, and amygdala. In insular cortex, labeled neurons extended more caudally and there were fewer labeled cells in cortex of the superior temporal sulcus as compared to previous cases. There was also a shift in the proportion of labeled cells in parahippocampal cortex, with fewer in area TH and more in area TF. Finally, in this case the caudal half of the inferior parietal lobule, including areas PG and Opt, contained labeled neurons.

Areas 23, 30, and 29. In two other cases injections were placed in posterior cingulate cortex as outlined in Figure 4. In one of these cases the injection involved areas 23a, 23b, 30, and 29 (Fig. 4A–F). In the other case the injection additionally encroached upon adjacent areas 23c and 19 (Fig. 4G). The basic pattern of labeled neurons was similar in both cases. In the former case there were five patches of labeled neurons in anterior areas 24a and 24b. In posterior cortex areas 31 and 23b below the splenial sulcus also contained labeled neurons. Additionally, labeled neurons occurred in area 19 adjoining the caudal border of area 23. In the frontal lobe labeled neurons were around and within the principal sulcus in areas 46 and 10 and there were two patches on the orbitofrontal surface in areas 11 and 14. In the temporal lobe labeled cells were located in patches along much of the caudal superior temporal sulcus (STS) in area TPO. Areas TL and TF of parahippocampal cortex and much of the medial part of the subiculum also contained labeled neurons.

In the parietal lobe labeled neurons were restricted to the most caudal part of the inferior parietal lobule (i.e., area Opt). Comparison of cases presented in Figures 3B and 4E indicates that the broader distribution of labeling in anterior parts of the inferior parietal lobule was associated with involvement of area 24, since injections restricted to area 23 resulted in labeling only in area Opt. Finally, in case 6, with the large injection, presented in Figure 4G, there was an overall enhancement in the density of labeled neurons in each area in comparison to the previous case, and the patchy organization of the projection cells was not apparent.

In these cases labeled neurons were organized in two laminar patterns. In the first, most labeled cells were in layer III and fewer were in layer V, especially in frontal cortex and areas 24, 31, 19, Opt, TL, and TF. In the second there was an approximately even distribution of cells in layers III and V, which was the case for cortex of the dorsal bank of the STS.

Small HRP injections

Although the previous two cases provided information about the overall topography of cortical afferents to posterior cingulate cortex, each injection involved more than one cortical subregion. In order to isolate further the sources of the cortical inputs to specific areas, a series of eight discrete HRP injections were made into posterior cingulate cortex.

Figure 5 presents a case in which only areas 23a and 23b were involved in the injection (see also Fig. 6A). Labeled neurons on the medial surface were organized in several patches with three in area 24a and two in area 23b, with the latter adjacent to the splenial sulcus and in the caudomedial lobule. Another large group of neurons spanned areas 23a, 30, 29a–c, and 29d (Figs. 5D, 6B,C). In rostral area 19 there were two clusters of labeled neurons. In the frontal lobe three small patches of labeled neurons were in and around the principal sulcus and two were in the orbitofrontal cortex. In the temporal lobe there was extensive labeling of neurons in areas TH and TL, limited labeling in the depths of the STS, and none occurred in the subiculum. The parietal lobe also contained labeled neurons in area Opt (Figs. 5E, 6D), as in previous cases with large posterior cingulate injections.

In a case that involved areas 30 and 23a (Fig. 7A) patches of labeled neurons were seen in many of the areas noted

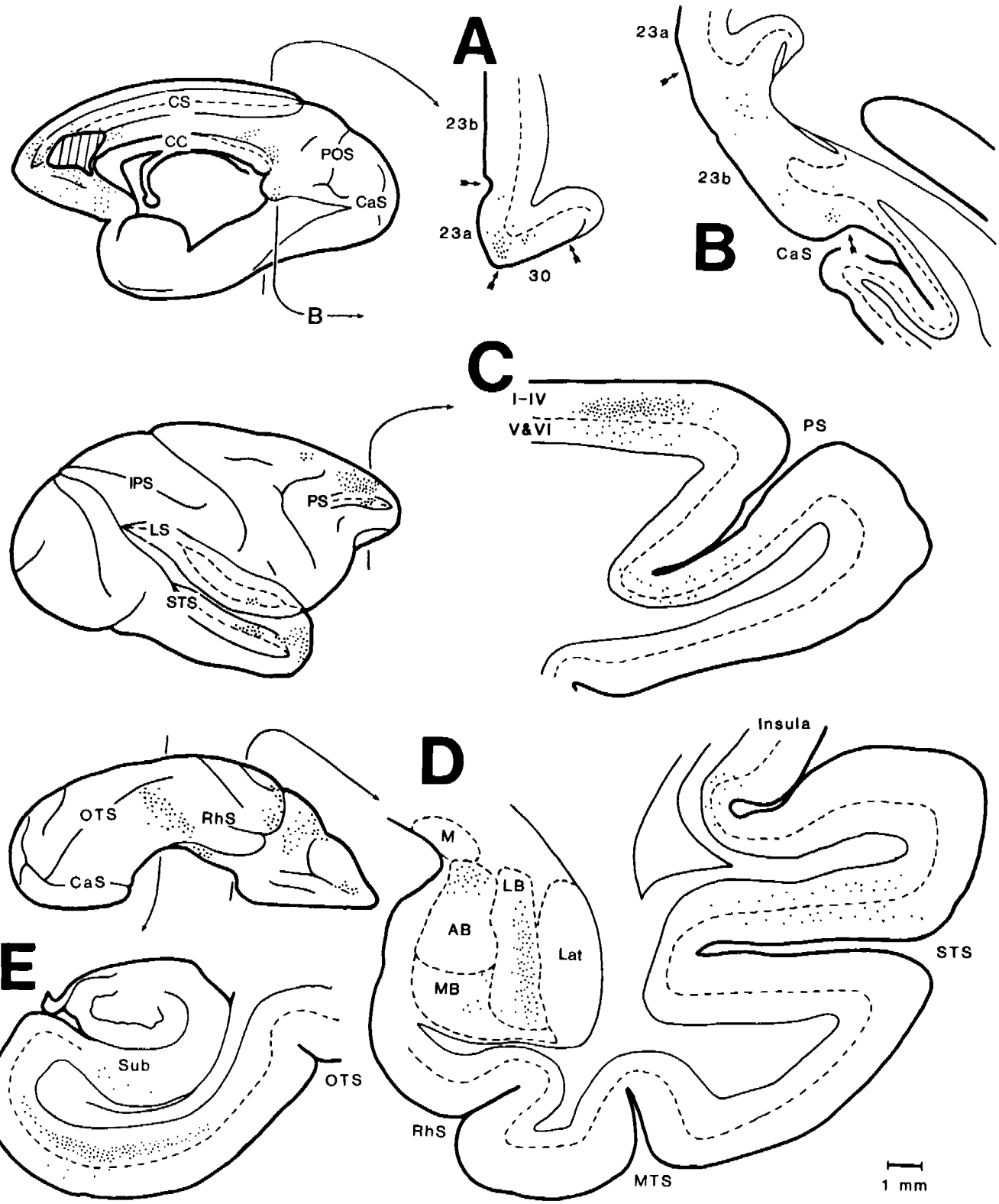

Fig. 2. Pattern of HRP-labeled neurons following an injection into rostral area 24. LS, lateral sulcus; RhS, rhinal sulcus; MTS, middle temporal sulcus; Amygdalar nuclei: M, medial; AB, accessory basal; MB, medial basal; LB, lateral basal; Lat, lateral.

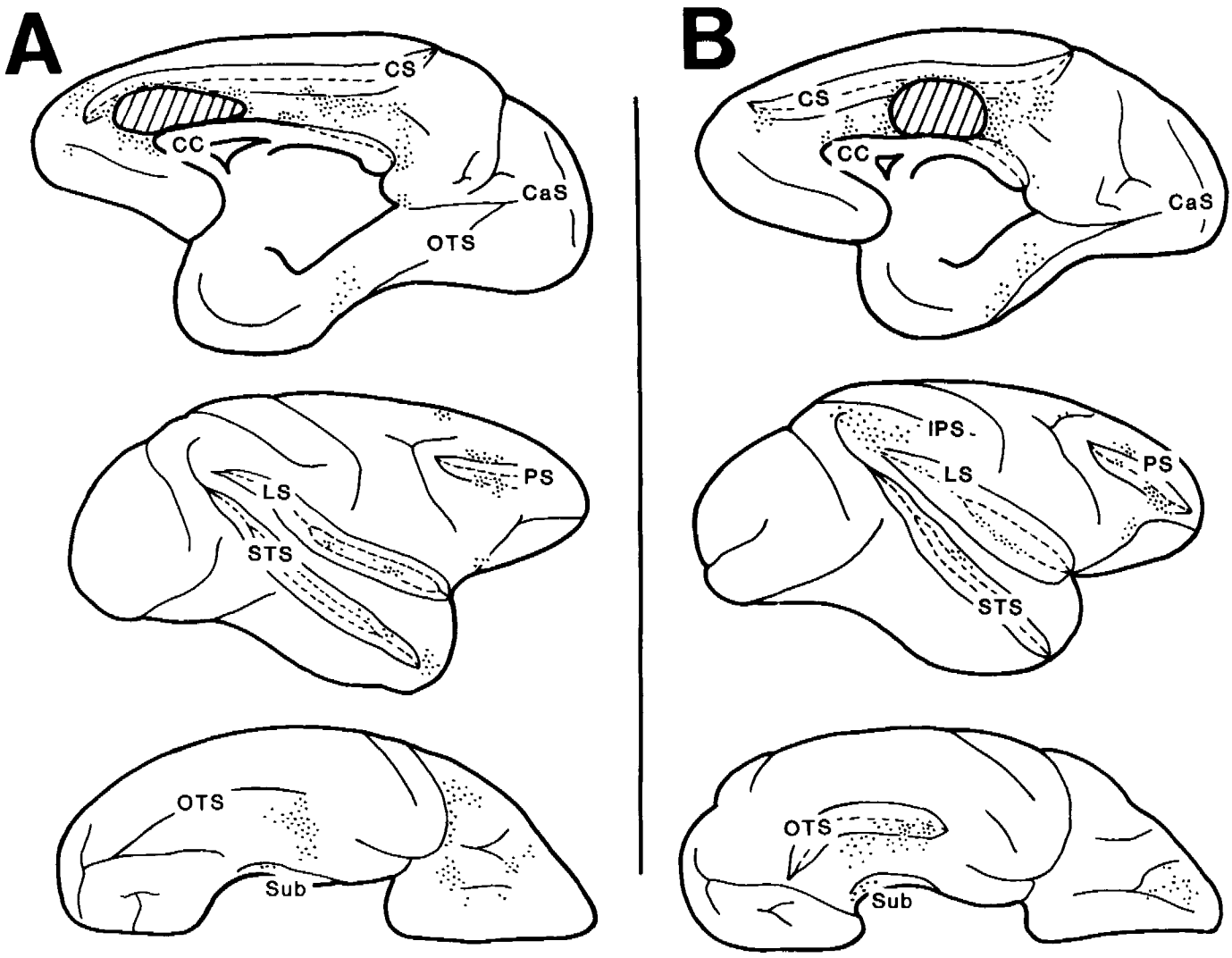

Fig. 3. Frequency of HRP-labeled cortical neurons following an area 24 injection (A) and a midcingulate gyrus injection that involved caudal area 24 and rostral area 23 (B).

above; however, there were a number of differences. For example, there was only one group of labeled neurons in area 19; there was greatly reduced labeling of neurons in the temporal lobe with none in the STS and only a limited number in area TF. Finally, there was one patch of labeled cells in orbitofrontal cortex.

Two other cases presented in Figure 7B and C involved only part of area 23b. The pattern of labeled neurons in the rostral area 23b case (Fig. 7B) was almost the same as in the case with involvement of both areas 23a and 23b (Fig. 5), although neurons in this case were mainly in areas TF and TL and none were in TH of parahippocampal cortex. There was also a small patch of cells in medial entorhinal cortex. In the final HRP case (Fig. 7C) no label was seen in neurons in area 7 or entorhinal cortex while more extensive labeling occurred along the upper bank of the STS. Lack of labeling in area Opt could have been due to small HRP injections into a zone that does not receive parietal input.

Comparison of the distribution of HRP-labeled neurons following small and large injections of posterior cingulate cortex suggests some of the following conclusions. First, the subiculum projects only to area 29 of posterior cortex, since only cases that involved area 29 had labeled cells in the subiculum and none were seen after areas 30 or 23 injections. Second, areas 24a and 24b are primarily responsible for projections to area 23, while area 24c does not appear to send axons to area 23. It is also interesting that the amount of cortical area 24 with labeled neurons was always larger

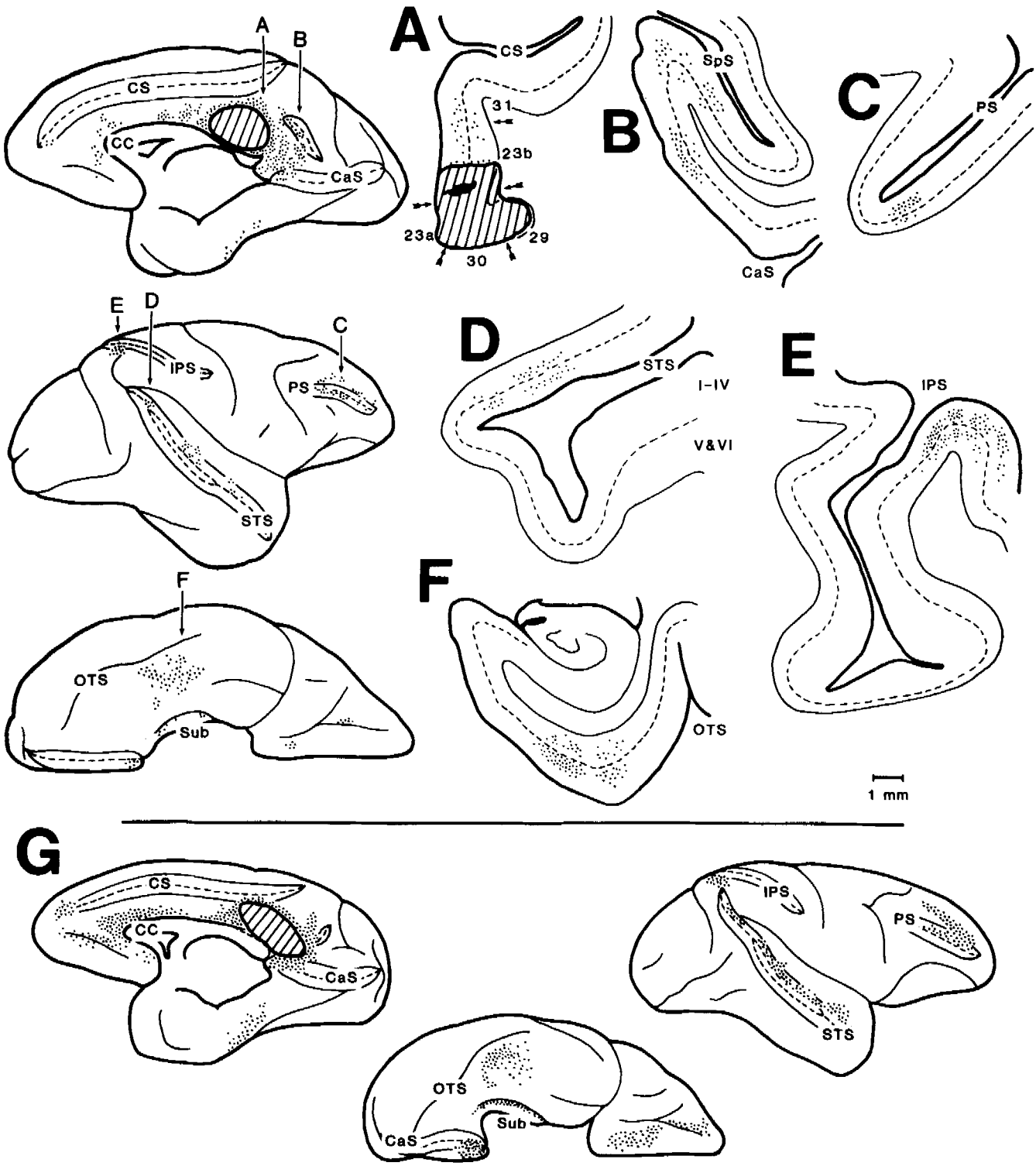

Fig. 4. Distribution of HRP-positive cortical neurons following large HRP injections into posterior cingulate cortex. SpS, splenial sulcus.

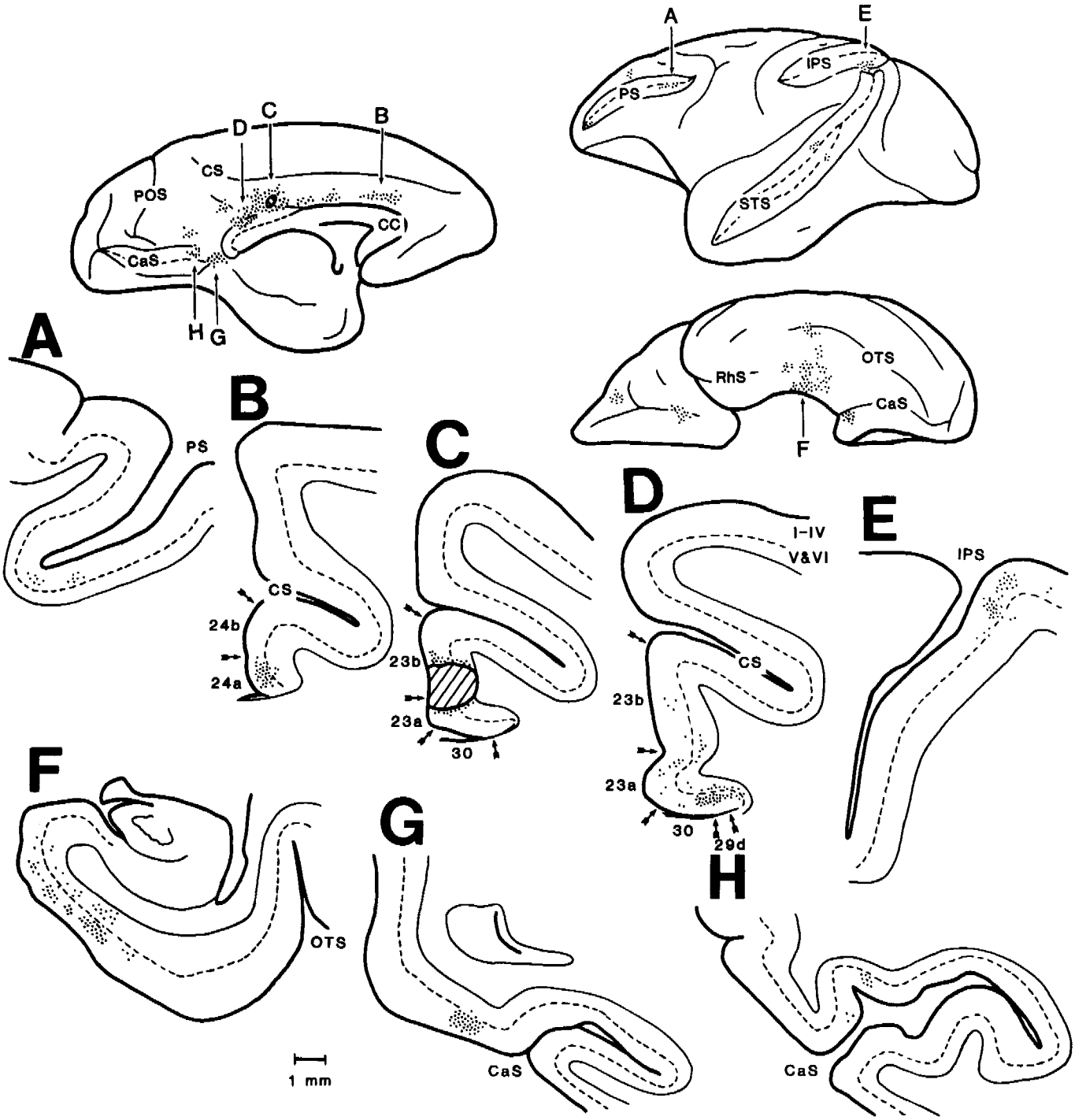

Fig. 5. Location of HRP-labeled cells following a very restricted HRP injection into posterior cingulate cortex that involved only areas 23a and 23b.

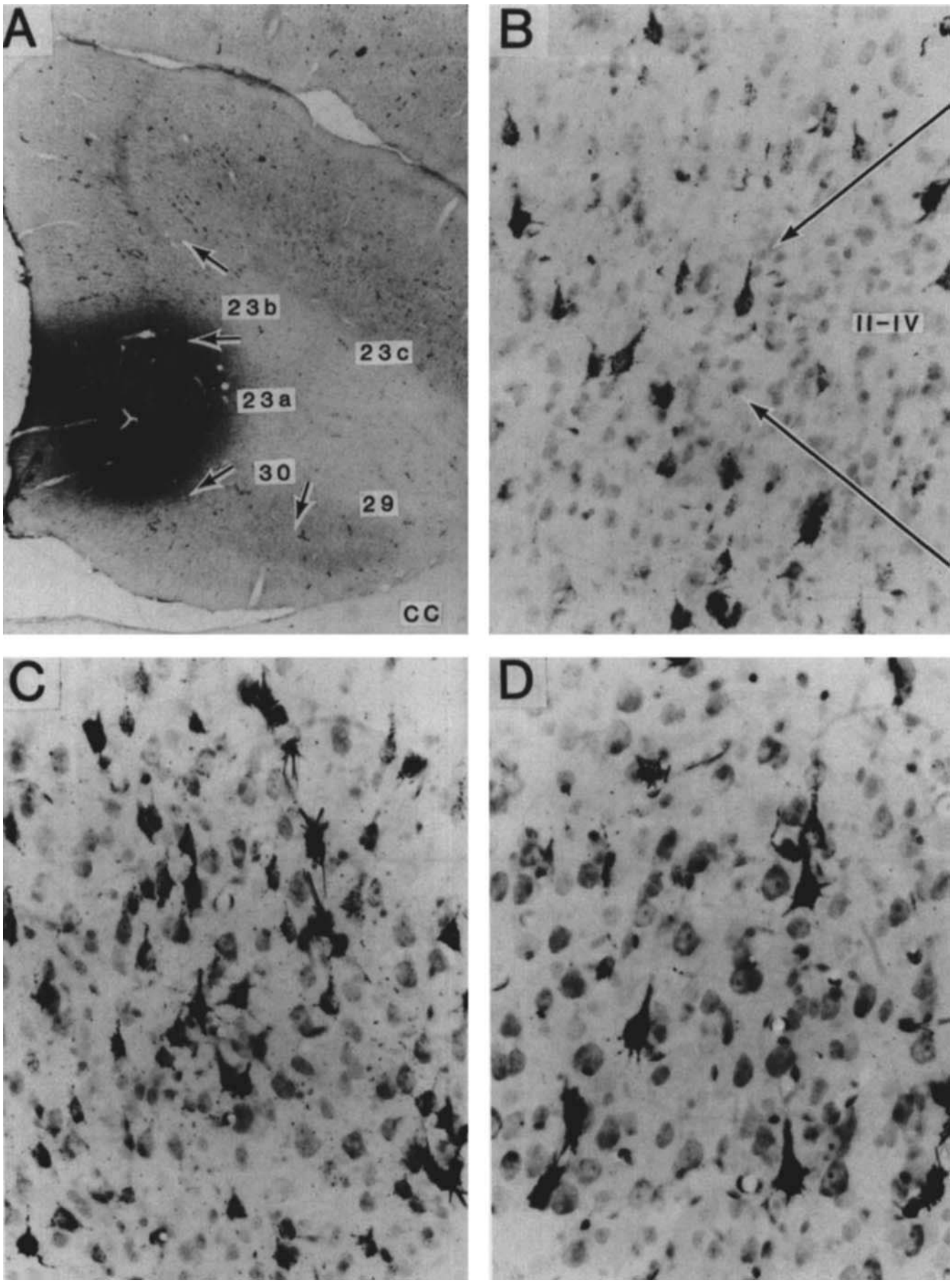

Fig. 6. Photomicrographs of the restricted area 23 HRP injection case presented in Figure 5. **A:** Injection site. ×22. Retrogradely labeled neurons were located in areas 29d and 30 (**B:** granular layers II–IV of area 29d are on right between arrows), layer III of area 30 (*C*), and layer III of area Opt (**D**).

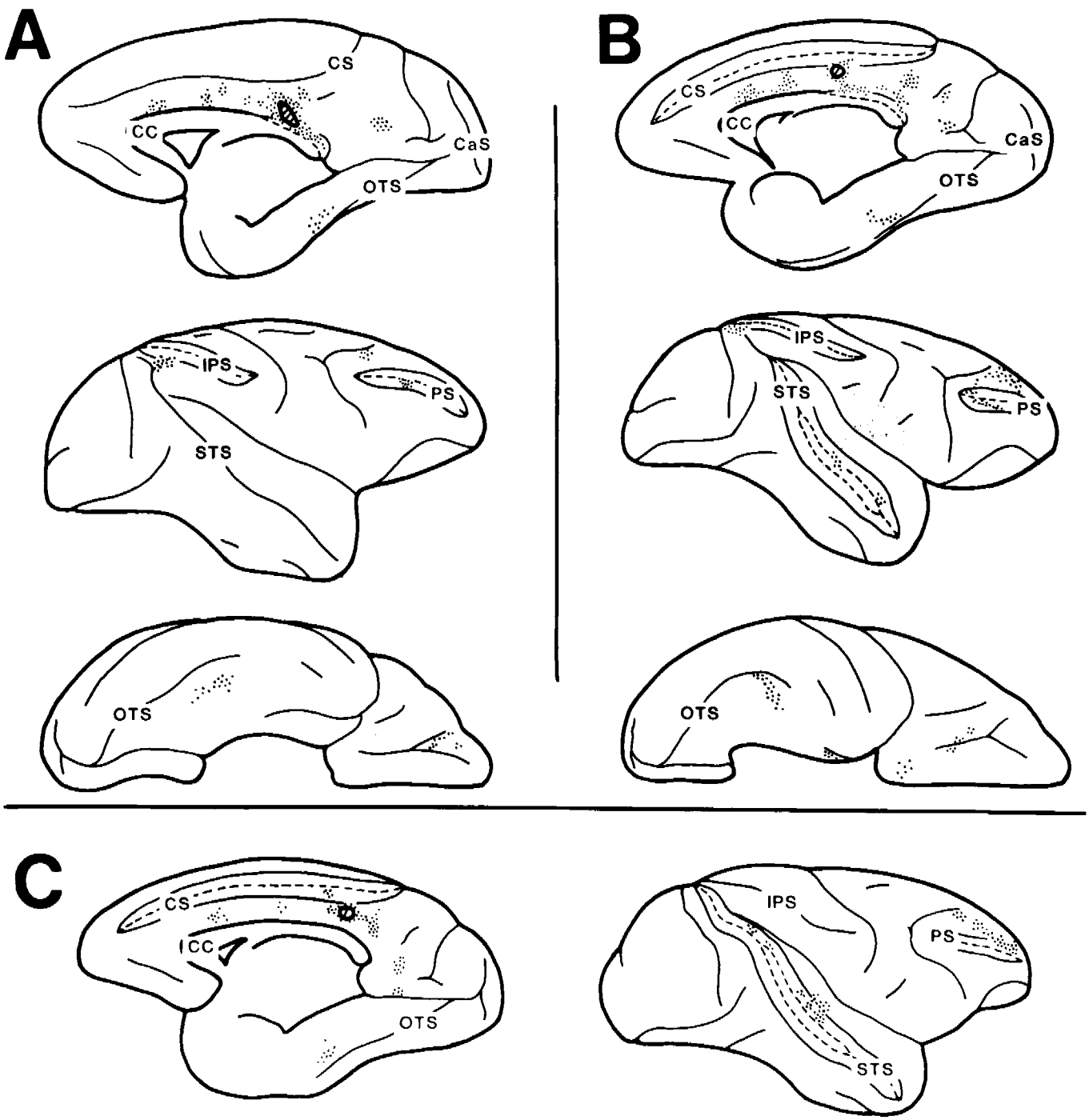

Fig. 7. A number of small posterior cingulate cortex HRP injections and their associated neuronal labeling pattern. A: Injection into areas 23a and 30. B: Injection into posterior area 23b. C: Injection into an intermediate level of area 23b.

than the small injection sites in area 23, suggesting some convergence of area 24 projections. Third, areas 29 and 30 project to areas 23a and 23b. Fourth, area 19 projects directly to areas 23a and 23b. Fifth, area PG projects to caudal area 24 while area Opt projects to area 23. Sixth, cortex of the STS projects mainly to area 23b, although the full extent of this connection with other areas like areas 29 and 30 cannot be determined with this material. Finally, there are two basic laminar patterns of projection neurons. Most cortical neurons that project to areas 30 and 23 are in layer III and fewer are in layer V, while cortex of the STS has an equal proportion of cells in layers III and V that project to area 23.

Amino acid injections

In order to evaluate the topography and laminar termination patterns of cortical inputs to cingulate cortex, a number of cases were examined in which ^{3}H-amino acids were placed into some of the major sources of cingulate afferents. Examples of each major category are presented below. The locations of autoradiographic grains are shown on the entire medial surface, but this description will be restricted to cingulate cortex.

Frontal lobe. Representative tritiated amino acid injections into lateral prefrontal cortex are presented in Figure 8. An injection into area 46 (Fig. 8A) that involved parts of the upper and lower bank of the principal sulcus had the most extensive termination in cingulate cortex. This included rostral area 24c and one patch of terminals in caudal area 24a bordering area 23. Most of the grains in posterior cingulate cortex were over areas 31, 23b,c, and 29a–c. Following injections into ventral area 46 (Fig. 8C) and lateral orbitofrontal area 12 (Fig. 8D), labeled terminals were observed in area 24 in both cases, while a case with an injection in area 8 failed to produce any labeling on the medial surface (Fig. 8B). In terms of laminar termination, grains were observed mainly over layers I–IIIa with lesser amounts in layer IV.

Parahippocampal gyrus. In general, injections into rostral parts of parahippocampal cortex produced less labeling in cingulate cortex than did caudal injections. Thus, an injection involving rostral and lateral parahippocampal cortex and adjacent area TE (Fig. 9A) had labeled terminals over areas 24a and 24b and only a sparse number of terminals in area 23. A more caudal injection that involved mainly area TL (Fig. 9B) additionally labeled terminals in area 24 rostral to those of the previous case. It also extensively labeled terminals in all divisions of area 23 and area 31. Of all parahippocampal injections an area TH case (Fig. 9C) produced the most extensive labeling in cingulate cortex including all divisions of areas 24 and 23 and parts of area 31. However, in none of these cases was label over the most caudal and ventral parts of cingulate cortex. In a case with an injection into areas TL and TF (Fig. 9D), extensive labeling occurred in areas 23a and 23b extending into the caudomedial lobule and into area 30. Area 24 showed only sparse labeling in this case. In all of these parahippocampal cases terminals were labeled over layer I, fewer were labeled in layers II and III, and the fewest were labeled in layer IV. Linear arrays of grains associated with axons were usually present in layers V and VI.

Lateral temporal cortex. Injections into cortex of the temporal pole (areas Pro and TS1) labeled terminals mainly in areas 24a–c (Fig. 10A), as would be expected from previous HRP cases (Figs. 2, 3A). Injections into other parts of the temporal lobe such as insular cortex (Fig. 10B) produced grains over areas 24b,c and 23b,c, while injections into caudal cortex of the STS (Fig. 10C) labeled terminals mainly in areas 23b,c and 31. The lack of labeling in area 23a in this case is consistent with previously described HRP cases.

Parietal lobe. An amino acid injection into the inferior parietal lobule that involved both areas Opt and PG (Fig. 11B) resulted in labeling in caudal areas 24a–c and much of areas 23 and 30. An injection into medial area 7 or PGm produced a more restricted labeling pattern such that terminals were primarily labeled in areas 24a–c, 23c, and 31. It should be pointed out that the labeling in cingulate cortex was not evenly distributed since there were zones that were devoid of terminations. Once again the predominant label was over layer I and less was over layers II and III. In these cases there was also substantial label over layer IV.

Amygdala. Large injections into the amygdala that included the accessory basal, lateral basal, and medial basal nuclei (Fig. 12) had the following features. Extremely dense labeling was over areas 25 and rostral areas 24a–c, but not caudal area 24. The laminar pattern of termination in area 24 differed from that of other afferents described so far in that the terminals were primarily in the deeper part of layer I and layer II.

DISCUSSION

The corticocortical connections of subareas of the cingulate cortex have been described in the monkey. Many of these connections are summarized in Figure 13. The following analysis considers the transfer of information to and among the cingulate areas in terms of connections that may subserve sensorimotor integration.

Sensory afferents

Visual. The previous article proposes that one of the major sources of visual input to area 23 is from the lateral posterior and medial pulvinar thalamic nuclei. The present study describes another pathway linking the visual system to cingulate cortex via area 19. The extent of area 19 projections to the cingulate cortex appears to be limited since only a few patches of neurons in layer III of the most rostral part of area 19 were labeled following area 23 HRP injections. Since most parts of the visual field in areas 17–19 do not have neurons that project to cingulate cortex, it is unlikely that topographically organized visual field information is relayed to the cingulate region. It is possible that visual field properties other than topographic receptive field information, such as motion, form, or color properties (Van Essen and Maunsell, '83), are transferred to cingulate cortex. It is also possible that limited visual cortical projections to cingulate cortex in monkey are due to divergent projections of area 19 into association cortices. Thus, outflow of area 19 through a ventral visual pathway of inferotemporal cortex (Ungerleider and Mishkin, '82) is projected in turn to cingulate cortex via parahippocampal areas and through a dorsal visual route via inferior parietal cortex to cingulate cortex directly.

Visual and cingulate cortical interconnections in the monkey differ significantly from those in the rat and rabbit (Vogt and Miller, '83; Vogt et al., '86). In these nonprimate species, which do not have area 19 or 23, reciprocal and topographically organized connections occur primarily between cingulate area 29d and visual areas 17 and 18. Regarding the laminar origin of these connections, in the rat

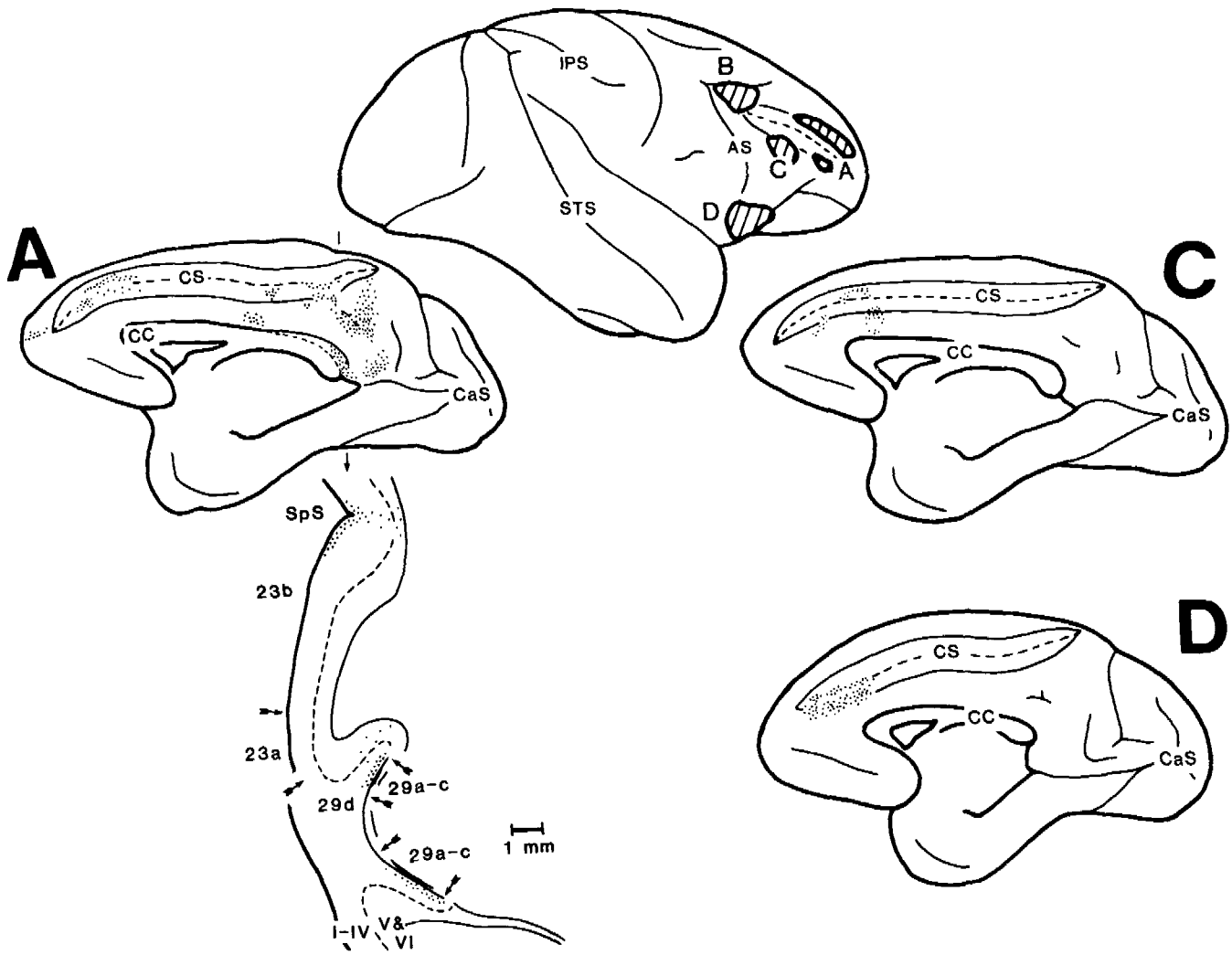

Fig. 8. Distribution of labeled terminals (dots) following ^{3}H-amino acid injections into prefrontal cortex (hatched). AS, arcuate sulcus. No labeling was present in cingulate cortex following an injection into area 8 (B).

the visual projection cells are mainly in layer V and less in layer III; in the rabbit most cells are in layers II and III and less in layer V; in the monkey visual projection neurons are limited to layer III. Also, area 24b has reciprocal connections with area 18 and to a lesser extent with area 17 in rat and rabbit, but no such connections appear to exist in monkey.

Auditory. As with visual cortical input, there are no direct primary auditory cortical efferents to the monkey cingulate cortex. However, there are auditory association areas in the superior temporal gyrus (STG) that receive afferents from auditory koniocortex (Pandya and Sanides, '73; Seltzer and Pandya, '78). It appears in the present study that most auditory input to cingulate cortex originates from the rostral part of the STG and terminates in area 25 and rostral area 24.

Multimodal. Anatomical and physiological studies have shown that prefrontal, insular, and posterior parietal cortices are multimodal areas. Thus, these areas receive multiple sensory afferents from unimodal parasensory association cortices (Pandya and Kuypers, '69; Jones and Powell, '70; Chavis and Pandya, '76). In these regions neuronal discharges are linked to more than one sensory modality, can occur during or after eye or arm movements, and respond to stimuli with motivational significance (Bignall and Imbert, '69; Schechter and Murphy, '75; Newman

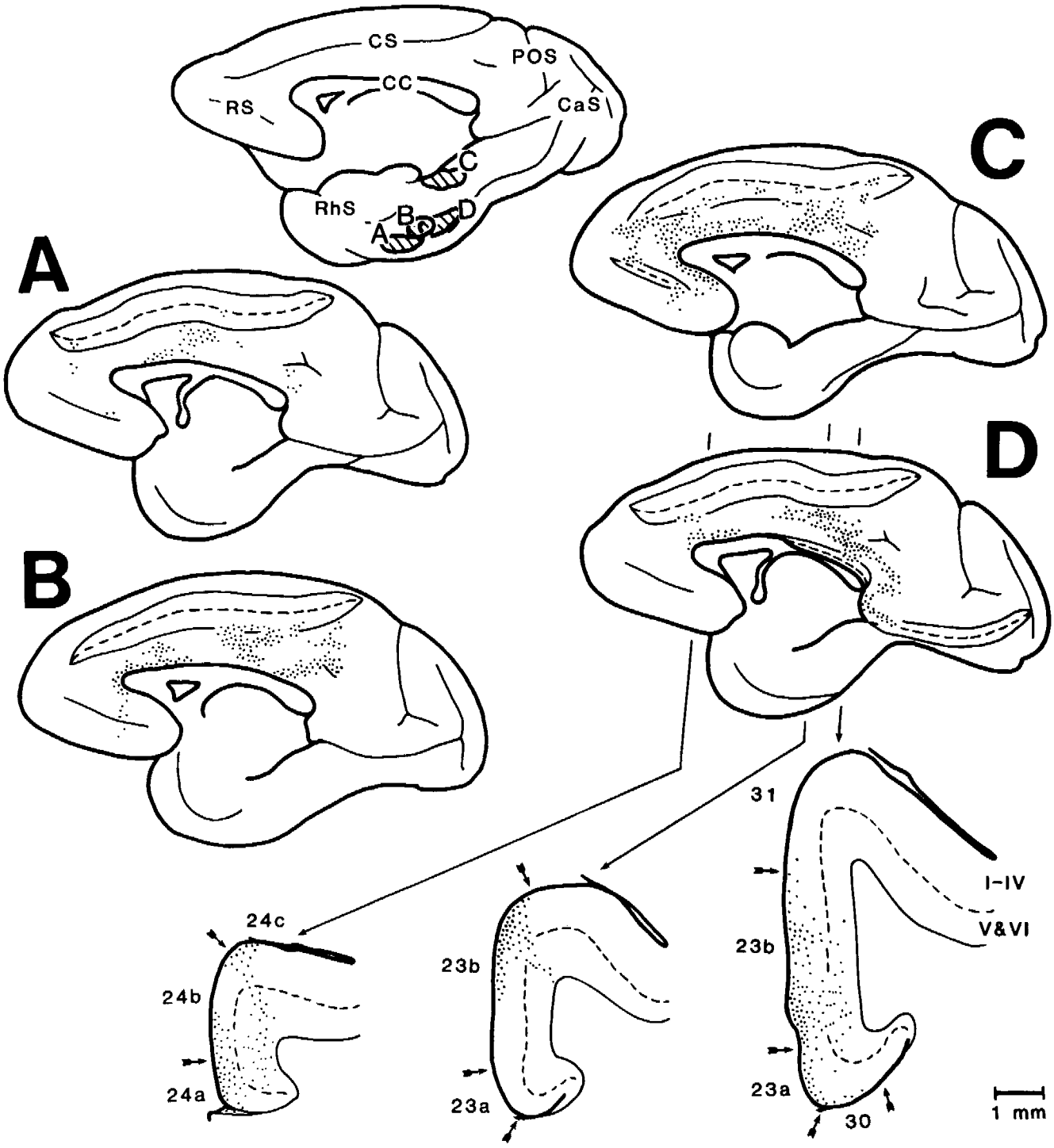

Fig. 9. Location of labeled terminals in cingulate cortex following ^{3}H-amino acid injections into parahippocampal cortex.

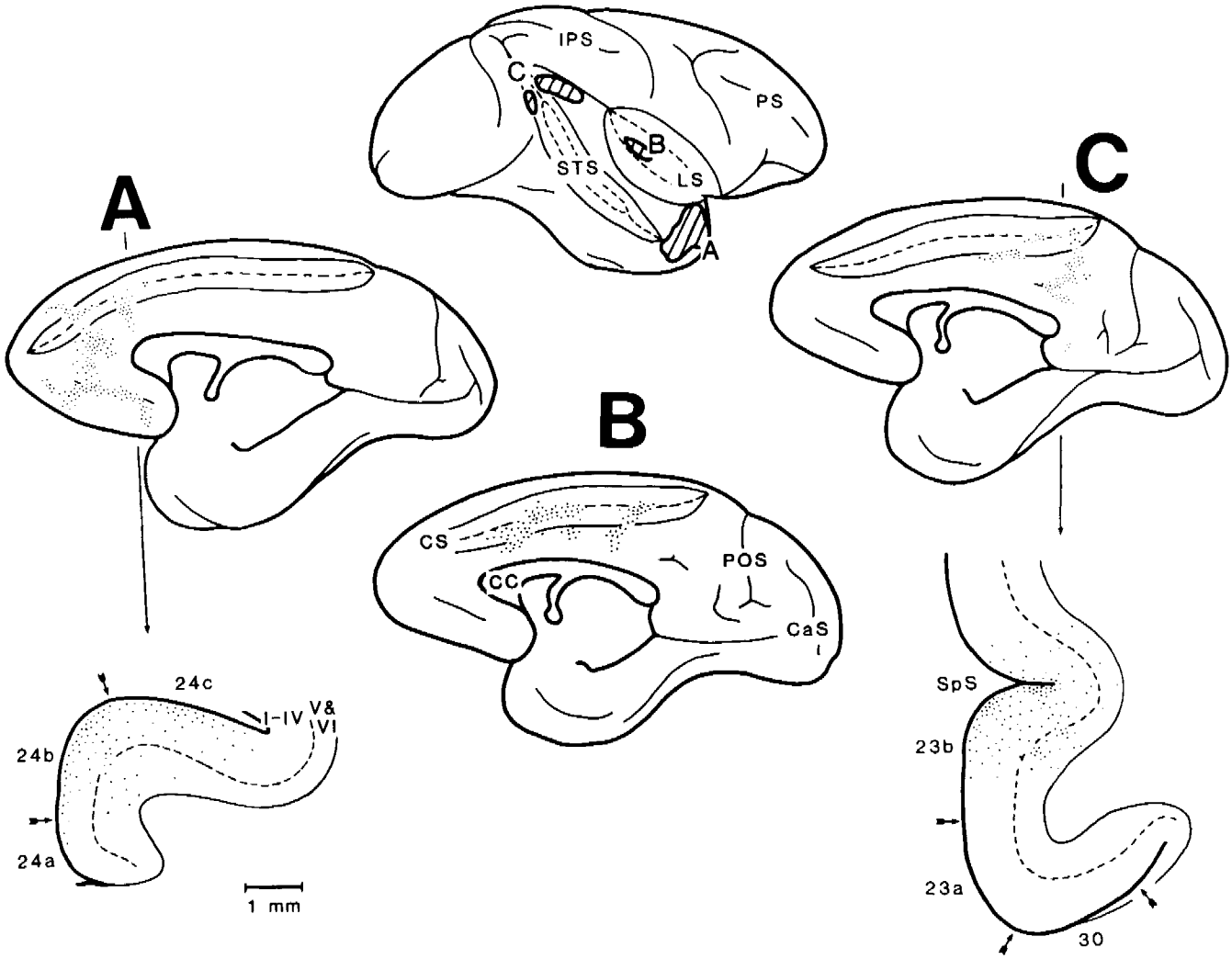

Fig. 10. Patterns of labeled terminals in cingulate cortex after lateral temporal lobe injections including the temporal pole (A), insula (B), and cortex of the superior temporal gyrus and sulcus (C).

and Lindsley, '76; Robinson et al., '78; Hyvärinen and Selepin, '79; Lynch, '80).

The connections of these multimodal areas with cingulate cortex have now been described. Prefrontal connections from area 46 are most pronounced to posterior cingulate areas 29, 30, 23, and 31 while orbital projections terminate mainly in rostral area 24 with a smaller contingent to caudal cortex. Parahippocampal areas TH, TL, and TF project extensively throughout anterior and posterior cingulate cortices. Parietal projections arising in PG terminate mainly in caudal areas 24a and b while those of Opt terminate mainly in areas 30, 23a, 23b, and 31 of posterior cingulate cortex. Finally, area TPO in the STS projects throughout cingulate cortex. These observations complement previously reported projections from the parietal lobe and other areas (Pandya and Kuypers, '69; Jones and Powell, '70; Baleydier and Mauguiere, '80; Pandya and Seltzer, '82; Petrides and Pandya, '84).

In view of the lack of direct projections from sensory to cingulate areas in monkey, an important source of sensory input to cingulate cortex likely comes via the multimodal areas. This may explain some attentional deficits in sensory space following ablations of cingulate cortex (Watson et al., '73).

Connections of premotor cingulate cortex, area 24c

It is possible that part of area 24c is a key link with the motor system in terms of corticocortical connections since

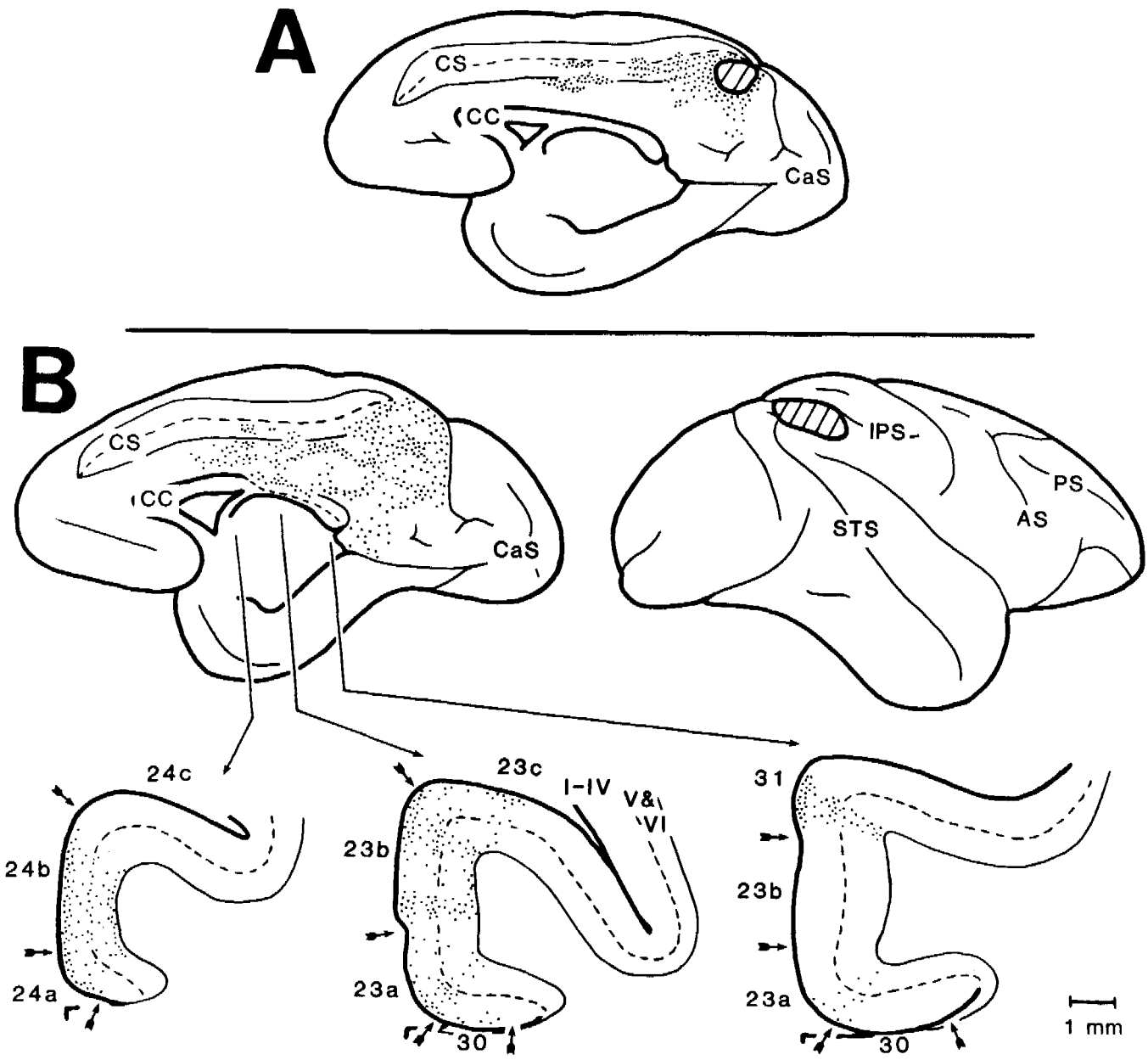

Fig. 11. Distribution of labeled terminals on the medial surface following ^{3}H-amino acid injections into medial parietal (A) and inferior parietal (B) cortices.

this area projects to motor and premotor cortices (Muakkassa and Strick, '79; Barbas and Pandya, '81). The previous article demonstrates that the ventral anterior, densocellular division of the medial dorsal, and limitans thalamic nuclei contribute major inputs to area 24c while the present analysis indicates that cortical inputs include those from area 23, prefrontal areas 46 and 12, the amygdala, the insula, cortex of the superior temporal sulcus, and area TG of the temporal pole. Since area 24 does not appear to receive direct input from area 19, area 23 may provide a critical link for integrating visual and motor activity via a transcingulate route. Auditory afferents to area 24c may be more direct from area TPO and not require area 23 as an intermediary.

In nonprimate species connections between medial parts of motor area 8 and cingulate area 29d appear to be a prominent form of motor and cingulate connections with areas 29d and 24b receiving most visual connections (Vogt

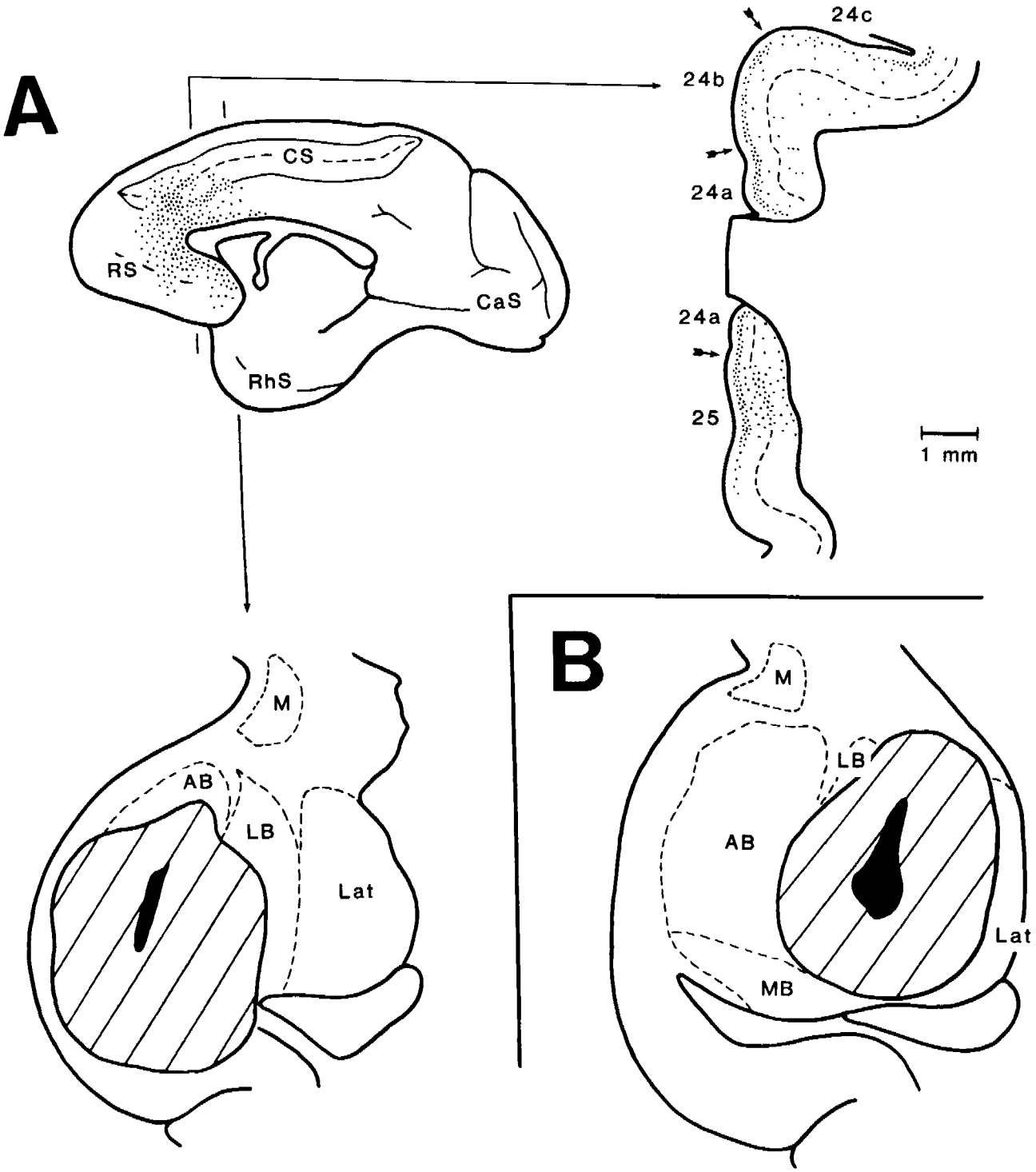

Fig. 12. Location of labeled terminals in rostral cingulate cortex following injections of ^{3}H-amino acids into the amygdala. Although two injections were placed in slightly different parts of the amygdala, terminal fields in cingulate cortex were labeled in essentially the same way in both cases.

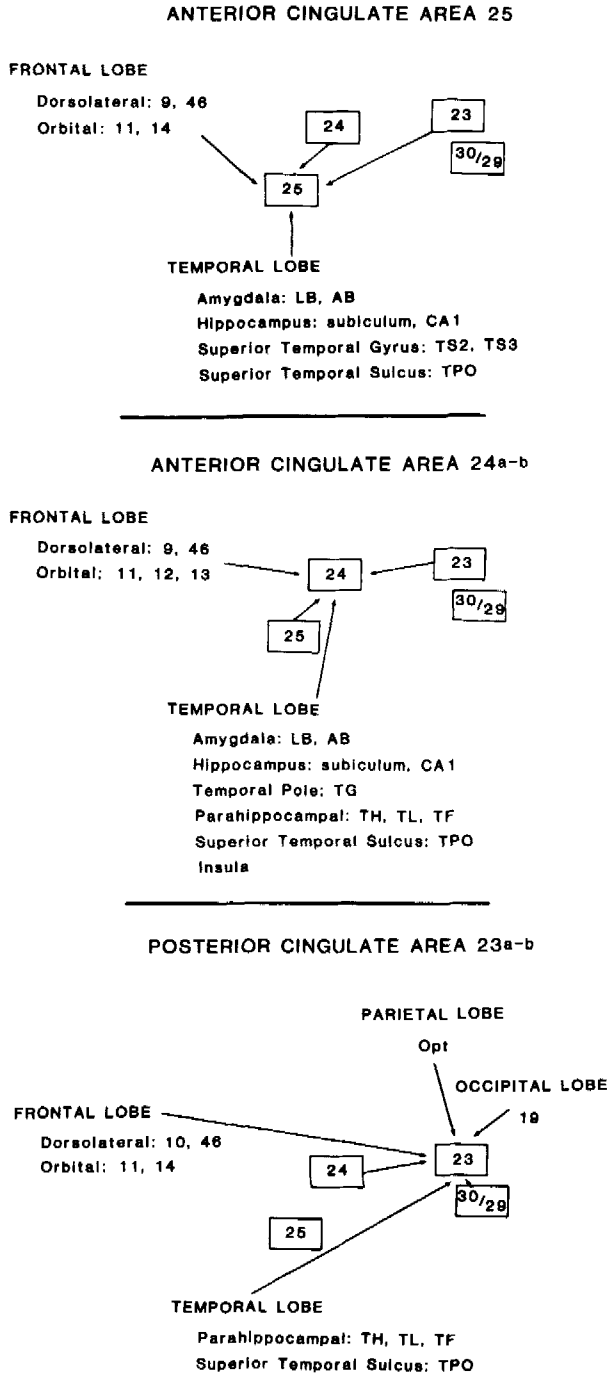

Fig. 13. Summary of the principal afferent cortical and amygdalar connections of cingulate areas 25, 24a,b, and 23a,b. Notice that rostral but not caudal areas 24a and b are illustrated. Caudal area 24 has an additional projection from area PG of the parietal lobe and no amygdalar input.

and Miller, '83; Vogt et al., '86). The relative importance of area 29d as a sensorimotor integration area may be greatly reduced in the monkey where areas 23 and 24c may be the predominant players.

Area 29 in the monkey does not project directly to premotor area 24c but does receive substantial multimodal input from area 46. Area 29 interacts with the motor system, like many cerebral cortical areas, via direct projections to the caudate and pontine nuclei (Schwab et al., '77; Royce, '82; Wiesendanger and Wiesendanger, '82). A gate control model has been proposed by Gabriel et al. ('86) that states that subicular inputs to cingulate cortex select between corticostriatal/corticopontine or corticothalamic projection neurons depending upon the state of phasic and tonic sensory inputs to the subiculum. In particular, there is a buildup of subicular neuronal discharge that precedes an active avoidance response to a conditioned sensory stimulus, and this might release central motor patterns. In the monkey, area 29, rostral area 24a, and area 25 all receive subicular input and are, therefore, candidates for this mechanism of interaction with the motor system.

Rostral vs. caudal area 24

Area 24 is not homogeneous in either the ventrodorsal or rostrocaudal plane. As noted in the previous article, area 24a is least differentiated cytoarchitecturally while areas 24b and 24c have more distinct laminar characteristics. We are aware of only one investigator (Sarkissov, '55) who recognized rostrocaudal differences in the cytoarchitecture of area 24 and who termed this transitional region area 23/24a–c. Although it is true that caudal area 24 has a poorly differentiated layer IV, we have not delineated this as a separate entity. However, there may be a connectional basis for pursuing this differentiation further, since the present study indicates that rostral and caudal area 24 differ in terms of their afferents. Thus, caudal area 24 receives parietal PG input but not amygdalar or STG afferents. In addition, the bulk of TH, TF, and TL projections terminate in caudal area 24 although the rostral areas also receive this input.

Intracingulate connections

Intracingulate connections may be viewed as organized in three tiers. In the rat and rabbit there is a ventral tier in which area 25 projects to areas 24 and 29, an intermediate tier in which area 24a is connected with areas 29a and 29b, and a dorsal tier in which area 24b is interconnected with dorsal and posterior areas 29c and 29d (Vogt and Miller, '83; Vogt et al., '86). In the monkey there is also a three-tier organization, but of a somewhat different composition. Thus, there is a ventral tier in which area 25 projects to area 24 and areas 29 and 30 project to caudal area 23. There is an intermediate tier in which area 24a is connected with areas 23a–b. Finally, in the dorsal tier, areas 24b and 24c are connected with areas 23b and 23c.

It should be emphasized that intracingulate connections between the anterior and posterior cortices represent a fundamental species difference between rodents and primates. Thus, in rodents anterior and posterior cingulate cortices are composed of areas 24 and 29, respectively, and

these are the areas that are reciprocally connected. In primates intracingulate connections are mainly between anterior area 24 and posterior area 23, not posterior area 29.

Although there are many possible connectional sequences by which limbic, sensory, and motor connections might be organized in cingulate cortex, one possible sequence is the following. Connections from the subiculum and area TH terminate in area 29, which in turn projects to areas 30 and 23a. The intermediate and dorsal tiers interconnect anterior and posterior cingulate cortices including those with area 24c containing a premotor cingulate area as noted above. According to this scheme area 23 in monkey is pivotal for interactions among allocortical temporal areas via areas 29 and 30 and visual cortices via area 19.

Proisocortical afferents

There are several proisocortical areas that project to cingulate cortex. The insula is one such input (Vogt et al., '79), which has been described as originating from agranular and dysgranular insular cortices (Mesulam and Mufson, '82). It is unclear in both of these studies, however, exactly where in cingulate cortex this input terminates. In the present study it has been shown that areas 24b and 24c and 23b and 23c receive the bulk of insular afferents.

Parahippocampal projections to cingulate cortex have also been reported (Vogt et al., '79; Baleydier and Mauguiere, '80) but can now be defined in some detail. First, these connections appear to be arranged in a loose topographic fashion such that rostral and medial parahippocampal cortices project primarily to area 24 while caudal and lateral parts of areas TF and TL project to posterior cingulate cortex. These projections are not segregated into entirely separate projection zones, however. Second, in terms of laminar origin, projections to rostral area 24 originate mainly in layer V while those to posterior cingulate cortex are mainly from neurons in layer III. Finally, most parahippocampal areas (TH, TL, and TF) terminate in areas 23 and 30, caudal area 24, and lightly in rostral area 24. Only large tritiated amino acid injections into area TH produce labeling of terminals in areas 29a–c. Areas TF and TL do not appear to project to area 29. These observations and those made above point to the pivotal role of area 23 in sensorimotor and limbic association processes.

Amygdalar connections

Projections of the lateral and accessory basal nuclei of the amygdala to anterior cingulate cortex are of interest for two reasons. First, as already noted above, these nuclei project to anterior area 24, thus differentiating anterior and posterior parts of area 24. Second, as also noted in a previous study (Amaral and Price, '84), the layer of termination is mainly in deep layer I and layer II. This contrasts with broader laminar projections to anterior area 24 of prefrontal, parahippocampal, temporal pole, and posterior cingulate (Pandya et al., '81) cortices, all of which project to layers I–V.

One interpretation of the above observations is that amygdalar projections are focused on layer II neurons in area 24. At present no extrinsic projections have been reported for layer II neurons. However, they could project intrinsic collaterals to neurons in layers III and V to influence neurons that project to other cortical areas. One possible function of the amygdalar input is in significance coding. Since some amygdalar neurons respond to visual stimuli that have been paired with rewarding or aversive stimuli (Rolls, '81), it is possible that they contribute to the role of anterior cingulate cortex in significance coding processes (Gabriel et al., '80).

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