

Pattern in the Laminar Origin of Corticocortical Connections

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ABSTRACT

The laminar origin of cortical projections to the frontal cortex was studied in 17 adult rhesus monkeys with the use of the retrograde transport of horseradish peroxidase (HRP). The frontal regions injected with HRP extended from the posterior periarculate region to the frontal pole. The architectonic boundaries of areas containing HRP-labeled neurons were determined from matched sections stained for the visualization of cell bodies, myelin, or acetylcholinesterase. The results showed that the laminar origin of both nearby and distant corticocortical projections was correlated with the architectonic differentiation of the regions giving rise to the projecting afferent fibers. Frontally directed projections from limbic cortices, which show a rudimentary laminar organization, emanated mainly from deep layers. On the other hand, projections from increasingly more differentiated cortices arose progressively from the upper (or supragranular) layers. This pattern was observed for projections originating along the axis of architectonic differentiation of the visual, somatosensory, auditory, motor, and prefrontal cortical systems. Thus, as the cortical architecture within each system changes from limbic areas toward the primary cortices, the origin of frontally directed projections shifts from predominantly infragranular to predominantly supragranular layers.

Key words: cortical architecture, connectional organization, cortical differentiation, limbic and sensory cortex

Studies on the laminar origin of corticocortical projections have concentrated on short axon connections between nearby regions within the same sensory modality. These studies suggest that projections directed away from primary sensory cortex originate mainly in layer III, and to a lesser extent from the deep layers (V and VI). On the other hand, neurons projecting toward the primary areas originate from layer III, but also in substantial numbers from the deep layers (Galaburda and Pandya, '83; Gilbert and Kelly, '75; Jones et al., '79; Jones and Wise, '77; Maunsell and Van Essen, '83; Rockland and Pandya, '79; Shatz, '77; Spatz, '77; Wong-Riley, '79). The above patterns seem to typify connections between regions subserving the same modality, but it is not clear what patterns underlie connections between other cortical regions. For example, one may ask what patterns characterize long axon connections, or connections which are not modality specific, or cross-modal connections? Some of these questions were addressed in the present study by investigating the laminar origin of projections to the prefrontal and premotor cortices of rhesus monkeys.

Unlike the primary cortices, whose connections are restricted to nearby cortical regions, the prefrontal cortex of

rhesus monkeys receives afferent fibers from a spectrum of sensory, motor, polymodal, and limbic cortices. Some of these afferent fibers originate within the frontal cortex and some originate in distant cortical regions. Like the sensory specific connections, most projections to the prefrontal cortex of rhesus monkeys originate in layers III, V, and VI. However, the proportion of projecting cells situated within each of the layers differs from one cortical region to the next (Barbas and Mesulam, '81, '85). For example, most projections from limbic areas emanate from the deep layers, but projections from regions close to the primary sensory areas originate mainly from layer III. The most striking morphological difference between limbic and parasensory areas is the degree of their architectonic differentiation. Limbic cortices have a rudimentary lamination, whereas parasensory areas are characterized by a more complex laminar organization. This suggests that the laminar origin of prefrontally directed projections may be associated with the architecture of the regions giving rise to the projections. The present study provides evidence consistent

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with this view. Thus, as the cortex shows a gradual laminar differentiation from limbic toward the primary areas (Sanides, '70, '72; see Pandya and Yeterian, '85, for review), the origin of frontally directed projections gradually shifts from predominantly infragranular to predominantly supragranular layers.

MATERIALS AND METHODS

The data were obtained from 17 adult rhesus monkeys. One subsector of the frontal cortex was injected with horseradish peroxidase (HRP) in each animal. The frontal cortex here refers to the prefrontal region, which extends from the rostral bank of the arcuate sulcus to the frontal pole, and to the premotor cortex, situated in the caudal bank of the arcuate sulcus. The zones injected with HRP included portions of Walker's ('40) prefrontal areas 10–12, 8, 45, 46, and the rostral part of the premotor area 6. With respect to anatomic landmarks, the injection sites were situated above and below the principal sulcus along its entire length (areas 10 and 46), anterior to the upper and lower limbs of the arcuate sulcus (areas 8 and 45), in orbital areas 11 and 12, or in the caudal bank of the arcuate sulcus (area 6).

The monkeys were anesthetized with sodium pentobarbital (35 mg/kg i.v.). Surgery was performed under aseptic conditions. The monkey's head was firmly positioned in a holder that left the cranium unobstructed for surgical approach. The femoral vein was catheterized for infusion of mannitol (Invenex, Ohio, 25%) to reduce the volume of the brain and avoid traumatic edema. A bone defect was made, the dura was retracted, and the cortex was exposed.

Injections of HRP (Miles, 20% aqueous solution) were made with a microsyringe (Hamilton, 75 N, 5 μ l) mounted on a microdrive that was attached to a carrier (Kopf). The needle was lowered to the desired site under microscopic guidance. Small amounts (0.05 μ l) of the injectate were delivered 1.5 mm below the pial surface at each of one or two adjacent sites separated by 1–2 mm over a 30-minute period. A survival period of 48 hours allowed HRP to be transported via axons from the injection site back to the parent cell bodies. The monkeys were then reanesthetized and perfused through the heart with saline until the blood was cleared. A timed fixation procedure then followed, during which 2 liters of fixative (1.25% glutaraldehyde, 1% paraformaldehyde in 0.1 M phosphate buffer at pH 7.4) were delivered over a 30-minute period. The fixative was followed by perfusion with 2 liters cold (4°C) sucrose phosphate buffer (10% sucrose in 0.1 M phosphate buffer, pH 7.4).

The brain was then removed from the skull, photographed, placed in sucrose buffer, and transferred to a freezing microtome where it was cut at 40 μ m. Sections were collected in a 0.1 M phosphate buffer (pH 7.4). Every tenth section was treated for the visualization of HRP according to a procedure in which tetramethylbenzidine is used as the chromogen. The tissue was mounted, dried, and counterstained with neutral red (Mesulam et al., '80).

Sections were examined microscopically under brightfield illumination. Outlines of brain sections and the location of labeled cells ipsilateral to the injection site were transferred from the slides onto paper by using an X-Y recorder (Hewlett Packard, 7044A) that was electronically coupled to the stage of the microscope. Counts of HRP-labeled neurons were obtained from every 20th section throughout the entire cerebral cortex. The architecture of regions containing labeled neurons was identified from matched sections

stained for cell bodies, myelin, or acetylcholinesterase (AChE). Cortical boundaries were determined by using criteria from both classical and, where available, recent studies.

RESULTS

Most labeled neurons were located in cortical layers III and V with a few in VI. The distribution of labeled neurons in these layers differed from one cortical region to the other in a manner consistent from case to case. Because of the similar trend in the distribution of labeled cells by layer in each architectonic region, data from all experiments having labeled cells within a given distinct area were pooled and are shown in Figure 1. Individual graphs represent systems of projections to the frontal cortex originating in ipsilateral visual, somatosensory, auditory, motor, and prefrontal cortices. Labeled neurons within each system were observed in ten or more cases following HRP injection in various sectors of the frontal cortex. Within each system adjacent architectonic zones were grouped into five categories with the least differentiated cortices on the left and progressively more differentiated cortices on the right. Pairs of bars represent the percentage of labeled cells in the upper and lower layers. Because it is sometimes difficult to determine the border between layers V and VI, particularly in the less-well-differentiated cortices, labeled neurons in the infragranular layers were considered together.

The cortical regions containing HRP-labeled neurons within each system were placed in one of five categories on the basis of architectonic studies that describe a progressive laminar differentiation and increased myelin content from limbic toward the primary areas (Bishop, '65; Sanides, '70; see Pandya and Yeterian, '85, for review). In architectonic terminology limbic cortical areas are referred to as periallocortices—or, for the slightly more differentiated regions, proisocortices. Limbic areas can be readily distinguished from adjacent cortices on the basis of several morphological features: They have a rudimentary laminar arrangement with a prominent deep and a sparsely populated upper layer. Limbic areas have a high cholinesterase and a low myelin content (Barbas and Pandya, '83; Gower, '81; Mesulam et al., '84; Sanides, '70, '72). The portion of the limbic cortex that lies at the foot of each sensory, motor, or prefrontal system, and forms the first, or primordial, step in cortical differentiation, is included in category 1 on the basis of architectonic and connectional grounds (see Galaburda and Pandya, '82; Pandya and Yeterian, '85, for reviews). At the other extreme, category 5 includes the most differentiated cortices situated immediately adjacent to or within the primary areas. The primary sensory areas here refer only to the true koniocortices, and include V1 in the visual system, 3b in the somatosensory system, and A1 (area KA of Sanides '70) in the auditory system. The term primary motor refers to area 4a and 4b (Vogt and Vogt, '19). Categories 2–4 show an intermediate architectonic differentiation, and regions were placed in one of these categories on the basis of architectonic studies that describe a progressive laminar differentiation in cortical systems (Barbas and Pandya, '82; Galaburda and Pandya, '83; Pandya and Yeterian, '85; Sanides, '70, '72).

Architectonic borders are at times difficult to delineate. However, because the five categories are relatively broad and include clusters of adjacent architectonic regions, errors in classifying labeled neurons to one architectonic zone are unlikely to affect the results significantly. In cases

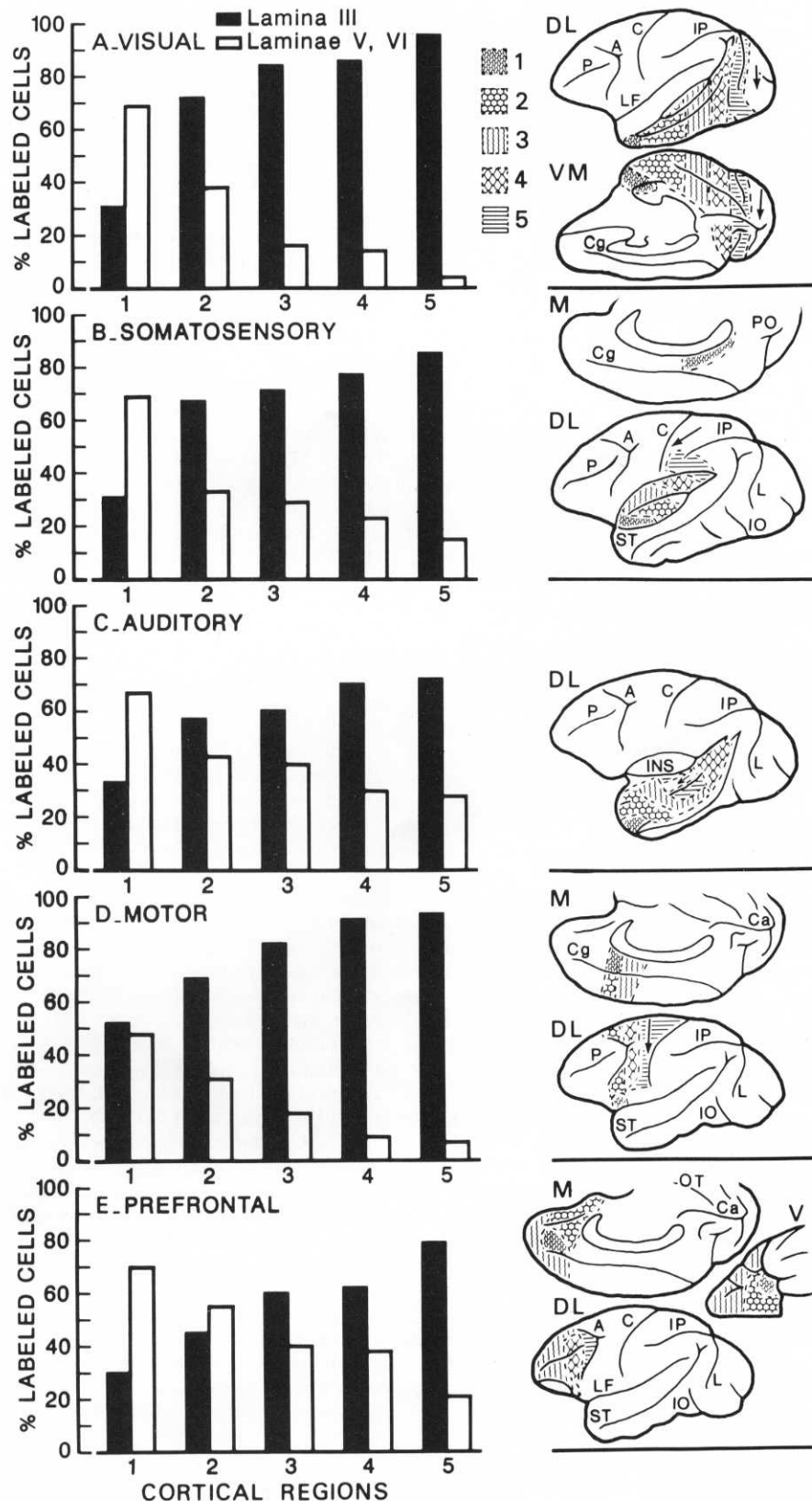


Fig. 1. The laminar distribution of ipsilateral frontally directed neurons originating in the least architecturally differentiated, or limbic cortical regions (1, left), and in progressively more differentiated cortices (5, right). Categories 1-5 in each system (A-E) represent groups of architectonic regions delineated with the aid of matched sections stained for the visualization of cell bodies, myelin, or AChE, based on descriptions of classical, and where available, recent studies describing cortical boundaries. The black (lamina III) and white (laminae V and VI) bars in each category (left)

add up to 100%. Outlines of the boundaries of regions 1-5 are shown on the dorsolateral (DL), ventromedial (VM), medial (M), and ventral (V) surfaces of the brain (right). The primary cortices are shown by arrows. Abbreviations for sulci on the right drawings are: A, arcuate; C, central; Ca, calcarine; Cg, cingulate; INS, insula; IO, inferior occipital; IP, intraparietal; L, lunate; LF, lateral fissure; OT, occipitotemporal; P, principal; PO, parietooccipital; ST, superior temporal.

where it was difficult to delineate architectonic boundaries, regions containing labeled neurons were placed in one of the five categories on the basis of anatomic landmarks. This decision was made because cortical architecture seems to change gradually in a way that is largely predictable by the distance from the primary areas (Galaburda and Pandya, '83; Sanides, '70, '72; Pandya and Yeterian, '85, for review).

The areas that contained labeled neurons following HRP injection in frontal cortical areas are shown diagrammatically by the five patterns on the surface of the brain (Fig. 1, right). Categories 1-5 (Fig. 1, left) include all regions that were found to project to the frontal cortical areas injected with HRP.

The classification of regions within the axis of visual cortical differentiation is based on both classical work (Bonin and Bailey, '47) and a recent study describing a progressive laminar differentiation within the visual system (Rosene and Pandya, '83). Distinct regions within extrastriate cortices were identified on the basis of recent studies describing architectonic features of specific visual cortices (see Van Essen, '79; Zeki, '78, for reviews; Covey et al., '82; Desimone and Ungerleider, '86; Maunsell and Van Essen, '83; Ungerleider and Mishkin, '79).

Labeled neurons in visual association areas were observed following HRP injection in areas 8 and 45 situated anterior to and in the rostral bank of the upper and lower limbs of the arcuate sulcus (five cases), in area 46 below the principal sulcus caudally (two cases), in anterior area 12 (two cases), and in area 11 (one case). Labeled neurons were observed in inferior temporal and extrastriate cortices. Figure 1A shows the laminar distribution of labeled neurons in the visual cortical areas ($n=6,431$). The areas included in each category are (from left to right) 1, proisocortex: ventral temporal polar and rhinal regions; 2, anterior TE: anterior inferior temporal cortex up to the level of the anterior middle temporal dimple; 3, posterior TE and MT: posterior inferior temporal gyrus and adjacent cortex within the depths and caudal bank of the superior temporal sulcus up to the level of the posterior middle temporal dimple; 4, anterior peristriate: anterior half of V4, and a medial parietooccipital region (area PO of Covey et al., '82) situated posterior to the medial parietal cortex; and 5, posterior peristriate: areas V3, ventral posterior (VP) and the V2-V4 border.

The architecture of the somatosensory system as a unit has not been as thoroughly investigated as that of other systems. However, several distinct architectonic regions within the somatosensory system have been described (Jones and Burton, '76; Mesulam and Mufson, '82; Pandya and Seltzer, '82; Roberts and Akert, '63; see Woolsey, '81, for reviews). In addition, a progressive architectonic differentiation has been described for the somatosensory cortex (Sanides, '70; see Pandya and Yeterian, '85, for review). On the lateral surface the somatosensory cortex originates in the proisocortices at the rostral frontal operculum and agranular insula and proceeds caudally toward the pericentral and parietal operculum, area PF, postcentral areas 2, 1, and koniocortical area 3b (Sanides, '70). On the medial surface area 23 forms the first step in the architectonic differentiation of the mediodorsal portion of somatosensory-related cortex, which includes the supplementary somatosensory area and area PE of the superior parietal lobule. Only area 23 of the medial parietal cortex contained a significant number of neurons retrogradely labeled from

the frontal injection sites. A few labeled neurons were also noted in area PE after injection of HRP in the premotor area 6. However, the premotor injections were situated in rostral area 6 and were largely outside the focus of projections from area PE (Petrides and Pandya, '84). The rest of the somatosensory-related projections to the frontal cortex appear to originate from the lateral surface.

Labeled neurons were observed in somatosensory association regions after HRP injection in area 46 above, and particularly below, the principal sulcus at its middle and caudal extent (four cases), in area 12 (two cases), in area 11 (one case), and in ventral and dorsal area 6 within the caudal bank of the lower and upper limbs of the arcuate sulcus (three cases). A small number of labeled neurons was also noted in somatosensory association areas following HRP injection in periarculate areas 8 and 45 (five cases). Figure 1B shows the distribution of labeled cells in the somatosensory system ($n=4,939$). The areas included in each category are 1, proisocortex: anterior part of the dorsal lateral fissure, the agranular insula, and area 23 (Sanides, '70); 2, dysgranular insula; 3, anterior operculum: the frontal opercular parts of areas 1 and 2; 4, SII: region situated in the pericentral operculum; and 5, post central: areas 1, 2, and 3a situated posterior to, and in the depths of the central sulcus, and areas PF, PFop and PGop situated between the dorsal lateral fissure at its caudal extent and the anterior part of the intraparietal sulcus (Pandya and Seltzer, '82). The few labeled cells found in area PE were included in this category.

The classification of regions along the axis of auditory cortical differentiation is based on the architectonic parcellation of Pandya and Sanides ('73), Seltzer and Pandya ('78), and Galaburda and Pandya ('83). Labeled neurons in auditory association regions were noted after HRP injection above the middle and rostral part of the principal sulcus (areas 46 and 10, two cases), in caudal area 12 (one case), anterior to the upper limb of the arcuate sulcus (two cases), and in area 11 (one case). Only a few labeled neurons were noted in auditory association cortices after HRP injection above and below the caudal half of the principal sulcus (three cases), or after HRP injection anterior to the arcuate sulcus at the junction of areas 8A and 45 (two cases).

Figure 1C shows the distribution of labeled cells in the auditory system ($n=4,540$). The areas included in each category are 1, proisocortex: dorsal polar region; 2, areas TS1-2, anterior area TAa: anterior part of the superior temporal gyrus, and the adjacent cortex in the superficial part of the rostral bank of the superior temporal sulcus. 3, areas TS3, middle TAa, paI: middle part of the superior temporal gyrus and adjacent TAa cortex, and anterior part of the caudal bank of the lateral fissure; 4, areas tpt, posterior TAa, ProA, relt, paAc: posterior extent of the superior temporal gyrus and the adjacent area TAa, and posterior half of the ventral lateral fissure; 5, area paAlt: region situated immediately below the primary auditory cortex.

The architecture of the motor system has not been as extensively investigated as that of some of the sensory systems. However, Sanides ('70) has described a progressive laminar differentiation within the motor cortical system that originates in cingulate area 24 on the medial surface and around the anterior part of the dorsal lateral fissure ventrally. Both of these proisocortices have strong reciprocal connections with the premotor (area 6) cortex (Damasio et al., '81; Jürgens, '84; Muakkassa and Strick, '79; Pandya et al., '81). The architecture of the entire motor system or

of portions of the motor system have also been investigated in classical (Bonin and Bailey, '47; Brodmann, '05; Vogt and Vogt, '19) and in recent (Barbas and Pandya, '81) studies.

Labeled neurons in motor and premotor regions were noted after HRP injection in area 6 at the caudal bank of the arcuate sulcus (three cases), above and below the posterior half of the principal sulcus (five cases), in areas 8 and 45 anterior to the arcuate sulcus (four cases), in area 12 (two cases), and in area 11 (one case). Figure 1D shows the distribution of labeled neurons in the motor system ($n=6,938$). The areas included in each category are 1, proisocortex: anterior half of area 24 below the cingulate sulcus, and a region above the anterior part of the dorsal lateral fissure; 2, anterior area 6: anterior half of area 6 corresponding to the Vogts' ('19) areas 6b β , 6ba, and 6a β ; 3, posterior area 24, MII: posterior portion of area 24, and the supplementary motor area (Woolsey et al., '51); 4, posterior area 6: posterior half of area 6 at the level of the spur of the arcuate sulcus; and 5, motor: precentral area 4a and 4b (Vogt and Vogt, '19).

Classification of the categories in the prefrontal cortex is based on the maps of Walker ('40) and on a recent study showing architectonic trends in the prefrontal cortex (Barbas and Pandya, '82). Retrogradely labeled neurons, reflecting connections among subsectors of the frontal cortex, were noted after injection of HRP in all frontal sites (17 cases). The zones injected with HRP included rostral area 6 in the caudal bank of the arcuate sulcus (three cases), areas 8 and 45 in the anterior periarculate zone (five cases), area 46 above and below the principal sulcus (five cases), area 12 (two cases), orbital area 11 (one case), and area 10 at the dorsolateral frontal pole (one case). Figure 1E shows the distribution of labeled neurons in the prefrontal system ($n=37,056$). The areas included in each category are 1, proisocortex: anterior medial region below the cingulate sulcus and a region next to the olfactory tubercle in the posterior orbitofrontal cortex. 2, orbital and medial areas 13, 14, 25; 3, areas 9–12; 4, area 46 at the posterior half of the periprincipalis region; and 5, areas 8 and 45 anterior to the arcuate sulcus.

Within each system the proportion of labeled neurons in the deep layers (V and VI) is high in the limbic areas (category 1). The contribution of layers V and VI to frontally directed projections decreases progressively toward regions of greater architectonic differentiation and is lowest in regions which lie adjacent to or within the primary cortices or in areas 8 and 45 within the prefrontal cortex (Figs. 1, 2). The proportion of labeled neurons in the supragranular and infragranular layers changes from limbic toward the primary areas in all five systems (Fig. 1A–E), but the magnitude of the change varies in degree. These differences in magnitude may be related to the breadth of origin of frontally directed projections within a given system. For example, the visual association projections originate from as far caudally as the highly differentiated area 18 (or V2) to as far rostrally as the ventral temporal pole that contains limbic proisocortex (Rosene and Pandya, '83); this extreme spread along the axis of visual cortical differentiation may account for the sharp laminar trend of supragranular to infragranular projections observed from regions 1–5 in Figure 1A. The least-dramatic gradient in the supragranular to infragranular ratio along the limbic-parakoniocortical axis is observed in the auditory system. However, relatively few projections to the frontal cortex were found to originate in the most highly differentiated parakoniocortical audi-

tory association areas (Barbas and Mesulam, '81, '85; Barbas, in preparation).

Labeled neurons were also noted in the inferior parietal area PG and in the depths of the rostral bank of the superior temporal sulcus. These regions, occupying a position between somatosensory, visual, and auditory association areas, have visuomotor and polymodal characteristics (Lynch, '80; Seltzer and Pandya, '78) and do not easily fit in the categories of Figure 1. The supragranular to infragranular percentage of labeled cells in the inferior parietal region was 69:31, and in the superior temporal sulcal region it was 67:33.

In summary, following HRP injections in the frontal cortex labeled neurons were observed mostly in layers III, V, and VI in visual, auditory, somatosensory, motor, and the prefrontal cortical systems. In all these systems labeled neurons in the least architectonically differentiated areas were located mainly in layers V and VI. A gradual increase in supragranular labeling was observed in regions that showed an increasing laminar differentiation.

DISCUSSION

The results indicate that the laminar origin of cortical projections to the frontal cortex of the rhesus monkey varied in accordance with the laminar differentiation of the cortical regions that gave rise to such projections. Thus, frontally directed projections from the least architectonically differentiated areas arose mainly from layers V and VI. Projections originating in regions with increasing laminar differentiation arose progressively from the supragranular layers.

The question arises of whether projections to other areas of the cerebral cortex show similar patterns of origin. The literature contains few quantitative data to assess possible trends, but some parallels can be made with projections to other regions. For example, corticocortical projections directed away from the primary sensory areas (termed "forward" connections) have been found to originate primarily in the supragranular layer III when the source is close to or within the primary areas. An example is a projection from V1 to V2. However, when "forward" projections originate in more distant (and less well differentiated) areas, there is always a small but consistent contribution from layer V (Rockland and Pandya, '79; Wong-Riley, '79). An example is a projection from V4 to the inferior temporal cortex. Projections from parasensory areas directed toward the primary areas have been referred to as "backward" connections. In the visual and auditory system of both monkeys and cats, "backward" projections are reported to originate in substantial numbers (estimated to be anywhere from 30% to a majority) from infragranular layers (Galaburda and Pandya, '79; Gilbert and Kelly, '75; Maunsell and Van Essen, '83; Rockland and Pandya, '79; Spatz, '77). Available evidence is insufficient to determine whether the laminar origin of "backward" projections also follows a regional pattern. However, descriptions of the laminar origin of projections to somatosensory, auditory, and visual areas seem to be consistent with a pattern that appears to parallel the architectonic differentiation of the projection zones (Galaburda and Pandya, '83; Jones et al., '79; Jones and Wise, '77; Shatz, '77). It should be noted that because laminar differentiation on the dorsolateral convexity decreases consistently with distance from the primary areas (Galaburda and Pandya, '83; Pandya and Seltzer, '82; Rosene and Pandya, '83; Sanides, '70, '72), "backward" con-

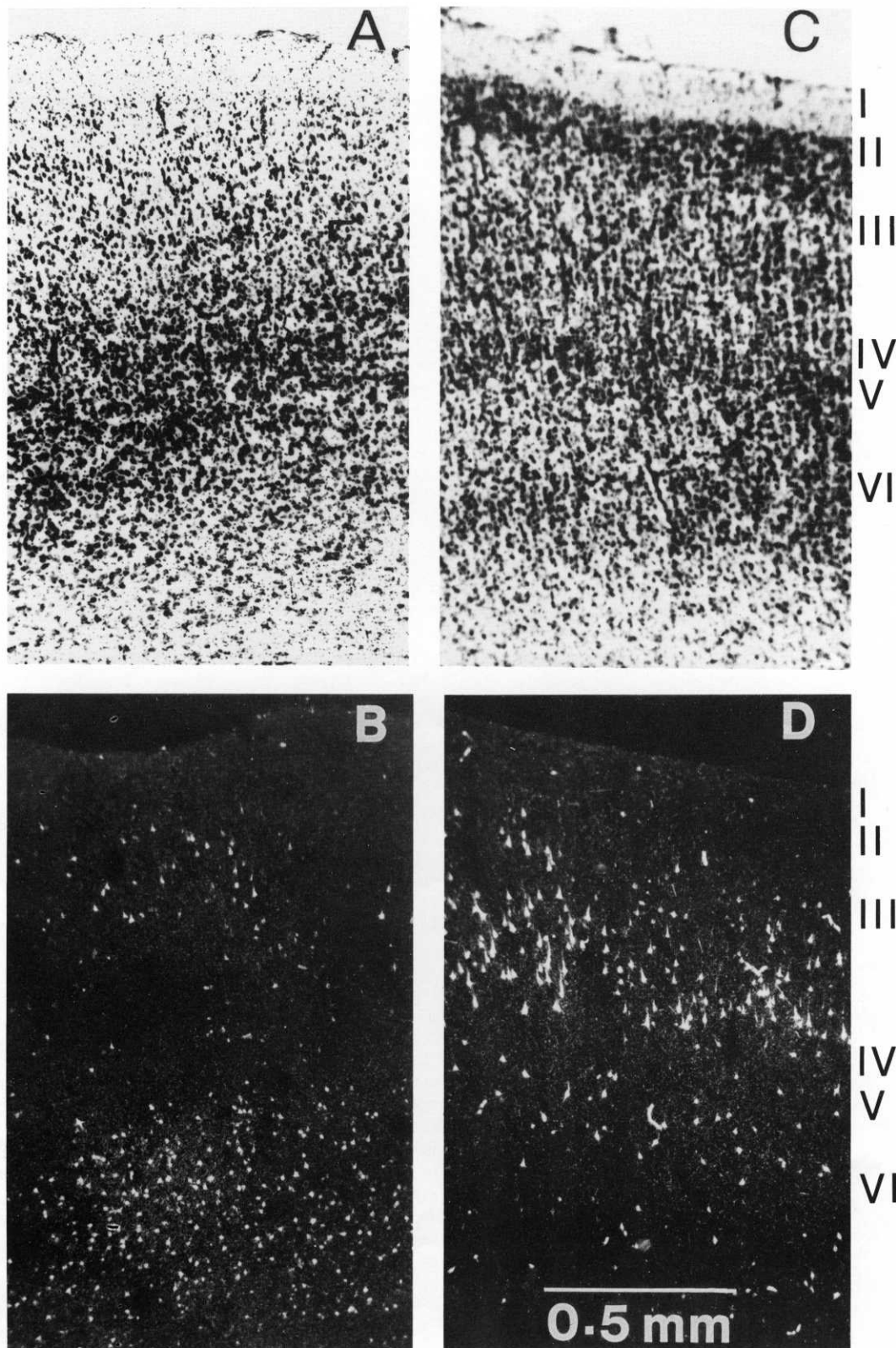


Fig. 2. Examples of architectonic and connectional characteristics of limbic (left), and of regions situated further away from limbic, and closer to primary, cortices (right). The brightfield photomicrographs in A and C show coronal sections stained with cresyl violet to show the cell bodies and their arrangement in layers. Limbic cortical areas (as in A) show a rudimentary laminar arrangement, where only a superficial and a prominent deep cell layer can be distinguished. On the other hand, cortices situated further away from limbic regions and closer to the primary areas have a more

differentiated laminar organization (C). The darkfield photomicrographs in B and D show the laminar distribution of prefrontally directed HRP-labeled neurons in one animal. Most labeled neurons originating in limbic areas are situated in the deep cortical layers (B). In contrast, labeled neurons found in areas further away from limbic areas are mostly situated in the superficial layers (D). A and B were taken from sections through the posterior orbitofrontal region and C and D through the somatosensory area SII.

nections always emanate from less-well-differentiated regions.

Laminar trends can also be observed in the origin of interhemispheric projections. In monkeys commissural connections of sensory cortices originate from the deep part of layer III when the source is close to the primary sensory areas (Jones et al., '75, '79; Jouandet and Gazzaniga, '79; Killackey et al., '83; Rockland and Pandya, '79; Tigges et al., '81; Weller and Kaas, '85). On the other hand, homotypical interhemispheric connections of regions situated at a distance from the primary cortices, such as parietal and prefrontal regions, originate from layer III, and albeit to a lesser extent, also from layer V (Andersen et al., '85; Caminiti and Sbriccoli, '85; Hedreen and Yin, '81; Jacobson and Trojanowski, '74; Schwartz and Goldman-Rakic, '84). Moreover, the contribution of layers other than III in both ipsilateral and interhemispheric connections seems to increase in sensory systems of mice, rats, hamsters, rabbits, and cats (Caminiti et al., '79; Innocenti, '80; Jacobson and Trojanowski, '74; Kelly and Wong, '81; Miller and Vogt, '84; Olavarria and Van Sluyters, '83; Ravizza et al., '76; Swadlow and Weyland, '81; Wise and Jones, '76; Yorke and Caviness, '75), which have an overall less-well-differentiated cortex. Further quantitative data are necessary to determine whether the principle which seems to underlie the pattern of connections to the frontal cortex applies for other corticocortical connections and for other species as well.

It is not clear why corticocortical projections from regions and species with more distinct laminar organization are largely restricted to supragranular layers but are more widespread and encompass layers V and VI in regions with more blurred laminar borders. The answer to this question may lie with events occurring during histogenesis (Jones and Wise, '77; Rakic, '74; Spatz et al., '70; Swadlow and Weyland, '81; Wise and Jones, '76) and may ultimately reflect on the evolutionary development of the cortex (Sanides, '70). The phylogenetically older limbic areas have prominent deep and rather sparsely populated upper layers (Fig. 2A). Newer cortical areas seem to have evolved by differentiation of the deep laminae, but also with the addition of the upper layers. The deep layers, which are the first to develop during histogenesis, may be phylogenetically older laminae throughout the cortex. In this context, it is conceivable that every cortical region has a "limbic" layer, or at least part of the deep layers may retain limbic characteristics. Deep layers, which are also the major source of corticofugal projections in all species (Kelly and Wong, '81; Lund et al., '76; Ravizza et al., '76), have been considered to participate in feedback mechanisms (Maunsell and Van Essen, '83; Rockland and Pandya, '79). The nature of signals conveyed from the deep layers to other cortices is not presently known, and the answer will ultimately lie in the realm of physiology. However, if deep layer projections are found to indeed participate in feedback mechanisms, they may convey signals associated with limbic functions, including the state of the internal milieu.

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