

The Origin of Corticospinal Projections from the Premotor Areas in the Frontal Lobe

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We determined the origin of corticospinal neurons in the frontal lobe. These neurons were labeled by retrograde transport of tracers after injections into either the dorsolateral funiculus at the second cervical segment or the gray matter of the spinal cord throughout the cervical enlargement. Using retrograde transport of tracer from the arm area of the primary motor cortex, we defined the arm representation in each premotor area in another set of animals.

We found that corticospinal projections to cervical segments of the spinal cord originate from the primary motor cortex and from the 6 premotor areas in the frontal lobe. These are the same premotor areas that project directly to the arm area of the primary motor cortex. The premotor areas are located in parts of cytoarchitectonic area 6 on the lateral surface and medial wall of the hemisphere, as well as in subfields of areas 23 and 24 in the cingulate sulcus. The total number of corticospinal neurons in the arm representations of the premotor areas equals or exceeds the total number in the arm representation of the primary motor cortex. The premotor areas collectively comprise more than 60% of the cortical area in the frontal lobe that projects to the spinal cord. Like the primary motor cortex, each of the premotor areas contains local regions that have a high density of corticospinal neurons.

These observations indicate that a substantial component of the corticospinal system originates from the premotor areas in the frontal lobe. Each of the premotor areas has direct access to the spinal cord, and as a consequence, each has the potential to influence the generation and control of movement independently of the primary motor cortex. These findings raise serious questions about the utility of viewing the primary motor cortex as the "upper motoneuron" or "final common pathway" for the central control of movement.

The term "premotor cortex" was originally applied to that portion of the frontal agranular cortex located rostral to the primary motor cortex (Fulton, 1935). Fulton stated that "strictly speaking, the premotor area is restricted to the superior part of area

6a" (Fulton, 1949, p 318) and indicated that it was related to the control of fore- and hindlimb movements. His review of this subject suggests that he considered the portion of area 6a inferior to the arcuate sulcus as the premotor area for oral-facial movements (Fulton, 1949). It is clear that Fulton's premotor cortex included that part of area 6 that lies on the medial wall of the hemisphere. Subsequently, this region was defined as the supplementary motor area (SMA; Penfield and Welch, 1951; Woolsey et al., 1952).

Classically, the premotor cortex has been viewed as functionally distinct from the primary motor cortex and as a center for the integration of complex skilled movements (Campbell, 1905; Fulton and Kennard, 1934; Jacobsen, 1934, 1935). Lesions of the premotor cortex in subhuman primates caused "a disorganization of more highly integrated voluntary movements producing a state akin to apraxia in man" (Fulton, 1935, p 313; see also Jacobsen, 1934, 1935). Electrical stimulation at different sites in the premotor cortex of humans and monkeys evoked movements of proximal and distal body parts (for historical review, see Fulton and Kennard, 1934; Fulton, 1949; Penfield and Welch, 1951; Woolsey et al., 1952; Wiesendanger, 1981). However, when the primary motor cortex was removed, stimulation of the premotor cortex could evoke movements of only proximal body parts (e.g., Vogt and Vogt, 1919; Foerster, 1936; Wiesendanger et al., 1973). Based on early anatomical studies, the premotor area was thought to lack substantial projections to the spinal cord (Fulton, 1949). These and other observations were consistent with a hierarchical concept of the cortical motor areas in which the premotor cortex was at the highest level (Campbell, 1905) and participated in the generation and control of distal movement through its projections to the primary motor cortex (area 4).

Since these early studies, there has been considerable progress in defining the anatomical location of the premotor cortex (Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Godschalk et al., 1984; Strick, 1985; Leichnetz, 1986; Ghosh et al., 1987; Dum and Strick, 1990). Based on the hierarchical concept, we have operationally defined the premotor cortex as that region in the frontal lobe that has direct projections to the primary motor cortex (area 4). According to this definition, the premotor cortex is heterogeneous and is comprised of multiple, spatially separate "premotor areas" (Pandya and Kuypers, 1969; Pandya and Vignolo, 1971; Künzle, 1978; Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Godschalk et al., 1984; Strick, 1985; Leichnetz, 1986; Ghosh et al., 1987). For example, the arm area of the primary motor cortex receives inputs from 3 regions within area 6: (1) the SMA on the medial wall of the hemisphere, (2) the arcuate premotor area (APA) in and around the caudal bank of the arcuate sulcus, and (3) the region in and

Received July 2, 1990; revised Oct. 4, 1990; accepted Oct. 9, 1990.

This work was initiated by support from the Eastern Paralyzed Veterans Association and sustained by funds from the Veterans Administration Medical Research Service and Rehabilitation Research and Development Service and by U.S. Public Health Service Grants 02957 and 24328. We wish to thank Mr. Mike Page for development of computer programs, Ms. Mary Lou Cherney and Sarah Fitzpatrick for their expert technical assistance, and Drs. Kenneth D. Hutchins and Anthony M. Martino for their assistance in some of the initial experiments.

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adjacent to the superior precentral sulcus (SPcS). The primary motor cortex also receives inputs from 2 regions of the frontal lobe that lie within subfields of areas 23 and 24 in the banks of the cingulate sulcus (Künzle, 1978; Muakkassa and Strick, 1979; Godschalk et al., 1984; Strick, 1985; Leichnetz, 1986; Ghosh et al., 1987; Dum and Strick, 1990) and have been termed the rostral and caudal cingulate motor areas (CMAr and CMAc; Hutchins et al., 1988; Dum and Strick, 1989). Thus, the anatomical organization of the premotor cortex is more complicated than previously recognized (for reviews, see Fulton, 1949; Woolsey et al., 1952; Humphrey, 1979; Wiesendanger, 1981; Wise, 1985).

In recent studies, we and others have begun to examine some of the afferent inputs to each of the premotor areas. For example, these studies have shown that the arm representation in the SMA receives projections from regions of the ventrolateral thalamus that are the site of termination of efferents from the basal ganglia (e.g., Schell and Strick, 1984; Wiesendanger and Wiesendanger, 1985a). In contrast, the arm representation in the APA receives projections from regions of the ventrolateral thalamus that are the site of termination for a set of cerebellar efferents (e.g., Schell and Strick, 1984; Matelli et al., 1989; Orioli and Strick, 1989). Another set of cerebellar efferents projects to regions of the ventrolateral thalamus that innervate the portion of the arm area of the primary motor cortex located on the crest of the precentral gyrus (Schell and Strick, 1984; Wiesendanger and Wiesendanger, 1985a,b; Matelli et al., 1989; Orioli and Strick, 1989). Based on these and other observations, we have proposed that each premotor area, along with the primary motor cortex, is a nodal point for a distinct set of afferent inputs from subcortical motor nuclei, such as the cerebellum and basal ganglia, and from cortical areas in the parietal lobe (Schell and Strick, 1984; Galyon and Strick, 1985; Strick, 1988; Dum and Strick, 1990). Thus, we view these cortical motor areas as components of anatomically distinct systems for the central control of movement (Schell and Strick, 1984; Strick, 1988; Dum and Strick, 1990). According to this view, these systems operate largely in parallel, but interact at the cortical level where the motor areas are densely interconnected.

An important consequence of our proposal is that it places the premotor areas at the same level of hierarchical organization as the primary motor cortex. This suggestion raises an important issue: To what extent do the premotor areas have outputs that are independent of the primary motor cortex? In fact, studies using retrograde transport techniques have provided evidence that some of the premotor areas project directly to the spinal cord (Catsman-Berrevoets and Kuypers, 1976; Biber et al., 1978; Murray and Coulter, 1981; Macpherson et al., 1982; Toyoshima and Sakai, 1982; Martino and Strick, 1987; Hutchins et al., 1988; Dum and Strick, 1989, 1990; Keizer and Kuypers, 1989). However, these studies did not specifically examine the areal extent and density of corticospinal projections from each of the premotor areas. Furthermore, the relationship between the premotor areas in the cingulate sulcus and the origin of corticospinal projections from this region has not been examined in detail.

To investigate these issues, we labeled cortical neurons that project to the spinal cord using retrograde transport techniques. We focused specifically on the origin of corticospinal projections from the premotor areas to cervical segments of the spinal cord. The size, number, density, and areal extent of corticospinal neurons in the premotor areas were compared with those found in the primary motor cortex. Finally, in another set of animals,

we defined the arm representation in each premotor area using the retrograde transport of tracer from the arm area of the primary motor cortex.

Our observations indicate that corticospinal projections to cervical segments of the spinal cord originate from the same areas of the premotor cortex that project to the arm area of the primary motor cortex. In fact, several quantitative measures indicate that the size of the corticospinal system from the premotor areas equals or exceeds that from the primary motor cortex. These findings raise serious questions about the utility of viewing the primary motor cortex as the "upper motoneuron" or "final common pathway" for the central control of movement.

Short reports of some of the data presented in this article have appeared previously (Dum and Strick, 1988).

Materials and Methods

Surgical procedures

We used retrograde transport of horseradish peroxidase (HRP) or wheat germ agglutinin conjugated to HRP (WGA-HRP) to determine the origin of projections from the frontal lobe to the spinal cord. These studies were performed on 6 pig-tailed macaques (*Macaca nemestrina*; 4.0–5.75 kg). An animal was prepared for surgery by restricting food and water for 6–12 hr and by pretreatment with dexamethasone (0.5 mg/kg, i.m., given 6 and 12 hr prior to surgery). The animal was initially anesthetized with ketamine (10 mg/kg, i.m.) and Nembutal (20 mg/kg, i.p.). Additional doses of ketamine (5–10 mg/kg, i.m.) and/or Nembutal (5 mg/kg, i.v.) were given as needed to maintain anesthesia. During surgery, each animal was given atropine (0.1 mg/kg) and antibiotics (Kefzol, 25 mg/kg, every 6 hr; Oxycillin, 25 mg/kg, every 4 hr; gentamicin, 1 mg/kg, every 8 hr) and was hydrated with intravenous fluids (lactated Ringer's solution, approximately 10–20 cc/hr). Respiration, heart rate, body temperature, and urinary output were monitored. Body temperature was maintained with a heating pad.

All surgical procedures were performed using sterile techniques. A laminectomy was performed over the appropriate segmental levels of the cervical spinal cord. The dura was opened, and the surface of the spinal cord was kept moist using warmed surgical-grade silicone. Thirty to 60 min prior to opening the dura, we gave a bolus of mannitol (1.5–2 gm/kg of a 25% solution, i.v.). The appropriate segmental level for injections was determined by identifying vertebrae and dorsal root entry zones (Hartman and Straus, 1933; Hill, 1974). We used 2 protocols to inject the spinal cord. In the first protocol ($n = 2$), we transected the dorsolateral funiculus at the second cervical segment (C2) using fine scissors. Then, crystalline HRP (34 mg; Sigma, Type VI) was packed into the lesion, and the area was covered with Gelfoam.

In the second protocol ($n = 2$), we injected WGA-HRP (Sigma; 2% in 0.5 M NaCl with 0.1 M mannose added) into the gray matter of specific cervical segments using a 1- μ l Hamilton syringe with a 32-gauge needle. A 2% solution of WGA-HRP was used because prior studies have shown that this concentration of tracer is not incorporated and transported by fibers of passage (for complete discussion, see Mesulam, 1982; Gibson et al., 1984). Injection sites were spaced 1–1.5 mm apart, except to avoid blood vessels. We angled the injection needle to enter the spinal cord by passing through the dorsal column. This was done to avoid damage to the dorsolateral funiculus, where most of the corticospinal tract descends. We made injections (0.05 μ l) at 2 depths along each track in order to completely fill the gray matter of the spinal cord with tracer. Following each injection, the needle was left in place at least 3 min and then withdrawn.

Upon the completion of either injection protocol, the spinal cord was covered with a thin sheet of surgical-grade Silastic and Gelfoam. The wound was closed in layers. The animal was returned to its home cage, and its recovery was carefully monitored throughout the survival period.

In 2 animals, multiple injections (8 tracks, 0.05 μ l/site) of WGA-HRP were made into the arm area of the primary motor cortex. The surgical procedures we employed were identical to those detailed in previous publications from this laboratory (Schell and Strick, 1984; Orioli and Strick, 1989). Tracer injections were made throughout the arm area of the primary motor cortex and included both the precentral gyrus and the anterior bank of the central sulcus (Woolsey et al., 1952). Injections

into the gyrus were placed at a depth of 1.5 mm, and those into the sulcus were placed at 1-mm intervals at depths from 1.5 to 4.5 mm.

After a 3–5-d survival period, all animals were reanesthetized with ketamine (20 mg/kg, i.m.) and Nembutal (36 mg/kg, i.p.). They were perfused transcardially using a 4-stage procedure (see also Rosene and Mesulam, 1978; Mesulam, 1982). The perfusates for animals with injections into the spinal cord included (1) 0.1 M phosphate buffer (pH, 7.4), (2) 2.5% glutaraldehyde in 0.1 M phosphate buffer, (3) 2.5% glutaraldehyde in 0.1 M phosphate buffer with 10% glycerin, and (4) 0.1 M phosphate buffer with 10% glycerin. Paraformaldehyde (2.5%) was substituted for the glutaraldehyde in the perfusates used in the animal with injections into the primary motor cortex. Following the perfusion, the brain was blocked *in situ* while the skull was held in a stereotaxic frame. The brain block included the arcuate sulcus rostrally and the intraparietal sulcus caudally. Then, both the brain and the spinal cord were stored in 0.1 M phosphate buffer with 10–20% glycerin at 4°C.

Histological Procedures

Four to 7 d later, the brain block was quick frozen in cold isopentane (Rosene et al., 1986). Serial coronal sections (50 μ m) of this block were cut on a microtome using a controlled freezing stage. Every tenth section was postfixated and processed for cytoarchitecture according to the technique outlined by Gower (in Mesulam, 1982). The remaining sections were processed for HRP using tetramethylbenzidine (TMB) as the substrate (Mesulam, 1982; Gibson et al., 1984). Spinal cord regions containing the injection sites also were sectioned at 50 μ m. Every tenth section of spinal cord was postfixated and processed for cytoarchitecture, and the remaining sections were processed for HRP using the TMB procedure.

Analytical procedures

At least every fourth section through the frontal cortex was examined for labeled neurons under bright-field and/or dark-field/polarized illumination. The outline of the section and the location of each labeled neuron was charted on an x-y plotter driven by linear potentiometers coupled to the microscope stage. At least every tenth spinal cord section through the injection site was examined and charted in a similar manner to determine the spread of HRP or WGA-HRP. The charts of individual sections were then entered into an IBM AT computer using a high-resolution digitizing tablet. These charts were used to reconstruct the distribution of labeled neurons in the frontal lobe. Two different types of reconstructions were generated: a flattened view of the lateral hemisphere along with the medial surface and a 3-dimensional view of the caudal bank of the arcuate sulcus.

Flattened reconstruction. In confirmation of prior studies, we found that all corticospinal neurons were located in layer V (e.g., Biber et al., 1978; Murray and Coulter, 1981; Toyoshima and Sakai, 1982; Nudo and Masterton, 1990). Therefore, we produced flattened reconstructions (Fig. 1) of the frontal lobe by “straightening” this layer. To do this, the charts of coronal sections were aligned on the junction of the medial wall with the lateral surface of the hemisphere, and this point of alignment was kept fixed. Then, layer V on the medial wall of the hemisphere (i.e., the superior frontal gyrus, cingulate sulcus, and cingulate gyrus) was unfolded and reflected upward, and the lateral surface of the hemisphere was unfolded and reflected downward. The anterior bank of the central sulcus also was included in the flattened reconstructions. To display this portion of the primary motor cortex in an appropriate perspective, it was angled with respect to the lateral convexity. The angle chosen was perpendicular to the average angle between the central sulcus and the midline. To prevent distortion of surface features of the lateral convexity, we did not flatten 2 sulci: the superior precentral and the arcuate. Labeled neurons in these regions were plotted on the surface directly over their respective sulci on the flattened reconstructions.

3-D reconstruction. The section outlines from the charts of coronal sections through the arcuate sulcus were carefully aligned. Then, the outline of the caudal bank of the arcuate sulcus and the position of labeled neurons in this region of the sulcus were digitized on an x-y tablet. Computer programs allowed us to rotate the reconstructed sulcus in any of the 3 major planes and view the sulcus from an optimal angle (see Fig. 10).

Density analysis. The flattened layer V from each coronal section was divided into 200- μ m bins. The number of cells in each bin was counted and color coded. The lightest colors (white and yellow) were assigned to the bins with the most cells and represent approximately the upper

10% of the bins containing labeled neurons. These were considered high-density bins. The locations of the color-coded bins were then plotted on a flattened reconstruction of the frontal lobe (see above).

Determining cell density for bins located in the central sulcus was somewhat more complicated because it traverses the lateral hemisphere at an angle to the midline. Consequently, coronal sections through this sulcus cut layer V at an angle and effectively sampled a larger width of the layer. To correct for this sampling bias, the number of cells in each bin in the central sulcus was multiplied by the cosine of the angle formed by the sulcus and the midline of the hemisphere. Because the sulcus curves, the average angle formed by 3 sections spanning the one under analysis was used for this calculation. No other stereological corrections were applied to our data.

A third procedure was used to determine the density of labeled neurons in the caudal bank of the arcuate sulcus. We rotated the 3-dimensional reconstruction of the sulcus to view it normal to its caudal bank. This region was then overlaid with a 200- μ m square grid. The labeled neurons within each grid square were counted to determine the number of cells per bin.

Cell size analysis. Labeled cells were viewed at 500 \times and measured on a digitizing tablet using a camera lucida attachment. The size of pyramidal-shaped cells was represented by the average of their maximum and minimum diameters. Unless otherwise noted, only cells cut parallel to their long axes were measured. All measured cells contained a complete nucleus and/or had prominent apical and basal dendrites. No corrections were made for tissue shrinkage.

Results

Cytoarchitecture of premotor areas on the medial wall

Before presenting our observations on the topographic distribution of corticospinal neurons, we will describe some of the features that characterize the cytoarchitecture in the region of the premotor areas. There have been numerous descriptions of the architectonics in this region (e.g., Brodmann, 1905; Vogt and Vogt, 1919; von Bonin and Bailey, 1947; Matelli et al., 1985; Barbas and Pandya, 1987; Vogt et al., 1987). However, the cytoarchitecture of the cortex within the motor areas on the medial wall of the hemisphere has not been fully described in prior reports. We have focused our analysis on those regions on the medial wall that project to cervical segments of the spinal cord. These cortical areas are located largely caudal to the arcuate sulcus and rostral to the central sulcus. We will not describe the architectonics of the cortex on the lateral surface of the hemisphere because several recent studies have been published on this subject (e.g., Sessle and Wiesendanger, 1982; Weinrich and Wise, 1982; Matelli et al., 1985; Kurata and Tanji, 1986; Barbas and Pandya, 1987).

Superior frontal gyrus

Portions of areas 4 and 6 are found on the superior frontal gyrus on the medial wall of the hemisphere (Figs. 1; 2A,D; 3). Four features characterize these cortical areas and allow them to be distinguished from others on the medial wall: (1) areas 4 and 6 have the thickest cortex on the medial wall, (2) the size of pyramidal-shaped cells increases with depth in layer III, (3) a granular layer IV is absent, and (4) layer VI is particularly thick in areas 4 and 6. The border between areas 4 and 6 is not sharp. However, area 6 on the medial wall of the hemisphere, like on the lateral surface, is distinguished from area 4 by the greater number and size of giant pyramidal cells in layer V of area 4 (Fig. 2A,D; see also Vogt and Vogt, 1919; Wise and Tanji, 1981; Macpherson et al., 1982; Sessle and Wiesendanger, 1982; Weinrich and Wise, 1982; Kurata and Tanji, 1986; Mitz and Wise, 1987). The border between these areas on the superior frontal gyrus lies approximately 7–8 mm caudal to the genu of the arcuate sulcus (Figs. 1, 3). Ventrally, both areas 6 and 4 extend

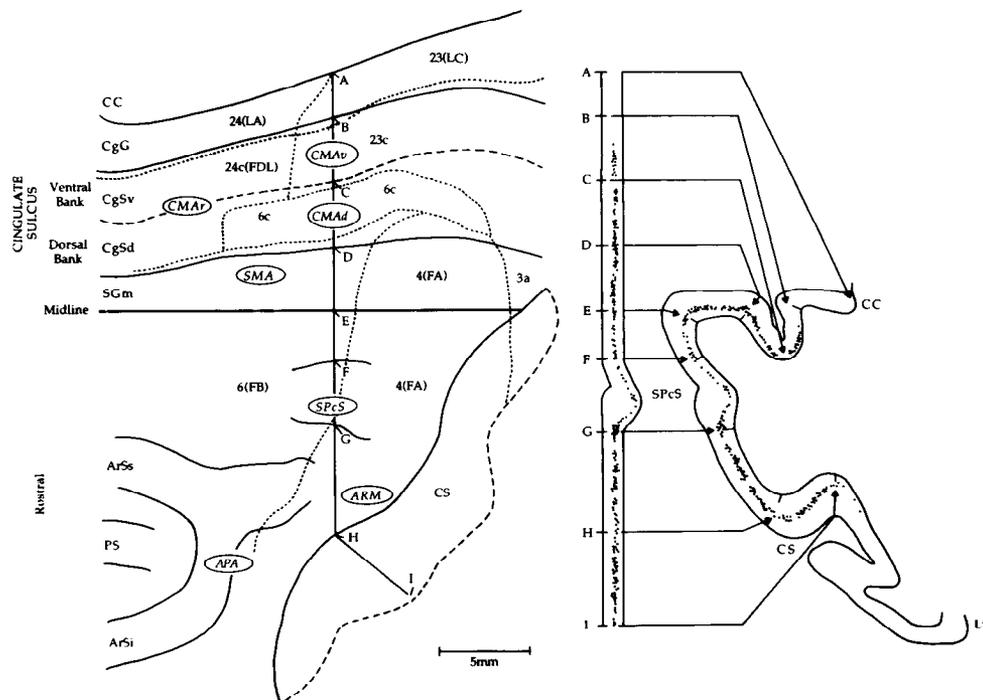


Figure 1. Schematic diagram of motor areas in frontal lobe. Individual coronal sections of cortex (*far right*) were straightened (*middle*) to form a flattened reconstruction (*left*) of the frontal lobe. The *vertical line* on the reconstruction indicates the level of the section displayed at the *right*. Each section was aligned on the junction of the medial wall with the lateral surface (i.e., the *midline*). *Capital letters* on the *middle panel* and on the *vertical line* in the reconstruction indicate the major points of unfolding (e.g., sulcal boundaries). The anterior bank of the central sulcus was projected perpendicular to the mean angle of the sulcus with respect to the *midline*. Note that the inferior and superior arcuate sulcus (*ArSi*, *ArSs*) and the *SPcS* were not flattened. Cytoarchitectonic regions are identified both by *numbers* (Brodmann, 1905) and by *letters in parentheses* (von Bonin and Bailey, 1947). *Dotted lines* indicate borders between these cytoarchitectonic regions. A *dashed line* indicates the fundus of each unfolded sulcus. The centers of the different cortical motor areas in the frontal lobe are indicated by the *circled lettering*. *APA*, arcuate premotor area; *ARM*, arm representation of the primary motor cortex; *CC*, corpus callosum; *CgG*, cingulate gyrus; *CgSd*, cingulate sulcus, dorsal bank; *CgSv*, cingulate sulcus, ventral bank; *CMAv*, caudal cingulate motor area, dorsal bank; *CMAr*, rostral cingulate motor area; *CS*, central sulcus; *LS*, lateral sulcus; *PS*, principal sulcus; *SGm*, superior frontal gyrus, medial wall; *SMA*, supplementary motor area.

for a short distance onto the dorsal bank of the cingulate sulcus. Some isolated giant pyramidal cells are found in the caudal portion of area 6 on the medial wall. This feature may have led Barbas and Pandya (1987) to split area 6 on the superior frontal gyrus into a caudal area 6DC and a rostral area MII.

Cingulate gyrus

The cytoarchitecture of the cingulate gyrus differs substantially from that of the superior frontal gyrus. For example, the cortex on the cingulate gyrus is the thinnest on the medial wall (cf. Fig. 2*B,C* with *A,D–F*). The cingulate gyrus has 2 major subdivisions in the region we examined: area 23 (LC in von Bonin and Bailey, 1947) and area 24 (LA in von Bonin and Bailey, 1947; Figs. 1, 2*B,E*; for a recent review, see Vogt et al., 1987). Classically, the presence of a distinct granular layer IV in area 23 has been used to distinguish it from area 24 (Fig. 2*B,C*; e.g., von Bonin and Bailey, 1947; Vogt et al., 1987). The border between these 2 areas is found several millimeters rostral to the level of the border between areas 4 and 6.

Cingulate sulcus

Areas 23 and 24 have been divided into a number of subfields that extend into the cingulate sulcus (e.g., Vogt et al., 1987). Rostrally, area 24c is found largely in the ventral bank of the sulcus. This subfield extends onto the dorsal bank of the sulcus at levels rostral to the genu of the arcuate sulcus (Fig. 1). Area

24c (the FDL of von Bonin and Bailey, 1947) is thicker than the cortex on the cingulate gyrus and, unlike the other subfields of area 24, contains an incipient granular layer (Fig. 2*F*). The presence of some relatively large pyramidal-shaped cells in layer V and in the deep part of layer III also distinguishes area 24c from the subfields of area 24 on the cingulate gyrus. The CMAr identified in a previous study lies within area 24c (Hutchins et al., 1988).

Caudally, area 23c is found largely in the ventral bank of the cingulate sulcus, beginning approximately 2–3 mm rostral to the area 4–6 border (Fig. 1). It extends onto the dorsal bank of the sulcus at levels caudal to the area 4–6 border. Area 23c is markedly thicker than the other subfields of area 23 on the cingulate gyrus (cf. Fig. 2*E* with *B*). It can be distinguished from area 24c because it has a larger number of granule cells in layer IV and a higher density of cells in the outer portions of layer III (cf. Fig. 2*E* with *F*).

In their classic study, von Bonin and Bailey (1947) noted that caudal portions of the dorsal bank of the cingulate sulcus contained a distinct subfield, which they termed FAL. We observed a comparable region in the dorsal bank of the cingulate sulcus with cytoarchitectonic features that are transitional between area 23c and area 6 (Figs. 1, 3). Because this region most resembles area 6 on the superior frontal gyrus, we consider it to be a subfield of that area. We have termed this region “area 6c” to indicate its topographic location in the cingulate sulcus. Area 6c is dis-

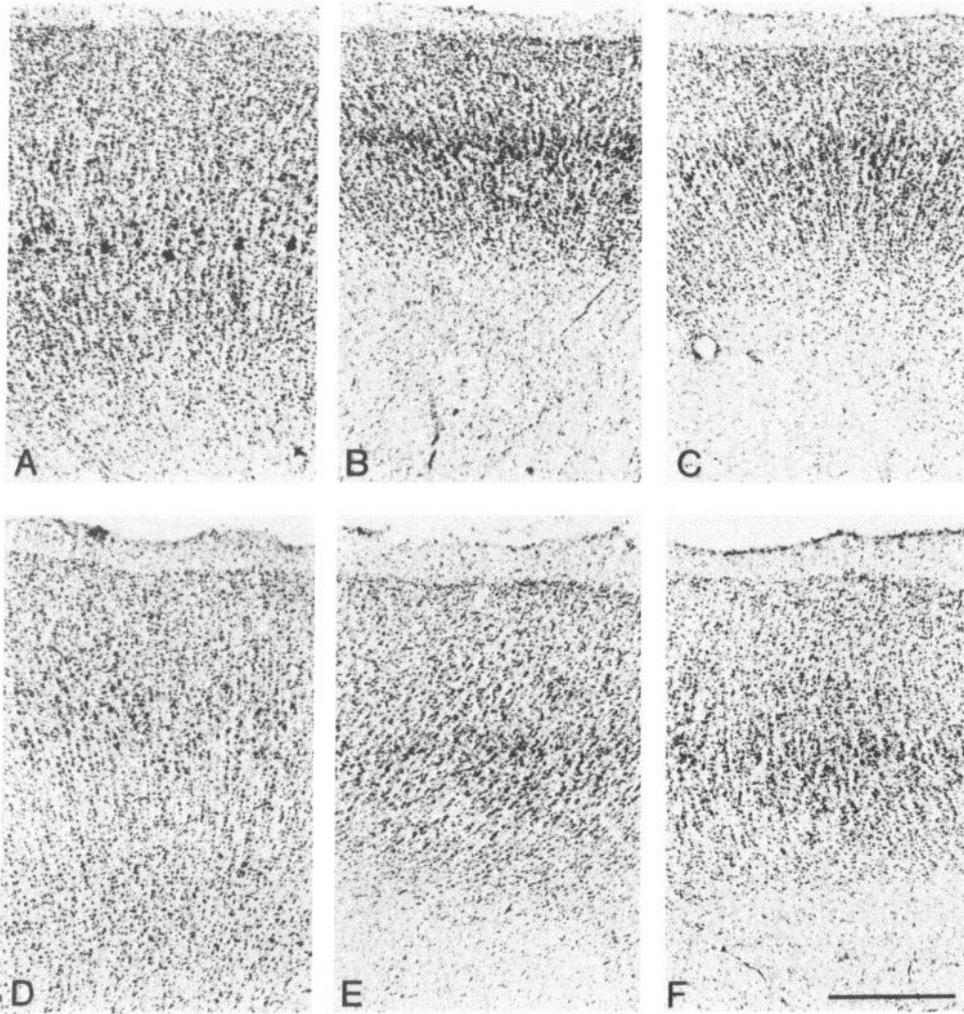


Figure 2. Cytoarchitecture of cortex on medial wall of hemisphere. These are photomicrographs of cresyl violet-stained sections from a monkey that received HRP into the dorsolateral funiculus at C2. *A*, Area 4 on the superior frontal gyrus. *B*, Area 23 on the cingulate gyrus. *C*, Area 24 on the cingulate gyrus. *D*, Area 6 on the superior frontal gyrus. *E*, Area 23c on the ventral bank of the cingulate sulcus, just caudal to the area 23–24 border. *F*, Area 24c on the ventral bank of the cingulate sulcus. Scale bar, 500 μ m.

tinguished from adjacent parts of areas 4 and 6 by a clear decrease in cortical thickness, particularly in layer VI (Fig. 3). It is distinguished from area 23c by the absence of a granular layer IV and the presence of a few large, pyramidal-shaped cells in layer V. Also, layers V and VI in area 6c are thicker than in area 23c. Previously, we considered the corticospinal projections from area 6c and area 23c to lie within the CMAc (Hutchins et al., 1988). However, the cytoarchitectonic differences between these subfields, the detailed patterns of their corticospinal projections (see below), and the results of recent connective studies (Holsapple and Strick, 1989) have led us to consider that portion of the CMAc in area 6c on the dorsal bank of the cingulate sulcus (CMA_d) as separate from that portion of the CMAc in area 23c on the ventral bank (CMA_v).

Location and extent of injection sites

We used 2 experimental approaches to determine the origin of corticospinal projections to cervical segments of the spinal cord. In one series of experiments ($n = 2$), we transected the dorsolateral funiculus at C2 and inserted HRP crystals into the lesion site. In the second series ($n = 2$), we injected WGA-HRP into the gray matter throughout multiple segments of the cervical spinal cord. We will present detailed descriptions of the injection sites and the cortical labeling of 1 representative animal from each series.

HRP into the dorsolateral funiculus

In order to label all the corticospinal fibers that travel in the lateral component of this tract, we placed HRP into the dorsolateral funiculus at C2. Sections of spinal cord rostral to the site of HRP placement demonstrated that axons were labeled throughout the full cross-sectional area of the ipsilateral lateral funiculus (Fig. 4*B*). In addition, we observed large numbers of labeled axons ipsilaterally in the lateral part of the ventral funiculus and in the lateral part of the dorsal column. Only small numbers of labeled axons were found in the medial part of the ventral funiculus. The only labeled axons found contralaterally were seen ventromedially in the dorsal column. Thus, the injection site completely covered the lateral component of the corticospinal tract, but spared other components of the corticospinal system, including those that travel in ipsilateral funiculi (e.g., Kuypers, 1960; Liu and Chambers, 1964; Kuypers and Brinkman, 1970; Ralston and Ralston, 1985).

WGA-HRP into the gray matter

In order to label those corticospinal neurons involved in the control of arm movements, we injected WGA-HRP into multiple segments of the cervical spinal cord. The injection needle was angled to pass through the dorsal columns (see Materials and Methods) to avoid damage and/or spread of the tracer to

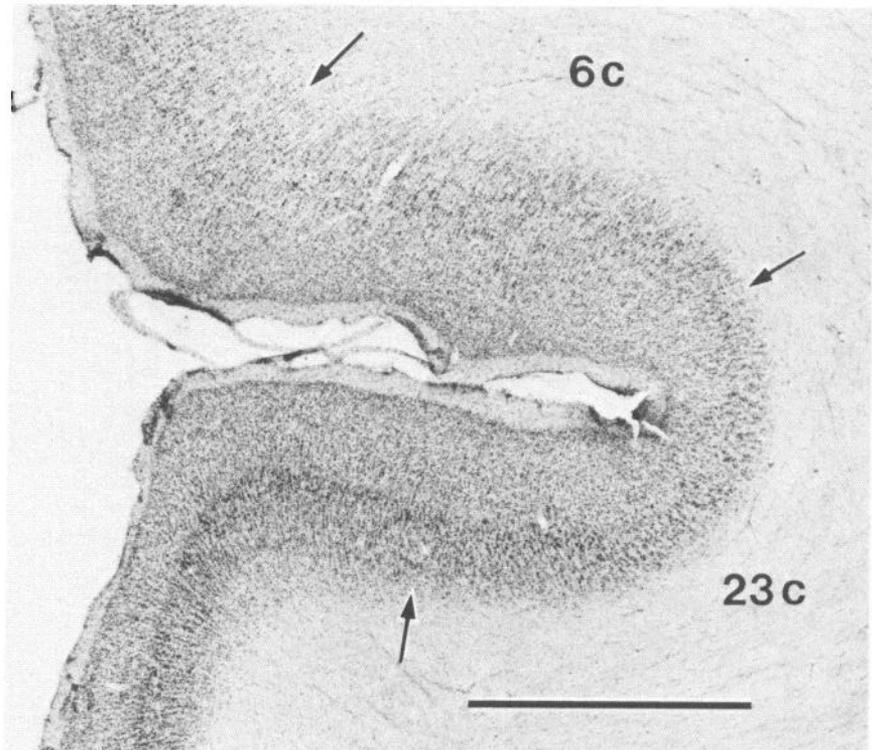


Figure 3. Cytoarchitecture in cingulate sulcus. The level of this section is close to the vertical line drawn on the flattened reconstruction in Figure 1. *Arrows* indicate the boundaries of areas 6c and 23c. Scale bar, 1.0 mm.

the lateral funiculus. In fact, on sections caudal to the injection site, we found labeled axons largely confined to the region of the lateral funiculus that was adjacent to the gray matter of the spinal cord (Fig. 4*A*). This is the region where propriospinal pathways are known to travel (Kuypers, 1981). This observation suggests that tracer uptake was limited to the gray matter within the injection site.

We defined the injection site in gray matter as the zone of staining that contained the densest reaction product (Mesulam, 1982). In this zone, labeled cells could not be distinguished from the staining of the neuropil. In the representative animal from this series, the injection site involved the entire dorsal horn, intermediate zone, and ventral horn from the sixth cervical segment (C6) to the first thoracic segment (T1; Fig. 5). Caudally, the injection site extended into the intermediate zone and ventral horn of the second thoracic segment (T2). Rostrally, the injection site partially involved the ventral horn and intermediate zone of the fourth and fifth cervical segments (C4, C5).

Distribution of corticospinal neurons in the frontal lobe *HRP into the dorsolateral funiculus at C2*

Multiple cortical areas in the frontal lobe contained substantial numbers of labeled neurons after HRP placement into the dorsolateral funiculus at C2 (Figs. 6, 7). Large numbers of labeled neurons were found in regions of area 4 located on the precentral gyrus, the anterior bank of the central sulcus, and the medial wall of the hemisphere. These parts of area 4 contain the forelimb and hindlimb representations of the primary motor cortex (e.g., Woolsey et al., 1952; Kwan et al., 1978; Wise and Tanji, 1981; Sessle and Wiesendanger, 1982).

In general, the number of labeled neurons on the lateral surface of the hemisphere gradually declined after the area 4–6 border. Only a few labeled neurons were found in the rostral

part of area 6 located medial to the superior limb of the arcuate sulcus and rostral to its genu (Figs. 6; 7, sections 176, 217, 245). However, there were 2 parts of area 6 on the lateral surface of the hemisphere that contained substantial numbers of labeled neurons. One of these was located in the caudal strip of area 6, which includes the shallow SPcS (Figs. 6; 7, sections 329, 357). The other was located in a more lateral part of area 6 (Figs. 6; 7, sections 217, 245, 289). Labeled neurons there were located largely in the caudal bank of the inferior limb of the arcuate sulcus and continued medially to include regions in and around the spur of this sulcus. This part of area 6 corresponds to the arm representation of the APA (Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Godschalk et al., 1984; Strick, 1985; Leichnetz, 1986; Matelli et al., 1986; Ghosh et al., 1987; Martino and Strick, 1987).

Substantial numbers of labeled neurons also were found in several cytoarchitectonic regions on the medial wall of the hemisphere. Labeled neurons on the superior frontal gyrus were found in the hindlimb representation of area 4 and in the regions of area 6 rostral to it (Figs. 6; 7, sections 217–357, area 4 on sections 385–481). These neurons were found as far rostrally as 2 mm beyond the genu of the arcuate sulcus. The part of area 6 on the superior frontal gyrus that contained labeled neurons coincides with the fore- and hindlimb representations of the SMA (e.g., Woolsey et al., 1952; Brinkman and Porter, 1979; Muakkassa and Strick, 1979; Wise and Tanji, 1981; Macpherson et al., 1982; Mitz and Wise, 1987; Hutchins et al., 1988).

Labeled neurons were found throughout a considerable rostrocaudal extent of both the dorsal and ventral banks of the cingulate sulcus (Fig. 6, 7). These neurons were located as far rostrally as 4 mm anterior to the genu of the arcuate sulcus and as far caudally as the end of the sulcus. Sites containing labeled neurons included all of area 6c (CMA) and substantial portions

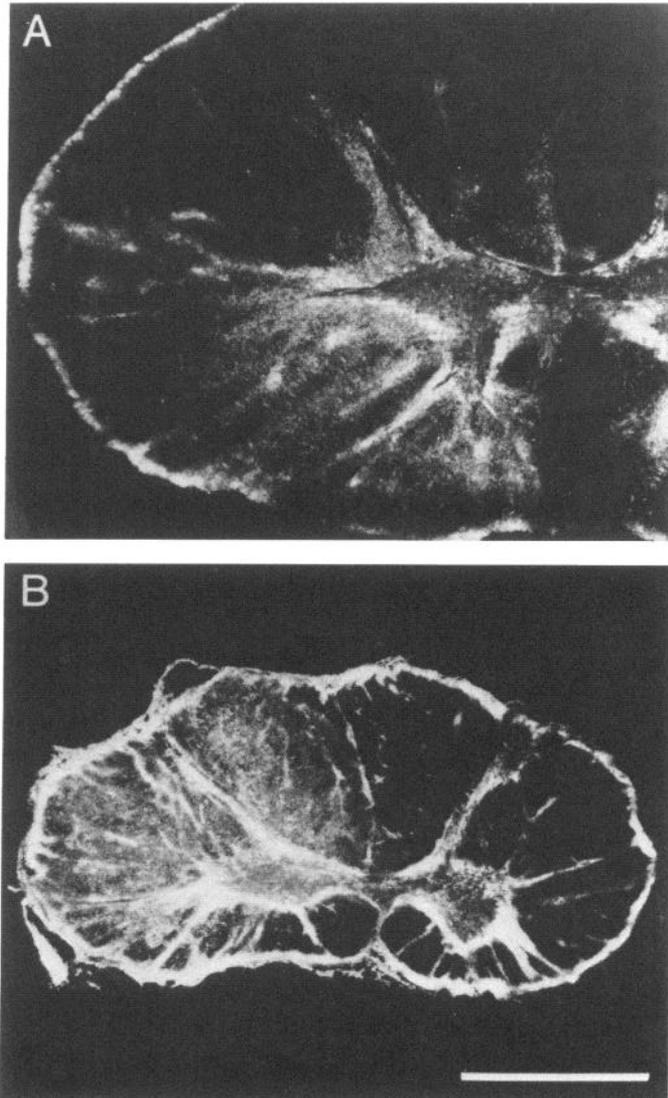


Figure 4. Spinal cord injection sites. These photomicrographs were taken under dark-field/polarized light illumination. *A*, Cross-section of the spinal cord caudal to an injection of WGA-HRP into the gray matter throughout C4–T2. Labeled axons caudal to the inject site were confined to the white matter immediately adjacent the gray matter. No labeled axons were visible in the more lateral regions of the dorsolateral funiculus. *B*, Cross-section of the spinal cord 1.5 mm rostral to the placement of HRP crystals into the dorsolateral funiculus at C2. Most of the HRP reaction product was confined to axons in the ipsilateral (*left*) dorsal columns, dorsolateral funiculus, and ventrolateral funiculus. The location of the labeled axons corresponds with the extent of the lesion observed in more caudal sections. Scale bar: 930 μ m for *A*; 2.0 mm for *B*.

of areas 23c (CMAv) and 24c (CMAR). Labeled neurons were rarely found on the cingulate gyrus. Thus, in addition to the primary motor cortex, corticospinal neurons were found in 6 different regions of the frontal lobe, which we have identified as premotor areas: the APA, the portion of area 6 around the SPcS, the SMA, the CMAR, the CMAd, and the CMAv.

As in prior studies (e.g., Jones and Wise, 1977; Murray and Coulter, 1981), we found that, on single sections through each motor area, labeled cortical neurons were arranged in irregular clusters (Figs. 6–9). These clusters were present after tracer injections into either the dorsolateral funiculus or the gray matter

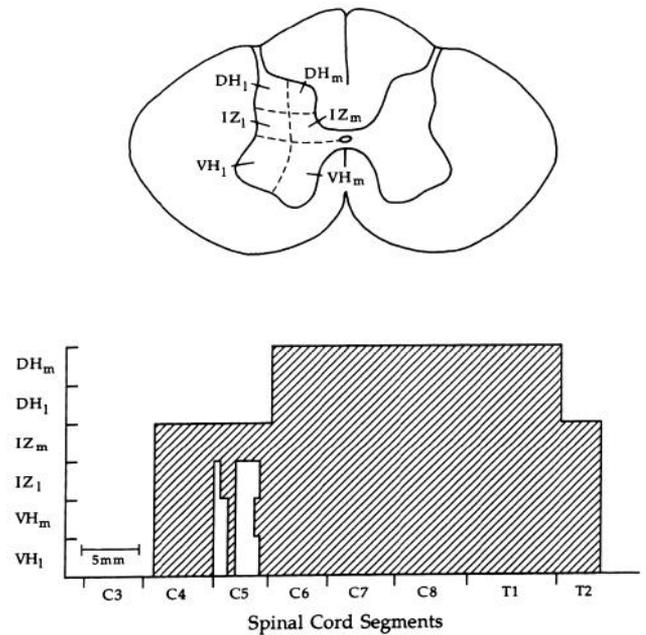


Figure 5. Diagrammatic representation of WGA-HRP injection site. *Top*, Drawing of a cross-section through C8 indicating the 6 zones of gray matter that were evaluated for reaction product. The zones included the medial (*m*) and lateral (*l*) part of the dorsal horn (DH), intermediate zone (IZ), and ventral horn (VH). *Bottom*, The histogram indicates the presence of reaction product within each of the 6 zones throughout the cervical enlargement.

of the spinal cord. However, “stripes” or “bands” of labeled neurons were not clearly evident in our surface reconstructions (Figs. 6, 8) or maps of neuron density (see Figs. 11, 12). Future studies will need to employ additional technical and analytic procedures (e.g., Johnson et al., 1989) to define the arrangement of these clusters of corticospinal neurons in each of the premotor areas.

WGA-HRP into cervical segments

Injections of WGA-HRP into the gray matter of the cervical spinal cord (C4–T2) resulted in neuronal labeling in parts of the same cytoarchitectonic areas as were labeled following funicular deposits of HRP at C2 (cf. Figs. 6, 8). Indeed, after injections into the cervical cord, we found substantial numbers of labeled neurons in the primary motor cortex and in each of the 6 premotor areas in the frontal lobe. However, these neurons were topographically restricted to specific parts of each region. This is in striking contrast to the more uniform distribution of labeled neurons observed after placement of HRP into the lateral funiculus.

Although their distribution was restricted, the number of corticospinal neurons found within each labeled region was greater in animals with injections of WGA-HRP than in those with the deposits of HRP. This difference was particularly evident in the numbers of labeled neurons in the arcuate sulcus (cf. Fig. 7, section 217, with Fig. 9, section 209). It is unclear whether this quantitative difference is due to (1) the tracer employed (WGA-HRP vs. HRP; e.g., Gonatas et al., 1979; Mesulam, 1982), (2) the site of injection and parameters of uptake (cut axons in the funiculus vs. gray matter injection sites; e.g., Brushart and Mesulam, 1980; Mesulam, 1982), or (3) variability among animals

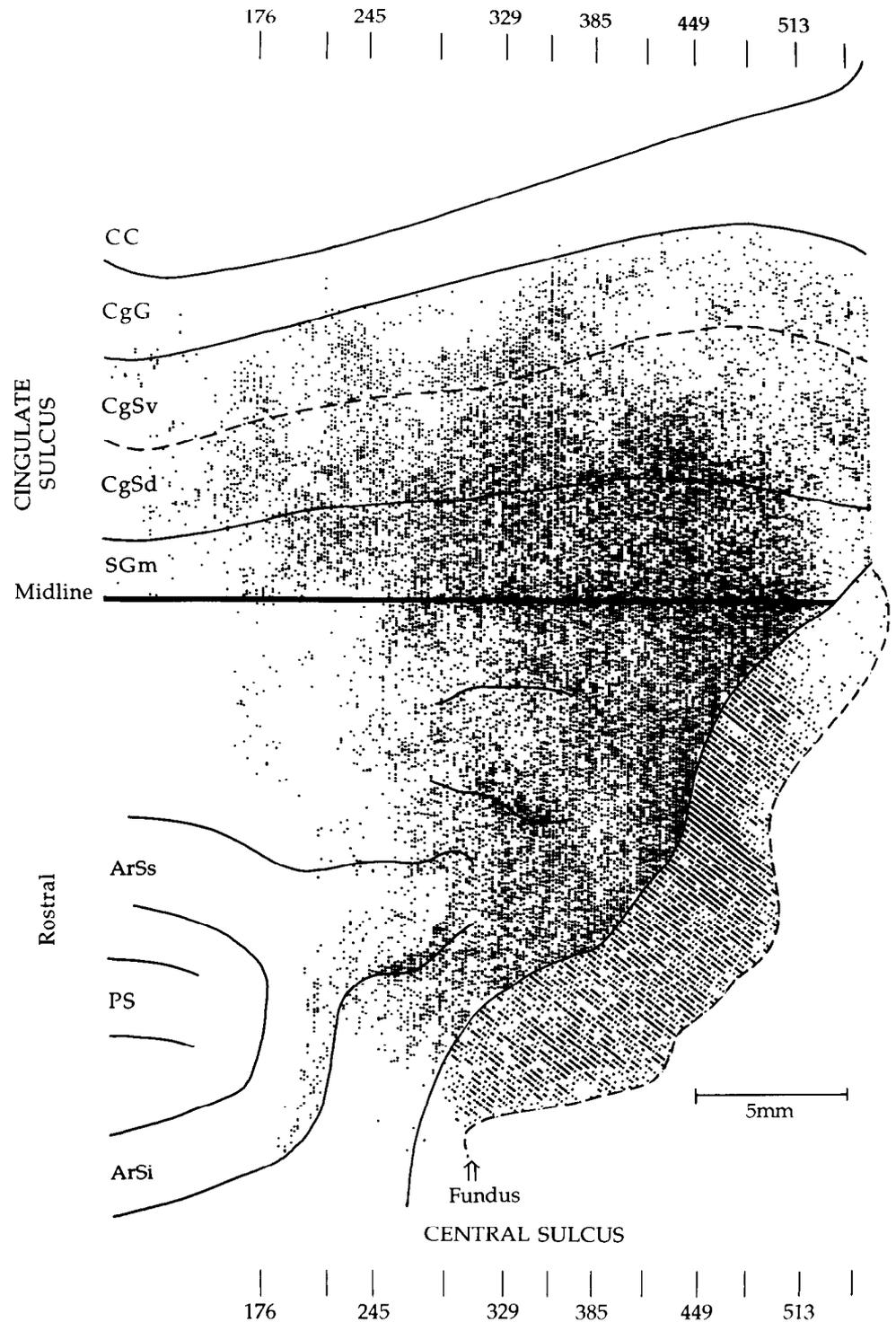


Figure 6. Map of corticospinal neurons in frontal lobe. HRP was injected into the contralateral dorsolateral funiculus at C2 (shown in Fig. 4B). Each labeled cell is represented by a dot. Every other 50- μ m section was used to construct this map. See Materials and Methods and Figure 1 for the reconstruction procedures and abbreviations. The numbered scale shows the location of sections illustrated in Figure 7.

in the number of pyramidal-tract axons (e.g., Russell and DeMeyer, 1961).

Within area 4, labeled neurons were confined to a region that began medially at the level of the SPCS and extended slightly lateral to the spur of the arcuate sulcus. Large numbers of labeled neurons were found on both the precentral gyrus and the anterior bank of the central sulcus. This labeled region corresponds to the forelimb representation in the primary motor cortex (e.g., Woolsey et al., 1952; Kwan et al., 1978; Sessle and Wiesen-

danger, 1982). No corticospinal neurons were found in the face representation of area 4, and very few were seen in the hindlimb representation. The absence of labeling in the hindlimb region of the primary motor cortex provides additional evidence for our claims that (1) corticospinal axons passing in the funiculi to lower levels of the cord were not involved by our injections into gray matter, and (2) tracer uptake in these animals was limited to cervical segments of the spinal cord.

Another group of labeled neurons was found in the region of

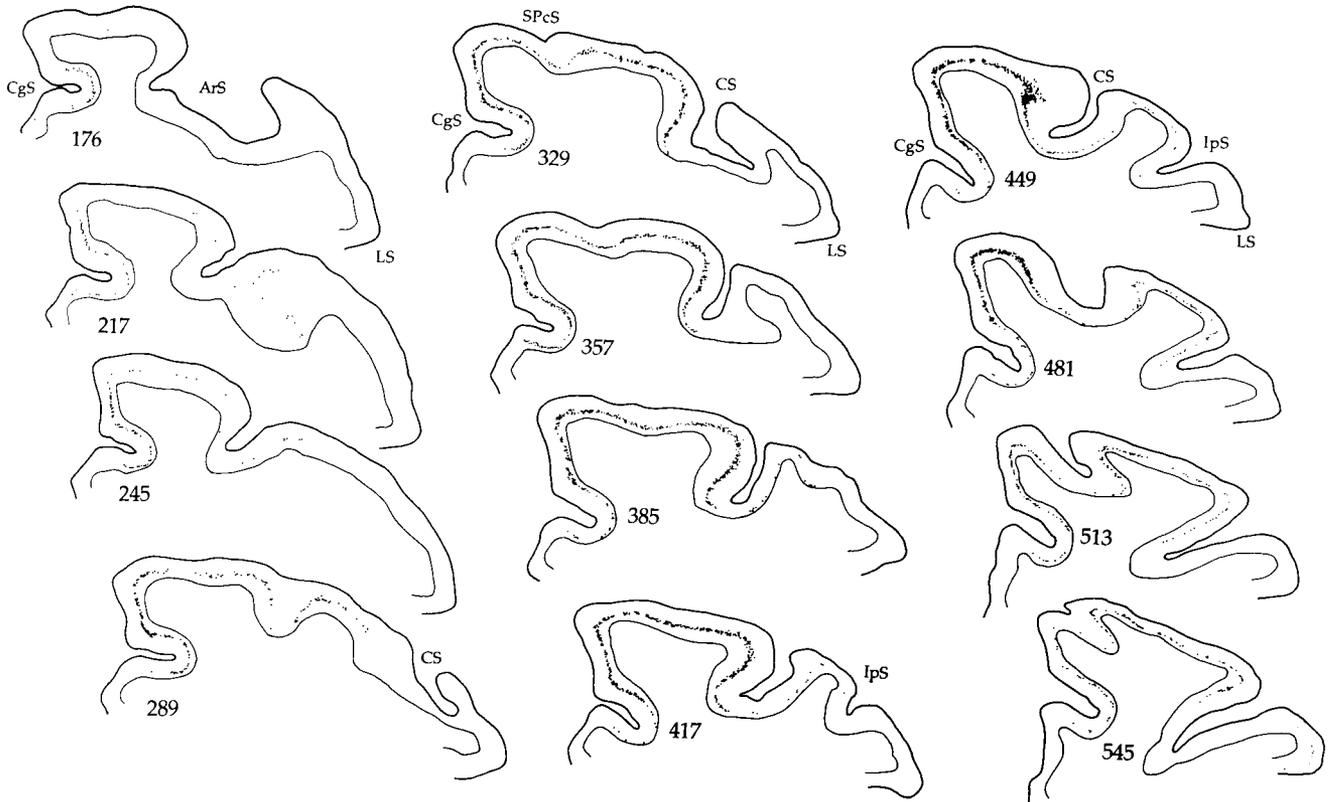


Figure 7. Plots of corticospinal neurons found on coronal sections through frontal lobe. The coronal sections are from the animal illustrated in Figure 6; the location of each section is indicated by the numbered scale in that figure. CgS, cingulate sulcus; IpS, intraparietal sulcus; other abbreviations are as in Figure 1.

area 6 that surrounds the lateral edge of the SPcS (Figs. 8; 9, sections 329, 357, 381). This group of labeled neurons merged caudally and laterally, with the main concentration of labeled neurons in the primary motor cortex. The labeled neurons in and around the SPcS overlap the arm representation of the premotor area located in this region of the cortex (e.g., Muakkassa and Strick, 1979; Godschalk et al., 1984; Kurata et al., 1985; Kurata, 1989). A small cluster of labeled neurons was located immediately caudal to the medial lip of the SPcS (Fig. 8). Neurons were labeled at this location only when gray matter injections included lower segments (C7–T1) of cervical spinal cord (Dum and Strick, 1989; He et al., 1989).

A distinct patch of labeled neurons also was found more laterally in area 6. These labeled neurons were buried in the caudal bank of the arcuate sulcus, particularly its inferior limb (Figs. 8; 9, section 209; 10). This area of labeling was isolated from the main concentration of labeled neurons in area 4 by a sparsely labeled region along the arcuate spur (Fig. 8; see also Nudo and Masterton, 1990). The topographic distribution of these neurons was best visualized on 3-D reconstructions of the caudal bank of the arcuate sulcus (Fig. 10). Such reconstructions demonstrated that corticospinal neurons tended to shift from a superficial position in the sulcus at caudomedial levels to the depths of the sulcus at more rostralateral levels. This region of corticospinal neurons corresponds to the arm representation of the APA (e.g., Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Godschalk et al., 1984, 1985; Martino and Strick, 1987; Gentilucci et al., 1988).

On the medial wall of the hemisphere, restricted portions of the superior frontal gyrus and the banks of the cingulate sulcus contained concentrations of labeled neurons. These labeled areas were separated by regions that either lacked or had few labeled neurons. This pattern of labeling is in marked contrast to the more uniform distribution of labeled neurons found on the medial wall after funicular injections of tracer (cf. Figs. 6, 8).

On the superior frontal gyrus, most corticospinal neurons were located in the region of area 6 that started at the level of the genu of the arcuate sulcus and extended caudally for approximately 6 mm. The largest number of these labeled neurons was found ventrally on the gyrus. Very few labeled neurons were observed in regions that extend either rostral to the genu of the arcuate sulcus or dorsally onto the lateral surface. Thus, these corticospinal neurons were located largely in a region that coincides with the arm representation of the SMA (e.g., Penfield and Welch, 1951; Woolsey et al., 1952; Brinkman and Porter, 1979; Muakkassa and Strick, 1979; Macpherson et al., 1982; Mitz and Wise, 1987; Hutchins et al., 1988).

Rostrally, the dorsal and ventral banks of the cingulate sulcus contained scattered clusters of labeled neurons (Figs. 8; 9, sections 133, 173). These corticospinal neurons were located in the region of area 24c that was rostral to the genu of the arcuate sulcus (Figs. 8; 9, sections 209, 237). This region of area 24c corresponds to the arm representation of the CMAr (Hutchins et al., 1988; Dum and Strick, 1989; He et al., 1989). The region of the dorsal and ventral banks of the cingulate sulcus that lies

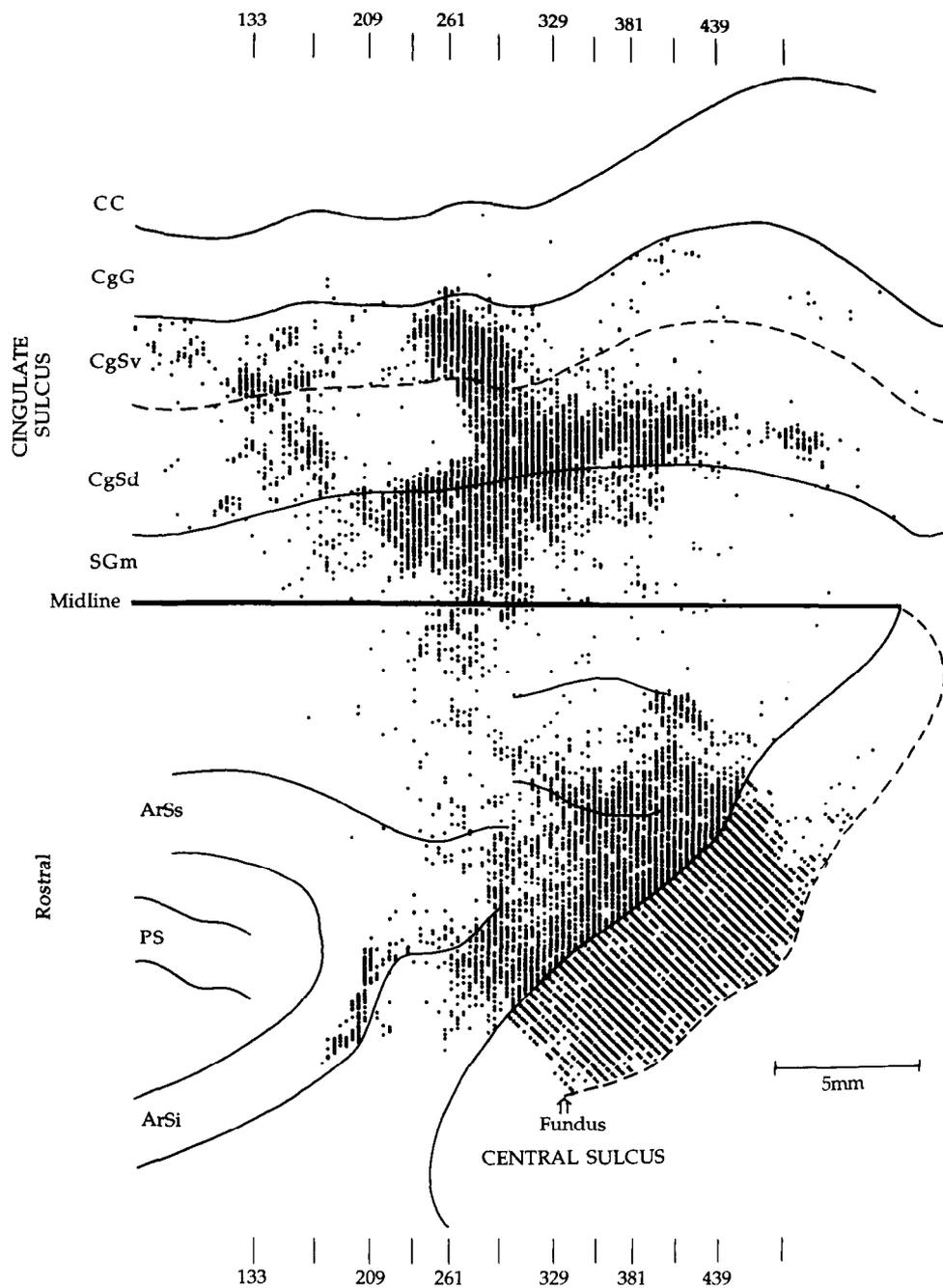


Figure 8. Map of corticospinal neurons in frontal lobe projecting to C4–T2. WGA-HRP was injected into the contralateral gray matter throughout C4–T2. Every fourth section was used to construct this map. See Figures 1 and 6 for conventions and methods of reconstruction.

3–4 mm caudal to the genu of the arcuate sulcus contained very few labeled neurons. Data from other studies indicate that this unlabeled region projects to lumbar segments of the spinal cord (Biber et al., 1978; Murray and Coulter, 1981; Macpherson et al., 1982; Hutchins et al., 1988; He et al., 1989).

Further caudally, the numbers of labeled neurons on the dorsal and ventral banks of the cingulate sulcus increased dramatically. The region of the dorsal bank that contained labeled neurons extended for a considerable rostrocaudal distance (over 8 mm). This group was followed by a small, separate cluster of labeled neurons (Figs. 8; 9, sections 293–481). All of the labeled neurons in this region of the dorsal bank were located in area 6c. The region of the ventral bank that contained labeled neurons was more limited in extent (3 mm; Figs. 8; 9, sections 261,

293, 329). These neurons were located in area 23c. In a subsequent section, we will present evidence that the region with corticospinal neurons in area 6c corresponds to the arm representation of the CMA_d and the region in area 23c corresponds to the arm representation of the CMA_v (see also Hutchins et al., 1988; Dum and Strick, 1989, 1990; He et al., 1989).

Using the surface maps, we measured the area of each cortical region that contained labeled neurons after injections of tracer into cervical segments of the spinal cord (Table 1). The total area of cortex in the frontal lobe that contained corticospinal neurons measured 226 mm². Only 37% of this area was located in the arm area of the primary motor cortex. The next largest area containing corticospinal neurons was the arm area of the SMA (19%). Smaller amounts of the cortex were allotted to the

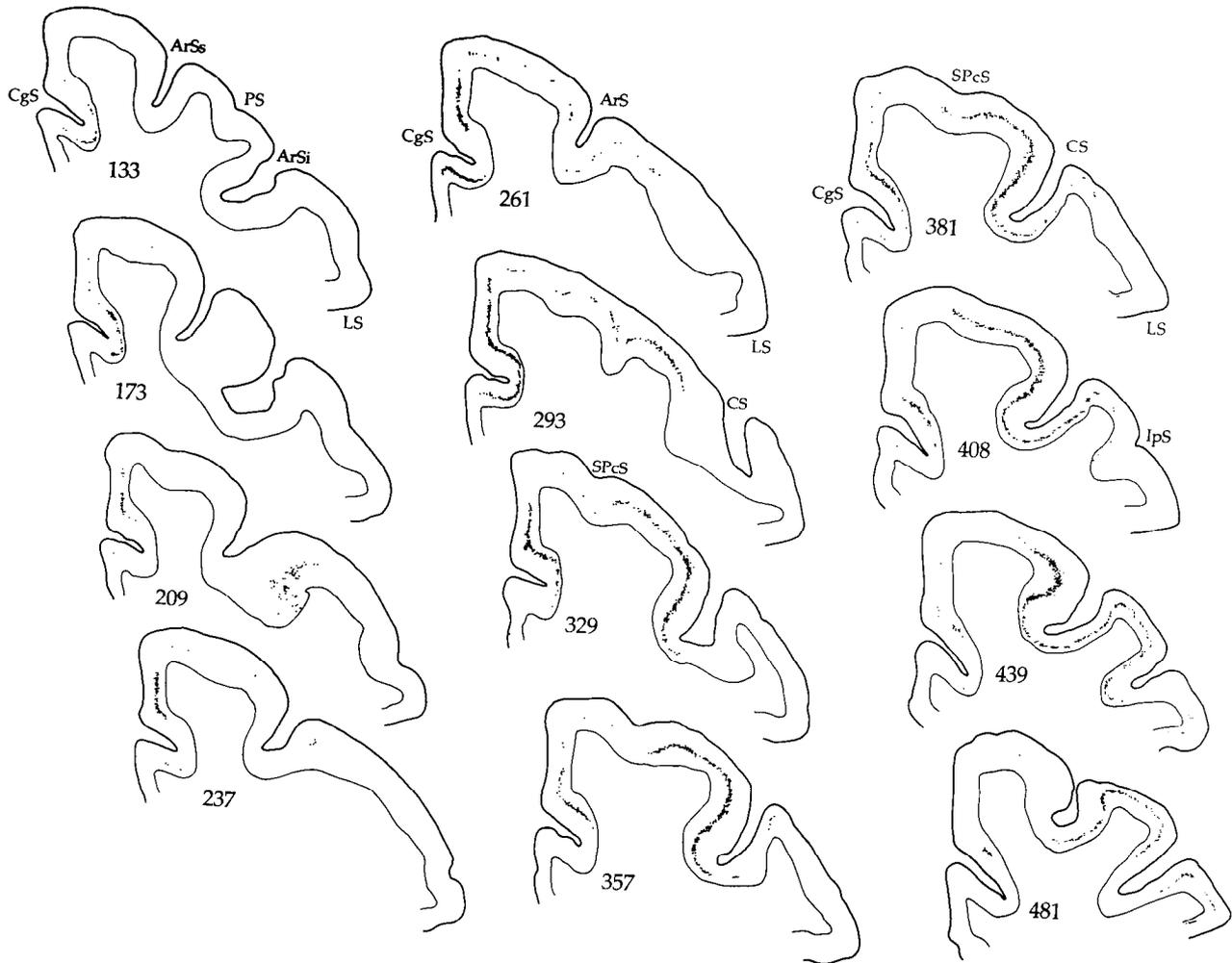


Figure 9. Plots of corticospinal neurons projecting to C4–T2 found on coronal sections through frontal lobe. The coronal sections are from the animal illustrated in Figure 8; the location of each section is indicated by the numbered scale in that figure. Abbreviations are as in Figures 1 and 7.

arm representations of the other premotor areas (CMAr, 11%; CMAAd, 10%; SPcS, 9%; APA, 8%; CMAv, 6%).

Density of corticospinal neurons in the motor areas

The surface maps of labeled neurons provide an accurate representation of the topographic distribution of corticospinal neurons in the frontal lobe. However, when every labeled neuron is plotted, these maps suffer from a tendency to distort the apparent density of corticospinal neurons at some sites. For example, the plot of labeled neurons saturated into a solid line at sites where there was a moderate to high density of corticospinal neurons. To overcome this and other shortcomings, we constructed surface maps that displayed the density of labeled neurons (for further description, see Figs. 11, 12 and Materials and Methods).

These maps demonstrated that high-density bins (i.e., bins in which the number of labeled neurons was in the upper 10% of the total sample of 200- μ m bins) were found in each of the 6 premotor areas, as well as in the primary motor cortex (Figs. 11, 12). High-density bins were scattered throughout the primary motor cortex. However, they were most frequently found on the edge and in the anterior bank of the central sulcus (Fig. 12). At more rostral portions of the primary motor cortex, there

was a decline in the density of labeled neurons. Then, the number of high-density bins increased in the premotor area at the lateral edge of the SPcS.

On the medial wall of the hemisphere, high-density bins were particularly concentrated in the CMAAd and CMAv (Fig. 11). Furthermore, a trough in density clearly separated the mass of high-density bins in the CMAAd (in area 6c) from those in the CMAv (in area 23c). Within the SMA, high-density bins were most concentrated ventrally near the edge of the cingulate sulcus.

In total, we found 450 high-density bins in the frontal lobe of the animal illustrated in Figures 11 and 12. Fifty-three percent of these were located in the arm representation of the primary motor cortex. The next largest groups of high-density bins were located in the arm area of the SMA (19%) and in the arm area of the CMAAd (15%). Smaller groups of high-density bins were found in the arm representations of the other premotor areas (CMAv, 7%; SPcS, 5%; CMAr, <1%; APA, <1%).

We determined the distribution of density bins for each premotor area and compared them with the distribution of density bins for the primary motor cortex (Fig. 13). The distributions for 2 premotor areas (CMAAd and CMAv) were remarkably similar to that of the primary motor cortex (χ^2 , $p = >0.1$). In contrast, the distributions for the APA and CMAr were highly

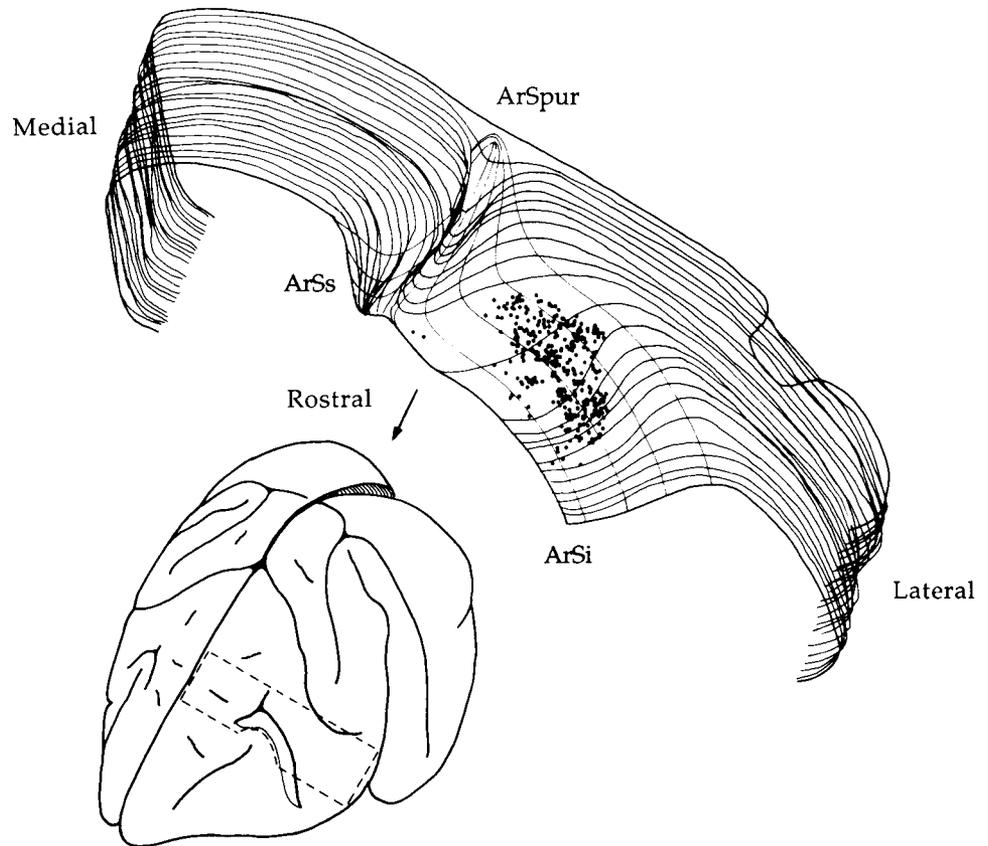


Figure 10. Corticospinal neurons in arcuate sulcus. This is a 3-D reconstruction of the caudal bank of the arcuate sulcus from the animal illustrated in Figures 8 and 9 (WGA-HRP into C4–T2). The labeled neurons (*dots*) from every other section are plotted along with the surface outline of every eighth section. The area reconstructed is indicated by the *dashed lines* on the diagram of the brain surface at the *lower left*. *ArSpur*, spur of the arcuate sulcus.

skewed toward low-density bins ($p = <0.0001$). The distributions in the remaining premotor areas were only slightly skewed toward low-density bins ($p = <0.05$).

Number of corticospinal neurons in the motor areas

We counted the number of labeled neurons found on every fourth section through each of the motor areas and multiplied this number by 4 to get the total number of corticospinal neurons in each area. In the animal illustrated (Figs. 8–12; WGA-HRP injections into gray matter), we found 42,912 corticospinal neurons in the frontal lobe that projected to cervical segments of the spinal cord. Less than 50% of these neurons were located in the arm area of the primary motor cortex (Table 1). Within the premotor areas, the largest numbers of corticospinal neurons were located within the arm area of the SMA (18.5% of the total) and in the arm area of the CMA_d (10.5%). Smaller numbers of corticospinal neurons were located in the arm representations of the other premotor areas. More corticospinal neurons ($n = 71,128$) were labeled in another animal with a more extensive injection of WGA-HRP into cervical segments of the spinal cord (from C2 to T1). As in the animal illustrated, less than 50% of these neurons were located in the arm area of the primary motor cortex (Table 1). Also, the arm area of the SMA contained more corticospinal neurons than any of the other premotor areas (12.2%). However, in this animal, larger percentages of corticospinal neurons were located in the arm areas of the APA and SPcS.

Size of corticospinal neurons in the motor areas

We determined the mean diameter of corticospinal neurons in each of the motor areas in the frontal lobe. Because other studies have shown that the size of corticospinal neurons varies with their level of segmental termination (e.g., Biber et al., 1978; Murray and Coulter, 1981; Toyoshima and Sakai, 1982), our analysis was restricted to an animal with tracer injections into cervical segments of the spinal cord (Figs. 8–12). The distribution of soma diameters for the total sample of corticospinal neurons in the frontal lobe ranged from 9 to 31 μm (Fig. 14). For comparative purposes, we have defined “large neurons” as those with soma diameters greater than 19 μm . Using this definition, we found large neurons in all of the motor areas of the frontal lobe except the CMA_r and the CMA_v (see Fig. 16). The greatest number of large corticospinal neurons was located in the arm area of the primary motor cortex. Thirty-one percent of the corticospinal neurons in this region were large, and these neurons represented 79% of the total number of large corticospinal neurons. Although a sizeable portion of the corticospinal neurons in the arm areas of the APA¹ and the SPcS were large (APA, 20%; SPcS, 21%), together these regions contained only 12% of all the large corticospinal neurons in the frontal lobe. A

¹ The somas of most of the neurons in the APA were not aligned parallel to the plane of sectioning. Consequently, the measurements of their soma diameter underestimated their size.

relatively small percentage of the corticospinal neurons in the arm areas of the SMA and CMAd were large (6% in each area). Within the arm area of the SMA, these neurons were concentrated caudally and ventrally on the superior frontal gyrus. Finally, corticospinal neurons in the arm areas of the CMAr and the CMAv were significantly smaller (Figs. 15, 16) than those found in the other motor areas of the frontal lobe (Mann-Whitney *U* test, $p = <0.001$).

Projections from the medial wall to the arm area of the primary motor cortex

A final goal of our experiments was to compare the location of those regions on the medial wall that project to cervical segments of the spinal cord with the premotor areas in this region of the cortex. A similar comparison for the arm area of the APA was the topic of a previous report (Martino and Strick, 1987). We defined the location of the arm representations in the premotor areas by making multiple injections of WGA-HRP into the arm area of primary motor cortex ($n = 2$; see Materials and Methods, Fig. 17). The results from 1 representative animal will be presented in detail. The injection site in this animal was defined as the zone of dense reaction product where labeled neurons could not be distinguished from the staining of neuropil (Mesulam, 1982; the dark line on the inset of Fig. 17). Based on this definition, the injection site involved a large portion of the arm area of the primary motor cortex on the precentral gyrus and in the anterior bank of the central sulcus. The lateral edge of the injection site may have encroached upon the face representation in the primary motor cortex (e.g., Woolsey et al., 1952; McGuinness et al., 1980; Huang et al., 1988). However, the location of the injection site is comparable to the location of labeled neurons found in the primary motor cortex of other animals after tracer injections into cervical segments of the spinal cord (Fig. 8; see also Martino and Strick, 1987; Dum and Strick, 1989).

Large numbers of corticocortical neurons were found in the SMA, CMAr, CMAd, and CMAv (Figs. 17, 18). In fact, the map of labeled neurons on the medial wall of the hemisphere in this animal was remarkably similar to those of animals with tracer injections into cervical segments of the spinal cord (cf. Figs. 17, 18 with 8, 11). Both corticocortical and corticospinal neurons within the SMA were densest at a level caudal to the genu of the arcuate sulcus (Fig. 18). In both instances, the arm representations in the CMAd and CMAv were larger and contained more efferent neurons than the arm representation in the CMAr. Also, corticocortical neurons, like corticospinal neurons, were absent from a region of the dorsal bank of the cingulate sulcus located between the CMAr and CMAd.

Even some of the fine details in the distribution of corticocortical neurons matched the distribution of corticospinal neurons. For example, there was a trough in the density of corticocortical neurons that separated the labeled neurons in the arm area of the CMAd from those in the CMAv (Fig. 18). This trough fell on the border between area 23c and area 6c. A similar trough was present in the density maps of corticospinal neurons (e.g., Fig. 11).² Finally, a small cluster of corticocortical neurons was found on the dorsal bank of the cingulate sulcus just caudal to

Table 1. Distribution of corticospinal neurons among the premotor areas and the primary motor cortex

Region	Area (mm ²)	WGA-HRP in C4-T2		WGA-HRP in C2-T1	
		<i>n</i>	%	<i>n</i>	%
Primary motor cortex	84	20,824	48.5	35,344	49.7
SPcS	20	3004	7.0	7032	9.9
APA	18	1716	4.0	6824	9.6
SMA	44	7952	18.5	8704	12.2
CMAd	22	4496	10.5	5664	8.0
CMAv	14	2900	6.8	4336	6.1
CMAr	24	1728	4.0	2056	2.9
Area 6DR ^a	— ^b	292	0.7	1168	1.6
	226	42,912	100.0	71,128	100.0

Results from 2 animals are included (WGA-HRP into C4-T2 and WGA-HRP into C2-T1).

^a Area 6DR of Barbas and Pandya (1987).

^b The surface area of this region was not included because it does not meet our definition of a premotor area (see Discussion).

the main group of labeled neurons in the CMAd. An analogous cluster of labeled neurons also was present in the maps of corticospinal neurons (cf. Figs. 11, 18). These observations indicate that precisely the same portions of the premotor areas that project to the arm area of the primary motor cortex also innervate the cervical segments of the spinal cord.

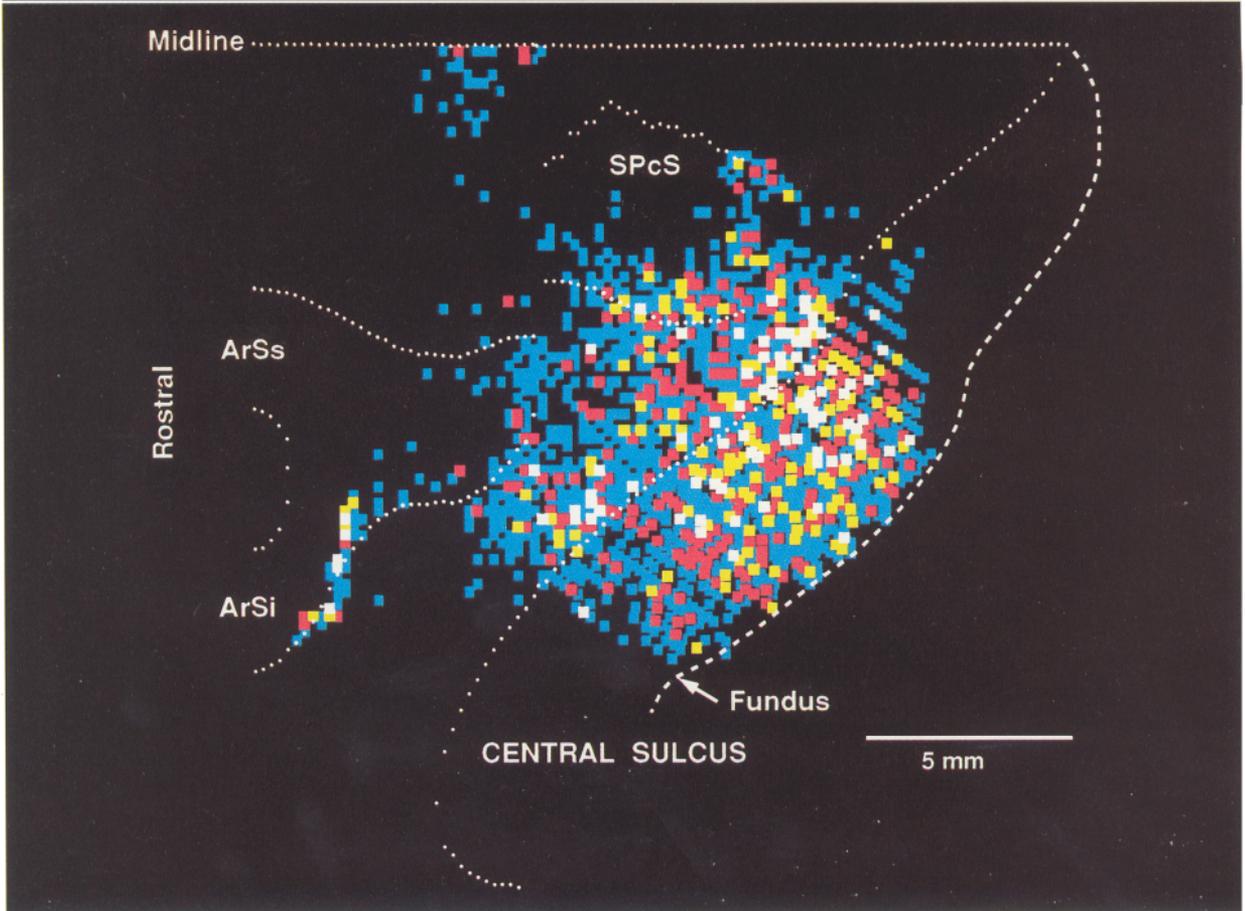
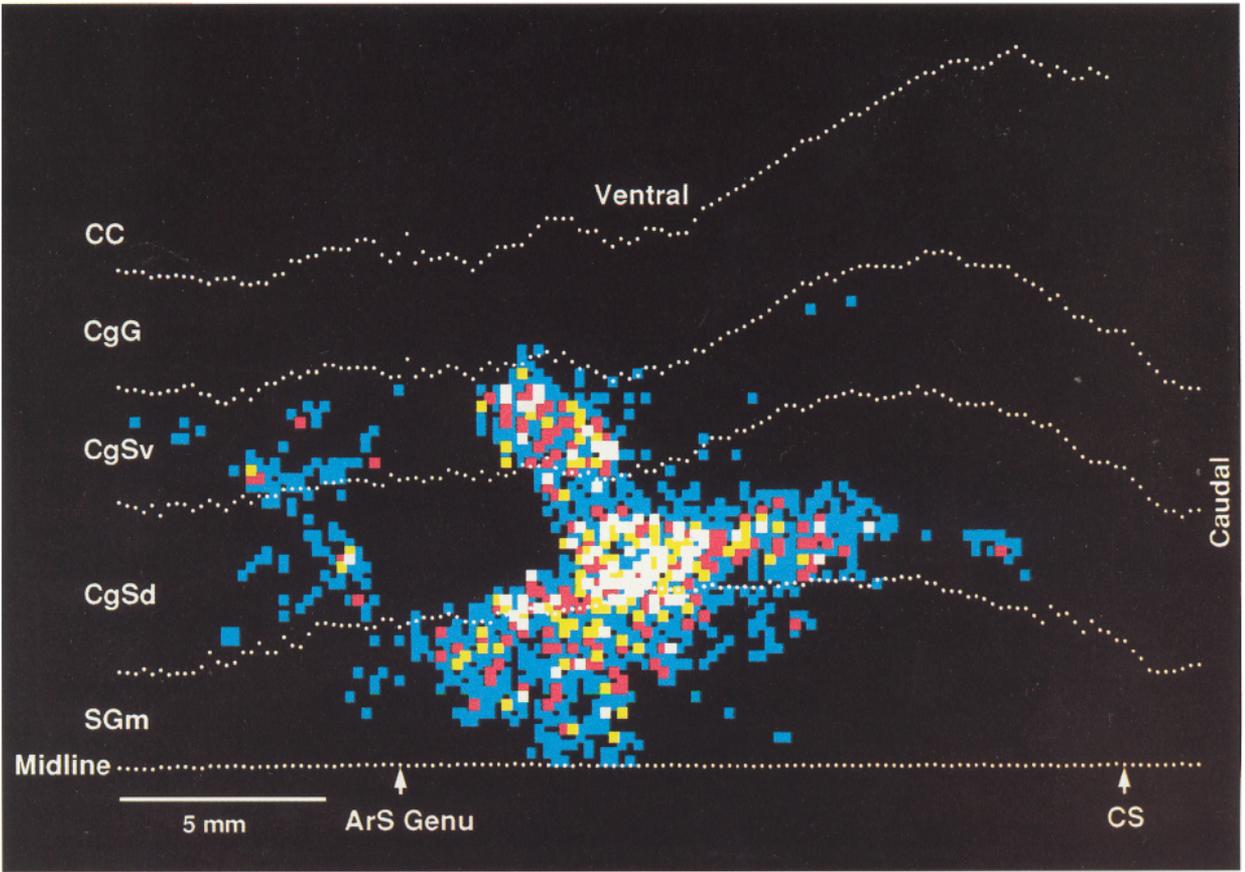
Discussion

Identification of the premotor cortex

As noted in the introductory remarks, we have defined the premotor cortex as those regions in the frontal lobe that project directly to the primary motor cortex. Based on this definition, we have found that the premotor cortex is composed of multiple, spatially separate areas (e.g., Muakkassa and Strick, 1979; Schell and Strick, 1984; Strick, 1985; Dum and Strick, 1990; see also Matsumura and Kubota, 1979; Godschalk et al., 1984; Leichnetz, 1986; Ghosh et al., 1987). These premotor areas are located in diverse cytoarchitectonic regions, including subfields of areas 6, 23, and 24. The present study demonstrates that the areas comprising the premotor cortex share another important feature, namely, that each has a projection to the spinal cord. Consequently, the premotor areas have the potential to influence the control of movement at both the cortical and the spinal levels.

The cortical regions included within our definition of the premotor cortex differ from those of others in several important respects. The original designation of the premotor cortex as a single cortical field (Fulton, 1935) included regions that we now consider separate premotor areas (SPcS, SMA, and CMAd). In addition, the APA, CMAr, and CMAv were excluded from the original definition by cytoarchitectonic criteria. Conversely, the original definition of the premotor cortex included a rostral portion of area 6 (i.e., the lateral part of area 6aB of Vogt and Vogt, 1919; 6DR of Barbas and Pandya, 1987). Because this cortical region lacks substantial direct projections to either the primary motor cortex or the spinal cord (e.g., Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Godschalk et al., 1984; Strick, 1985; Barbas and Pandya, 1987; Ghosh et al.,

² Another trough in the density of corticocortical neurons was present on the superior frontal gyrus (Fig. 18). However, a comparable trough was not clearly apparent at this location in the density maps of corticospinal neurons (e.g., Fig. 11).



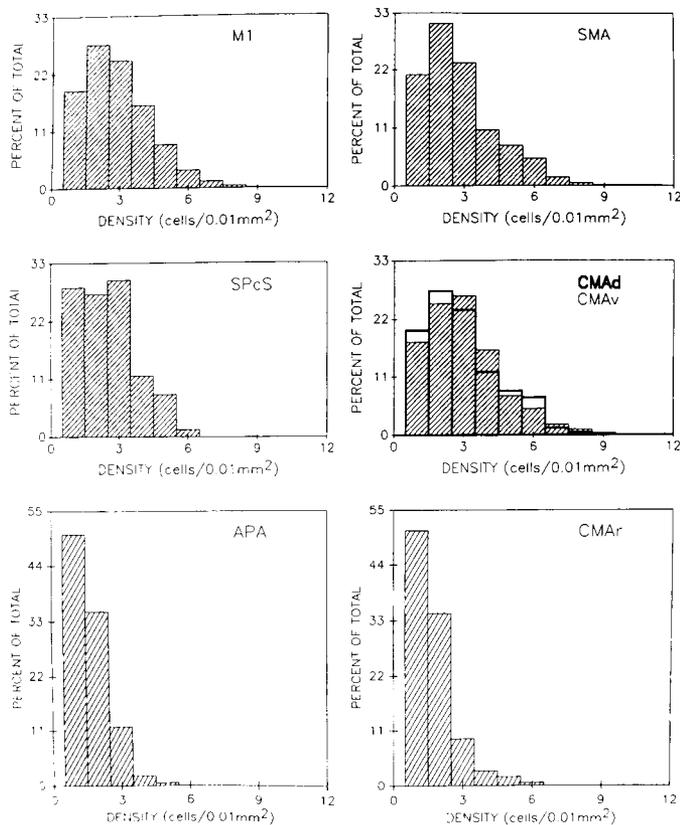


Figure 13. Histograms of density distribution of corticospinal neurons in motor areas of frontal lobe. The data in this figure are from the animal illustrated in Figures 8–12 (WGA-HRP into C4–T2). Cell counts were determined for 200- μm bins along every fourth coronal section. *M1*, primary motor cortex.

1987; Dum and Strick, 1990), we believe that it should no longer be considered functionally as part of the premotor cortex.

It is important to note that our definition of the premotor cortex does not include all the cortical regions in the frontal lobe that may be associated with the control of limb movement. There are considerable data that suggest that the prefrontal cortex is involved in the planning, initiation, facilitation, and inhibition of motor responses (for review, see Goldman-Rakic, 1987; Fuster, 1989). In fact, some neurons in the prefrontal cortex display changes in activity that are tightly locked to limb movements (e.g., Kubota and Niki, 1971; Niki, 1974a,b; Watanabe, 1986). Furthermore, widespread areas of the frontal lobe

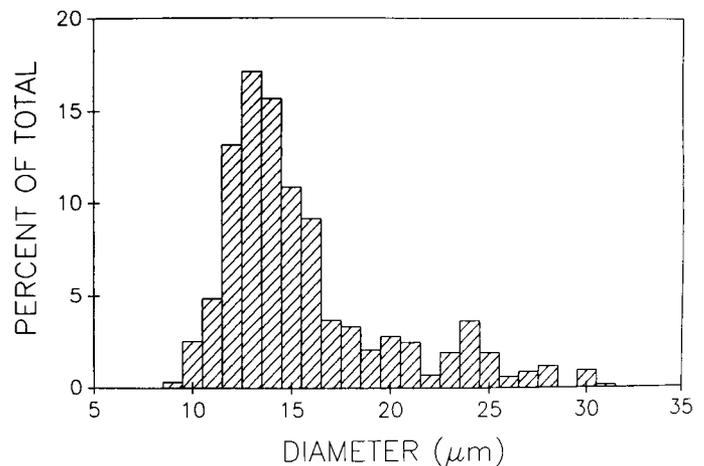


Figure 14. Soma diameters of corticospinal neurons in arm representations of motor areas in frontal lobe. The data in this figure are from the animal illustrated in Figures 8–12 (WGA-HRP into C4–T2). These measurements represent the average of the maximum and minimum soma diameter. Large neurons in this sample were defined as those measuring more than 19 μm .

contribute to basal ganglia and cerebellar loops (e.g., Brooks and Thach, 1981; Glickstein et al., 1985; Alexander et al., 1986; Goldman-Rakic, 1987) and, through these connections, may participate in the generation and control of movement. We suggest that the term “premotor cortex” should be reserved for those cortical areas that have the unique potential to influence directly motor output at the level of both the primary motor cortex and the spinal cord. Other cortical areas that do not fit this definition but clearly have a function in the generation and control of limb movement might be included within the broad term “nonprimary motor areas” (Wise et al., 1990).

Location of the individual premotor areas

An important consequence of the present study is a more complete definition of the location and extent of the “arm” representation in the premotor cortex. In total, the premotor cortex appears to contain at least 6 arm areas. In this section, we will briefly review the anatomical and physiological evidence that distinguishes these areas from each other and from the primary motor cortex.

One of the premotor areas is the APA, which is largely buried in the caudal bank of the arcuate sulcus. Woolsey et al. (1952) included part of this region within the head and neck represen-

Figure 11. Density of corticospinal neurons in frontal lobe: medial wall of hemisphere. The data in this figure are from the animal illustrated in Figures 8–12 (WGA-HRP into C4–T2). The conventions used in this figure are the same as those for Figure 12. The genu of the arcuate sulcus (*ArS Genu*) and the junction of the central sulcus (CS) with the midline are indicated by *arrows*. The number of cells per bin is color coded as follows: *white*, 6–11; *yellow*, 5; *red*, 4; *blue*, 2–3. Note that each of the premotor areas on the medial wall contains at least 1 high-density bin. The percentage of the total bins at each level is 5% (highest density level), 5%, 8%, 42% (lowest density level illustrated), and 40% (density level not illustrated). Abbreviations are as in Figure 1.

Figure 12. Density of corticospinal neurons in frontal lobe: lateral surface. The data in this figure are from the animal illustrated in Figures 8–11 (WGA-HRP into C4–T2). In this view, however, the SPcS was opened in a medial direction to display the density of labeled neurons within it. The procedures used for dividing cortex into bins (200 μm on a side) and for correcting density counts for the angulation of the central sulcus are described in Materials and Methods. The number of cells per bin is color coded as follows: *white*, 6–10; *yellow*, 5; *red*, 4; *blue*, 2–3. Bins containing only 1 cell are not displayed. The white and the yellow levels contain the upper 10% of the bins (high-density bins). Note that each premotor area contains at least 1 high-density bin. The density in the arcuate sulcus is not accurately displayed because this region was not flattened (see Figure 10). The percentage of the total bins at each level is 4% (highest density level), 6%, 12%, 45% (lowest density level illustrated), and 33% (density level not illustrated). See Materials and Methods and Results for further details.

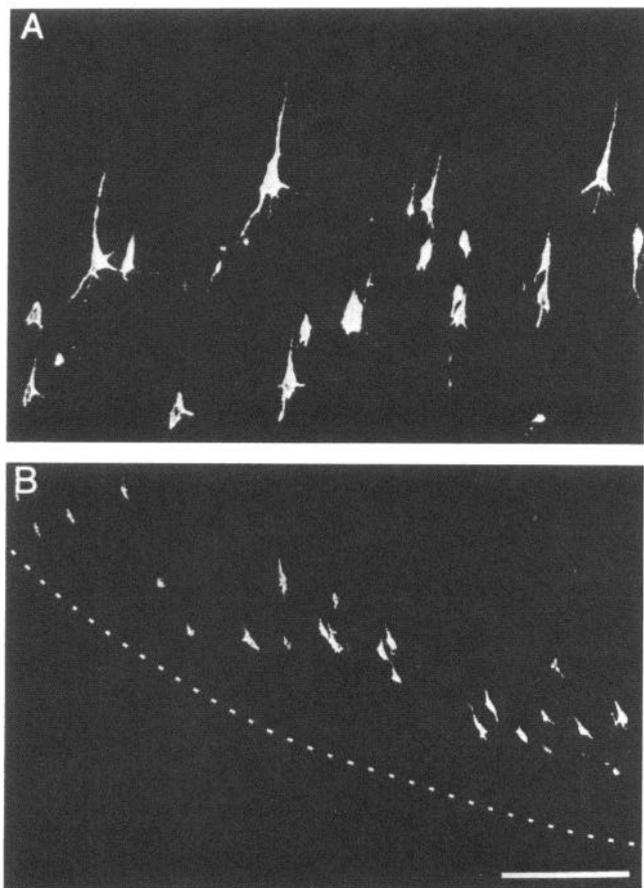


Figure 15. Corticospinal neurons. These photomicrographs were taken under dark-field/polarized light illumination. *A*, Corticospinal neurons located in the primary motor cortex. *B*, Corticospinal neurons located in the arm representation of the CMAv in area 23c on the ventral bank of the cingulate sulcus. The dashed line indicates the border between cortical layer VI and white matter. Scale bar, 250 μm .

tation of the primary motor cortex. However, movements of the digits and wrist have been evoked by intracortical stimulation in the caudal bank of the arcuate sulcus (Gentilucci et al., 1988). In addition, single neurons recorded in this sulcus in awake monkeys show changes in activity related to distal forelimb movements (Kubota and Hamada, 1978; Rizzolatti et al., 1981, 1988; Godschalk et al., 1985; Kurata and Tanji, 1986; Okano and Tanji, 1987). Anatomical studies provide further support for an arm representation in the APA by demonstrating that it projects to the arm area of the primary motor cortex and cervical segments of spinal cord (Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Godschalk et al., 1984; Martino and Strick, 1987; Dum and Strick, 1989). Anatomical studies also demonstrate that the corticocortical and thalamocortical connections of the APA, as well as its cytoarchitecture, are very different from those of the primary motor cortex (Schell and Strick, 1984; Matelli et al., 1985, 1986, 1989; Barbas and Pandya, 1987; Dum and Strick, 1990). These observations support our proposal that the APA is a distinct entity with a separate arm representation.

A second premotor area is located in the region of the cortex surrounding the SPcS. The existence of an arm representation and even a premotor area at this site has been controversial. In

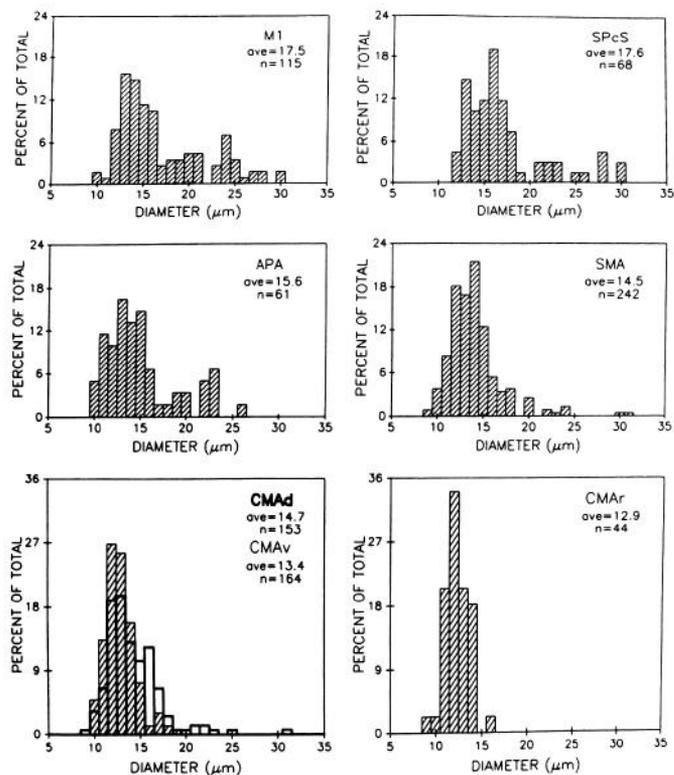


Figure 16. Soma diameters of corticospinal neurons in arm representations of premotor areas and primary motor cortex. The data in this figure are from the animal illustrated in Figures 8–12 (WGA-HRP into C4–T2). Note that large corticospinal neurons (soma diameter, >19 μm) are found in 4 premotor areas (the SPcS, SMA, APA, and CMAv). *M1*, primary motor cortex.

fact, some studies have included all or part of the SPcS within the primary motor cortex (e.g., Brodmann, 1905; von Bonin and Bailey, 1947; Woolsey et al., 1952; Sessle and Wiesendanger, 1982). Early physiological studies attributed the region around the SPcS with some unique characteristics and distinguished it from the primary motor cortex (e.g., Bucy and Fulton, 1933; Hines, 1937; Denny-Brown and Botterell, 1948). More recent anatomical and physiological data continue to indicate differences between this cortical area and the adjacent primary motor cortex. The thresholds for evoking movement in the SPcS are higher than those in the primary motor cortex (Kurata et al., 1985; Kurata, 1989). In awake trained monkeys, many neurons around the lateral edge of the SPcS change their activity in relation to distal forelimb movements and display “set-related” activity (Kurata et al., 1985; Kurata, 1989). In contrast, neurons with set-related activity are comparatively rare in the primary motor cortex. The SPcS and primary motor cortex also differ in that the SPcS has dense projections to the medullary reticular formation and the primary motor cortex does not (Keizer and Kuypers, 1989). The results of the present study indicate that large numbers of corticospinal neurons are found in and around the SPcS. This is the same region that contains a spatially separate group of labeled neurons following tracer injections into the arm area of the primary motor cortex (Muakkassa and Strick, 1979; Godschalk et al., 1984). Thus, there is both anatomical and physiological evidence to support the proposal that the cortex around the SPcS contains a premotor area with an arm representation distinct from the primary motor cortex.

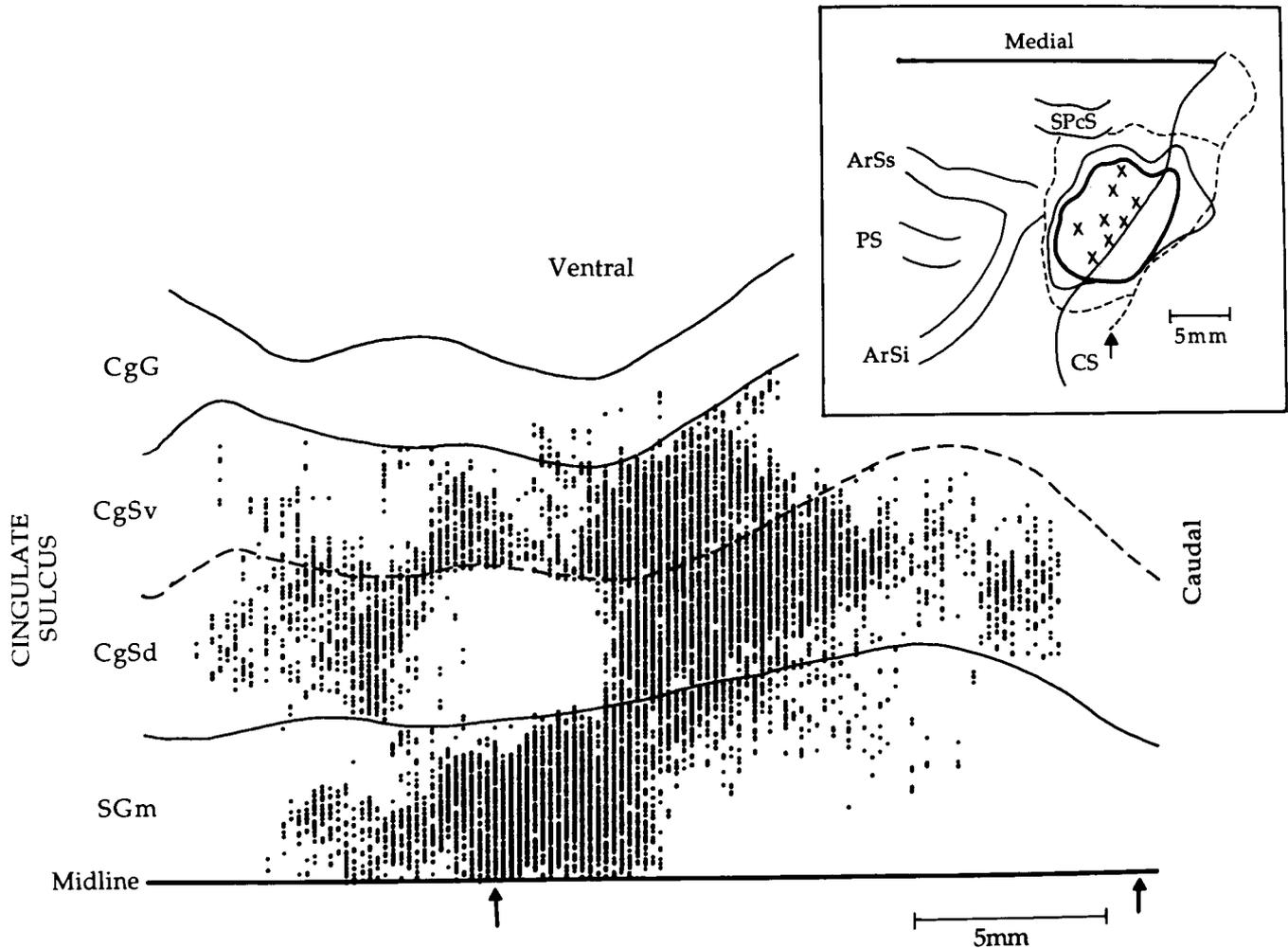


Figure 17. Map of cortical neurons projecting from premotor areas on medial wall to arm area of primary motor cortex. WGA-HRP was injected into the arm area of the primary motor cortex. The spread of tracer is indicated on the flattened reconstruction of the frontal lobe (*inset at upper right*). *X*'s mark the site of needle penetration into the cortex. A *heavy line* encircles the densest region of reaction product, and a *lighter line* indicates the "halo" that surrounded it. The *dashed line* encircles the region of almost continuous cell labeling that surrounded the injection site. Every fourth section was used to reconstruct the distribution of labeled neurons (*dots*) on the medial wall. The genu of the arcuate sulcus (*left arrow*) and the junction of the central sulcus with the midline (*right arrow*) are indicated. See Figures 1, 6, and 8 for conventions and methods of reconstruction. Note that neurons projecting to the arm area of the primary motor cortex are located in the same regions that project to cervical segments of the spinal cord (cf. Fig. 8).

Four additional premotor areas, each of which has an arm representation, are located on the medial wall of the hemisphere (see also Muakkassa and Strick, 1979; Hutchins et al., 1988; Dum and Strick, 1989, 1990). One of these is the SMA, which has long been recognized as separate from the primary motor cortex (Penfield and Welch, 1951; Woolsey et al., 1952). There is a close correspondence between the location of corticospinal neurons in the SMA projecting to cervical segments of the spinal cord and other anatomical and physiological maps of arm representation on the superior frontal gyrus (e.g., Penfield and Welch, 1951; Brinkman and Porter, 1979; Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Macpherson et al., 1982; Godschalk et al., 1984; Mitz and Wise, 1987). For example, corticospinal neurons that project to cervical segments are most concentrated within regions of the superior frontal gyrus that lie 3–4 mm caudal to the genu of the arcuate sulcus. Apparently, this is the only site within the superior frontal gyrus where intracortical stimulation evokes arm movements (Macpherson

et al., 1982; Mitz and Wise, 1987; Alexander and Crutcher, 1990). Thus, there is general agreement that a large part of the arm representation within the SMA lies on the superior frontal gyrus, caudal to the genu of the arcuate sulcus.

There is some disagreement, however, about the complete extent of arm representation within the SMA. Woolsey et al. (1952) indicated that part of its arm representation extended ventrally from the superior frontal gyrus into the depths of the dorsal bank of the cingulate sulcus. In other studies, stimulation in this region of the dorsal bank evoked movements of the hindlimb (Penfield and Welch, 1951; Macpherson et al., 1982; Mitz and Wise, 1987). In the present study, the portion of the dorsal bank of the cingulate sulcus that lies ventral to the SMA arm representation on the superior frontal gyrus lacked projections either to cervical segments of the spinal cord or to the arm area of the primary motor cortex. Indeed, we and others have found that this region of the dorsal bank projects to lumbar segments of the spinal cord (Biber et al., 1978; Murray and

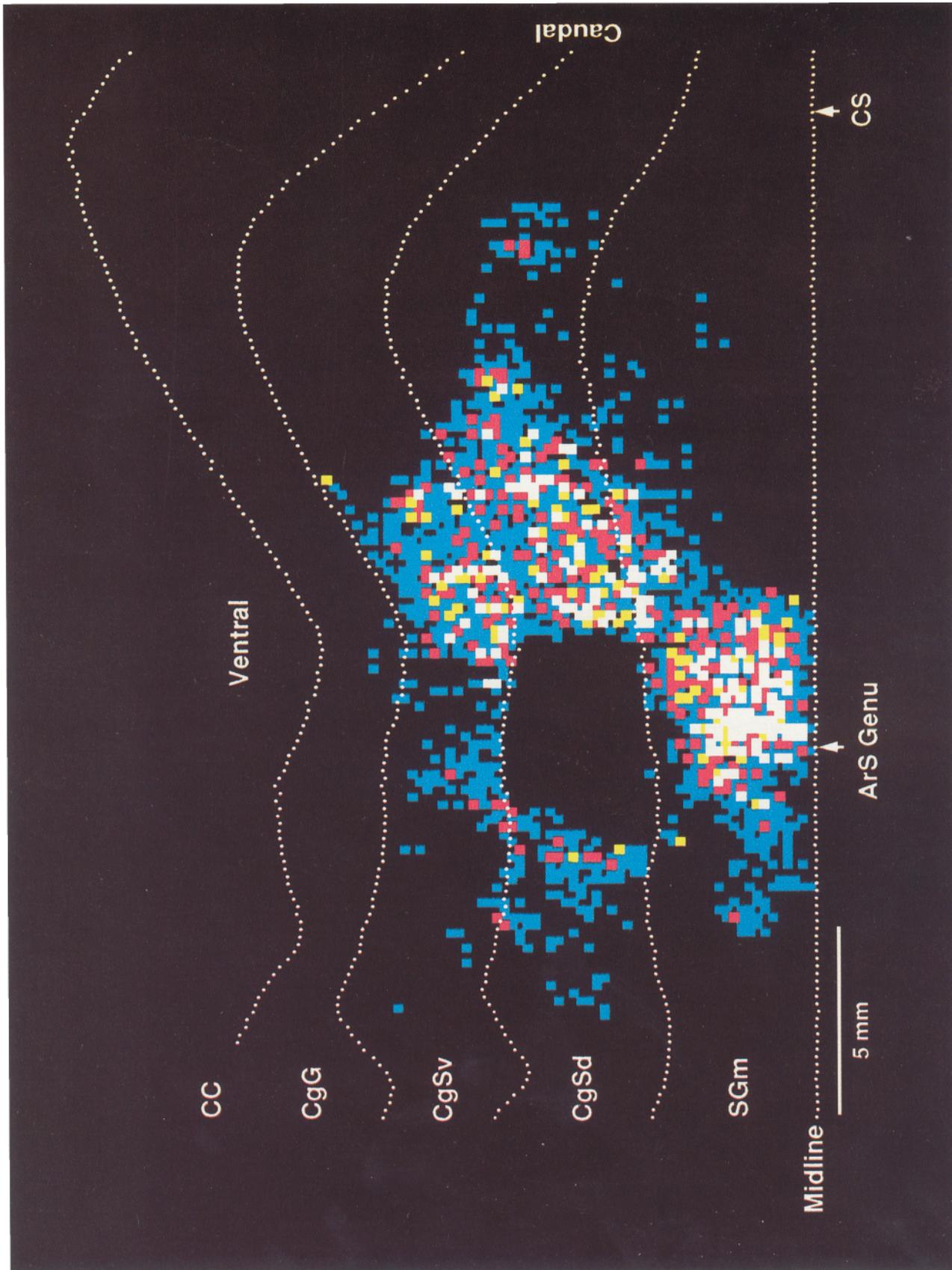


Figure 18. Density of cortical neurons projecting from premotor areas on medial wall to arm area of primary motor cortex. The data in this figure are from the animal illustrated in Figure 17 (WGA-HRP into the arm area of the primary motor cortex). The conventions used in this figure are the same as those for Figure 11. The genu of the arcuate sulcus (left arrow) and the junction of the central sulcus with the midline (right arrow) are indicated. The number of cells per bin is color coded as follows: white, 10–24; yellow, 9; red, 7–8; blue, 3–6. Bins containing 1–2 cells are not displayed. Note that there is a trough in density that separates the corticocortical neurons on the dorsal bank (in the CMAAd) from those on the ventral bank (in the CMAV).

Coulter, 1981; Macpherson et al., 1982; He et al., 1989). Thus, most of the available evidence suggests that the arm area of the SMA is largely confined to the superior frontal gyrus.

Two additional premotor areas, the CMA_d and the CMA_v, are located more caudally in the cingulate sulcus (see also Hutchins et al., 1988; Dum and Strick, 1989, 1990). Although our initial description treated these areas as a single cortical region (Hutchins et al., 1988), they span 2 distinct cytoarchitectonic fields. The CMA_v resides in area 23c, and the CMA_d resides in area 6c (see also von Bonin and Bailey, 1947; Vogt et al., 1987). In addition, the present study demonstrates that tracer injections into either the arm area of the primary motor cortex or cervical segments of spinal cord result in a high-density region of labeled neurons in the CMA_d that is separated from that in the CMA_v by a trough in labeled neurons. Furthermore, recent anatomical studies in our laboratory indicate that the subcortical and cortical projections to the 2 portions of the CMA_c differ. For example, the CMA_v, but not the CMA_d, is interconnected with regions of the prefrontal cortex adjacent to the principal sulcus (Lu and Strick, 1990). The CMA_v receives thalamic input from a caudal portion of the ventralis lateralis pars caudalis (VL_c; Holsapple and Strick, 1989), a site of termination of cerebellar efferents (e.g., Percheron, 1977; Stanton, 1980; Kalil, 1981; Asanuma et al., 1983a,b). In contrast, the CMA_d receives thalamic input from a portion of the ventralis lateralis pars oralis (VL_o) (Holsapple and Strick, 1989), a site of termination of pallidal efferents (e.g., Nauta and Mehler, 1966; Kuo and Carpenter, 1973; Kim et al., 1976; DeVito and Anderson, 1982). Thus, the available anatomical evidence supports the division of the CMA_c into 2 premotor areas with separate arm representations.

Before proceeding, we would like to clarify a potential source of confusion about the CMA_d. Woolsey et al. (1952) considered this region to be a part of the SMA and indicated that it contained the representation of the proximal hindlimb (cf. Fig. 8, 17 with Woolsey et al., 1952, p 255, their Fig. 132B). However, using stimulation techniques comparable to Woolsey et al. (1952), Penfield and Welch (1951) evoked forelimb movements when they stimulated this approximate location on the dorsal bank of the cingulate sulcus (see, e.g., their Fig. 5, points 19, 52). We have confirmed prior observations that the architecture in the region of the CMA_d differs from that of the SMA on the adjacent superior frontal gyrus (Mauss, 1908; Brodmann, 1909; von Bonin and Bailey, 1947; Toyoshima and Sakai, 1982). The large injections of tracer employed in the present study produced a region of labeled neurons that continued uninterrupted from the SMA to the CMA_d. However, after tracer injections limited to lower cervical segments of the spinal cord or small injections into the arm representation of the primary motor cortex, there was a clear separation between the labeled neurons in the SMA and those in the CMA_d (Strick, 1985; Hutchins et al., 1988; Dum and Strick, 1989, 1990; He et al., 1989). Taken together, these observations support our conclusion that the CMA_d contains an arm representation distinct from that in the SMA.

The fourth premotor area and arm representation on the medial wall is located in the banks of the cingulate sulcus at levels rostral to the genu of the arcuate sulcus. This premotor area resides in a subfield of area 24 and was termed "CMA_r" (Hutchins et al., 1988; Dum and Strick, 1990). Besides its connections with the primary motor cortex and spinal cord (Künzle, 1978; Leichnetz, 1986; Martino and Strick, 1987; Dum and Strick, 1990), little is known about the CMA_r. However, in awake

primates, Shima et al. (1991) have recorded the activity of neurons in the CMA_r, CMA_d, and CMA_v. All 3 regions contained neurons whose activities were related to the execution of stimulus-triggered and self-paced movements of the distal forelimb. Many neurons in the cingulate motor areas (60%) discharged before distal muscles became active in the task. Compared to the CMA_d and CMA_v, the CMA_r contained a higher concentration of neurons that were preferentially active during self-paced movements. Also, neurons with changes in activity long before the onset of self-paced movements (0.5–2.0 sec) were particularly abundant in the CMA_r. These observations provide additional evidence for distinguishing the CMA_r from the more caudal premotor areas in the cingulate sulcus. Furthermore, they support our proposal that the cingulate motor areas are involved in the generation of arm movements.

Contribution of the premotor areas to the corticospinal system

One of the major results of the present study is our finding that the total number of corticospinal neurons in the arm representations of the premotor areas equals or exceeds the total number in the arm representation of the primary motor cortex. Furthermore, the premotor areas collectively comprise more than 60% of the cortical area in the frontal lobe that projects to the spinal cord. As much as 40% of the corticospinal neurons in the frontal lobe originate from the premotor areas on the medial wall of the hemisphere (i.e., SMA, CMA_d, CMA_v, and CMA_r). Up to 18% of the corticospinal system in the frontal lobe originates from a single premotor area, the SMA. These observations are consistent with the findings of Russell and DeMyer (1961) that, on average, 29% of the pyramidal tract at the medullary level originates from area 6 and 31% originates from area 4.

Individually, the contribution of each premotor area to the corticospinal system may not appear substantial. For example, the area of the arm representation in the SMA is approximately half the area of the arm representation in the primary motor cortex. Also, the number of corticospinal neurons in the SMA is less than half that of the primary motor cortex. However, several studies suggest that the primary motor cortex is actually composed of functional subdivisions. In the squirrel monkey, the arm area of the primary motor cortex contains 2 spatially separate representations of the hand, which receive different concentrations of "deep" and "cutaneous" afferent input (Strick and Preston, 1978a,b, 1982a,b). A similar organization may be present in the arm and leg representations of macaques (Lamour et al., 1980; Lemon, 1981; Wise and Tanji, 1981; Sato and Tanji, 1989). Thus, it may be more appropriate to compare individual premotor areas with one of the subdivisions of the primary motor cortex.

A second major result of the present study is that each of the premotor areas contains local regions that have a high density of corticospinal neurons. In fact, the overall density distributions of corticospinal neurons in the CMA_d and CMA_v were not significantly different from that in the primary motor cortex. These observations suggest that the local density of corticospinal output from some of the premotor areas is comparable to that from the primary motor cortex.

These 2 major results emphasize that a substantial component of the corticospinal system originates from the premotor areas in the frontal lobe. Each of the premotor areas has direct access to the spinal cord, and, as a consequence, each has the potential to influence the generation and control of movement independently of the primary motor cortex. This conclusion contrasts

sharply with the classical viewpoint that the primary motor cortex is the main source of motor signals in the corticospinal tract. In fact, some have viewed the primary motor cortex as the "upper motoneuron" or the "final common pathway" for the cortical control of movement (for review, see Phillips and Porter, 1977; Kuypers, 1981; Hepp-Reymond, 1988). This view is clearly reflected in Fulton's statement that area 4 "serves as a funnel through which highly organized movement-patterns are ultimately discharged" (Fulton, 1949, p 393). It is now clear that the primary motor cortex is only one of a number of cortical areas that have the potential to influence motor function at the spinal level.

Influence on spinal mechanisms

Large corticospinal neurons are thought to have a special role in movement initiation, in part because they provide a substantial portion of the monosynaptic input from the motor cortex to motoneurons (for review, see Phillips and Porter, 1977; Evarts, 1981). We found that "large" corticospinal neurons (mean diameter, $> 19 \mu\text{m}$) are present not only in the primary motor cortex, but also in 4 out of 6 premotor areas. Although the primary motor cortex contains the highest percentage of large corticospinal neurons (31%), these neurons comprise as much as 20% of the population of corticospinal neurons originating from the APA and the SPcS. In this respect, the corticospinal system originating from the premotor areas differs from that in the parietal lobe, where few if any large corticospinal neurons are present (Jones and Wise, 1977; Murray and Coulter, 1981; Toyoshima and Sakai, 1982). The presence of large corticospinal neurons in the premotor areas is consistent with the hypothesis that these cortical regions participate in the actual generation of movement.

On the other hand, most (92%) of the corticospinal neurons in the premotor areas are "small" (mean diameter, between 9 and $19 \mu\text{m}$). Small neurons also make up the vast majority (69%) of the corticospinal population in the primary motor cortex. The small size of these neurons, however, should not preclude them from having an important function in motor control and/or participating in the generation of limb movement. The results of recent physiological studies in the primary motor cortex indicate that some presumably small corticospinal neurons with more slowly conducting axons make monosynaptic connections with motoneurons (Fetz and Cheney, 1980; Buys et al., 1986). Furthermore, some small corticospinal neurons change their activity before the onset of EMG activity and movement (e.g., Evarts, 1966; Fromm and Evarts, 1981).

The functional contribution of corticospinal projections from the premotor areas cannot be fully evaluated until the patterns of spinal termination of efferents from these areas are determined. Results from preliminary studies (R. P. Dum and P. L. Strick, unpublished observations; see also Brinkman, 1982; Cheema et al., 1983) suggest that the corticospinal projections from the CMA_d, CMA_v, and SMA terminate most heavily in the intermediate zone of the spinal cord. In this respect, the pattern of termination of corticospinal projections from the premotor areas is like that from the primary motor cortex (Kuypers, 1960; Liu and Chambers, 1964; Kuypers and Brinkman, 1970; Cheema et al., 1984; Ralston and Ralston, 1985). The intermediate zone of the spinal cord contains many interneurons that project to motoneurons (for review, see Kuypers, 1981). Thus, the limited evidence available suggests that the cortico-

spinal projections from the premotor areas have direct access to spinal cord mechanisms concerned with motor output.

Functional implications of spinal access for the premotor areas

Our observations suggest a new perspective on the involvement of the premotor areas in the generation and control of movement. As noted in the introductory remarks, classically, the cortical motor areas were viewed as organized in a hierarchical manner in which the premotor cortex occupied a level superior to that of the primary motor cortex. The generation of motor commands was thought to proceed in a serial fashion from the premotor cortex to the primary motor cortex and hence to the spinal cord (e.g., Campbell, 1905; Fulton, 1949; for recent reviews, see Wiesendanger, 1981; Freund and Hummelsheim, 1985; Wise, 1985). Thus, the premotor areas have been thought to influence the control of movement (especially that of distal body parts) primarily through their connections with the primary motor cortex.

The results of studies on the origin of subcortical inputs to the premotor areas (reviewed in the introductory remarks) began to raise questions about a strictly serial model of motor control at the cortical level (e.g., Schell and Strick, 1984; Wiesendanger and Wiesendanger, 1985a,b; Matelli et al., 1989; Orioli and Strick, 1989). For example, Schell and Strick (1984) proposed that the arm area of the SMA is a target of pallidothalamic efferents, and in contrast, the arm area of the APA is a target of cerebellothalamic efferents. Furthermore, they suggested that the projections from the cerebellum and basal ganglia to the premotor areas were independent of those to the primary motor cortex. The organization of parietal lobe projections to the arm areas of the SMA, APA, and primary motor cortex appears to be organized along similar lines (Galyon and Strick, 1985; Matelli et al., 1986; Dum and Strick, 1990). Briefly, each cortical area receives its most substantial input from a different region of the parietal lobe. Some parietal lobe regions project to both the primary motor cortex and either the APA or the SMA. However, no parietal lobe region has substantial projections to both premotor areas. Thus, the premotor areas receive a unique pattern of input from the parietal lobe, as well as from subcortical motor centers.

The parallel and independent nature of the inputs to the cortical motor areas led us to hypothesize that the premotor areas function, in part, at the same hierarchical level as the primary motor cortex (Strick, 1988; Dum and Strick, 1990). The results of the present study add further support for this hypothesis by demonstrating that, like the primary motor cortex, each premotor area has direct access to the spinal cord. Indeed, our findings indicate that the corticospinal system from the premotor areas is numerically as substantial as that from the primary motor cortex. Thus, we propose that the generation and control of movement at the cortical level are mediated by parallel outputs from the premotor areas, as well as from the primary motor cortex.

By making this proposal, we do not mean to imply that the premotor areas influence the control of movement only via their corticospinal projections; nor do we mean to imply that the premotor areas function only in parallel with the primary motor cortex. The direct connections of the premotor areas with the primary motor cortex and their participation in cerebellar and basal ganglia loops have long been thought to provide the anatomical substrate for serial interactions between the premotor

areas and the primary motor cortex (e.g., Brooks and Thach, 1981; Ito, 1984; Glickstein et al., 1985; Alexander et al., 1986). Instead, we wish to emphasize a viewpoint that has been somewhat neglected, namely, that the premotor areas have parallel outputs directly to the spinal cord that may be independent of these serial interactions.

Many different functions have been attributed to the premotor cortex (e.g., visual guidance of movement, bimanual coordination, movement sequencing, preparation for movement, building associations between motor responses and arbitrary stimuli, postural mechanisms to support movement and trajectory control; e.g., Moll and Kuypers, 1977; Roland et al., 1980; Brinkman, 1984; Freund and Hummelsheim, 1985; Passingham, 1988; Halsbad and Freund, 1990; for review, see Wiesendanger, 1981; Wise, 1985). Perhaps these diverse viewpoints on the function of the premotor cortex are appropriate and reflect the functions of all 6 of the premotor areas. Thus, it is possible that each of these premotor areas may be differentially involved in one or another of these aspects of motor behavior. In fact, one potential consequence of the parallel input-output organization we propose for the motor areas in the frontal lobe is that this anatomical arrangement may facilitate the concurrent processing of different aspects of movement. Now that the locations of the premotor areas have been more precisely identified in primates, it should be possible to use combined behavioral and physiological methods to examine the contributions of individual premotor areas to motor control.

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