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Corticospinal Terminations in Two New-World Primates: Further Evidence That Corticomotoneuronal Connections Provide Part of the Neural Substrate for Manual Dexterity

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Anterograde transport of 2–10% WGA-HRP was used to examine the pattern of termination of efferents from the primary motor cortex to cervical segments of the spinal cord in cebus (*Cebus apella*) and squirrel (*Saimiri sciureus*) monkeys. We have compared the pattern of termination in these monkeys because of marked differences in their manipulative abilities. Both primates have pseudo-opposable thumbs; however, only cebus monkeys use independent finger movements to pick up small objects.

We found that corticospinal terminations in cervical segments of the cebus monkey are located in three main zones: a dorsolateral region of the intermediate zone, a dorsomedial region of the intermediate zone, and the ventral horn. The projection to the ventral horn in these monkeys is particularly dense at C8–T1 segments, where terminations form a "ring" that encircles the lateral motoneuronal cell group. In contrast, there are only two main zones of terminations in the squirrel monkey: a dorsolateral region of the intermediate zone and a dorsomedial region of the intermediate zone. As others have noted, efferents from the primary motor cortex of squirrel monkeys have, at best, only sparse terminations within the ventral horn. Thus, there are marked differences between cebus and squirrel monkeys in the extent of corticospinal terminations within the ventral horn. These observations provide further support for the concept that monosynaptic projections from the primary motor cortex to motoneurons in the ventral horn provide part of the neural substrate for dexterous movements of the fingers.

[Key words: cervical spinal cord, hand movement, motor control, primary motor cortex]

The hand endows most primates with a number of special motor skills. For example, selected primates can perform a "precision grip" in which an object is grasped between two fingers without the use of the palm (e.g., Napier, 1956, 1961). Hand movements, such as a precision grip, are clearly the basis for the enhanced dexterity of some primates. In fact, the capacity of selected primates to manufacture and use tools may derive, in part, from their ability to perform relatively independent movements of the fingers.

Yet, the appropriate peripheral apparatus is, in itself, not sufficient to explain the unique motor capacities of some primates. There are multiple instances of animals that possess similar hands, but differ in their ability to perform dexterous movements of the fingers (e.g., Torigoe, 1985; see Napier and Napier, 1985). For example, two species of new-world primates, cebus monkeys and squirrel monkeys, have similar hands with pseudo-opposable thumbs. However, recent behavioral studies have demonstrated that the cebus monkey and the squirrel monkey differ markedly in their manual dexterity (Fragaszy, 1983; Costello and Fragaszy, 1988). Because the thumbs of these two monkeys cannot rotate about the carpo-metacarpal joint, it was thought that neither primate was capable of performing a precision grip (e.g., Napier and Napier, 1967, 1985). In spite of this anatomical constraint, the cebus monkey is capable of performing relatively independent finger movements and uses a precision grip to pick up small objects and manipulate tools (Antinucci and Visalberghi, 1986; Westergaard and Fragaszy, 1987; Costello and Fragaszy, 1988). In contrast, the squirrel monkey is incapable of performing relatively independent movements of the fingers and does not use a precision grip for any activity (Fragaszy, 1983; Costello and Fragaszy, 1988). Instead, the squirrel monkey uses a "power grip" in which an object is grasped by using a sweeping motion that involves all the fingers of the hand working in concert. The differences in grip usage between the two species of monkey cannot be explained by differences in the mobility of joints in the wrist or hand (Fragaszy et al., 1989).

In the present study, we explored the possibility that the cebus and squirrel monkey have different neural substrates for generating and controlling finger movements. Specifically, we hypothesized that efferents from the primary motor cortex terminate directly on hand motoneurons in the cebus monkey, but not in the squirrel monkey. This hypothesis is based on results from prior anatomical, physiological, and behavioral studies that suggested that the ability to perform highly fractionated movements of the fingers depends on a monosynaptic connection between the primary motor cortex and hand motoneurons (for references, see Kuypers, 1981).

There already is evidence from prior studies that the squirrel monkey lacks substantial projections from its primary motor cortex to the ventral horn (Harting and Noback, 1970; Tigges

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et al., 1979). However, there is little information available on corticospinal connections in the cebus monkey (Petras, 1968). Therefore, we used anterograde transport techniques to define the pattern of projections from the primary motor cortex of the cebus monkey to the cervical spinal cord. We also examined this projection in the squirrel monkey for comparison.

We found that there is a major difference between the cebus and squirrel monkey in the pattern of corticospinal terminations in the cervical spinal cord. The cebus monkey has abundant corticospinal terminations in the regions of the ventral horn where the cell bodies of hand motoneurons are located. In contrast, comparable terminations at this site are absent in the squirrel monkey. Thus, our results suggest that the differences in corticomotoneuronal connections between cebus and squirrel monkeys may be part of the basis for the differences in hand function between these two primates. Furthermore, our results provide additional support for the concept that the direct corticomotoneuronal connection is part of the neural substrate for relatively independent movements of the fingers.

A brief report of some of the results has been presented previously (Bortoff and Strick, 1990).

Materials and Methods

We used anterograde transport of wheat germ agglutinin conjugated to horseradish peroxidase (WGA-HRP) to label the terminations of efferents from the primary motor cortex within cervical segments of the spinal cord in two new-world primates: the squirrel monkey (*Saimiri sciureus*, $n = 2$) and the tufted capuchin (*Cebus apella*, $n = 2$).

Surgical procedures

One day prior to surgery, each animal was pretreated with dexamethasone (0.5 mg/kg, i.m.). The animal was restricted from food and water 6–12 hr prior to surgery. On the day of surgery, the animal was anesthetized with ketamine HCl (25 mg/kg, i.m.) and sodium pentobarbital (20 mg/kg, i.p.). Supplemental doses of ketamine (5–10 mg/kg, i.m.) were given as needed during the surgery. Prior to surgery, the animal was given atropine (0.1 mg/kg) and antibiotics (Kefzol, 25 mg/kg, every 6 hr; oxacillin, 25 mg/kg, every 4 hr; and gentamicin, 1 mg/kg, every 8 hr). Body temperature, heart rate, and respiration were monitored. We maintained body temperature with a heating pad.

All surgical procedures were performed using sterile techniques. The animal was mounted in a Kopf stereotaxic frame. A craniotomy was performed over the primary motor cortex and the dura was incised and reflected to expose the cortical surface. Multiple unilateral injections of WGA-HRP (Sigma, lot 27F-4034, dissolved in 0.5 M NaCl with 0.1 M mannose) were made into the forelimb representation of the primary motor cortex. We injected 10% solutions of WGA-HRP into the cortex of one cebus and one squirrel monkey and allowed the animals to survive for 4.5 d to promote the maximal anterograde transport possible. In a second cebus and squirrel monkey, we injected 2% solutions of WGA-HRP and allowed these animals to survive only 3 d to eliminate the possibility of transneuronal transport of the conjugate (Mesulam, 1982).

In all animals, multiple injections (0.05 μl) were made using a Hamilton syringe with a 32-gauge fixed needle. Injections were spaced 1 mm apart, except to avoid surface blood vessels. After each injection, the needle was left in place for 2–3 min. In the squirrel monkey, 11 injections were made into the "arm" area of primary motor cortex (see Fig. 2*B*) using the maps of Welker et al. (1957) and Strick and Preston (1978, 1982) as a guide. Each injection was placed 1.5 mm below the cortical surface. In the cebus monkey, injections were made 1.5 and 3 mm rostral to the central sulcus in the "arm" area of primary motor cortex according to the maps of Asanuma and Rosén (1972) and Shinoda et al. (1979). The most rostral injections were placed 1.5 mm below the surface. To include the anterior bank of the central sulcus in the injection site, injections near the sulcus were made at three depths (1.5, 3.0, and 4.5 mm) (see Fig. 2*A*).

Following the last injection, the edges of the cut dura were apposed and the dura was covered with surgical grade Silastic strips that were glued to the edges of the bone defect. Then, the bone flap was replaced, and the wound was closed in anatomical layers. The animal was returned to its home cage, where recovery was carefully monitored.

After the survival period, animals were reanesthetized and perfused transcardially using a four-step procedure (Rosene and Mesulam, 1978; Mesulam, 1982). The perfusates included (1) 0.1 M phosphate buffer solution, pH 7.4 (PBS); (2) 2.5% paraformaldehyde in PBS; (3) 2.5% paraformaldehyde in 10% glycerin and PBS; and (4) cold 10% glycerin in PBS. The spinal cord and the brain were removed and stored in PBS with 10–20% glycerin at 4°C for 5–7 d. The cervical spinal cord was divided into two blocks (C2–C5 and C6–T2). The brain was blocked to include the injection site and adjacent cortical areas.

Histological procedures

The brain and spinal cord blocks were quick-frozen in cold isopentane (Rosene et al., 1986). Transverse sections of spinal cord and coronal sections of brain were cut at 50 μm intervals on a microtome. Every 10th section was postfixed and reacted with cresyl violet for cytoarchitecture, according to Gower (in Mesulam, 1982). The remaining sections were processed for HRP using a tetramethylbenzidine (TMB) method, which incorporates the procedures of Mesulam (1982) and Gibson et al. (1984).

Analytical procedures

The outlines of sections and the locations of injections sites, labeled processes, and tissue landmarks (e.g., blood vessels, spinal lamina) were plotted and stored using a computerized charting system (Minnesota Datametrics). This system uses optical encoders to sense x-y movements of the microscope stage and stores the coordinates of charted structures on an IBM-compatible computer.

Injection site analysis. At least every fourth section of the frontal cortex was examined under bright-field and dark-field illumination with polarized light and plotted to define the extent of the injection site. The injection site was considered to include the densely stained regions adjacent to the needle track, but not the adjacent region with light background staining where individual neurons could be distinguished (Mesulam, 1982). The sections stained with cresyl violet were examined under bright-field illumination to determine the area 3a/4 border using the appearance of a granular layer IV as the defining criterion (Lucier et al., 1975; Jones and Porter, 1980; Strick and Preston, 1982).

Analysis of spinal terminations. Sections of cervical and upper thoracic spinal cord were examined under dark-field illumination with polarized light for anterograde transport. Detailed drawings of corticospinal fibers and their terminal fields, along with section outlines were made using a camera lucida (e.g., see Figs. 3–5). Adjacent sections stained with cresyl violet were then examined under bright-field illumination and the boundaries of spinal laminae (Rexed, 1952) were added to the drawings.

Density analysis. To quantitatively analyze anterograde transport, we performed a gradient density analysis of spinal cord terminations. The images of individual sections were viewed under dark-field illumination with polarized light using a Newvicon video camera (Dage-MTI series 68) and analyzed using an IBM-compatible computer with an "image capture" board (Imaging Technologies, FG-100). Images were captured at a magnification that resulted in pixels measuring 4.8 × 5.7 μm.

To begin the density analysis, the section with the densest terminations was captured. The illumination was adjusted so that the distribution of intensities throughout the gray matter of this section fell within the 256 gray levels available for analysis. This illumination level was then used during the capture of the images of the remaining sections. Next, we subtracted the image of a "blank slide" (i.e., a slide with only a coverslip and mounting media) from the image of each section. The resulting image had approximately 245 intensity levels (Fig. 1). Then, we measured the peak intensity of "background" staining in regions of gray matter that do not receive any corticospinal input (e.g., the ventral horn ipsilateral to the cortical injection site). We used this value to set the threshold for the intensity level considered a termination (Fig. 1). In the example illustrated, the highest intensity level of background staining averaged a value of 22. Intensity values at and below this level were assigned the color black in pseudocolor images of termination density (see Figs. 9, 10). The remaining intensity levels were then divided into four populations that were color coded (Fig. 1, inset). The brightest 10% of the population of pixels was assigned the color white, and the next 30% of the population was assigned the color yellow (Fig. 1; see Figs. 9, 10). The lower 40% and 20% of the pixel population were

assigned the colors red and blue. We termed the upper 40% of the pixel population "dense pixels." We chose this cutoff because there was a close match between the location of dense pixels defined by this criterion and the location of the densest terminations when the sections were viewed with the microscope (compare Fig. 6 to Figs. 9, 10). Therefore, we regarded the dense pixels as representing regions of peak density of corticospinal termination and termed them the "dense terminations." All the surgical and experimental procedures we employed were approved by the institutional animal care and use committees.

Results

We will describe and illustrate the data obtained from the cebus and squirrel monkey that received injections of 10% WGA-HRP into the arm representation of primary motor cortex. This data was representative of that from the animals that were injected with 2% WGA-HRP. However, the monkeys injected with 10% WGA-HRP had the highest contrast between background and reaction product. No evidence of transneuronal transport of WGA-HRP was seen in any of the spinal cord sections examined in this study.

Location and extent of injection site

Cebus monkey. Based on maps of the primary motor cortex of the cebus monkey (Asanuma and Rosén, 1972; Shinoda et al., 1979; J. E. Hoover and P. L. Strick, unpublished observations), the spread of WGA-HRP in the animal illustrated filled the finger, wrist, and elbow representations (Fig. 2*A*). Tracer may have extended into the shoulder representation of the primary motor cortex, but not to the face and leg representations. Tracer involved the portions of area 4 in the anterior bank of the central sulcus, but did not extend to the depths of the anterior bank where area 3a is located (Fig. 2*A*) (Brodmann, 1912; Bucy, 1935; von Bonin, 1938; Lucier et al., 1975).

Squirrel monkey. Based on maps of the primary motor cortex of the squirrel monkey (Welker et al., 1957; Strick and Preston, 1978, 1982), the spread of WGA-HRP in the animal illustrated filled the representations of the fingers, wrist, and elbow, and may have involved the shoulder representation as well (Fig. 2*B*). Tracer spread caudally beyond area 4 to involve a portion of the adjacent area 3a (Fig. 2*B*).

Corticospinal tracts. Three corticospinal tracts were present throughout the cervical spinal cord of both cebus and squirrel monkeys (Figs. 3–5). The main corticospinal tract traveled in the *contralateral* dorsolateral funiculus (cd-CST). A second, less dense tract was present in the *ipsilateral* dorsolateral funiculus (id-CST). A third tract was created by a relatively small number of fibers that were located in the *ipsilateral* ventral funiculus (iv-CST) (Figs. 3–5). Thus, in both cebus and squirrel monkeys, the primary motor cortex of one hemisphere projects to the cervical cord via pathways that travel bilaterally in the spinal cord. Corticospinal tracts of comparable size and location have previously been described in the squirrel monkey (Tigges et al., 1979), macaque (Verhaart, 1954; Liu and Chambers, 1964; Kuypers, 1987), chimpanzee (Leyton and Sherrington, 1917; Fulton and Sheehan, 1935; Kuypers, 1963), and human (Russell, 1898; Nathan and Smith, 1955; Schoen, 1964; Nathan et al., 1990).

Most fibers originating from the cd-CST and the id-CST entered the gray matter through the lateral border of laminae V–VII (Figs. 3–7). We saw some fibers from the cd-CST cross to the opposite side by passing through the commissures dorsal and ventral to the central canal. Most fibers from the iv-CST crossed the midline in the commissure ventral to the central canal, although single fibers from the iv-CST were seen to terminate on the ipsilateral side. All three corticospinal tracts were markedly diminished in intensity and size by the T2 segment (Fig. 3).

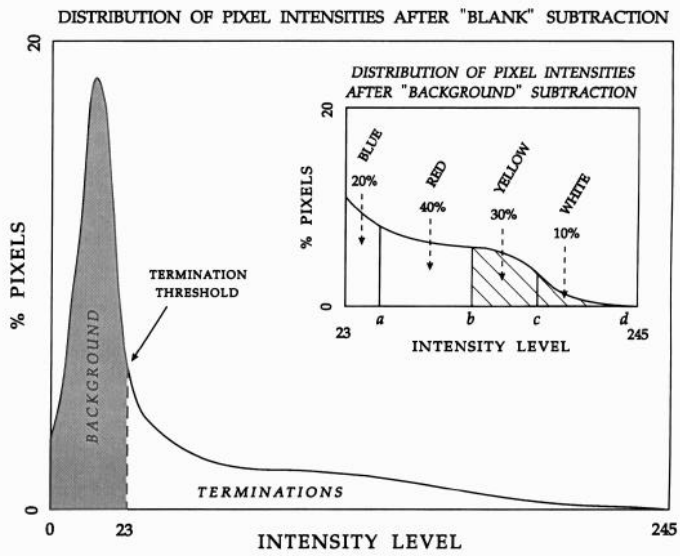

Figure 1. Sample distribution of pixel intensities from a gradient density analysis of corticospinal terminations in the spinal cord. The curve represents the distribution of pixel intensities following substraction of the "blank slide" (see Materials and Methods). This distribution is taken from the gray matter of T1 contralateral to an injection site in the primary motor cortex of a cebus monkey. Black = 0 or no intensity; the brightest pixel intensity = 245. Intensity levels below the termination threshold (=23) represent "background" staining. *Inset,* Intensity distribution of corticospinal terminations following subtraction of the "background" staining. The four populations of terminations and the colors used to indicate them in pseudocolor figures are shown in this diagram (e.g., white = brightest 10% of the population of pixels considered terminations). *a–d,* The intensity level at the upper boundary of each population. The *hatched area* indicates the brightest 40% of the pixels (i.e., yellow + white in Figs. 9 and 10), which we have termed "dense" terminations.

Corticospinal terminations

Cebus monkey. In the cebus monkey, there were three major zones of corticospinal terminations within laminae contralateral to the injected hemisphere (Figs. 3, 6, 9). One of these zones of termination was located in the medial parts of laminae V–VII in a region termed the internal basal nucleus (nucleus of the posterior commissure) (Kuypers, 1960). This region of the spinal cord is a dorsomedial portion of the "intermediate zone" (Kuypers, 1981). Terminations at this site were found from C2 to T2 (Figs. 3, 5) and their density was as high as anywhere in the spinal cord (Figs. 3, 5, 6, 9). Fibers from both the cd-CST and iv-CST appear to contribute to this zone of termination.

A second major zone of termination was the most extensive and was located in the central and lateral parts of laminae V–VII, that is, the dorsolateral portion of the intermediate zone (Figs. 3, 5, 6, 9). Terminations in this portion of the intermediate zone also were found from segment C2 to T2. Multiple patches of "dense terminations" (i.e., the brightest 40% of the pixels considered terminations) were present throughout this zone. The labeling in the dorsolateral portion of the intermediate zone was separated from that in the dorsomedial portion by a small region in laminae VI and VII that either lacked or had a particularly low density of termination (Figs. 3, 5, 6, 9).

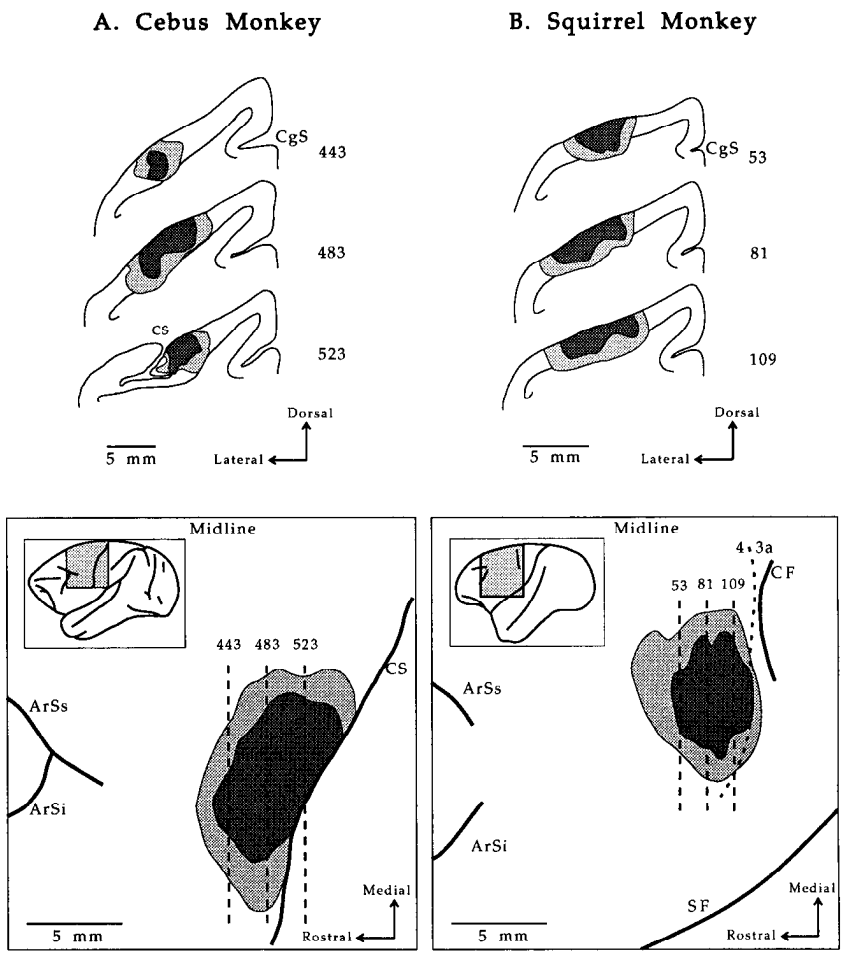

Figure 2. WGA-HRP injection sites. *A*, Cebus monkey. *B*, Squirrel monkey. *Top*, Coronal sections through each injection site. *Numbers* indicate the location of each section on the diagram below. *Bottom*, Flattened reconstruction of each injection site. The *darkly shaded region* indicates the area of dense label surrounding the needle penetrations; the *lightly shaded region* indicates the periphery of tracer spread. *Dashed lines* through the injection site indicate the location of corresponding coronal sections shown above. *Inset*, Lateral surface of the cortex. The *shaded region* on the lateral surface represents the area shown in the flattened reconstruction. The area 3a/4 border is indicated by the *dashed line* rostral to the central fissure. *ArSi*, Inferior arcuate sulcus; *ArSs*, superior arcuate sulcus; *CF*, central fissure; *CS*, central sulcus; *CgS*, cingulate sulcus; *SF*, sylvian fissure.

The third major zone of corticospinal termination in the cebus monkey was located in the ventral horn, lamina IX. The terminations at this site were surprisingly extensive and dense, particularly in segments C8–T1 (Figs. 3, 5–7, 9). In fact, reaction product covered over 86–93% of the cross-sectional area of lamina IX in these segments. Furthermore, dense terminations were present over 25% of the area of lamina IX in C8 and 38% of the area of lamina IX in T1 (see Fig. 11). Of the total area of the spinal cord at C8–T1 that received corticospinal terminations, 25–30% was located in the ventral horn. In segments C5–C7, corticospinal terminations in lamina IX were less dense and extensive. Reaction product in the ventral horn represented only 6–12% of the total area of corticospinal terminations and covered 16–27% of the cross-sectional area of the ventral horn (see Fig. 11). Dense terminations were preferentially located at the dorsal and lateral edges of the ventral horn (Fig. 3) and represented only 2–4% of lamina IX (Fig. 9). No dense terminations were found in lamina IX at C2–C4, and reaction product covered less than 10% of the area of the ventral horn at this segmental level (Fig. 5).

Many of the terminations in lamina IX of C6–T1 appeared to arise from corticospinal fibers that travel in the most ventral part of the cd-CST (Figs. 3, 6, 7). These fibers entered lamina IX directly from the tract in the funiculus (Fig. 7). We did not observe any evidence that the fibers entering directly into lamina IX were branches of those entering the gray matter through laminae V–VII. This arrangement suggests that an important component of the corticospinal terminations in the ventral horn of the cebus monkey arises from fibers that are separate from those that terminate in the intermediate zone.

The corticospinal terminations in lamina IX of segments C8–T1 formed a unique pattern (Figs. 3, 6, 8, 9). Dense terminations created a "ring" that encircled the ventral horn. Corticospinal terminations in the center of the ring were considerably less dense and even absent at some sites. The ring of dense terminations tended to thicken along the dorsal edge of lamina IX. Large motoneurons in these segments also tended to be more concentrated around the edges of lamina IX (Fig. 8). Thus, there was considerable overlap between the dense corticospinal terminations and the location of many of the large motoneurons in segments C8–T1.

Some corticospinal terminations also were located outside the three main zones described above, but none of these additional sites contained dense terminations. For example, contralateral to the injection, in segments C2–T2 some sparse terminations were present in the central and medial portions of lamina IV and trace amounts of label were seen in lamina III (Figs. 3, 5). Both ipsilateral and contralateral to the injection site, sparse terminations were present in dorsomedial portions of lamina VIII and trace amounts of label also were found in medial portions of lamina VII. No terminations were found at any segmental level in either contralateral or ipsilateral laminae I and II.

Squirrel monkey. Only two major zones of corticospinal terminations were present in the spinal cord of the squirrel monkey contralateral to the injection site (Figs. 4, 6, 10). One zone was

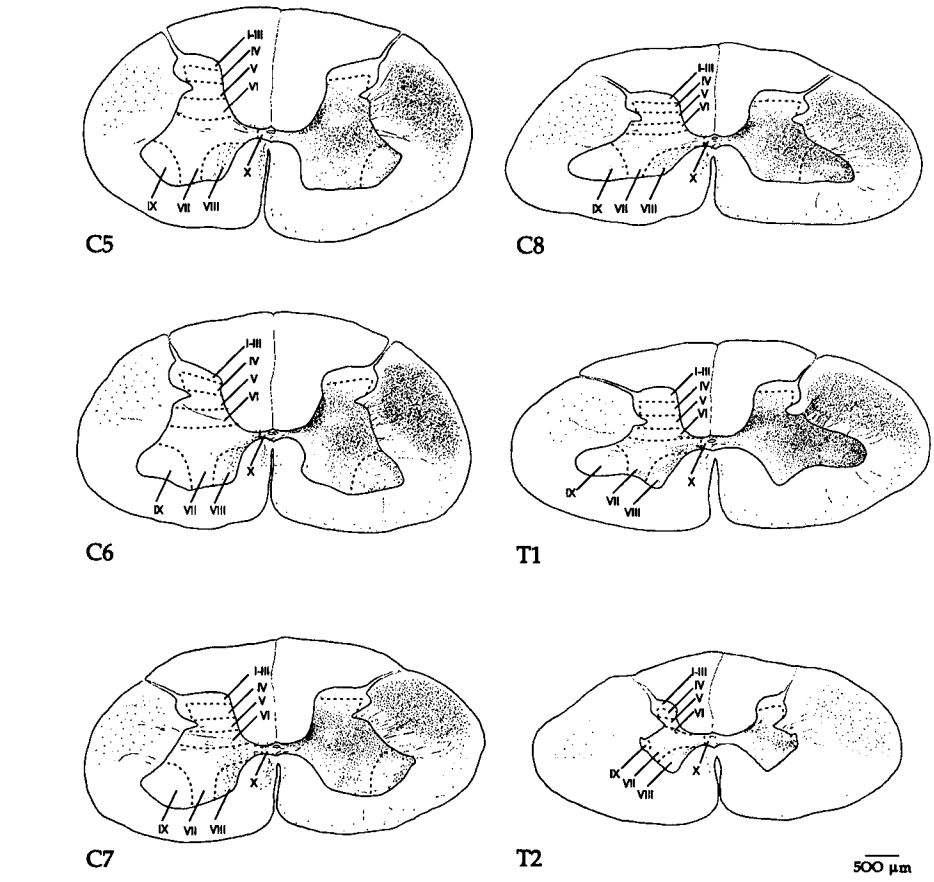

Figure 3. Corticospinal terminations at C5–T2 in the cebus monkey. *Stippling* indicates the relative density and distribution of labeling seen in sections reacted with the TMB technique. Rexed's laminae were determined from adjacent sections stained with cresyl violet. Note three regions of dense terminations: a dorsomedial region of the intermediate zone, a dorsolateral region of the intermediate zone, and lamina IX.

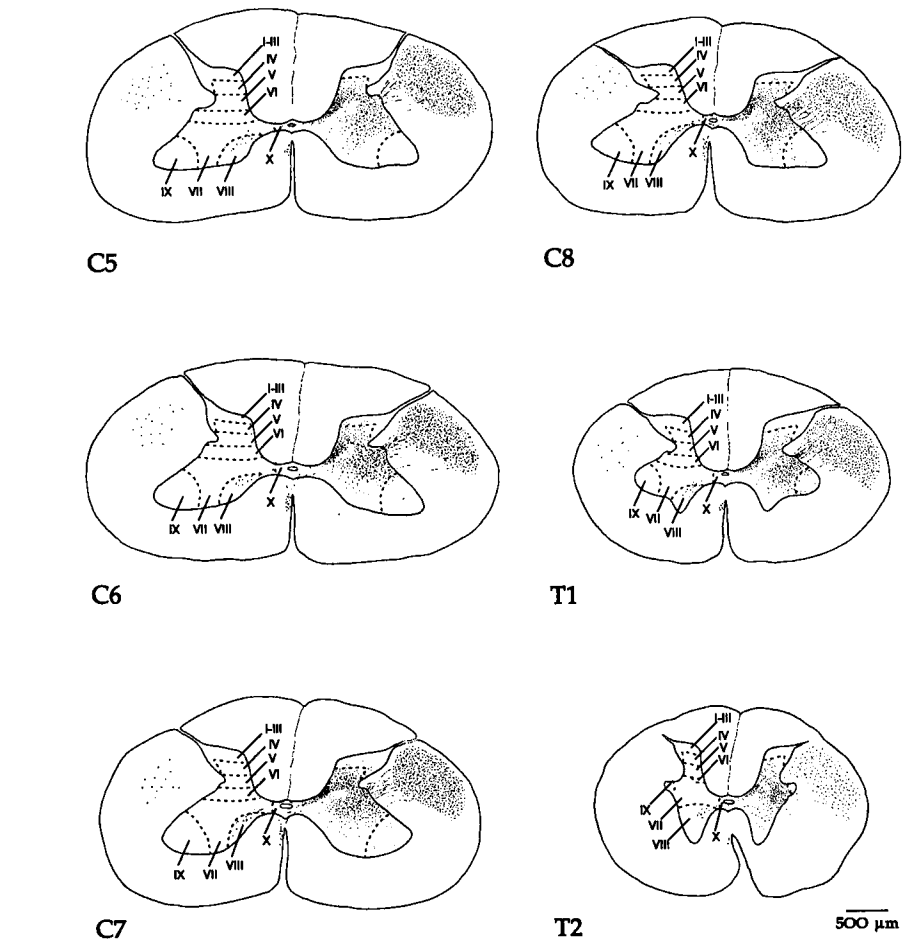

Figure 4. Corticospinal terminations at C5–T2 in squirrel monkey. The conventions for this figure are the same as those used in Figure 3. Note only two regions of dense terminations: dorsomedial and dorsolateral regions of the intermediate zone.

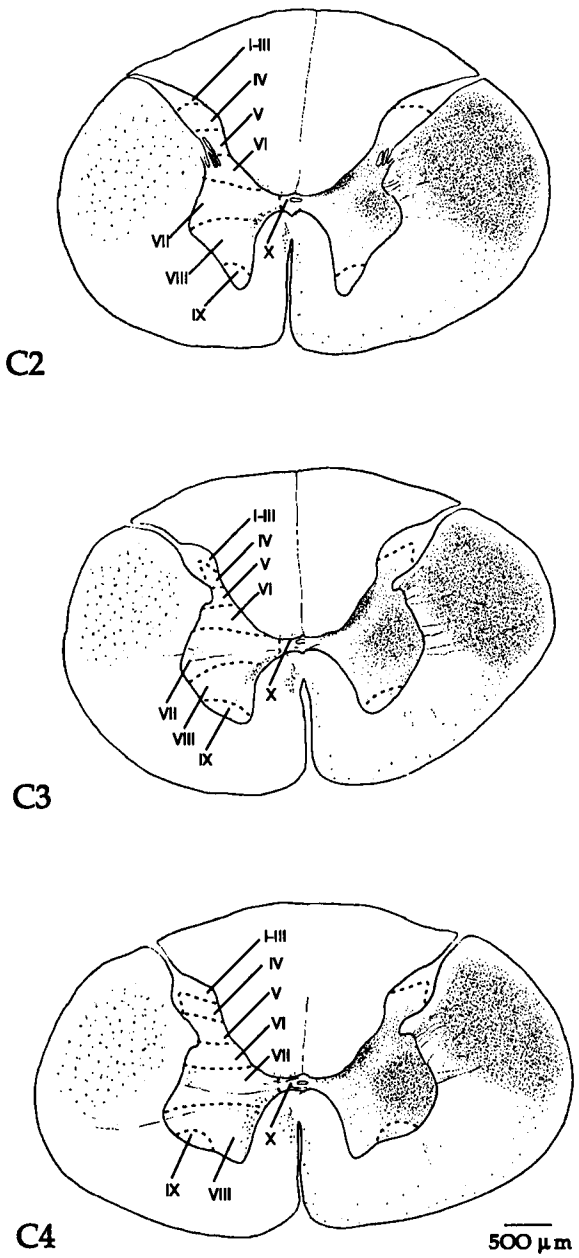

Figure 5. Corticospinal terminations at C2–C4 in cebus monkey. The conventions for this figure are the same as those used in Figure 3. Note the two regions of termination in the intermediate zone.

located in a dorsomedial portion of the intermediate zone and the other was located in a dorsolateral portion of the intermediate zone. The location and density of corticospinal terminations in these two regions of the intermediate zone were fully comparable to the pattern of termination in the intermediate zone of the cebus monkey. However, the third zone of termination that was present in the ventral horn of the cebus monkey was largely absent in the squirrel monkey.

The region of the ventral horn of the squirrel monkey where motoneurons were located received only sparse corticospinal terminations (Figs. 4, 6, 10). Label was found in only 5% of the cross-sectional area of lamina IX in C8 (Fig. 11). No label was found in lamina IX of C5, and less than 2% of lamina IX contained label in C6 and C7 (Fig. 11). Corticospinal terminations in lamina IX of C8 and T1 were largely confined to a small region near the border with lamina VII (Figs. 4, 6, 10). Dense terminations were present in lamina IX only at T1, but these covered less than 1% of the cross-sectional area of this lamina (Fig. 11).

The remaining corticospinal labeling (outside the major zones of termination) was comparable to what was found in the cebus monkey with one exception. Contralateral to the injection site, sparse terminations were located in laminae III and IV of the squirrel monkey (Fig. 4). This labeling was somewhat more abundant than that seen in the cebus monkey (compare Figs. 3, 4). The increased terminations in laminae III and IV of the squirrel monkey may be due to the slight involvement of somatic sensory cortex (e.g., area 3a) in the injection site (see also Harting and Noback, 1970; Tigges et al., 1979).

Discussion

Terminations in the ventral horn

One of the major results of the present study is the finding that efferents from the primary motor cortex terminate densely in the ventral horn of the cebus monkey. In fact, at segments C8 and T1, the terminations in lamina IX were as dense as anywhere in the gray matter of the spinal cord. At T1, dense terminations occupied nearly 40% of lamina IX. In contrast, a comparable pattern of corticospinal termination does not exist in the squirrel monkey. Corticospinal efferents terminate in the ventral horn only at segments C8 and T1, and the terminations at these levels are sparse, at best. Prior studies also reported only sparse corticospinal terminations in lamina IX in the squirrel monkey (Harting and Noback, 1970; Tigges et al., 1979). Indeed, Tigges et al. (1979) observed, as did we, that the few terminations present in the ventral horn were located exclusively along the VII/IX border. Thus, there are striking differences between these two new-world primates in the pattern of corticospinal input to the ventral horn.

It is important to note that the presence of dense terminations in the ventral horn does not, in and of itself, guarantee that an input makes direct connections with motoneurons. Some of the labeling we have designated as terminations is likely to represent fibers of passage and the preterminal arborizations of corticospinal axons in the gray matter. Similarly, the absence of terminations in lamina IX does not rule out the possibility of monosynaptic connections with motoneurons. It is well known that motoneuron dendrites extend for considerable distances outside of lamina IX in the macaque (e.g., Lawrence et al., 1985; for an example of this phenomenon in the cat, see Rose and Richmond, 1981). There is the possibility that some of the dense terminations in the intermediate zone may actually represent monosynaptic input to the more distal portions of motoneuron dendrites. The only anatomical method that can unequivocally demonstrate monosynaptic connectivity is electron microscopic analysis. In the absence of this analysis, we cannot rule out the possibility that some corticospinal fibers synapse on the distal dendrites of motoneurons in the squirrel monkey. Thus, a conservative interpretation of our results is that the proximal dendritic arbors of motoneurons in the cebus monkey are very likely to receive heavy corticospinal input, while those of the squirrel monkey do not.

It is arguable whether even the distal dendritic arbors of motoneurons in the squirrel monkey receive corticospinal input. Physiological methods (e.g., Lloyd, 1941; Hern et al., 1962; for references and review, see Phillips and Porter, 1977; Kuypers, 1981; Hepp-Reymond, 1988) have failed to demonstrate mono-

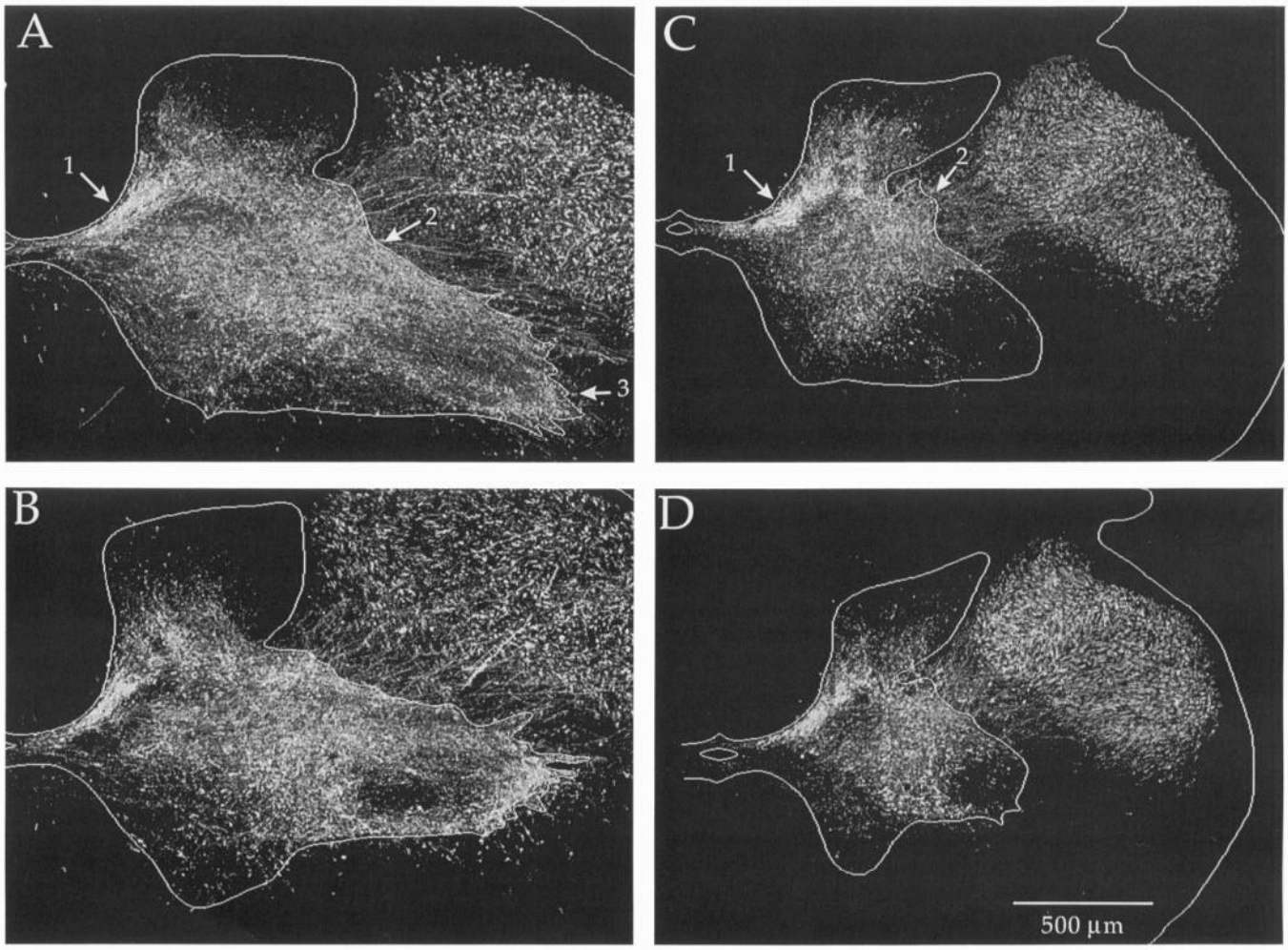

Figure 6. Corticospinal terminations and cd-CST in cebus and squirrel monkeys. These images were "captured" using the imaging system described in Materials and Methods and were taken under dark-field illumination with polarized light. *A*, cebus monkey, C8; *B*, cebus monkey, T1; *C*, squirrel monkey, C8; *D*, squirrel monkey, T1. *Arrows* point to regions of dense termination at C8. Note that dense terminations are present in three regions in the cebus monkey, and only two in the squirrel monkey.

synaptic input from corticospinal fibers to motoneurons in animals like the cat that have dense terminations in the intermediate zone, but lack corticospinal terminations in the ventral horn (e.g., Chambers and Liu, 1957; Nyberg-Hansen and Brodal, 1963; Flindt-Egebak, 1977). Conversely, the same methods demonstrate corticomotoneuronal connectivity in animals like the macaque, which have substantial corticospinal terminations in the ventral horn (e.g., Bernhard et al., 1953; Bernhard and Bohm, 1954; Preston and Whitlock, 1960, 1961). Thus, it seems reasonable to conclude that the presence of dense corticospinal terminations in lamina IX of the cebus monkey provides evidence for a corticomotoneuronal connection in this primate, whereas the near absence of terminations in lamina IX of the squirrel monkey argues against such a connection in this animal.

Comparison between the cebus monkey and other primates. When the present results on cebus monkeys are compared with those from similar studies on macaques, it is clear that there are some interesting differences between these primates in the pattern of corticospinal termination within the ventral horn. Corticospinal terminations in C8–T1 of macaques are restricted to dorsal and dorsolateral portions of lamina IX (e.g., Kuypers, 1960; Liu and Chambers, 1964; Kuypers and Brinkman, 1970; Cheema et al., 1984; Ralston and Ralston, 1985; Leichnetz, 1986). The motoneurons that innervate predominantly flexor and intrinsic muscles of the hand are located at this site (Jenny and Inukai, 1983; for additional discussion, see Kuypers, 1981). In contrast, we found that in the cebus monkey nearly 90% of the cross-sectional area of lamina IX at C8–T1 receives corticospinal input. If the distribution of motoneuron pools in the cebus monkey is similar to that of the macaque, then corticospinal terminations in the cebus monkey fall within motoneuron pools that innervate hand extensors as well as hand flexors. Thus, in terms of the number of different motoneuron pools innervated, corticomotoneuronal input in the cebus monkey is likely to be more extensive than that in macaques. In fact, the distribution of corticospinal terminations in the ventral horn of the cebus monkey appears to be almost as extensive as that described for the chimpanzee and human (Kuypers, 1964, 1981; Schoen, 1964; Petras, 1968, 1969). This suggests that analysis of the corticospinal system in the cebus monkey may yield important insights into the function of this system in higher primates.

The results of prior anatomical and physiological studies suggest that corticomotoneuronal synapses in macaques and ba-

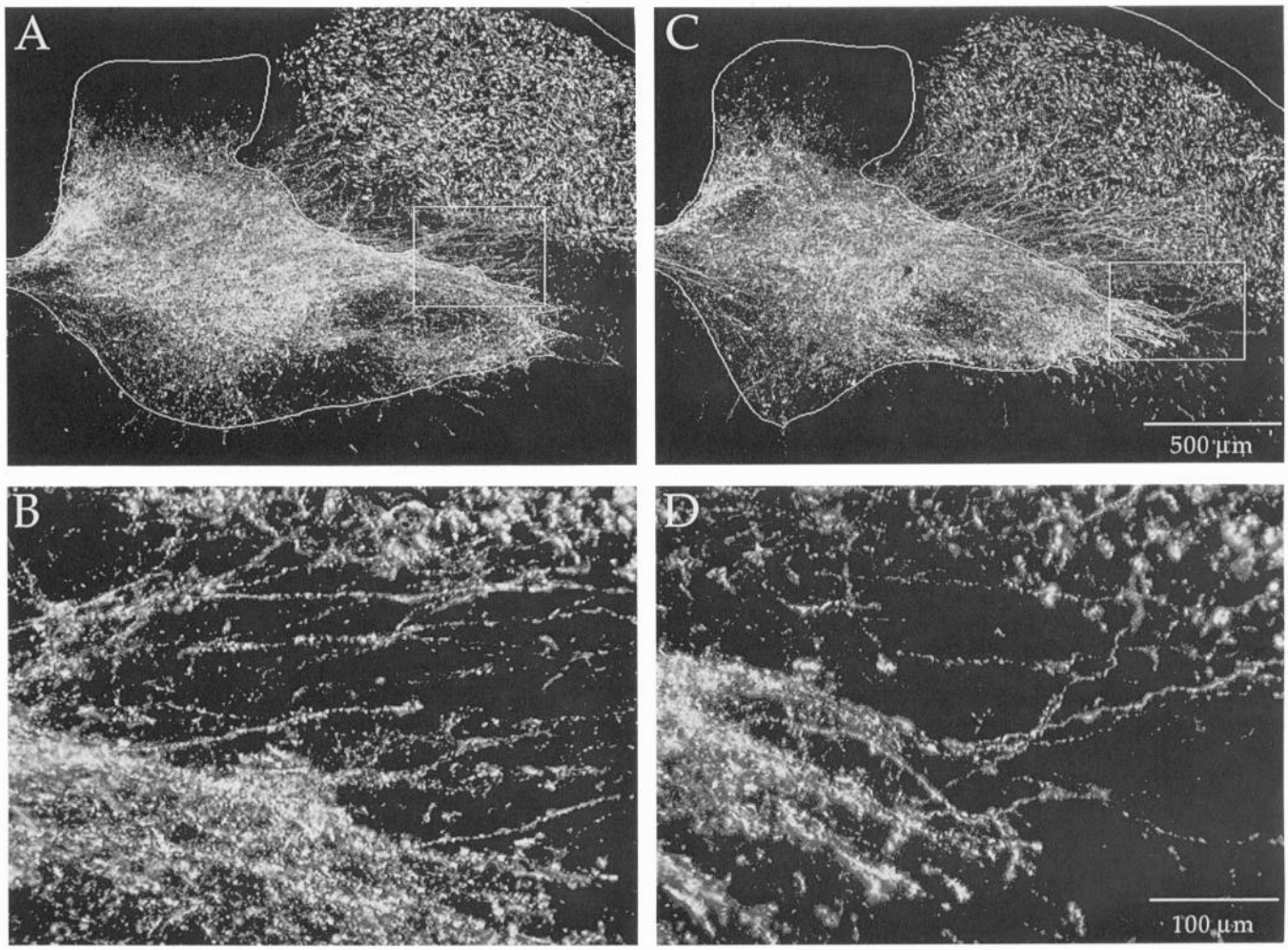

Figure 7. Corticospinal terminations and fibers entering the ventral horn in the cebus monkey. These images were "captured" using the imaging system described in Materials and Methods and were taken under dark-field illumination with polarized light. *A*, Rostral C8. *B*, Higher magnification of *boxed region in A*. Note the presence of many labeled fibers that leave the ventral portion of the cd-CST and enter directly into lamina IX. *C*, T1. *D*, Higher magnification of *boxed region in C*. Note fibers entering the ventral most portion of lamina IX.

boons contact largely the dendrites of motoneurons and that few of these synapses are made with motoneuron somas (e.g., Clough et al., 1968; Porter and Hore, 1969; Jankowska et al., 1975; Shinoda et al., 1981; Lawrence et al., 1985). However, the unique ring-like pattern of corticospinal terminations within the ventral horn at C8–T1 of the cebus monkey suggests that this may not be the case for this primate. The ring of terminations tended to align with a ring-like arrangement of motoneuron cell bodies. Thus, corticospinal input to lamina IX is densest where motoneuron somas are densest. Perhaps this association indicates that a significant component of the corticomotoneuronal input in the cebus monkey makes synapses on or near the somas of motoneurons innervating hand muscles.

Does a unique set of fibers contribute to the corticomotoneuronal connection? We saw many examples of corticospinal fibers in the cebus monkey that traveled directly from the tract in the dorsolateral funiculus to the ventral horn. These fibers were located in a ventral portion of the tract and were separate from the more dorsal fibers that entered the spinal cord gray matter at the lateral edge of laminae V–VII. These observations suggest that a portion of the corticomotoneuronal system in the cebus monkey arises from a distinct set of corticospinal fibers.

The phenomenon of corticospinal fibers entering the ventral horn directly without traversing the intermediate zone occurs much more frequently in the cebus monkey than in the macaque (e.g., compare our chartings with those of Kuypers, 1960; Liu and Chambers, 1964; Ralston and Ralston, 1985). Shinoda et al. (1981) found that only 1 of the 54 corticospinal fibers they labeled entered the ventral horn of the macaque without passing through the intermediate zone. Thus, the population of corticospinal fibers that projects directly to motoneurons appears to be more extensive in the cebus monkey than in the macaque.

Terminations in the intermediate zone

Although as much as 30% of the corticospinal input terminates in the ventral horn of the cebus monkey, it is clear that the majority of corticospinal terminations are located within the intermediate zone of the spinal cord. This also appears to be true for corticospinal terminations in the squirrel monkey, macaque, chimpanzee, and human (for references and review, see Kuypers, 1981). Thus, the importance of corticospinal projections to interneurons should not be underemphasized.

According to Kuypers, the corticospinal system from area 4 has multiple components (e.g., Kuypers, 1981, 1982). The

smallest is part of his "medial motor system" and consists of fibers that terminate in ventromedial parts of the intermediate zone in the spinal cord. These fibers originate predominantly from regions of the primary motor cortex that contain the representation of axial and proximal body musculature (Kuypers and Brinkman, 1970). The largest component contributes to the "lateral motor system" of Kuypers and consists of fibers that distribute to the dorsal and lateral parts of the intermediate zone. The corticomotoneuronal projection was included in this system. The corticospinal fibers that comprise the lateral system arise predominantly from caudal regions of the primary motor cortex where the representation of distal extremity muscles is located.

The pattern of corticospinal termination we saw in the cebus monkey suggests that the organization of the intermediate zone is more complicated than suggested by the Kuypers model. Some of the sparse terminations that were present in the intermediate zone of the cebus monkey are typical of the medial motor system of Kuypers. However, we found dense terminations at two spatially separate sites within the region of the intermediate zone that is part of the lateral system. One of these was located within lateral and central regions of laminae V–VII. This portion of the intermediate zone has long been considered the major site of termination for efferents from area 4 of primates (e.g., Kuypers, 1960; Liu and Chambers, 1964; Petras, 1968; Harting and Noback, 1970; Tigges et al., 1979; Cheema et al., 1984; Ralston and Ralston, 1985; see Heffner and Masterton, 1975). It is also the major site of termination of efferents from the primate red nucleus (e.g., Kuypers et al., 1962; Miller and Strominger, 1973; Holstege et al., 1988).

The second site of dense termination within the intermediate zone was located within medial regions of laminae V–VII. This site included the region of the spinal cord termed the internal basal nucleus (or the nucleus of the spinal posterior commissure) (Kuypers, 1960; Petras, 1969; Tigges et al., 1979). Although some prior studies of corticospinal projections from area 4 in primates have found terminations in this dorsomedial region of the intermediate zone (e.g., Kuypers, 1960; Schoen, 1964; Harting and Noback, 1970; Kuypers and Brinkman, 1970), dense terminations were not observed at this site. One potential reason we observed dense terminations in the dorsomedial region of the intermediate zone may be that the methods we used (i.e., anterograde transport of 2–10% WGA-HRP) enhanced the labeling of a fiber system that was not as well labeled by the methods used in several of the prior studies (e.g., degeneration, amino acid transport) (see also Leichnetz, 1986). Indeed, the absence of dense labeling within the dorsomedial portion of the intermediate zone is particularly evident in studies that used amino acids as tracers (e.g., Coulter and Jones, 1977; Tigges et al., 1979). If this explanation is correct, then it raises the possibility that the dorsomedial terminations originate from a fiber system that is separate from the system which gives rise to terminations in the dorsolateral portion of the intermediate zone. This possibility should be explored in future studies.

The results of anatomical and physiological studies performed largely on cats have demonstrated that interneurons projecting directly to cervical motoneurons are located in both dorsolateral and dorsomedial regions of the intermediate zone (Illert et al., 1977, 1978, 1981; Molenaar, 1978; Molenaar and Kuypers, 1978; Grant et al., 1980; Alstermark et al., 1984; Alstermark and Kümmel, 1986, 1990a,b; Hongo et al., 1989a,b). In fact, recent studies indicate that the motoneurons that innervate intrinsic forepaw muscles receive monosynaptic excitation or inhibition from interneurons located in both regions of the intermediate zone (Hongo et al., 1989a; T. Hongo, personal communication). If these interneurons exist in primates, then the dense corticospinal terminations we observed in the two regions of the intermediate zone may represent two separate disynaptic pathways from area 4 to hand motoneurons. At this point, there is not enough information on the comparative properties of interneurons within dorsomedial and dorsolateral regions of the intermediate zone to speculate on the potential differences between these two pathways to motoneurons. However, when these disynaptic pathways are considered together with corticomotoneuronal connections, it is clear that the corticospinal system from area 4 contains at least three potentially independent routes for influencing hand motoneurons.

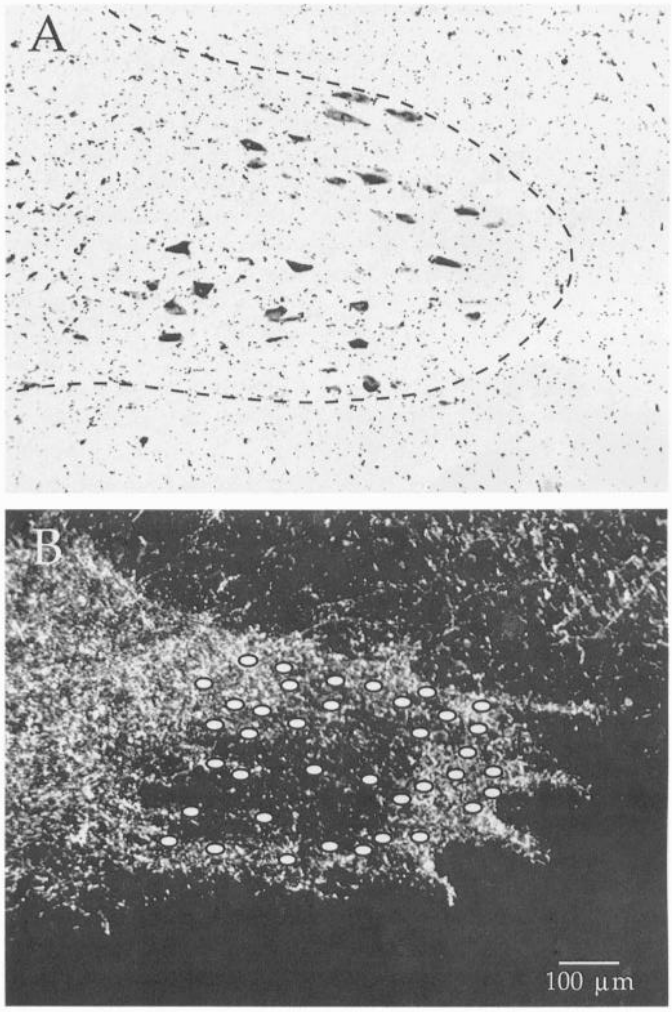

Figure 8. Location of motoneuron somas and corticospinal terminations at T1 of the cebus monkey. *A*, "Captured" image of cytoarchitecture in ventral horn of T1. *Dashed line* indicates approximate gray/white border. Note that the somas of large motoneurons tend to be located at the periphery of lamina IX, whereas they are less concentrated in the center of the lamina. *B*, "Captured" image of corticospinal terminations in the ventral horn using dark-field illumination with polarized light. The locations of motoneuron somas in this section were determined using bright-field illumination and are indicated by the *solid white circles*. Note the overlap between the location of motoneurons and dense corticospinal terminations.

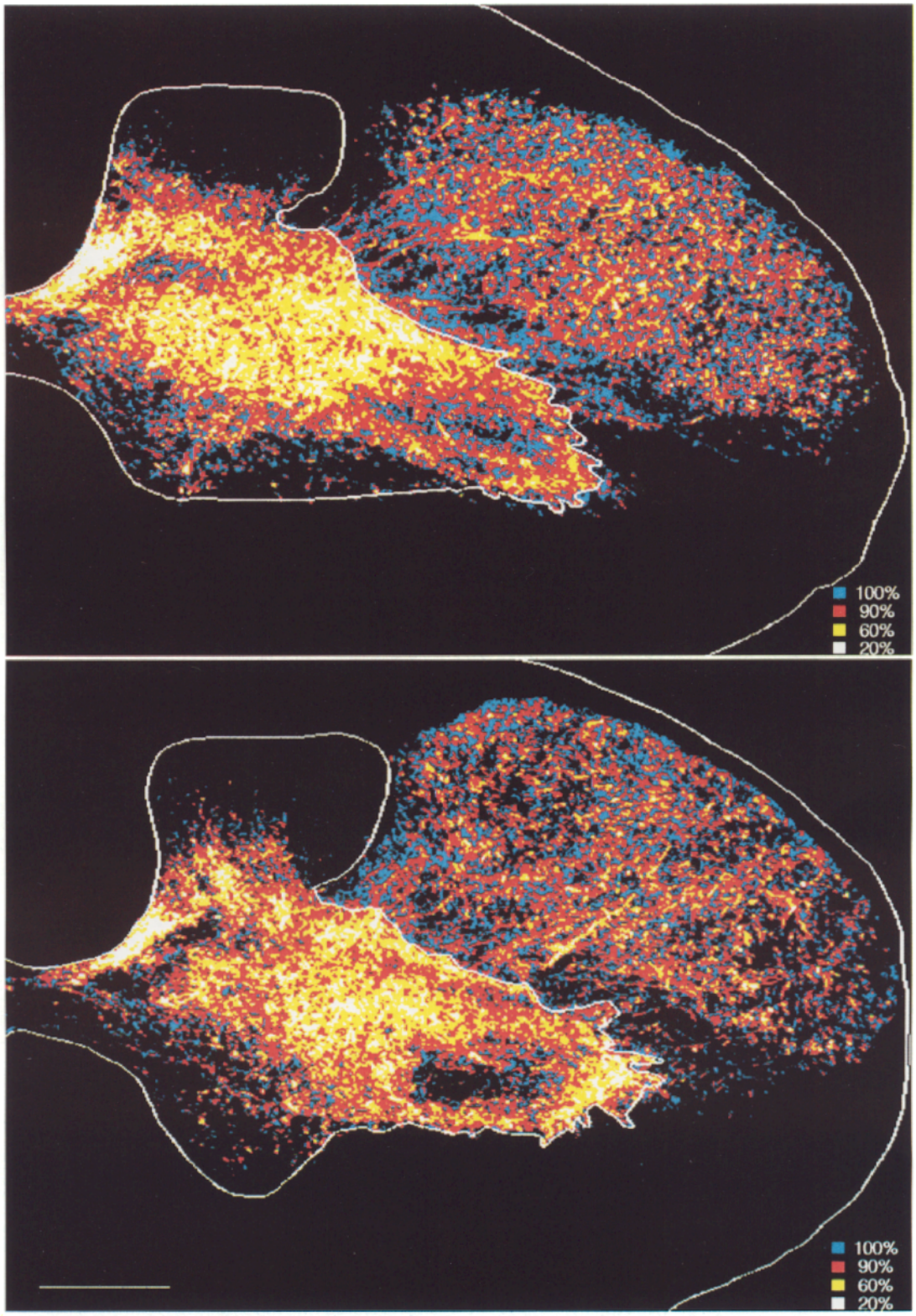

Figure 9. Gradient density analysis of corticospinal terminations in the cebus monkey. *Top*, C8. *Bottom*, T1. Pixel intensity levels were divided into five groups (e.g., *white* represents approximately the brightest 10% of the terminations within a segment). The legend indicates the upper percentage of each range and the numbers correspond to *a–d* in Figure 1. Note that the ventral horn of the cebus monkey has a substantial amount of dense terminations. Scale bar, 400 μm.

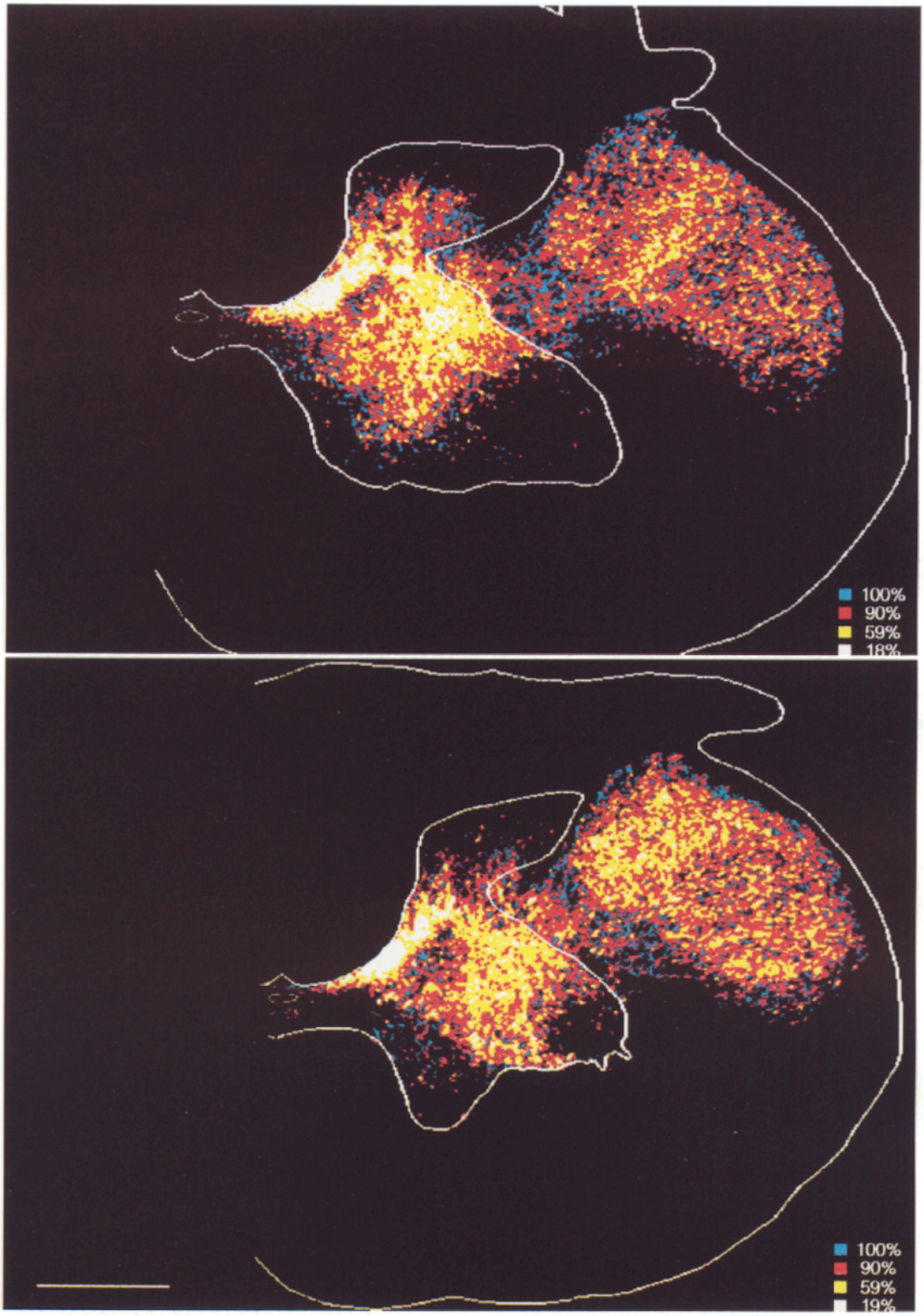

Figure 10. Gradient density analysis of corticospinal terminations in the squirrel monkey. *Top*, C8. *Bottom*, T1. The conventions for this figure are the same as those used in Figure 9. Note that the ventral horn of the squirrel monkey lacks dense terminations. Scale bar, 400 μm.

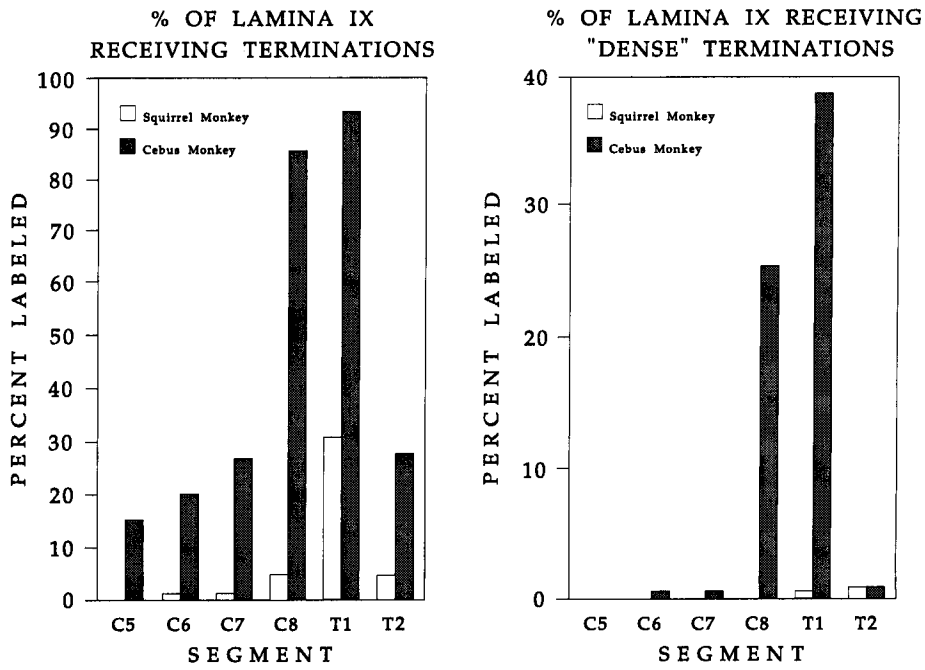

Figure 11. Analysis of corticospinal termination in lamina IX. *Left*, Percentage of the cross-sectional area of lamina IX with corticospinal tract terminations. *Right*, Percentage of the cross-sectional area of lamina IX with *dense* terminations (i.e., pixels in the upper 40% of the density range = white and yellow range in Figs. 1, 9, 10).

The corticomotoneuronal connection: part of the neural substrate for dexterity

Prior studies have provided multiple lines of evidence that corticomotoneuronal connections are part of the neural substrate for relatively independent movements of the fingers (for references and review, see Kuypers, 1981). One of the aims of the present study was to test the hypothesis that differences in corticomotoneuronal connections between cebus and squirrel monkeys provide part of the basis for the differences in manipulative abilities between these primates. As noted in the introductory remarks, recent behavioral studies of cebus and squirrel monkeys have shown that these two primates differ markedly in their ability to perform relatively independent movements of the fingers. Both primates have pseudo-opposable thumbs. Yet, the cebus monkey uses a variety of different "precision" grips to pick up small objects and is capable of producing highly fractionated movements of the fingers (Costello and Fragaszy, 1988). The precision grip used most often by these primates is opposition of the thumb and index finger. However, cebus monkeys are also known to pick up objects without the use of the palm by opposing the thumb and the tips of other fingers, as well as by opposing adjacent fingers. The extensive manipulative abilities of this primate are particularly apparent in observations of finger movements during the usage of tools (Klüver, 1937; Westergaard and Fragaszy, 1985, 1987; Fragaszy and Visalberghi, 1989). In contrast, the squirrel monkey is not able to perform relatively independent movements of the fingers. Consequently, this primate does not use a precision grip for fine motor tasks (Fragaszy, 1983; Costello and Fragaszy, 1988). Instead, to pick up small objects the squirrel monkey uses a whole-hand sweeping motion and moves all of its fingers in concert.

In the present study, we found that there is a major difference in the pattern of corticospinal terminations between cebus and squirrel monkeys. Cebus monkeys have surprisingly dense terminations in the ventral horn, particularly in cervical segments where the motoneurons that innervate hand muscles are located. Using the same techniques, we found little evidence for corticospinal terminations in the ventral horn of the squirrel monkey. On the other hand, the two primates have similar patterns of corticospinal termination outside the ventral horn. Based on these observations, we propose that the differences in manipulative abilities between cebus and squirrel monkeys are due, at least in part, to differences in corticomotoneuronal connectivity. Certainly, other factors could contribute to the behavioral differences between the two species of primates. For example, the primary motor cortex of the cebus monkey could have finger representations that are larger and more distinct than those in the primary motor cortex of the squirrel monkey. However, our observations provide further support for the concept that corticomotoneuronal connections provide an important part of the neural substrate for manual dexterity.

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