Chapter 28

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Motor Functions of Cerebral Cortex

INTRODUCTION

Primary and Secondary Motor Cortex Areas

Anyone who has seen the victim of a cerebral stroke can appreciate the importance of motor cortex in performing normal movements. Typically, such patients are incapable of using one or more contralateral limbs and frequently cannot speak fluently. The loss of control is most notable in the muscles of the hands and face. Furthermore, many patients are unable to regain normal control of the paralyzed muscles, indicating that other regions cannot compensate to perform these motor functions.

Clinical and experimental evidence indicates that the cerebral cortex plays a crucial role in both the programming and the execution of normal voluntary movements. The relevant cortical areas can be broadly divided into two groups: *primary* motor cortex, which has relatively direct anatomical and functional relation to muscles and is important for the normal *execution* of movements, and *secondary* motor cortical areas that are synaptically more remote from the periphery and are more involved in *programming* movements under particular circumstances. The locations of these cortical regions in monkeys and humans are shown in Figure 28-1. The largest of these areas, the *primary motor cortex* (MI) lies on the precentral gyms, in Brodmann's area 4. Electrical stimulation. of the primary motor cortex produces specific and repeatable movements, with the lowest stimulus thresholds of any cortical area. MI contains a somatotopic map of the representation of body muscles. Electrical stimulation of secondary areas generates movements more rarely; these movements are more complex and variable and require stronger stimulus currents. These secondary motor areas include the *premotor cortex* (PMC), which lies anterior to MI, in the lateral portion of Brodmann's area 6, and the *supplementary motor cortex*, or supplementary motor area (SMA), which lies in the medial portion of area 6, largely in the medial bank of the sagittal sulcus. Both of these regions are also somatotopically organized and are interconnected with each other and MI. Still further rostral, in Brodmann's area 8, are the *frontal eye fields,* which are concerned with movements of

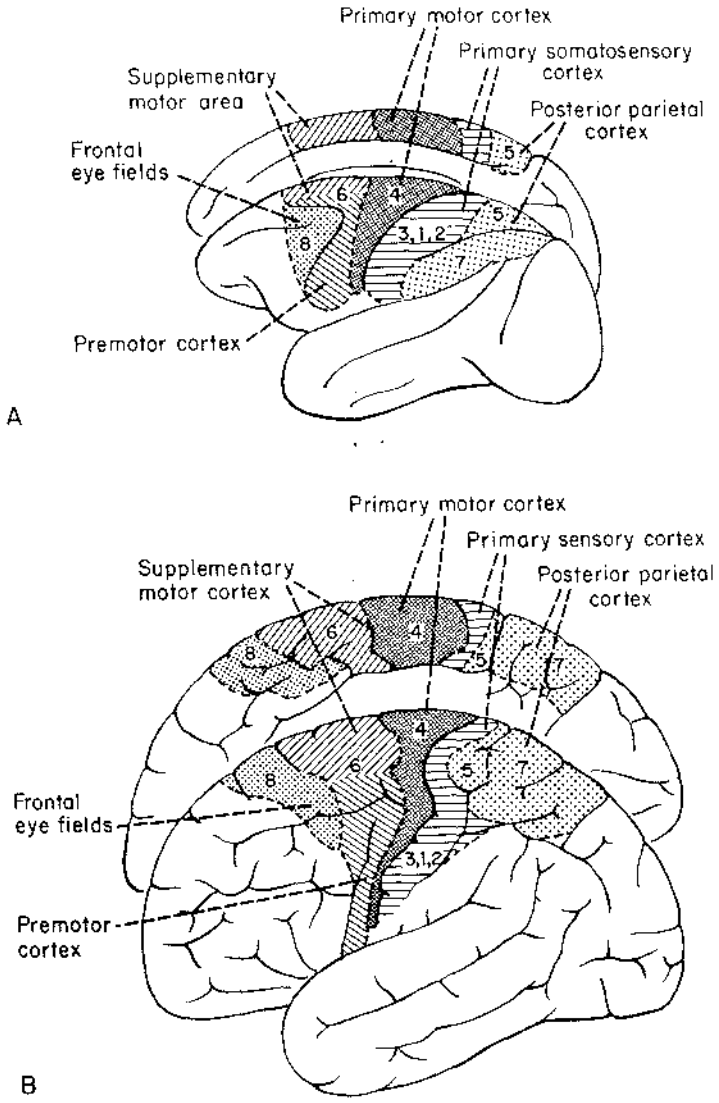


Figure 28-1 Major motor areas of cerebral cortex in *(A)* macaque monkey and *(B)* man. Numbers refer to Brodmann's designation of cortical regions with different cytoarchitectonic features. (From Brodmann, K Vergleichende Lokalisationslehre der Grosshirnrinde. Leipzig, Barth, 1909.)

the eyes. Finally, the *posterior parietal cortex,'* comprising Brodmann's areas 5 and 7, appears to be involved in programming directed movements of the limbs and eyes to targets in space.

In addition to electrical stimulation, other lines of experimental evidence support a functional distinction between primary and secondary motor cortical areas. *Lesions* in primary motor cortex of primates tend to produce paresis or paralysis, obvious deficits in generating muscle activity. Lesions in secondary motor regions produce more subtle deficits, called apraxias, which are the inability to perform certain types of movements under particular conditions. Finally, the recording of *neuronal activity* during movements has revealed that many primary motor cortex cells discharge strongly in relation to muscle activity, whereas neurons in secondary motor areas tend to be active under particular conditions that give rise to movements. This chapter reviews the evidence that primary motor cortex is predominantly involved in the execution of movements whereas secondary motor areas are more concerned with motor programming. The major emphasis is on primary motor cortex, which has been studied most extensively and is best understood.

The Pyramidal and Extrapyramidal Systems

The cerebral cortex may influence movements through two major output pathways: the pyramidal and the extrapyramidal systems. While these two systems normally work together to control movement and posture, their functions are distinguished by neurologists who classify motor deficits as "pyramidal" or "extrapyramidal." The *pyramidal system* consists of cortical neurons whose axons descend through the medullary pyramids; the vast majority continue to the spinal cord via the corticospinal tracts, but some terminate in the brain stem reticular formation. The *extrapyramidal system* comprises the remaining motor systems, including the descending tracts from brain stem to spinal cord, the basal ganglia and the cerebellum. Inclusion of many different centers in the extrapyramidal system limits the usefulness of this classification, as discussed in Chapter 26.

Organization of Pyramidal Tract Neurons

The corticospinal tract exists only in mammals and increases in size along the phylogenetic scale.[24, 36a] In humans, each pyramid contains about one million fibers. About 60% of the pyramidal tract arises from cells in precentral cortex (approximately 30% from Brodmann's area 4 and 30% from area 6); the remaining 40% of the pyramidal tract arises from postcentral cortex. Figure 28-2 illustrates the course of precentral and postcentral pyramidal tract fibers in the macaque. The precentral pyramidal tract neurons originate in both primary and secondary motor areas and terminate preferentially in the more ventral laminae of the cord, which contain motoneurons and interneurons involved in movement. The number and proportion of corticospinal fibers terminating among motoneurons becomes progressively greater from prosimians, through monkeys and apes, to humans. Postcentral pyramidal tract cells tend to terminate more dorsally in the spinal cord,

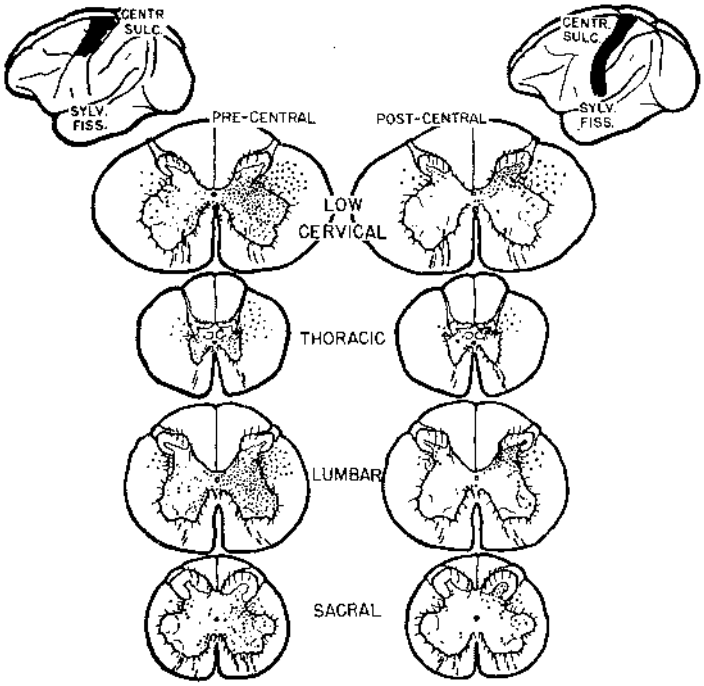


Figure 28-2 Course and termination of pyramidal tract fibers from precentral and postcentral cortex of the monkey. Heavy dots and line segments show the course of fibers descending in lateral and ventral corticospinal tracts. Light dots show sites of termination of corticospinal fibers. (From Kuypers, H. G. J. *Brain* 83:161-184, 1960.)

among interneurons relaying peripheral input from afferent fibers to motoneurons and to higher centers. This postcentral component of the pyramidal tract may be more involved in regulating sensory function by presynaptic and postsynaptic modulation of transmission of afferent impulses.

The cortical origin of the pyramidal tract has been documented most clearly by retrograde transport of horseradish peroxidase (HRP) from the spinal cord or the pyramids. In the monkey, corticospinal cells labeled with HRP are extensively distributed over several cortical fields, including Brodmann's areas 8, 6, and 4 precentrally, and areas 3, 1, 2, 5, and 7 postcentrally (Fig. 28-3A). Sagittal sections of the cerebral cortex reveal that the somata of pyramidal tract neurons all reside in layer 5 of the cortex (Fig. 28-3B). The labeled corticospinal cells appear to be grouped in clusters, which on surface reconstructions tend to form mediolateral bands.[18]

Most of the pyramidal tract fibers are small—90% are less than 4 um in diameter—and about half are unmyelinated. Thus the majority of pyramidal tract fibers are slowly conducting. The large Betz cells in motor cortex contribute about 2% of all pyramidal tract fibers. In the primate, single pyramidal tract cells typically distribute terminals to many motoneuron pools.[1]

PRIMARY MOTOR CORTEX (MI)

Somatotopic Organization

Effects of Stimulation on Muscles

The cortical motor areas have been delimited and mapped by observing the movements evoked by electrically stimulating the cortex. The primary motor cortex (MI), which has the lowest threshold sites, is organized somatotopically much like the

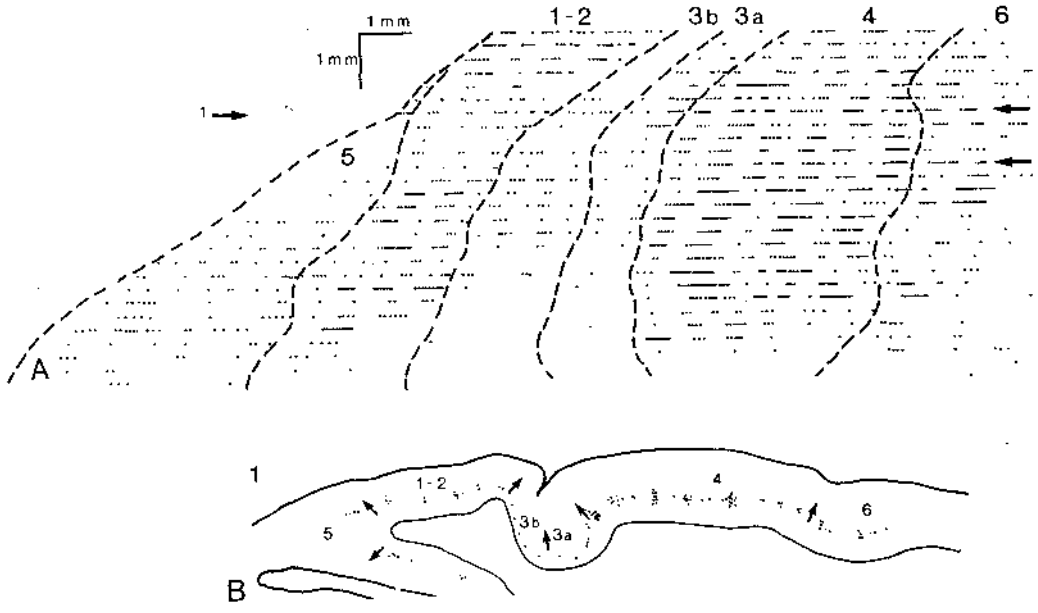


Figure 28-3 Cortical location of pyramidal tract neurons labeled by retrograde transport of horseradish peroxidase (HRP) from contralateral thoracic spinal cord of the cynomolgus monkey. *A,* Location of labeled cells projected on flattened cortical surface. *B,* Representative sagittal section through cortex at arrow in A. Numbers denote Brodmann's areas. (From Jones, E. G.; Wise, S. P. *J. Comp. Neurol.* 175:391-438, 1977.)

primary somatosensory cortex. Thus stimulating adjacent cortical sites evokes movements of adjacent body parts. The representation of the somatic musculature in MI of the monkey is summarized in Figure 28-4A. The motor map in the precentral gyrus provides the most extensive and detailed cortical representation of limb muscles. The anatomical distortion of the simunculus figure (Fig. 28-4A) indicates that a proportionately larger region of cortex is devoted to those body parts capable of finer motor control, such as the tongue, digits, and toes. The greater cortical area devoted

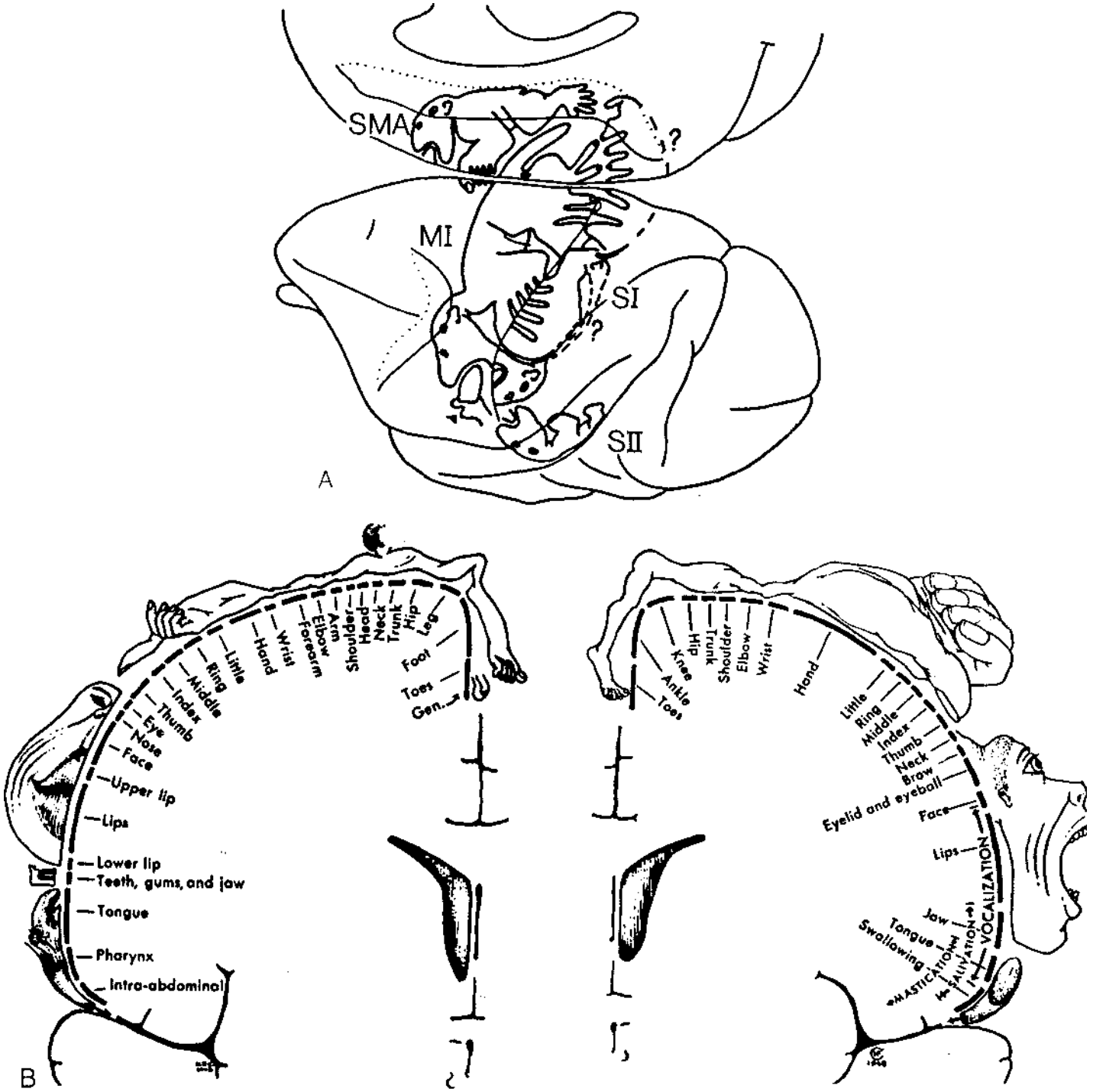


Figure 28-4 Somatotopic organization of motor cortical areas in monkeys and humans. *A,* The summary of body regions activated by cortical surface stimulation in an anesthetized macaque monkey. MI = primary motor cortex; SMA = supplementary motor cortex; SI = primary somatosensory cortex; SII = secondary sensory cortex. *B,* Relative size and location of primary motor cortex areas devoted to different body parts in humans. Sensory input is shown at left; motor output representation is shown at right. *(A,* After Woolsey, C. N. In Harlow, H. F.; Woolsey, C. N. *Biological and Biochemical Bases of Behavior,* Madison, Wis., Univ. of Wisconsin Press, 1958; *B,* reprinted with permission of Macmillan Publishing Company from Penfield, W.; Rasmussen, A. T. *Cerebral Cortex of Man. A Clinical Study of Localization of Function.* Copyright © 1950 by Macmillan Publishing Company, renewed 1978 by Theodore Rasmussen.)

to these regions contains a larger number of interneurons concerned with controlling this output and also provides more efferent cells that project to the brain stem and spinal cord.

Many of the fine movements evoked by motor cortex stimulation in the monkey are mediated by the pyramidal tract. This is illustrated by experiments in which the pyramidal tract was sectioned. Figure 28-5 summarizes the results of an experiment in which Woolsey and colleagues' sectioned the pyramidal tract unilaterally in monkeys and then mapped the movements evoked by stimulating the cortex on both sides. Movements elicited from the normal side, with the pyramidal tract intact (Fig. 28-5, right), were diverse and commonly involved distal finger and toe movements. The cortical distribution is in general agreement with the summary map of Figure 28-4A. Although movements could also be evoked by stimulating the cortex with the pyramidal tract sectioned (Fig. 28-5, left), these movements were more restricted and involved mainly proximal joints such as the knee and elbow. Moreover, these movements required stimulus intensities two to three times higher than those of corresponding points on the side with the intact pyramidal tract. This experiment demonstrates that the pyramidal tract is important in mediating outputs from motor cortex to motoneurons of distal muscles.

A comparable somatotopic motor map for human cortex was obtained by Penfield and colleagues,[25] who stimulated the surface electrically during neurosurgical procedures to identify the functions of cortical sites. As in the monkey, the most medial portions of human motor cortex are devoted to the leg and the more lateral regions to the arm and face, as indicated in Figure 28-4B. Again, the relative area of cortex devoted to the thumb and tongue greatly exceeds their relative anatomical size. Some of this topographic organization of human motor cortex had already been deduced by the neurologist Hughlings Jackson by observing the typical progression of epileptic seizures. The so-called "Jacksonian march" of epileptic activity begins with twitches of the thumb and then proceeds to involve the hand and more proximal parts of the body, and eventually the face. Reasoning that these peripheral symptoms

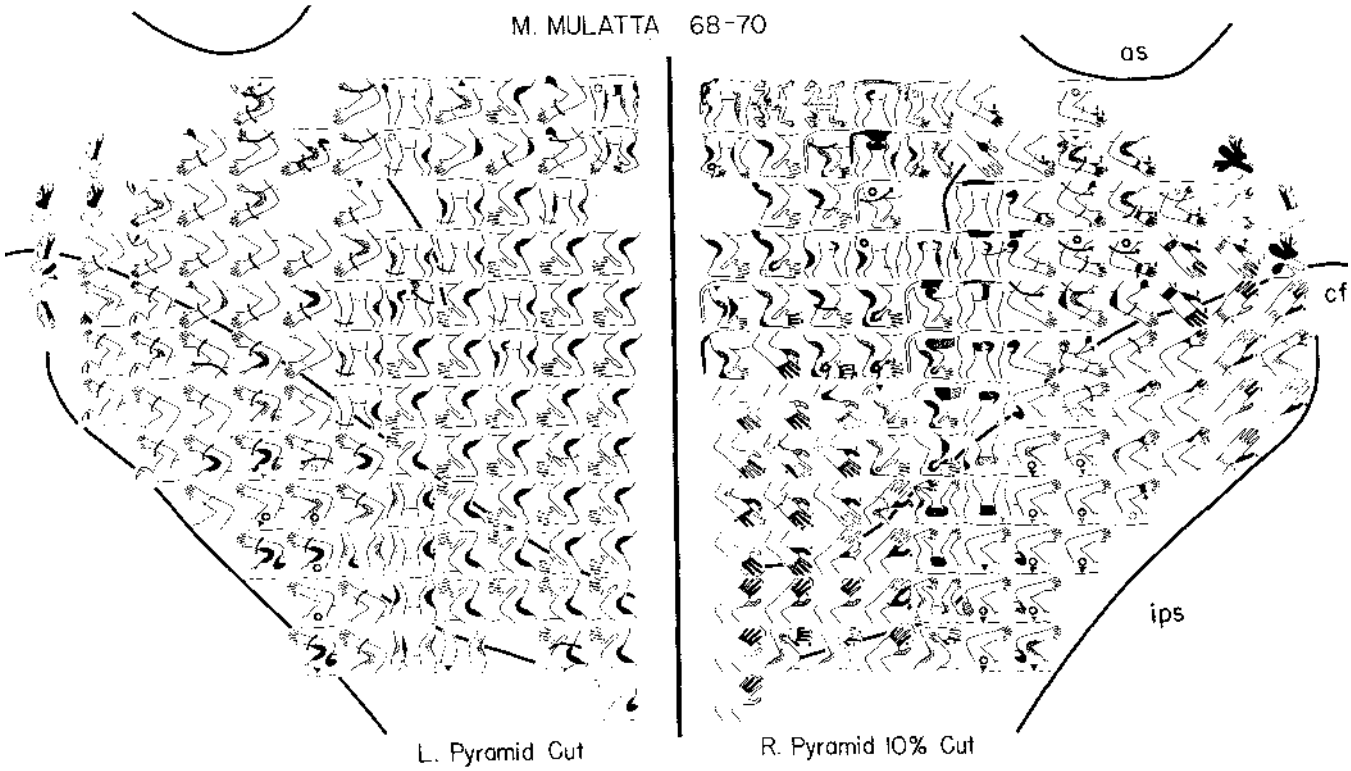


Figure 28-5 Figurine map illustrating movements evoked by electrical stimulation of pre- and postcentral cortex of macaque monkey with a unilateral pyramidal tract section. Figurines are located at the cortical points that evoked movements of the joints indicated. Pyramidal tract from left hemisphere was sectioned and from right hemisphere was largely intact. c.f. - central fissure; i.p.s. = intraparietal sulcus; a.s. = arcuate sulcus. (After Woolsey, C. N.; Gorska, T.; Wetzel, A.; Erickson, T. C., Earls, F. J.; Allman, J. M. Brain Res. 40:119-123, 1972.)

reflect the spread of epileptic activity through adjacent cortical areas, Jackson deduced much of the relative cortical representation of the musculature shown in Figure 28-4B.[1]

Conscious human patients whose precentral gyrus is electrically stimulated often report that the evoked movements are involuntary. Precentral stimulation evokes simple, stereotyped motor responses, rather than any conscious impulse to move, indicating that the primary motor cortex is relatively close to the output of the motor system. At many sites of human motor cortex electrical stimulation produces relaxation of musculature rather than muscle contraction.

In addition to evoking involuntary movements and arresting voluntary movements, electrical stimulation of motor cortex may also evoke somatic sensations. About a third of the precentral cortex sites stimulated by Penfield and Boldrey[25] evoked experiences of tingling or numbness—similar to the sensations produced by stimulating postcentral cortex. These sensations could be evoked from precentral sites even after ablation of adjacent postcentral regions that normally process somatic sensation (see Chap. 15), suggesting that precentral cortex may also be involved in somatic sensation.

Because cortical stimulation evokes movements that involve many muscles, it has been argued that movements rather than muscles are represented in motor cortex. In this view, the primary motor cortex sends command impulses that signal brain-stem and segmental circuitry to generate coordinated activity of many motoneuron pools. The alternative view is that motor cortex cells ultimately control individual muscles, and that their activity is coordinated by inputs from higher centers. To test these alternatives, Chang, Ruch, and Ward[5] dissected ankle muscles in anesthetized monkeys and measured the tensions produced by repetitive stimulation of different cortical sites. Each muscle could be made to contract from stimulation of a wide region of cortex, but the sites of lowest threshold were more localized. Stimulation of some low-threshold sites evoked contraction of specific muscles in isolation, whereas stimulation of other sites caused several muscles to contract together, suggesting that MI can affect both single and multiple muscles.

Effects of Stimulation on Motoneurons

The effects of corticospinal projections have been analyzed in more detail by recording intracellularly the excitatory postsynaptic potentials (EPSPs) evoked in motoneurons by cortical stimulation.[26,27] In primates, some corticospinal cells make monosynaptic connections with motoneurons. Figure 28-6A illustrates corticomotoneuronal EPSPs recorded in motoneurons innervating arm muscles of the baboon.[26] As the stimulus intensity increases and recruits more corticomotoneuronal cells, the amplitude of the EPSPs also increases (Fig. 28-6B). Above a certain stimulus intensity the size of the EPSP increases no further, suggesting that the whole "colony" of corticomotoneuronal cells projecting to that motoneuron has been recruited. To estimate the cortical extent of the motoneuron's colony, Phillips and Porter[26] measured the current spread of the cortical stimuli by measuring the threshold intensity required to evoke a response in single pyramidal tract cells as a function of distance from the lowest threshold point. The threshold typically increased as the square of the distance, as shown in Figure 28-6C. Using this relation, the extent of the cortical colonies was estimated to range from 2 to 10 mm^2 for different motoneurons. EPSPs in distal motoneurons reached their maximum at lower stimulus intensities than those in proximal motoneurons, suggesting that the cortical colonies of distal motoneurons were more localized in the cortex. Moreover, motoneurons of distal muscles also received larger maximal EPSPs than those of proximal muscles. Thus, motoneurons of distal muscles received a greater net synaptic input from cortex, and this originated from a smaller cortical area.

The spatial distribution of cortical colonies was determined by mapping the cortical points from which minimal corticomotoneuronal EPSPs could be evoked in hindlimb motoneurons of the monkey.[16] The cortical distributions of these colonies were irregular in shape, typically between 3 and 7 mm^2, and the colonies projecting to motoneurons of different muscles overlapped extensively. Different motoneurons of the same pool sometimes received monosynaptic EPSPs from different cortical areas, suggesting that some corticomotoneuronal cells may project to specific motoneurons within the pool. Cortical stimulation also evoked disynaptic inhibitory postsynaptic potentials (IPSPs) in motoneurons; these inhibitory effects are mediated in part by the Ia inhibitory interneurons, which receive monosynaptic input from the cortex.

The relative magnitudes of the monosynaptic inputs to motoneurons descending from motor cortex and those arriving from Ia muscle spindle afferents suggest that the cortical and reflex inputs are somewhat different for each muscle. The size

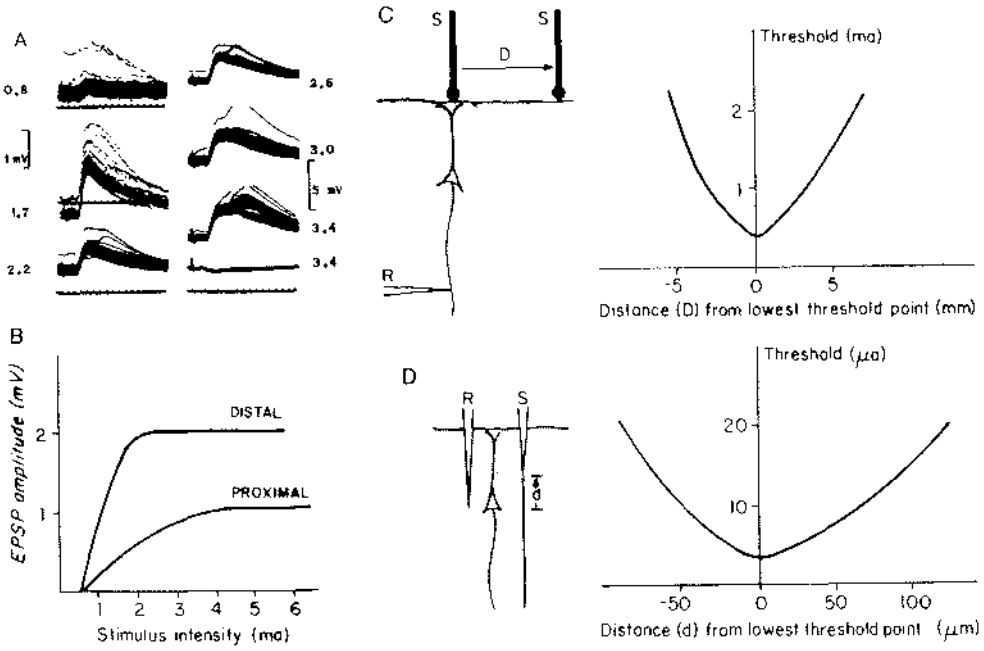


Figure 28-6 Effects of cortical stimulation. *A,* corticomotoneuronal excitatory postsynaptic potentials (CM-EPSPs) evoked in a motoneuron by increasing intensity of cortical surface stimulation. *8,* Size of CM-EPSP as function of stimulus intensity for motoneuron of distal and proximal muscle. C, Spread of cortical surface stimulus as measured by the threshold intensity required to activate pyramidal tract cell; typical curve of threshold in milliamperes, as a function of distance (D) of the stimulating electrode (S) from the best point (for 0.2 ms anodal pulse). *D,* Spread of intracortical microstimulation as measured by threshold intensity required to activate cortical cell; typical curve of threshold in microamperes, as a function of distance (d) of the stimulating electrode (S) from the best point (for 0.2 ms cathodal pulse). R represents recording electrode. *(A, B,* and C from Phillips, C. G.; Porter, R. *Prog. Brain Res.* 12:222-242, 1964 *[8* and C modified]. *D* after Stoney, S. D.; Thompson, W. D.; Asanuma, H. *J. Neurophysiol.* 31:659-669, 1968.)

of the maximal EPSP from these two sources is represented in Figure 28-7A by the width of the arrows converging onto motoneurons innervating hand and finger muscles of the baboon. The extensor digitorum communis (EDC) motoneurons receive the largest corticomotoneuronal EPSPs, which exceed the magnitude of the Ia-EPSPs from EDC muscle afferents. Other motoneurons, such as those of the hypothenar muscles (Uh), receive greater net synaptic input from muscle spindles than from cortical inputs.

Not only does electrical stimulation of MI produce monosynaptic EPSPs in primate motoneurons, but repetitive cortical stimulation, which mimics the bursts of activity recorded in corticospinal cells, enhances the effectiveness of EPSPs beyond simple summation. Figure 28-7B shows that repetitive stimulation (200/s) of the Ia muscle afferent produced algebraic summation of successive Ia-EPSPs, whereas repetitive stimulation of motor cortex produced an increase in the size of successive corticomotoneuronal EPSPs. This increase was not due simply to recruitment of additional corticospinal cells, since the amplitudes of the descending volleys remained constant. Neither could the increase be due to recruitment of excitatory spinal interneurons, since the latency and shape of the EPSPs did not change, but only their amplitude. Such facilitation of corticomotoneuronal EPSPs enhances the effectiveness of high-frequency activity, which typically occurs at the onset of movement (see Fig. 28-14).

Intracortical Microstimulation

The experiments described above employed cortical surface stimulation, which can spread over considerable distances, limiting the spatial resolution of the effective sites. To evoke discrete responses from more circumscribed intracortical sites, Asanuma and Rosen' delivered intracortical microstimulation through microelectrodes. This technique has provided three-dimensional maps of low-threshold output sites in the depth of the cortex. To quantify the effective spread of stimulus currents, Asanuma and colleagues [3la] measured the stimulus intensities required to activate a pyramidal tract neuron as a function of the distance of the stimulating electrode. As the electrode was moved from the lowest threshold point, threshold intensities increased as the square of the distance (see Fig. 28-6D). The effective radius of a 10-ua current pulse was found to be 80 to 90 pm.

Using intracortical microstimulation to evoke activity in a given muscle, Asanuma and Rosen' found that the low-threshold points for individual

muscles were located in a cylindrical volume of cortex perpendicular to the cortical surface (see Fig. 28-12). The diameters of these columnar zones ranged from 0.5 to several millimeters. These observations suggested a columnar organization of output cells to specific muscles, analogous to the columnar arrangement in sensory cortex of cells with inputs from particular receptors. However, in addition to activating cells directly, repetitive microstimulation is very effective in evoking responses transsynaptically, via fibers that are activated directly. This could explain why the low-threshold points for evoking muscle responses with repetitive stimulation have the same distribution as the afferent and efferent fibers. These fibers could activate the corticospinal output cells, which are located in cortical layer V (see Fig. 28-3B).

Cortical Connections

Cortical Neurons and Their Targets

The operations of the motor cortex can best be understood in the context of its input and output connections. On the basis of cell morphology and fiber distributions, anatomists have distinguished five layers within motor cortex. Unlike other cortical areas, primary motor cortex lacks a prominent layer IV containing granule cells, so the precentral gyrus is also called "agranular cortex." Drastically simplified, cortical cells can be classified into two basic types: pyramidal and nonpyramidal. *Pyramidal* cells, so called because of their pyramidal somata, have a long apical dendrite directed toward the cortical surface and short basal dendrites issuing from the base of the soma. Their extensive dendritic tree suggests that they integrate synaptic input from several layers. Axons of the pyramidal cells leave the cortex for other cortical and subcortical targets, making them the main cortical output cell; in addition, axon collaterals of pyramidal cells usually provide local intrinsic connections. *Nonpyramidal* cells, on the other hand, have small dendritic trees that sample input from a more restricted region; because their axons remain within the cortex and arborize locally, they are interneurons. Nonpyramidal cells include stellate, basket, and granule cells, some of which are inhibitory.

As illustrated in Figure 28-8, pyramidal cells in each cortical layer send axons to specific targets. The pyramidal cells in layers II and III project to other cortical regions. The more superficial cells project to ipsilateral cortical areas, notably to secondary motor areas (SMA and PMC) and to postcentral sensory cortex; the deeper cells in layer III send axons through the corpus callosum to the motor cortex of the opposite hemisphere. These two superficial cortical layers in turn receive their input from other cortical regions. Thus, layers II and III are largely concerned with intercortical

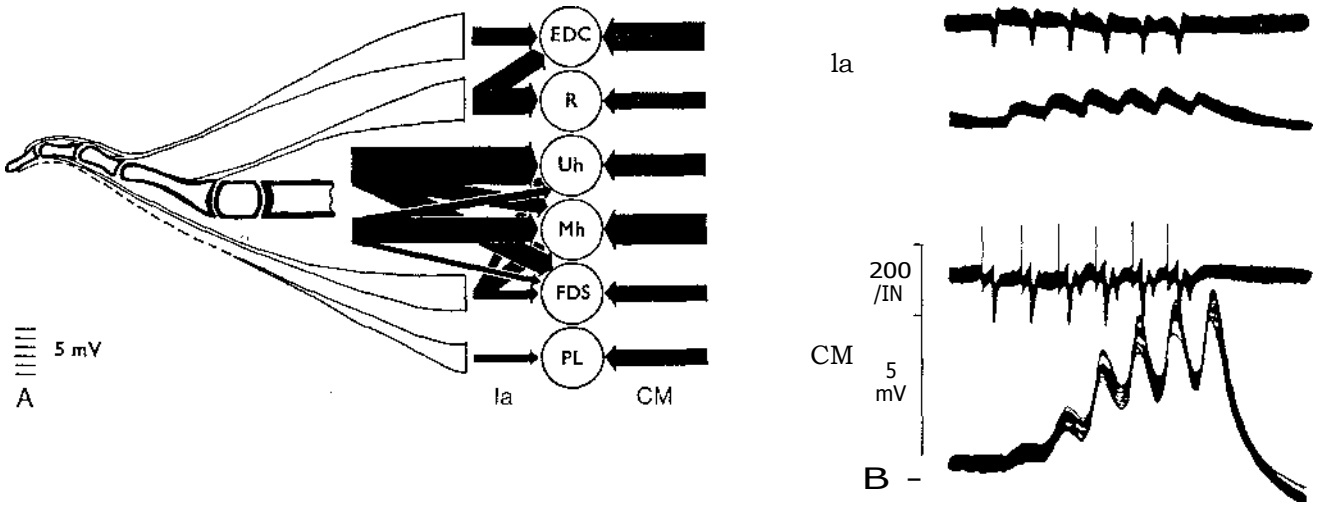


Figure 28-7 Comparison of monosynaptic excitatory postsynaptic potentials (EPSPs) evoked in forelimb motoneurons from cerebral cortex (CM) and from Ia afferent fibers. *A,* Total synaptic input to different types of motoneurons. Thickness of arrows represents the relative size of maximal EPSP. EDC = extensor digitorum communis; R = remaining dorsiflexors of wrist; Uh = intrinsic hand muscles innervated by ulnar nerve; Mh = intrinsic hand muscles innervated by median nerve; FDS = flexor digitorum sublimis; PL = palmaris longus. *B,* High-frequency stimulation evokes facilitation of successive corticomotoneuronal (CM) EPSPs *(bottom)* but not Ia EPSPs *(top).* Upper records show that arriving volleys, recorded on cord dorsum, are constant. *(A* from Clough, J. F. M.; Kernell, D.; Phillips, C. G. *J. Physiol. [Lond.]* 198:145-166, 1969. *B,* from Phillips, C. G.; Porter, R. *Prog. Brain Res.* 12:222-242, 1964.)

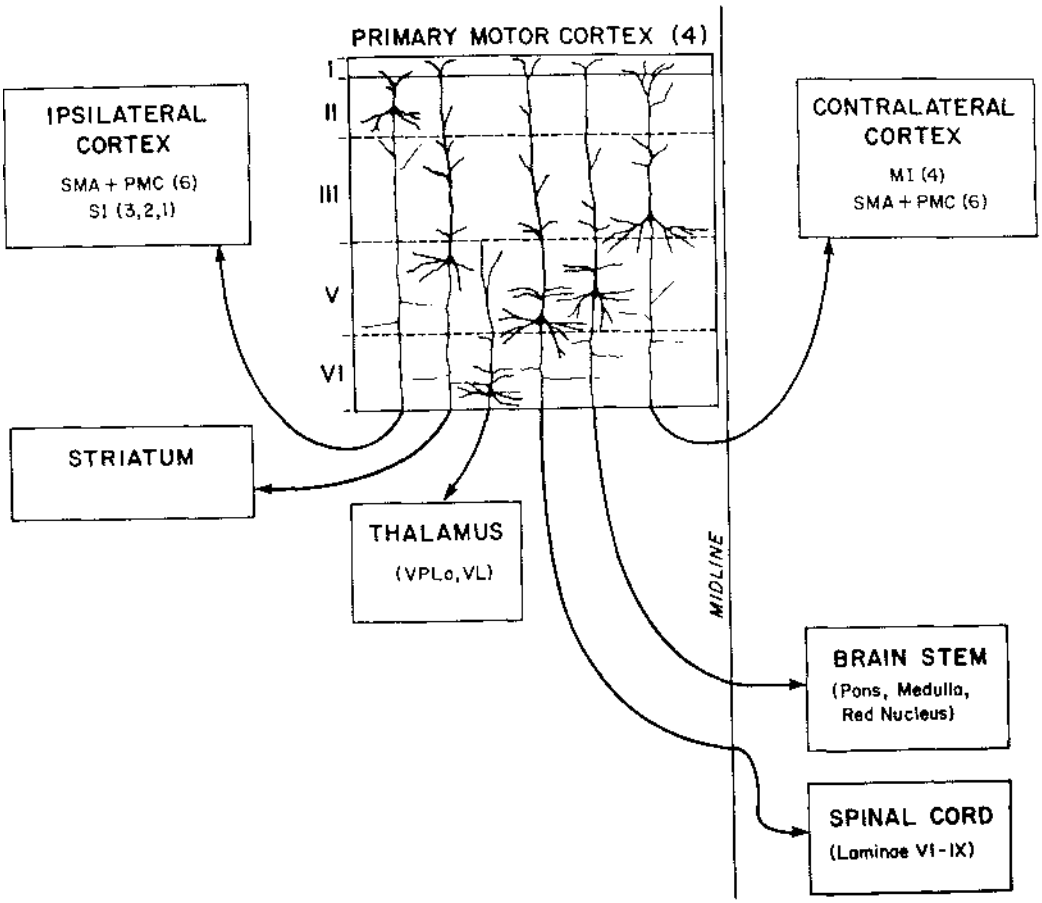


Figure 28–8 Targets of projections from pyramidal cells in different layers of primary motor cortex. Cells projecting to targets across the midline are shown at right. Numbers refer to Brodmann's architectonic designations. VPLo = nucleus ventralis posterior lateralis oralis; VL = nucleus ventralis lateralis; SMA = secondary motor area; PMC = premotor motor cortex. (From Jones, E. G. In Jones, E. G.; Peters, A., eds. *Cerebral Cortex*, vol. 5, 113–184. New York, Plenum Press, 1986.)

communication between somatotopically related areas.

Most of the outputs to subcortical targets arise from pyramidal cells in layer V. The corticospinal cells lie deepest in layer V and include the largest pyramidal cells in motor cortex, the so-called Betz cells. Cells in successively more superficial portions of layer V project to successively more proximal brain-stem targets, namely to the medulla, pons, and red nucleus; the most superficial layer V cells project to the striatum. A few pyramidal cells send branching connections to more than one of these targets, but the majority project to only one site.

Layer VI contains smaller pyramidal cells with long apical dendrites, whose axons project to the thalamus, particularly the ventrolateral nucleus. Many layer VI cells also send recurrent connections to upper cortical layers.

Sources of Inputs to Primary Motor Cortex

The major inputs to primary motor cortex (MI) arise from other cortical areas and from thalamic nuclei. Interconnections between *ipsilateral* cortical regions are diagrammed in Figure 28-9. These cortical areas are all reciprocally connected in a somatotopically organized manner. The most massive connections are those that interconnect homologous pre- and postcentral cortex sites. These inputs to motor cortex provide cutaneous and proprioceptive somatosensory information (and motor cortex, in turn, provides information about motor commands, which can modulate the activity of sensory cortex cells). However, postcentral cortex is not the only source of sensory input, since somatic stimuli can still evoke responses in motor cortex after ablation of postcentral cortex. MI is also reciprocally connected with the SMA and PMC. As discussed below, these secondary motor areas are commonly considered to be sources of motor commands to primary motor cortex. Afferent connections from other cortical areas converge in the superficial layers, among the cells that project back to the same cortical regions.

Contralateral motor cortical regions are connected through the corpus callosum. The corpus callosum preferentially interconnects those regions related to limb girdle and axial musculature (face and trunk regions), suggesting that it helps to integrate motor control of these midline structures. The hand and foot areas of motor cortex (like those of

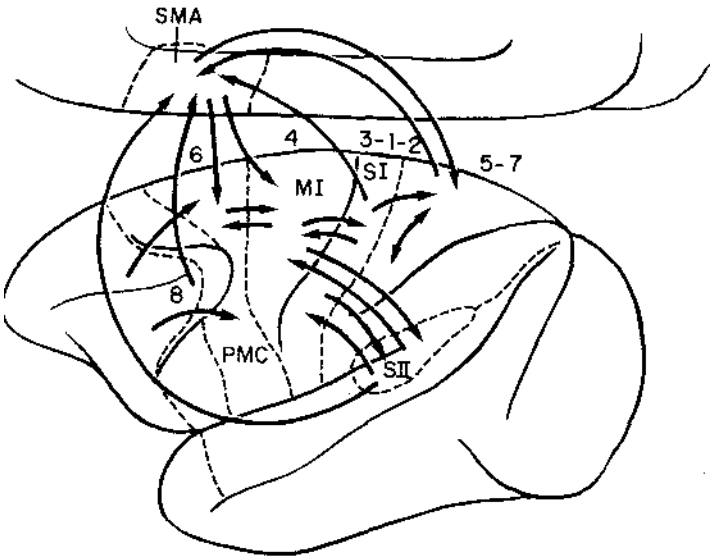


Figure 28-9 Major interconnections between cortical areas involved in motor control. Numbers indicate Brodmann's areas and arrows indicate direction of projection. Regions are reciprocally interconnected in a somatotopic manner. SMA = supplementary motor area. (After Wiesendanger, M. In Towe, A. L.; Luschei, E. S., eds, *Handbook of Behavioral Neurophysiology*, vol. 5, pp 401-491. New York, Plenum Press, 1981.)

sensory cortex) are not interconnected with the contralateral side. The supplementary and premotor cortex areas are also interconnected with their contralateral counterparts. Surprisingly, sectioning the corpus callosum does not noticeably disrupt motor coordination of proximal or distal limb muscles.

The main *thalamic* input to primary motor cortex comes from the ventrobasal nucleus (nucleus ventralis lateralis caudalis [VLc] and nucleus ventralis posterolateralis oralis [VPLo], using the nomenclature of Olszewski[23]), which relays information about peripheral events arriving from the spinothalamic tract as well as central commands arriving from the cerebellar nuclei. Recent evidence reveals that the primary and secondary motor cortical areas each receive their thalamic inputs from separate nuclei, which in turn transmit inputs from different sources. As schematized in Figure 28-10, the VPLo and VLc nuclei relay impulses from the rostral dentate nucleus and from spinothalamic cells to primary motor cortex; nucleus ventralis lateralis oralis (VLo) transmits input from the basal ganglia (globus pallidus and substantia nigra) to the supplementary motor cortex, and nucleus X relays information from the caudal dentate nucleus to the lateral premotor cortex. The existence of separate subcortical input pathways to each of the three motor areas implies that the basal ganglia and caudal dentate nucleus could influence primary motor cortex only indirectly, via relays through their secondary motor fields.

In addition to these "specific" motor relay nuclei, the thalamus also provides input to motor cortex from "nonspecific" nuclei such as the intralaminar and reticular nuclei; these are thought to regulate the general excitability of cortical neurons (Chap. 15).

Somatic Sensory Input to Motor Cortex

Most cells in motor cortex receive somatic input, which can be readily demonstrated by their responses to peripheral stimulation. In the unanesthetized primate, two thirds of the MI cells respond clearly and consistently to adequate somatic stimulation. Most cells can be driven by passive joint rotation, usually flexion or extension of one or more joints. Other motor cortex cells respond to cutaneous stimulation, such as touching skin or brushing hairs; their receptive fields are similar in size to those of postcentral cortex cells. A few precentral cells receive both deep and cutaneous input. About a third of the precentral neurons show no clear somatosensory responses, although a few respond to visual or auditory stimuli.

Cells encountered in a vertical electrode penetration through the motor cortex tend to respond to input of the same modality (deep or cutaneous) and to receive input from the same joint or overlapping receptive fields. This tendency for motor

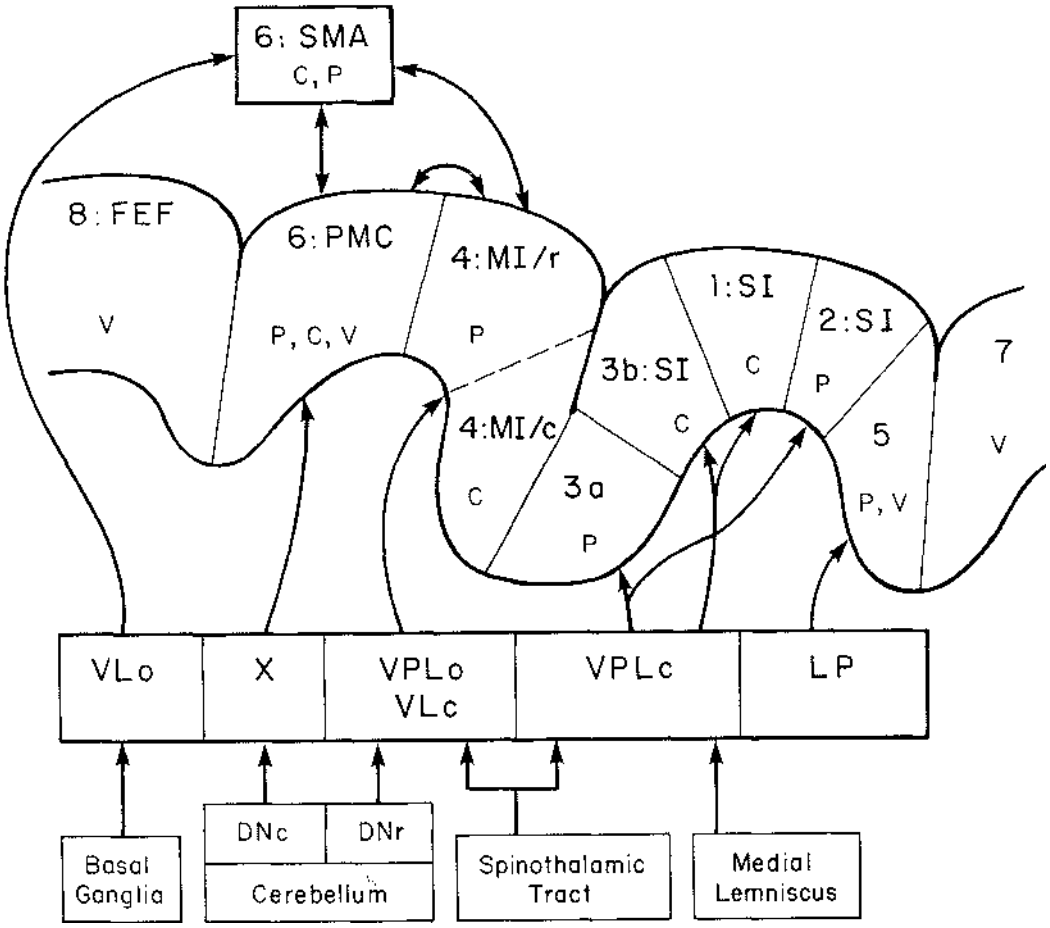


Figure 28-10 Schematic sagittal section through pre- and postcentral cortex, showing Brodmann's cytoarchitectonic areas and their thalamic inputs. The predominant sensory modality represented in each area is symbolized by C (cutaneous), P (proprioceptive), or V (visual). Note the separate thalamocortical pathways to the three motor cortical areas. Primary motor cortex (MI) is connected reciprocally with ventralis posterolateralis oralis (VPLo) and ventralis lateralis caudalis (VLc); supplementary motor area (SMA), with ventralis lateralis oralis (VLo); and premotor cortex (PMC), with area X. Input from cerebellum is relayed via the caudal and rostral components of the dentate nucleus (DNc and DNr, respectively). (After Jones, E. G. In Jones, E. G.; Peters, A, eds. *Cerebral Cortex,* vol. 5,113-114. New York, Plenum Press, 1986. Schell, G. R.; Strick, P. L *J. Neurosci.* 4:539-560, 1984.)

cortex cells in a vertical "column" to have similar input resembles the columnar organization of sensory cortex cells and is readily understood as a consequence of the radial distribution of the afferent axons.

The input from peripheral receptors is distributed in motor cortex in a somatotopic map, which is in register with the motor output map shown in Figure 28-4. This map summarizes the source of somatic input to most neurons at each cortical site; however, cells with inputs from other regions and modalities are considerably intermingled in motor cortex—more so than in sensory cortex. This heterogeneity of inputs has allowed investigators to emphasize different features of the distribution of cells with sensory inputs in motor cortex. For example, in awake macaques, Murphy and colleagues[22] found that neurons driven by stimulation of different forearm regions are distributed in a set of roughly concentric rings (Fig. 28-11). In the central region most cells respond to input from the fingers; surrounding rings contain cells responsive to wrist, elbow, and shoulder. These groupings are by no means exclusive, since neurons receiving input from adjacent joints were substantially intermingled.

In monkeys, the inputs from cutaneous and deep receptors project to two separate regions of area 4. Neurons in a rostral zone of precentral cortex respond predominantly to passive joint movements, while cells in a more caudal zone respond primarily to cutaneous input.[32, 33] This segregation of proprioceptive (p) cells rostrally and cutaneous (c) cells caudally is illustrated in the schematic sagittal section through pre- and postcentral cortex in Figure 28-10. This figure also indicates the predominant somatic modality represented in each Brodmann's area. Primary motor and sensory cortical areas are composed of alternating zones with predominantly proprioceptive and cutaneous input, and are bounded rostrally and caudally by regions that receive visual input (v).

Input-Output Relations

Woolsey's finding[37] that the somatotopic map of peripheral input to motor cortex was in broad register with the map of output effects evoked by cortical stimulation suggested a close functional relationship between input and output, which has been confirmed on the level of single neurons.

Using extracellular microelectrodes Rosen and Asanuma[29] compared the sensory responses of individual cortical neurons in the precentral hand area of the squirrel monkey with the movements evoked by microstimulation at the same sites. Figure 28-12 summarizes their results for a series of penetrations in the thumb area. Microstimulation evoked different thumb movements at different sites; the low-threshold sites for evoking flexion were distributed in an output zone oriented perpendicular to the cortical surface. Similar zones could be demonstrated for extension, adduction, and abduction. The sensory responses of neurons recorded in each zone were closely related to the output; for example, cutaneous receptive fields were located on the part of the thumb lying in the direction of the movement evoked by the stimulation. Similarly, cells driven by passive thumb extension were found in the zone whose stimulation evoked extension. Similar close relations between the sensory responses of cells and the movement evoked by microstimulation were also observed for the concentric regions illustrated in Figure 28-11.

These input-output relations have a simple functional interpretation. The cutaneous input from receptors that would be directly activated by movement could function to assist in grasp reflexes and placing reflexes by increasing activity of the relevant output cells; indeed, the motor cortex plays an important role in such reflexes. Similarly, the proprioceptive input from stretch

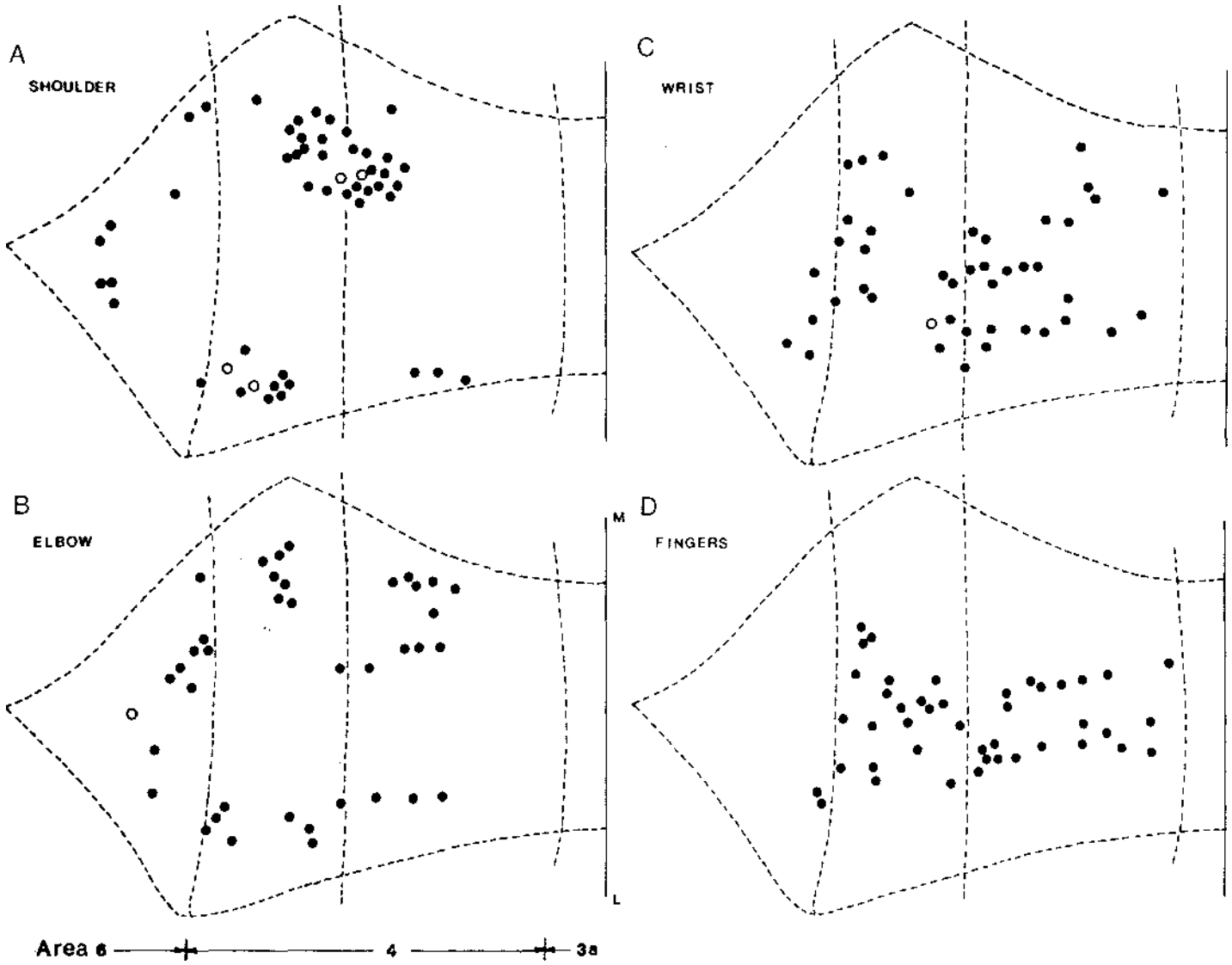


Figure 28-11 Distribution of sensory input from different forelimb joints in motor cortex of the macaque. The precentral gyrus was unfolded onto a flat plane, and boundaries between Brodmann's areas represented by vertical dashed lines. M = medial; L = lateral. Many points also represent output effects on the same joints evoked by microstimulation. (From Murphy, J. T.; Kwan, H. C.; MacKay, W. A.; Wong, Y. C. *J.* Neurophysiol 41:1120–1131, 1978.)

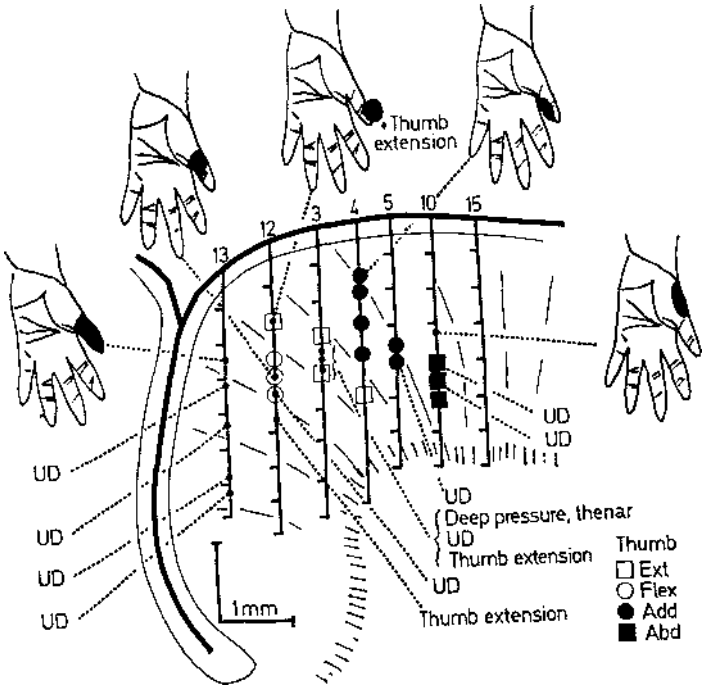


Figure 28-12 Relation between sensory input and motor output evoked by intracortical microstimulation in precentral cortex of monkey. Repetitive stimulation at 5 [La evoked thumb movement at sites indicated by symbols corresponding to movements listed at lower right and evoked no movement at sites with bars. Peripheral inputs to cells are indicated by diagrams representing their cutaneous receptive fields, or by the description of adequate proprioceptive stimulus; some cells were undriven (UD). (From Rosen, I.; Asanuma, H. *Exp. Brain Res.* 14:257-273, 1972.)

receptors to cells that facilitate muscle activity could function to overcome load perturbations in a manner similar to the segmental stretch reflex (see Chap. 24). Further evidence for such a transcortical stretch reflex from unit recordings in behaving monkeys is described below.

Coding of Movement Parameters by Motor Cortex Cells

While the effects of electrical stimulation and lesions demonstrate that motor cortex plays a role in controlling movements, these techniques cannot reveal which parameters of movement it controls. The movement variables that are coded in the activity of precentral cortex cells can be investigated only by observing neuronal activity in awake, behaving animals. In such "chronic unit recording" studies, the activity of single neurons is recorded with a movable microelectrode. Relevant behavioral responses are trained through operant conditioning techniques, which gradually "shape" the animal's behavior by selectively rewarding those responses that are closest to the desired final behavior. Thus, chronic recording studies can document the activity of cells under particular behavioral conditions designed to test hypotheses about the functions of the recorded neurons. For example, a repeatable movement in response to sensory signals is ideal for investigating the relative timing of cell activity involved in generating a simple voluntary response. On the other hand, to determine whether motor cortex cells are preferentially involved in coding limb position or force one can train the animal to move different loads through the same displacement—a task designed to dissociate the force and displacement. Experiments can also be designed to demonstrate the neural changes involved in preparing to make a particular movement.

Relative Timing of Cell Activity: Reaction Time Responses

One strategy in studying the generation of voluntary movement has been to determine the relative timing of changes in neural activity in different motor structures when the animal performs a simple movement. Those structures with neurons discharging earlier could presumably "drive" those that are activated later. The timing of neural activity is usually investigated by rewarding the animal for performing a rapid, stereotyped movement as soon as possible after detecting a sensory cue. An example of such a *reaction-time* task is the rapid release of a depressed lever when a light is turned on. This paradigm is a voluntary analogue of a segmental reflex, such as the tendon jerk; however, the delay between the stimulus and the behavioral response—the reaction time—is much longer, on the order of 100 to 200 ms. This latency depends on the amount of training and the stimulus modality. Reaction times are increasingly longer for responses evoked by proprioceptive, auditory, and visual stimuli, respectively. Some of this difference is accounted for by the different afferent conduction times for each sensory modality.

In monkeys trained to release a bar after a visual stimulus, many precentral pyramidal tract cells change their activity 10 to 100 ms prior to electromyographic (EMG) activity in the agonist wrist muscles. The changes in activity of these pyramidal tract neurons is more tightly linked with initiation of muscle activity than with occurrence of the light, indicating that they are more related to the movement than the sensory cue.'°

The routing of neural impulses between a reaction time stimulus and the voluntary response remains largely unresolved. Experiments using the reaction time task have not revealed a simple sequential activation of successive centers. The problems are illustrated by experiments designed to determine whether cerebellar cells might precede activation of motor cortex neurons. Figure 28-13 shows that the onset times of neural discharge in the cerebellar nuclei and motor cortex during the same motor responses are distributed over several hundred milliseconds and exhibit considerable overlap. Similar overlapping distributions characterize the onset of activity of cells in other motor regions. Thus, serial activation of different motor centers cannot be established by measuring neural onset times, because the cells within each region—including motoneuron pools—are recruited over times much longer than the conduction times between regions. Moreover, the duration of most movements greatly exceeds the conduction times, allowing any recurrent loops between regions to be traversed repeatedly during a single movement. Consequently, the appealing notion that initiation of movement involves sequential activation of cells in hierarchically related centers has proved difficult to confirm experimentally. Indeed, the distributions illustrated in Figure 28-13 suggest that cells in different regions are recruited more or less in parallel rather than in a strictly serial manner.

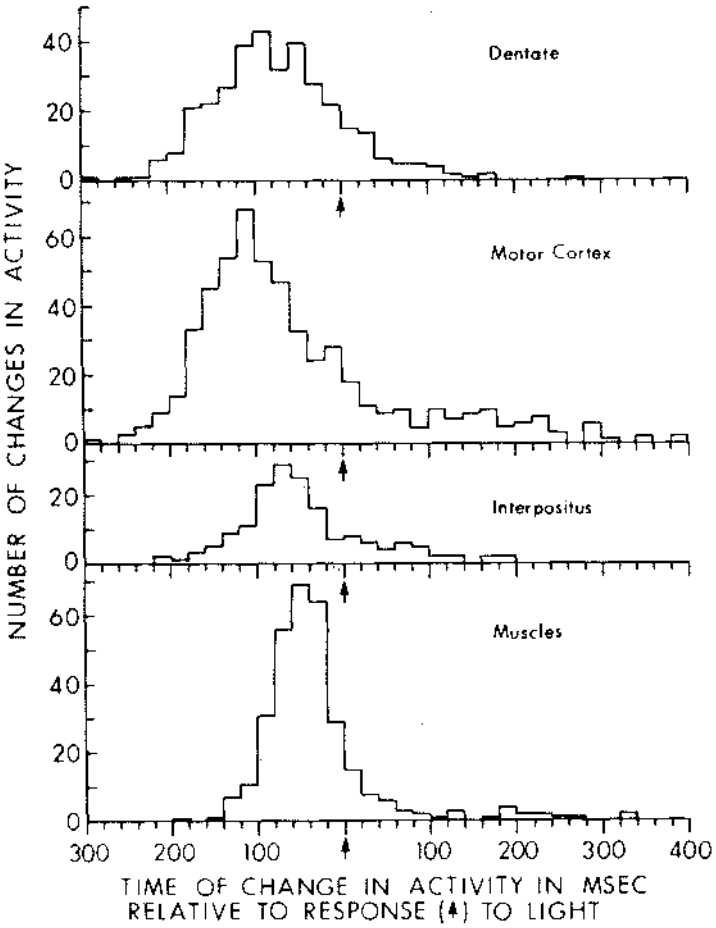


Figure 28-13 Relative timing of onsets of change in neural discharge in motor cortex, cerebellum, and forelimb muscles during active wrist movements in a monkey. Although the distributions show differences in timing, they overlap extensively. (From Thach, W. T. *J.* Neurophysiol. 41:654-674, 1978.)

Relation to Active Force

The activity of motor cortex cells during movements could potentially code a variety of movement parameters. To determine whether activity of pyramidal tract neurons is more strongly related to limb position or to the force required to move the limb, Evarts[10] trained monkeys to move a handle through the same displacement while lifting different loads. The discharge of most motor cortex cells was more closely related to the force exerted or to changes in force than to displacement of the wrist. Similarly, when the monkey was required to hold the handle steady against different externally applied forces, pyramidal tract neurons again discharged in proportion to the isometric force exerted.

The fact that activity of motor cortex neurons covaries with force is still not sufficient evidence to prove that they are causally involved in generating force. Such a causal linkage can be demonstrated by showing that some of the pyramidal tract neurons also have excitatory effects on agonist muscles." Such effects have been demonstrated by the technique of spike-triggered averaging, in which the action potentials of a cortical neuron are used to trigger a computer that averages the muscle (EMG) activity occurring in the time interval after the spike. Some pyramidal tract neurons produce a postspike increase in average activity of co-activated limb muscles, as shown in Figure 28-14C. The magnitude and latency of this "postspike facilitation" suggest that this neuron is a corticomotoneuronal (CM) cell and that the extensor carpi ulnaris (ECU) is one of its target muscles. Typically, the discharge of CM cells facilitates several co-activated muscles, indicating that they exert a divergent influence on a "muscle field."

The discharge of a CM cell facilitates the activity of its target muscles in proportion to its firing rate. Figure 28-14 illustrates the activity of a typical CM cell during wrist movements against an elastic load (which requires a force proportional to dis-

placement). The average of many extension responses (Fig. 28-14B) indicates that this CM cell fires with a phasic burst of activity at movement onset, when extra force is required to overcome inertial and elastic loads. The initial phasic discharge of CM cells begins about 80 ms before activity of their target muscles. This lead time is considerably longer than the latency of the post-spike facilitation, which peaks about 10 ms after the spike; therefore, much of this early discharge helps bring the motoneurons to firing threshold. The initial burst is followed by a tonic discharge during the period that the monkey exerts a constant force. The tonic firing rate of CM cells increases with the level of maintained force.' Besides facilitating their target muscles, the discharge of some CM cells also exerts inhibitory effects on antagonists of the target muscles.

While motor cortex output cells discharge in proportion to active force, this relationship is not invariant in all behavioral conditions. Pyramidal tract neurons fire more strongly in relation to finely controlled wrist and finger movements than to rapid ballistic movements.° Similarly, CM cells that facilitate finger muscles are more active during a precision grip task than during a power grip task, although in the latter condition their target muscles are even more active?' These observations are consistent with the behavioral effects of lesions, which suggest that motor cortex cells are particularly important in controlling fine finger movements; these neuronal recordings indicate further that pyramidal tract neurons are much less involved in rapid forceful movements.

Load Compensation Responses

The accurate control of voluntary movement involves a continual balance between centrally originating command signals and sensory feedback from the periphery. When a movement is suddenly resisted by an unexpected increase in the load, several neural mechanisms are activated to increase the motor output and overcome the perturbation. The stretch of an active muscle by a sudden load increase produces a series of muscle responses. The initial electromyographic response, called Ml, is mediated by the segmental stretch reflex and has a latency of 25 to 30 ms in man (Fig. 28-15). Between 50 and 90 ms there often appears a second response, M2, whose mediation has generated considerable controversy and experimentation. Phillips suggested that this long-latency EMG response could be mediated by CM

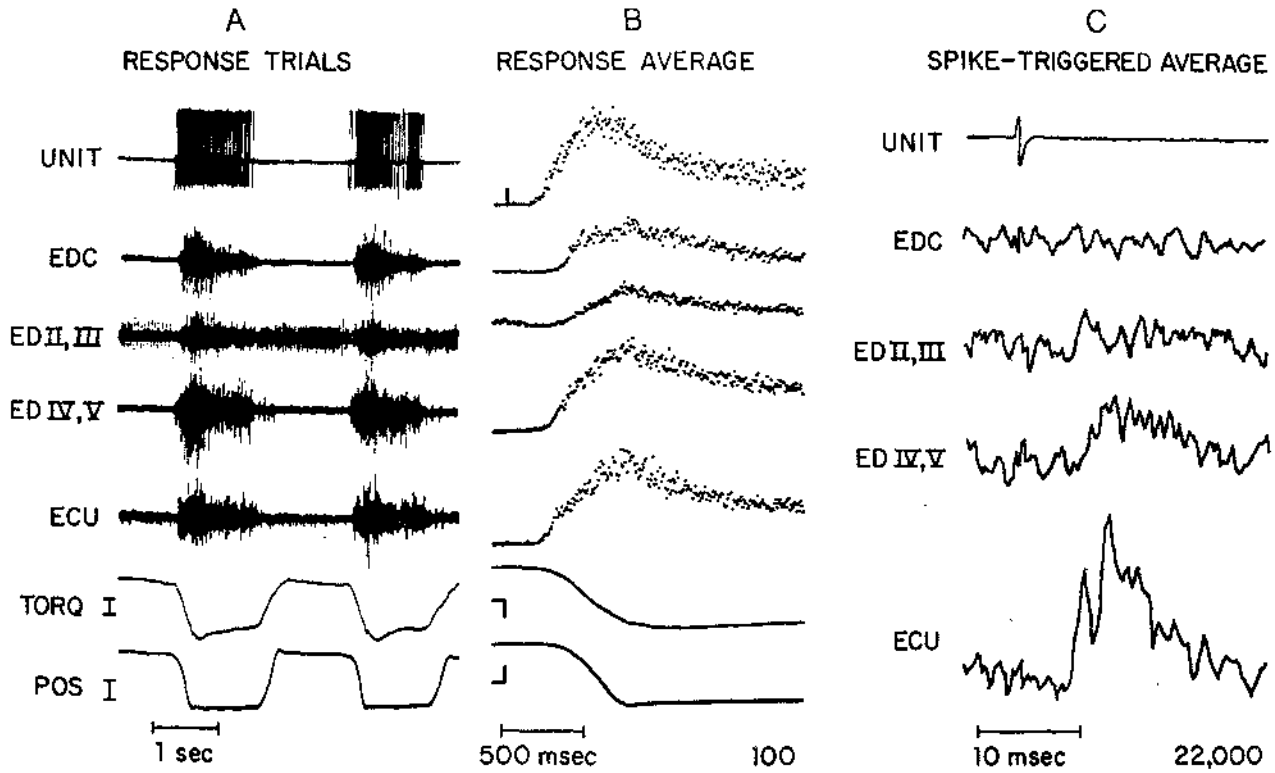


Figure 28-14 Response of motor cortex output cell during alternating flexion and extension of wrist. *A,* From top, activity of cortical unit and coactivated extensor muscles, wrist torque, and position. 8, Averages of activity and movement parameters for 100 extension responses. C, Spike-triggered averages of rectified electromyographic (EMG) activity show postspike facilitation of extensor carpi ulnaris (ECU). (From Fetz, E. E.; Cheney, P. D. *J. Neurophysiol.* 44:751-774, 1980.)

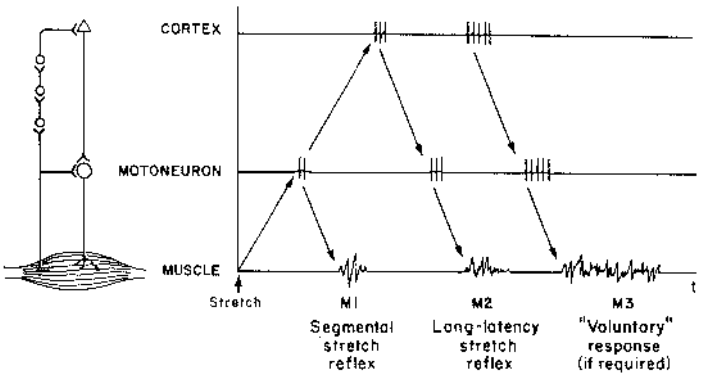


Figure 28–15 Schematic diagram of pathways mediating segmental and transcortical contributions to electromyographic (EMG) responses evoked by muscle stretch.

cells that form part of a transcortical stretch reflex, analogous to the segmental reflex. [25b] Indeed, in monkeys generating active limb movements, unexpected load increases that stretch the agonist muscle evoke excitatory responses in task-related pyramidal tract neurons. For example, the pyramidal tract neuron in Figure 28-16 fired with active elbow flexion (A) and responded with an additional burst when a transient load increase opposed flexion (B); moreover, the cell's activity dropped following a load decrease, which assisted the flexion (C). [8] Such responses in CM cells would produce changes in muscle activity that would help to overcome the load change. While motor cortex output clearly contributes to the "functional stretch reflex," other pathways and mechanisms may also be involved. Finally, subjects prepared to resist the perturbation often show a still later response (M3), which is associated with a voluntary muscle contraction (Fig. 28-15).

Preparatory Set

Prior to execution of a voluntary movement, cortical cell activity may also change in preparation to make the response. For example, a driver waiting at a red light is prepared (or set) to step on the gas pedal when the light changes. Experiments designed to investigate the neural mechanisms involved in such a "motor set" have typically involved monkeys trained to respond after two successive stimuli: the first is an instructional stimulus which indicates the type of movement to be

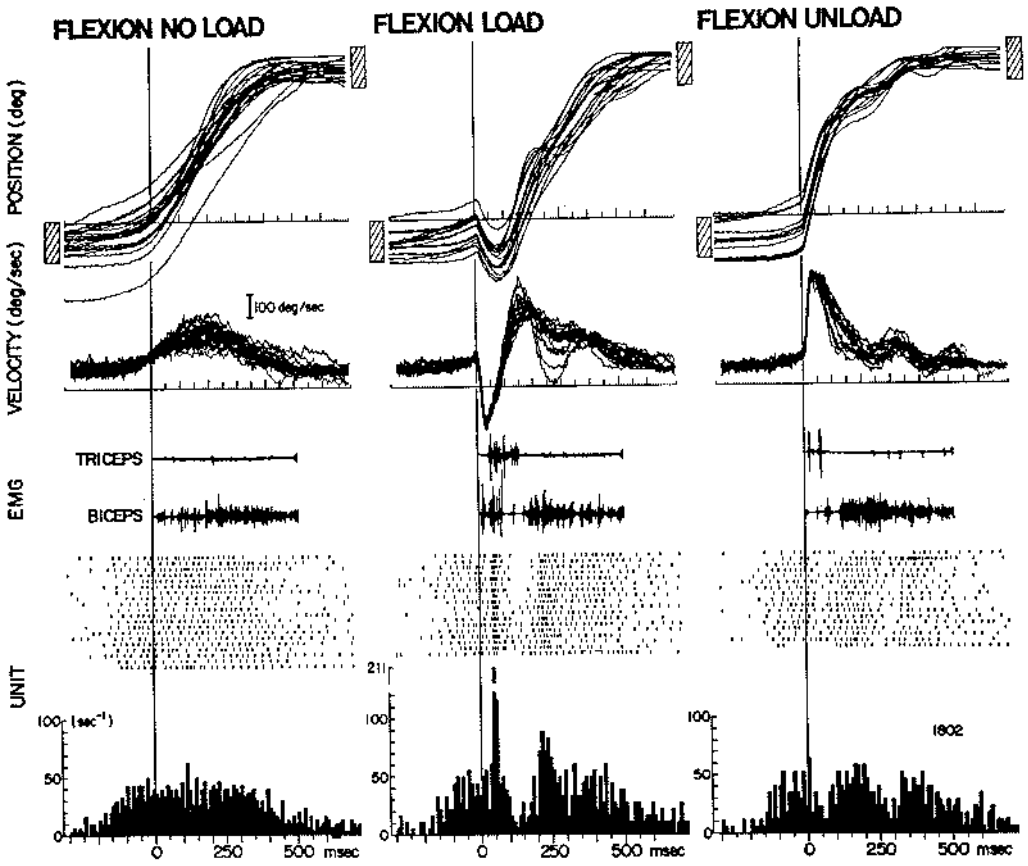


Figure 28-16 Responses of motor cortex cell and elbow muscles in a monkey during normal elbow flexion *(A)* and with brief increases *(B)* and decreases (C) of the flexion load. (From Conrad, B.; Matsunami, K.; Meyer-Loman, J.; Wiesendanger, M.; Brooks, V. B. *Brain Res. 71:507-*514, 1974.)

made to a subsequent trigger stimulus. For example, Evarts and Tanji" used a red light to instruct the monkey to pull a handle when the handle was subsequently perturbed, and a green light to instruct the monkey to push the handle. During the long delay between the visual instruction stimulus and the proprioceptive trigger stimulus caused by the handle perturbation, many motor cortex cells changed their firing rates, suggesting that they were involved in preparing to make the correct movement. Moreover, the response of many pyramidal tract neurons to the perturbation of the handle depended on which movement the monkey was prepared to make, suggesting that the peripheral input to these cells was also influenced by the set. The changes in the proprioceptive responses to the perturbation were usually those that would assist in the subsequent movement.

Coding of Movement Parameters by Population Responses

While most neuronal recording experiments to date have concerned the responses of single neurons in relation to movement parameters, the generation of a movement clearly involves large populations of cells. Thus the coding of response parameters must involve the coordinated activity of neuronal populations. Recording simultaneously from a group of motor cortex neurons in monkeys making wrist movements, Humphrey and colleagues[15] found that an appropriately weighted average of their firing rates could match the time course of force, and the population average matched force better than the discharge of any single neuron. Moreover, by using different sets of weighting factors, the discharges of the same cells could be made to match also the position trajectory, or the rates of change of position or force. The weighting factors derived from one set of movements would predict the time course of these parameters in subsequent movements. The match between the predicted and the observed movement parameters improved with the number of task-related motor cortex cells included in the weighted average. Figure 28-17C illustrates the firing rates of five motor cortex cells during one cycle of wrist movement. Figure 28-17D shows that the fit between the weighted unit activity and the time course of the force improves as more neurons are included in the weighted average *(bottom to top)*. This happens because each additional cell is added with a weight that would further decrease the remaining error. More remarkably, with different weighting factors, the activity of the same population could be used to match a variety of different movement parameters.

The discharge patterns of neuronal populations have also been used to match the direction of limb movement in space by a kind of vector addition. Georgopoulos and colleagues" trained monkeys to move a handle from the center of a circle to any of 12 equidistant points on its circumference. They found that many motor cortex neurons fired with movements in several directions, but that neurons usually showed the greatest average activity with movement in one "preferred" direction. They assigned a vector to each neuron that pointed in its preferred direction. Assuming that for every direction of movement, the neuron made a vector contribution (in its preferred direction) that was proportional to its mean firing rate during that movement, they found that the sum of the vectors of the neuronal population pointed in the direction of the limb movements. Again, the direction predicted by the vector sum of the population discharge became more accurate as more cells were included.

These studies indicate that close correlates of various movement parameters may be derived from the activity of neuronal populations. Moreover, the appropriate function of the population activity matches the mechanical parameters with increasing accuracy as the number of cells included is increased. Although such functions of population discharge can provide good descriptive matches with movement variables, this does not provide a causal explanation of how the nervous system controls these parameters.

Effects of Motor Cortex Lesions

Spasticity and Paralysis

Lesions of motor cortex in humans may result from cortical strokes, missile wounds, or surgical excisions required to treat epilepsy or to remove tumors. Damage to primary motor cortex initially produces flaccid paralysis of the body parts represented in the affected region. Within one to two weeks the ability to move the proximal joints is often regained. At the same time spasticity appears, becoming most severe and permanent in the distal muscles; spastic muscles are hyperactive and show exaggerated stretch reflexes. The most severe and long-lasting deficits occur in the extensors of the wrist and fingers.

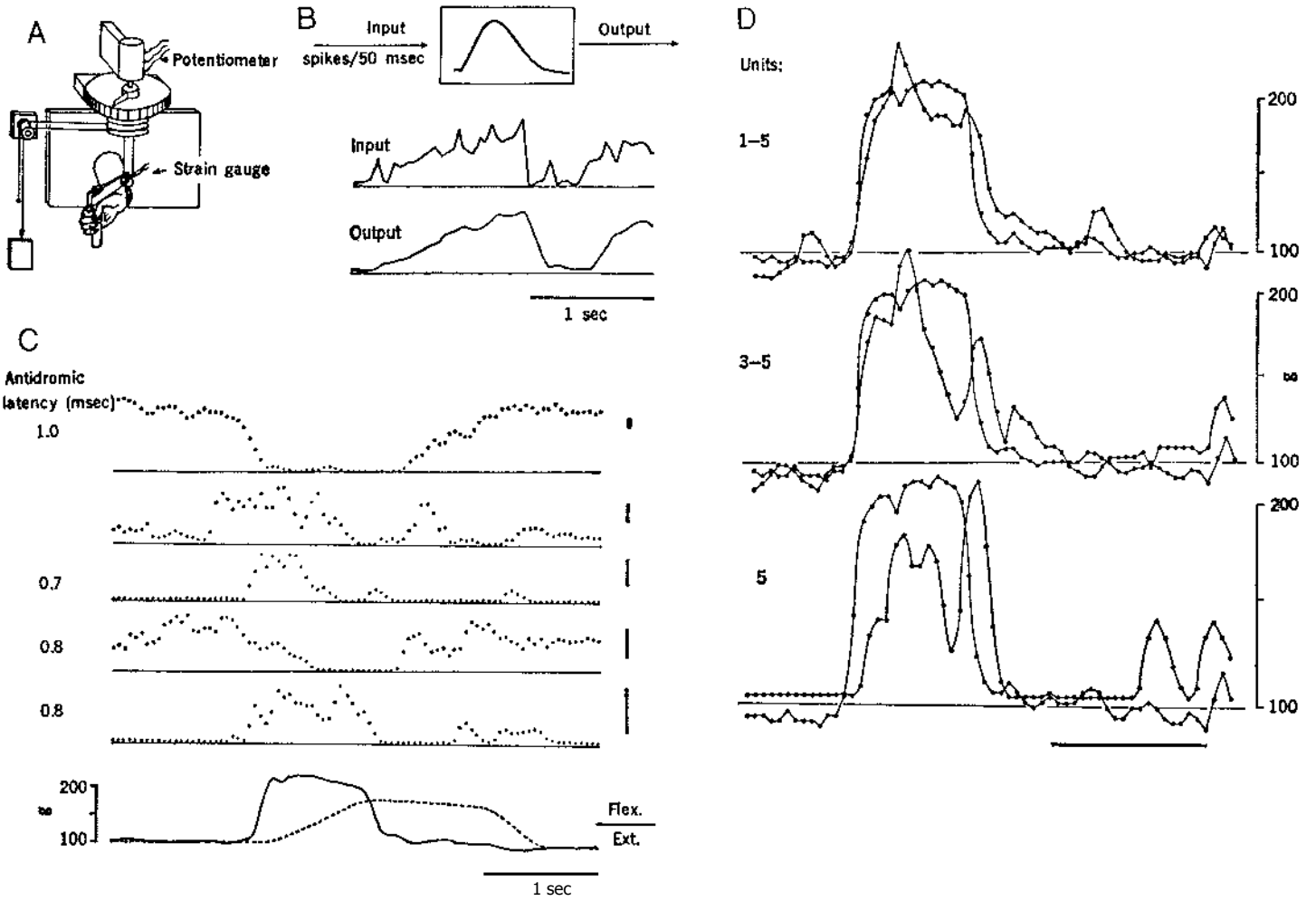


Figure 28-17 Population coding of movement parameters. *A,* Monkey's task involved alternating wrist movements against a constant load. *B,* Firing rate of cortical neurons was smoothed by a filter as shown. C, Smoothed firing rates of five simultaneously recorded motor cortex cells during a single trial (bars = 10 spikes/sec); the antidromic latencies of the four pyramidal tract neurons are given at left. Bottom traces show force (solid line) and displacement (dashed line). *D,* Matches between the force trace and the weighted averages of different numbers of cells: *Bottom,* single cell (No. 5); *middle,* three cells (Nos. 3-5); *top;* all five cells (Nos. 1-5). (From Humphrey, D. R.; Schmidt, E. M.; Thompson, W. D. *Science* 170:758-762. Copyright 1970 by the Ws.)

Damage to primary motor cortex also impairs the ability to move joints independently. For example, after a lesion in the foot area, the ankle typically cannot be extended without concomitant flexion of the knee. Also, after damage to the precentral hand area, the fingers can be flexed only as a group. These muscle "synergies" permanently replace the normal independent control of joints.

In contrast with clinical cases, which often involve additional complications, experimental ablation or cooling studies in animals provide more controlled conditions for testing cortical function.[9] The effects of cortical ablation are less severe in carnivores than in primates. After total decortication, a cat or dog can regain the ability to stand and walk, although it permanently loses tactile placing reflexes (the ability to correctly place the paw on a surface following tactile contact) and hopping reactions (the ability to reposition the paw when moving relative to the surface). In carnivores, subcortical centers are sufficient to generate righting responses and locomotion, but the cortex is necessary to perform learned responses appropriate to the external environment.

Primates are more severely and permanently affected by cortical damage. Ablation of the precentral hand area in the chimpanzee initially produces complete paralysis of the hand. After a month, crude grasping responses return, but the movements remain slow and inept and the fingers show persistent spastic flexion. Removal of the entire motor cortex produces maximal paralysis and spasticity, with hypertonia in flexors of the arm and extensors of the leg. In higher primates (apes and humans), lesions of motor cortex also

produce a positive Babinski reaction. While tactile stimulation of the foot pad normally evokes plantar (downward) flexion of the toes, after lesions of precentral cortex or the pyramidal tract the same stimulus evokes upward movement of the foot and toes. Babinski's sign has become a classic clinical test for damage to the pyramidal system.

Recovery from cortical ablation depends upon several factors. In primates the consequences of cortical removal can be considerably less severe if the cortex is ablated in stages which are separated by months or years. Following such gradual decortication, some monkeys recover the ability to make rudimentary movements. Also, recovery from cortical injury is considerably greater when the damage occurs early in life. An infant monkey deprived of its precentral cortex compensates almost completely for the loss.

Effects of Pyramidal Tract Lesions

The corticospinal tract may be selectively and completely sectioned at the medullary pyramids, producing an animal whose remaining motor functions are subserved by the extrapyramidal system. The behavioral consequences of pyramidal tract section were extensively described by Tower: [2]

The most conspicuous result of unilateral pyramidal lesion in the monkey is diminished general usage and loss of initiative in the opposite extremities. . . . When both sides are free to act, initiative of almost every sort is delegated to the normal side, but if the normal side is restrained, the affected side can, with sufficiently strong excitation, be brought to act.

The affected side shows a paresis—a loss of fine control of movement, particularly in the distal muscles. The skillful use of the hand in precise movements is entirely lost. Although the limb can still be used in postural activity and in reaching and grasping, the movements are clumsy and require considerable attention and effort.

Unilateral pyramidal section also produces hypotonia in muscles of the opposite side. Contralateral muscles exhibit abnormally low resistance to passive stretch and slowed tendon reflexes. Reflexes evoked by cutaneous stimulation also have higher thresholds. Reactions to pinprick and abdominal reflexes either are abolished or are harder to elicit and slower. Contact placing is abolished and proprioceptive placing is more difficult to elicit. The ability to reach for and grasp objects remains but is much clumsier. Also, the ability to manipulate objects and release a grasp is impaired.

Pyramidal lesions in the chimpanzee produce similar but more severe deficits. Discrete control of the digits is profoundly impaired, and the grasp reflex becomes so hyperactive that it is impossible to release objects. The chimpanzee, like humans, shows the classic Babinski sign after pyramidal section.

MOTOR FUNCTIONS OF OTHER CORTICAL AREAS

A goal-directed movement, such as reaching for an object, requires that the activities of many muscles be coordinated in a manner appropriate to environmental conditions. While primary motor cortex is involved mainly in *executing* movements, other cortical areas are more involved in the prior stages of *programming* the limb movements to be appropriate for the particular context or goal. Programming the patterns of muscle activity is largely accomplished by three interconnected cortical areas: the supplementary motor cortex, the premotor cortex, and the posterior parietal cortex (see Figs. 28-1 and 28-9). Each region appears to specialize in different aspects of movement contro1.36

Supplementary Motor Cortex

The supplementary motor area (SMA) lies anterior and medial to primary motor cortex, largely in the medial surface of the hemisphere. Movements evoked by electrical stimulation of the SMA require higher intensities and longer stimulus trains than those evoked from precentral cortex. Like MI, the SMA is somatotopically organized, with the head anterior and hindlimb posterior. The evoked movements are often more complex and prolonged than the simple muscle contractions obtained from precentral cortex. For example, evoked responses may involve orientation of the limb or body, or coordinated movements such as opening the hand. These movements may outlast the duration of the stimulus and sometimes are elicited on both sides of the body. Neurosurgeons stimulating the SMA in awake patients have evoked vocalization with associated facial movements, coordinated movements of the limbs, and also inhibition of voluntary movements.

Excision of the SMA in human patients has resulted in transient speech deficits, or aphasias, which typically disappear after several weeks. The loss of the SMA also results in a persistent slow-

ness in generating repetitive movements. Lesions of the SMA in monkeys has produced interesting apraxias of reaching and bimanual coordination. Monkeys with unilateral ablation of the SMA cannot coordinate their hands in a bimanual task. Faced with a horizontal plastic plate containing holes stuffed with raisins, a normal monkey quickly presses the raisins out with one hand and catches them with the other hand cupped below. After a unilateral lesion of the SMA the two hands cannot be coordinated independently, but instead move together in a similar manner, as if the intact SMA now controlled both hands. Sectioning the corpus callosum abolishes the bimanual deficit, suggesting that each SMA normally communicates with both hemispheres. [3]

Combined unilateral lesions of the SMA and premotor cortex abolish the ability of a monkey to reach around a transparent barrier to obtain a visible slice of apple with its contralateral hand. [19] Instead, the monkey persists in reaching for the apple directly and repeatedly hits the plastic plate. The same monkey has no problems performing the task using its other hand, indicating that its comprehension and motivation are intact. This apraxia lasts for at least two years. In contrast, a monkey with a lesion of primary motor cortex can reach around such a barrier, albeit clumsily.

Single unit recordings in the SMA of conscious monkeys also suggest that SMA cells may play a role in coordinating movements of the two limbs. Many cells fire in a similar way for comparable movements of the ipsilateral and contralateral arm. Such bilateral responses are found for cells related to distal as well as proximal joint movements. Some SMA cells respond to somatic stimulation; these are often driven by manipulation of multiple joints or bilateral somatic stimuli.

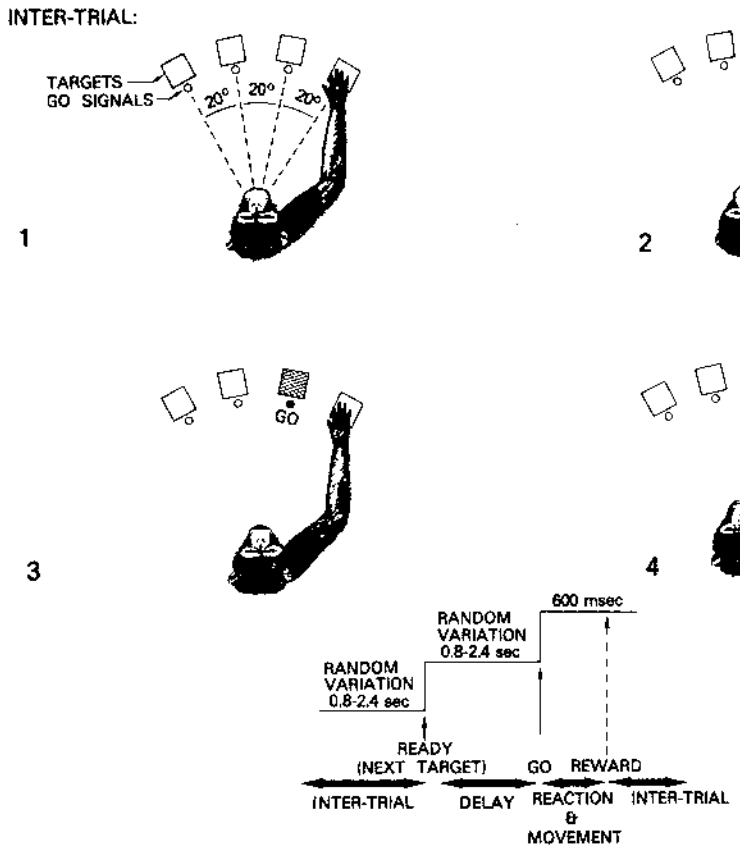
That the SMA is involved in programming sequences of movements has been revealed by measuring cerebral blood flow in conscious human subjects. Increases of cortical neural activity is correlated with localized increases in blood flow, which can be detected by monitoring the circulation of radioactive xenon with an array of radiation detectors around the scalp." Subjects performing the simple motor task of squeezing a spring between the thumb and forefinger showed clear increases in blood flow in both the primary motor and sensory cortex contralateral to the active hand. When they performed a more complex sequence of finger movements, touching the thumb successively with each of the other fingers in turn, their blood flow increased over the SMA bilaterally as well as over sensorimotor cortex. Furthermore, when the subjects simply *thought* about the sequential movements without performing them, regional blood flow again increased over the SMA, but not over sensorimotor cortex, suggesting that the SMA is involved in programming complex sequential movements.

Premotor Cortex

The premotor cortex (PMC) lies anterior to primary motor cortex on the lateral surface of the hemisphere in area 6 (see Fig. 28-1). PMC is comparable in size to MI in monkeys, but in humans it is almost six times larger than MI. Unlike MI and the SMA, PMC makes only a minor contribution to the corticospinal tract; instead, its descending output is directed largely to the medullary reticular formation. Electrical stimulation of PMC is much less likely to evoke movements than stimulation of MI, or even of the SMA. The elicited movements often involve the proximal musculature and require much higher stimulus intensities than those evoked from MI or the SMA.

In humans, lesions involving PMC produce weakness in shoulder and hip muscles and difficulty in abduction and elevation of the contralateral arm. Limb movements are also slower, as evidenced by delayed muscle activation. PMC lesions may also produce an inability to move the two arms simultaneously in a coordinated fashion (called movement-kinetic apraxia).

Like some cells in MI, many neurons in PMC discharge when a monkey is preparing to make a particular movement. In the experiment illustrated in Figure 28-18, [35] a monkey was trained to depress the one key of a set that was illuminated (the instructional stimulus), but only after another small light (the trigger stimulus) had been turned on. Most of the task-related cells in PMC, like those in MI, responded during the execution of the movement; others responded to the instructional cues (see also Fig. 31-13). However, certain PMC cells exhibited a sustained increase in discharge throughout the delay between the instructional cue and the trigger stimulus. This set-related discharge was often directionally specific, occurring only when the monkey was preparing to move in a particular direction. This discharge was not simply related to a subliminal excitation of agonist motoneurons, since it typically stopped with the onset of the movement. PMC contains a higher proportion of cells related to motor set than does MI. Similar "set-related" cells also have been observed in the SMA and prefrontal cortex.



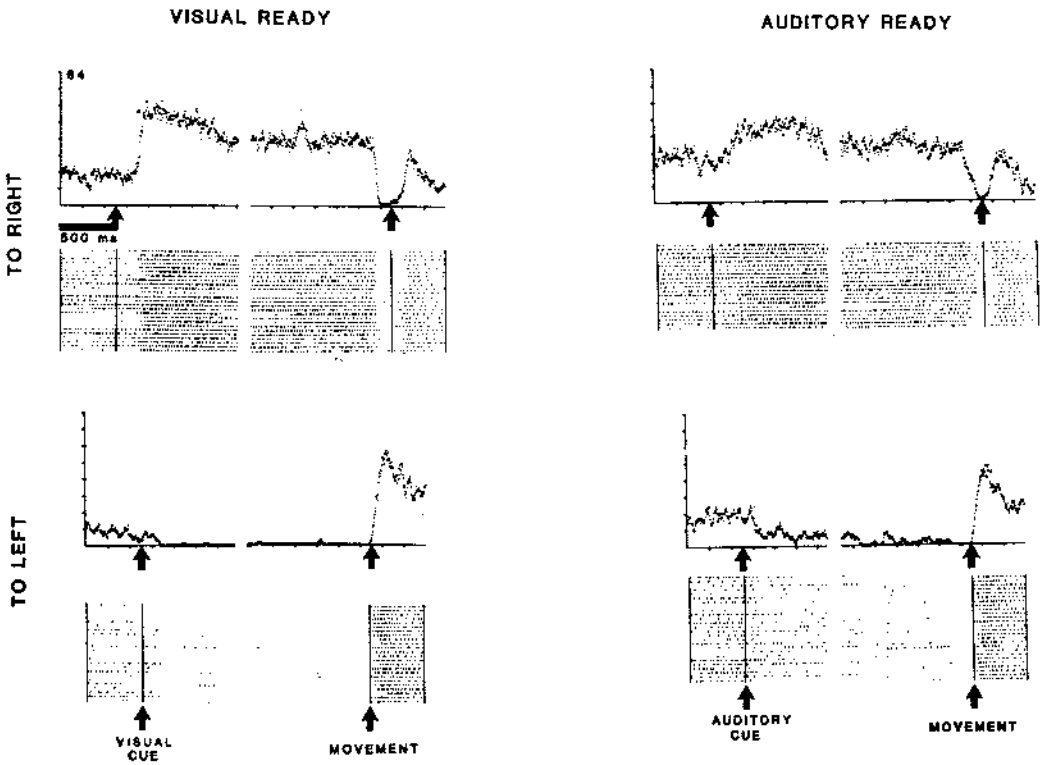


Figure 28-18 Set-related activity in a premotor cortex cell. *Top:* Behavioral paradigm. The monkey rested its hand on one of four keys during the intertrial period (1), observed the ready light appear at another key (2), then at a random time saw a go signal (3) and moved to the illuminated key (4). *Bottom:* Set-related discharge in this premotor cell occurred whenever the monkey was prepared to move to the right, whether the cue was visual (left) or auditory (right). This cell was also inhibited after instructions to move to the left *(bottom).* (From Weinrich, M.; Wise, S. P. *J. Neurosci.* 2:1329-1345, 1982.)

Frontal Eye Fields

The frontal eye fields lie anterior to the PMC in Brodmann's area 8 (see Fig. 28-1). Efferent projections from the frontal eye fields travel via the internal capsule to pontine regions controlling eye movements and to the superior colliculus, which also is involved in the generation of saccadic eye movements (see also Fig. 20-19).

Electrical stimulation of the frontal eye fields in primates and carnivores typically causes conjugate movement of both eyes to the opposite side; stimulation at some sites may cause the eyes to move obliquely upward or downward, with the horizontal component away from the stimulated side. Stimulation of a particular site in the frontal eye fields evokes saccades with a characteristic direction and amplitude, which are largely independent of the stimulus parameters and the initial position of the eyes in the orbit. Thresholds for evoking saccades are raised if the subject is fixating or tracking a visual target. Stimulation of the frontal eye fields may also evoke head movement to the opposite side and can sometimes produce autonomic responses such as dilatation of both pupils and lacrimation.[2]

Unilateral ablation of area 8 produces a sustained deviation of both eyes toward the side of the lesion and impairs voluntary eye movements to the opposite side. Unilateral lesions of area 8 may also produce deviation of the head to the side of the lesion. Bilateral ablation of the frontal eye fields can impair the ability to gaze laterally in either direction. Although the eyes are capable of following a moving target, they always drift back to the central position. Bilateral ablation can also destroy the ability to attend visually to objects in the peripheral visual field. These deficits are usually temporary, and eye movements often recover within several days after the lesion.

The activity of neurons in the frontal eye fields is related to eye or head movements. Many cells fire before or after voluntary saccades in a given direction.[4] Cells which discharge before voluntary saccades in a particular direction have been recorded at the sites with lowest thresholds for evoking those saccades. While many cells exhibit a burst of firing immediately before the saccade, certain "visuomovement" cells exhibit sustained activity between presentation of a visual target and the saccade to the target, reminiscent of the behavior of certain PMC neurons. Other frontal eye field neurons discharge with gaze in a certain direction, as well as pursuit in this direction. A third type of cell in Brodmann's area 8 is related exclusively to head movements.

Taken together, this evidence suggests that the frontal eye fields are involved in generating voluntary gaze and saccades. However, their role is not completely analogous to that of area 4 for limb movements, since lesions of the frontal eye fields cause only temporary impairment of eye movements. The frontal eye field cells are probably involved in mediating visually evoked saccades, but they apparently exert their influence in conjunction with or through the superior colliculus (see also Chap. 20).

Posterior Parietal Cortex

In addition to the anterior premotor regions described above, the posterior parietal cortex (areas 5 and 7) also appears to be involved in programming limb movements. Humans with lesions of posterior parietal cortex show classic signs of an apraxia—an inability to make directed limb movements in a particular context, in the absence of motor weakness. Their symptoms can be described as a sensory and motor neglect of the opposite hemifield of extrapersonal space. They cannot reach accurately for objects and appear to neglect information from the contralateral hemifield. Such neglect is particularly pronounced with parietal lesions of the nondominant hemisphere (see Chap. 31).

Mountcastle and colleagues[20] the activity of certain neurons in areas 5 and 7 of monkeys are specifically related to active reaching movements. Some neurons discharged only when the monkey reached for a desirable object, such as food, in its immediate extrapersonal space, but did not fire during similar limb movements that were not directed toward acquiring an object of interest. A related class of cells fired preferentially during active manipulation of objects of interest. Area 7 contains comparable oculomotor cells that fire specifically when the monkey moves its eyes toward an object of interest, but not during spontaneous eye movements. These workers suggested that these posterior parietal neurons may generate a motor command to acquire objects of interest, either manually or visually, in extrapersonal space. (An alternative interpretation is described in the discussion of the parietal lobe in Chap. 31).

DISTRIBUTED CORTICAL MOTOR FUNCTION

This chapter has adopted the view that primary motor cortex is preferentially involved in the execution of movements, whereas secondary motor

areas are more involved in programming. While this dichotomy provides a useful framework, the view that these functions are exclusively localized in separate cortical regions must be recognized as overly simplistic. Some of the evidence discussed suggests that generation of movement involves continual interactions between- different cortical regions. First, the neural connections between primary and secondary cortical areas are reciprocal, not serial, and each area has its own subcortical input and output connections. Second, although the various motor regions have neurons with response properties consistent with their proposed function, each area actually contains a mixture of cell types, all of which are present to some extent in the other areas. Cortical neurons with similar response properties might be interconnected and act together. Such a distributed representation could explain the recovery of some functions that are temporarily lost after lesions. Finally, the relative timing of cell responses in different regions during a reaction time movement largely overlap, suggesting that all areas are activated more or less simultaneously. Thus, attributing the functions of motor programming and execution to different cortical regions is more a matter of relative degree than an absolute dichotomy. In a similar way, cortical and subcortical centers must also interact continuously and cooperatively in producing movements.

BIBLIOGRAPHY

Recommended Reviews

Evarts, E.V. Role of motor cortex in voluntary movement. *Handbook of Physiology*. 2:1083-1121, 1981.
Review of motor cortex cell activity in relation to movements and transcortical reflexes.

Humphrey, D.R. Cortical control of reaching. In Talbott, R.E.; Humphrey, D.R., eds. *Posture and Movement,* 51-112. New York, Raven Press, 1979.
The roles of secondary motor cortex areas in programming limb movements.

Phillips, C.G.; Porter, R. Corticospinal neurones. Their role in movement. Monographs of the Physiological Society, London, Academic Press, 1977.
A *comprehensive review of the role of motor cortex and pyramidal tract in control* of *movement.*

REFERENCES

1. Asanuma, H.; Rosen, I. Topographical organization of cortical efferent zones projecting to different forelimb muscles in the monkey. *Exp. Brain Res.* 14:243-256, 1972.
2. Bucy, P.C., ed. *The Precentral Motor Cortex*. Urbana, Ill., Univ. of Illinois Press, 1949.
3. Brinkman, C. Supplementary motor area of the monkey's cerebral cortex: Short- and long-term deficits after unilateral ablation and the effects of subsequent callosal section. J. *Neurosci.* 4:918-929, 1984.

3a. Brodmann, K. Vergleichende Lokalisationslehre der Grosshirnrinde. Leipzig, J.A. Barth, 1909.

4. Bruce, C.J.; Goldberg, M.E. Physiology of the frontal eye fields. *Trends Neurosci.* 7:436 441, 1984.
5. Chang, H.T.; Ruch, T.C.; Ward, A.A., Jr. Topographic representation of muscles in motor cortex in monkeys. *J. Neurophysiol.* 10:39-56, 1947.
6. Cheney, P.D.; Fetz, E.E. Functional classes of primate corticomotoneuronal cells and their relation to active force. *I. Neurophysiol.* 44:775-791, 1980.
7. Clough, J.F.M.; Kernell, D.; Phillips, C.G. The distribution of monosynaptic excitation from the pyramidal tract and from primary spindle afferents to motoneurones of the baboon's hand and forearm. J. *Physiol. (Lond.)* 198:145-166, 1968.
8. Conrad, B.; Matsunami, K.; Meyer-Loman, J.; Wiesendanger, M.; Brooks, V.B. Cortical load compensation during voluntary elbow movements. *Brain Res.* 71:507-514, 1974.
9. Denny-Brown, D. *The Cerebral Control of Movement.* Springfield, Ill., Charles C Thomas, 1966.
10. Evarts, E.V. Relation of pyramidal tract activity to force exerted during voluntary movement. *J. Neurophysiol.* 31:14-27, 1968.
11. Evarts, E.V.; Tanji, J. Reflex and intended responses in motor cortex pyramidal tract neurons of monkey. J. *Neurophysiol.* 39:1069-1080, 1976.
12. Fetz, E.E.; Cheney, P.D. Postspike facilitation of forelimb muscle activity by primate corticomotoneuronal cells. *J. Neurophysiol.* 44:751-772, 1980.
13. Fromm, C.; Evarts, E.V. Relation of motor cortex neurons to precisely controlled and ballistic movements. *Neurosci. Lett.* 5:259-266, 1977.
14. Georgopoulos, A.P.; Kalaska, J.F.; Crutcher, M.D.; Caminiti, R.; Massey, J.T. The representation of movement direction in the motor cortex: single cell and population studies. In Edelman, G.; Gall, W.E.; Cowan, W.M., eds. *Dynamic Aspects of Neocortical Function,* 501-529. New York, John Wiley & Sons, 1984.
15. Humphrey, D.R.; Schmidt, E.M.; Thompson, W.D. Predicting measures of motor performance from multiple spike trains. *Science* 170:758-762, 1970.
16. Jankowska, E.; Padel, Y.; Tanaka, R. Projections of pyramidal tract cells to a-motoneurones innervating hind-limb muscles in the monkey. *J. Physiol.* 249:637-667, 1975.
17. Jones, E.G. Connectivity of the primate sensory-motor cortex. In Jones, E.G.; Peters, A., eds. *Cerebral Cortex,* vol. 5, 113-184. New York, Plenum Press, 1986.
18. Jones, E.G.; Wise, S.P. Size, laminar and columnar distribution of efferent cells in the sensorimotor cortex of monkeys. *J. Comp. Neurol.* 175:391-438, 1977.
19. Moll, L.; Kuypers, H.G.J.M. Premotor cortical ablations in monkeys: contralateral changes in visually guided reaching behavior. *Science* 198:317-319, 1977.
20. Mountcastle, V.B.; Lynch, J.C.; Georgopoulos, A.; Sakata, H.; Acuna, C. Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. J. *Neurophysiol.* 38:871-908, 1975.
21. Muir, R.B.; Lemon, R. N. Corticospinal neurons with a special role in precision grip. *Brain Res.* 261:312-316, 1983.
22. Murphy, J.T.; Kwan, H.C.; MacKay, W.A.; Wong, Y.C. Spatial organization of precentral cortex in awake primates.

III. Input-output coupling. J. *Neurophysiol.* 41:1120-1131, 1978.

Olszewski, J. *The Thalamus of the Macaca Mulatta: An Atlas for Use with the Stereotaxic Instrument.* Basel, Karger, 1952.

4. Patton, H.D.; Amassian, V.E. The pyramidal tract: its excitation and functions. *Handbk. Physiol.* 2:837-861, 1960.
5. Penfield, W.; Rasmussen, A.T. *Cerebral Cortex of Man. A Clinical Study of Localization of Function.* New York, Macmillan, 1950.

5a. Phillips, C.G. Motor apparatus of the baboon's hand. *Proc. R. Soc. Lond. [Biol.]* 173:141-174, 1969.

5b. Phillips, C.G.; Porter, R. Cortical spinal neurones. Their role in movement. Monographs of the Physiological Society. London, Academic Press, 1977.

6. Phillips, C.G.; Porter, R. The pyramidal projection to motoneurones of some muscle groups of the baboon's forelimb. *Prog. Brain Res.* 12:222-242, 1964.
7. Porter, R. The corticomotoneuronal component of the pyramidal tract: corticomotoneuronal connections and functions in primates. *Brain Res. Rev.* 10:1-26, 1985.
8. Roland, P.E.; Larsen, B.; Lassen, N.A.; Skinhoj, E. Supplementary motor area and other cortical areas in organization of voluntary movements in man. *J. Neurophysiol.* 24:91-100, 1980.
9. Rosen, I.; Asanuma, H. Peripheral afferent inputs to the forelimb area of the monkey cortex: input-output relations. *Exp. Brain Res.* 14:257-273, 1972.
3. Schell, G.R.; Strick, P.L. The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. *J. Neurosci.* 4:539-560, 1984.
I. Shinoda, Y.; Yokota, J-I.; and Futami, T. Divergent projection of individual corticospinal axons to motoneurons of multiple muscles in the monkey. *Neurosci. Lett.* 23:7-12, 1981.

31a. Stoney, S.D.; Thompson, W.D.; Asanuma, H. Excitation of pyramidal tract cells by intracortical microstimulation: effective extent of stimulating current. *J. Neurophysiol.* 31:659-669, 1968.

32. Strick, P.L.; Preston, J.B. Two representations of the hand in area 4 of a primate. *J. Neurophysiol.* 48:139-159, 1982.
33. Tanji, J.; Wise, S.P. Submodality distribution in sensorimotor cortex of the unanesthetized monkey. J. *Neurophysiol.* 45:467-481, 1981.
34. Thach, W.T. Correlation of neural discharge with pattern and force of muscular activity, joint position and direction of intended next movement in motor cortex and cerebellum. *J. Neurophysiol.* 41:654-676, 1978.
35. Weinrich, M.; Wise, S.P. The premotor cortex of the monkey. J. *Neurosci.* 2:1329-1345, 1982.
36. Wiesendanger, M. Organization of secondary motor areas of the cerebral cortex. *Handbk. Physiol.* 2:1121-1147, 1981.

36a. Wiesendanger, M. The pyramidal tract: its structure and function. In Towe, A.L.; Luschei, E.S., eds. *Handbook of Behavioral Neurophysiology,* vol 5, Motor Coordination, 401-491. New York, Plenum Press, 1981.

37. Woolsey, C.N. Organization of somatic sensory and motor areas of the cerebral cortex. In Harlow, H.F.; Woolsey, C.N., eds. *Biological and Biochemical Bases of Behavior.* Madison, Wis., Univ. of Wisconsin Press, 1958.
38. Woolsey, C.N.; Gorska, T.; Wetzel, A.; Erickson, J.C.; Earls, F.J.; Allman, J.M. Complete unilateral section of the pyramidal tract at the medullary level in *Macaca mulatta. Brain Res.* 40:119-123, 1972.