37
Voluntary Movement: The Primary Motor Cortex

"…. The physiology of movements is basically a study of the purposive activity of the nervous system as a whole."

—Gelfand et al., 1966

ONE OF THE MAIN FUNCTIONS OF THE BRAIN is to direct the body's purposeful interaction with the environment. Understanding how the brain fulfils this role is one of the great challenges in neural science. Because large areas of the cerebral cortex are implicated in voluntary motor control, the study of the cortical control of voluntary movement provides important insights into the functional organization of the cerebral cortex as a whole.

Evolution has endowed mammals with adaptive neural circuitry that allows them to interact in sophisticated ways with the complex environments in which they live. Adaptive patterning of voluntary movements gives mammals a distinct advantage in locating food, finding mates, and avoiding predators, all of which enhance the survival potential of the individual and a species.

The ability to use fingers, hands, and arms in voluntary actions independent of locomotion further helps primates, and especially humans, exploit their environment. Most animals must search their environment for food when hungry. In contrast, humans can also "forage" by using their hands to cook a meal or simply punch a few buttons on a telephone and order takeout. The central neural circuits responsible for such non-locomotor behavior emerged from and remain intimately associated with the phylogenetically older circuits that control the forelimb during locomotor behaviors.

In this and the following chapter we focus on the control of voluntary movements of the hand and arm in primates. In this chapter we describe the cortical networks that control voluntary movement, particularly the role of the primary motor cortex in the generation of motor commands. In the next chapter we address broader questions about cortical control of voluntary motor behavior, in particular how the cerebral cortex organizes the stream of incoming sensory information to guide voluntary movement.

Voluntary movements differ from reflexes and basic locomotor rhythms in several important ways. By definition they are intentional —they are initiated by an internal decision to act—whereas reflexes are automatically triggered by external stimuli. Even when a voluntary action is directed toward an object, such as reaching for a cup, the cause of action is not the object but an internal decision to interact with the object. The presence of the object provides only the opportunity for acting. Voluntary actions involve choices between alternatives, including the choice not to act. Furthermore, they are organized to achieve some goal in the

near or distant future.

Voluntary movements often have a labile, context-dependent association with sensory inputs. The same object can evoke different voluntary actions or no response at all depending on the context in which it appears. That is, the neural circuits controlling voluntary behavior are able to differentiate between an object's physical properties and its behavioral salience.

The nature and effectiveness of voluntary movements often improve with experience. The motor system can learn new behavioral strategies or new reactions to familiar stimuli to improve behavioral outcomes, and it can learn new skills to cope with predictable variations and perturbations of the environment.

Thus the neural control of voluntary movement involves far more than simply generating a particular pattern of muscle activity. It also involves processes that are usually considered to be more sensory, perceptual, and cognitive in nature. As we shall see, these processes are not rigidly compartmentalized into different neural structures or neural populations.

Motor Functions Are Localized within the Cerebral Cortex

For centuries it was believed that the human cerebral cortex was responsible for only higher-order, conscious mental functions. In the middle of the 19th century the English neurologist John Hughlings Jackson made the controversial proposal that a specific part of the cerebral cortex anterior to the central sulcus has a causal role in movement. He reached this conclusion from treating patients with epileptic seizures that were characterized by repeated spasmodic involuntary movements that sometimes resembled fragments of purposive voluntary actions.

During each episode the seizures always spread to different body parts in a fixed temporal sequence that varied from patient to patient, a pattern called *Jacksonian march*. Jackson concluded that paroxysmal neural activity generated by epileptic foci located near the central sulcus caused the involuntary seizures. He speculated that the progression of seizures across the body resulted from the spread of paroxysmal activity across

small clusters of neurons lying along the central sulcus, each of which controlled movement of a different body part. Jackson's proposal that a discrete cortical region is involved in the control of movement was a strong argument for the localization of different functions in distinct parts of the cerebral cortex. His observations, along with contemporaneous studies by Pierre Paul Broca and Karl Wernicke on the language deficits resulting from specific cortical lesions, laid the foundation for the modern scientific study of cortical function.

It was not until later in the 19th century, however, when improved anesthesia and aseptic surgical techniques allowed direct experimental study of the cerebral cortex in live subjects, that conclusive experimental evidence for a discrete region of the cerebral cortex devoted to motor function was possible. Gustav Fritsch and Eduard Hitzig in Berlin and David Ferrier in England showed that electrical stimulation of the surface of a limited area of cortex of different surgically anesthetized mammals evoked movements of parts of the contralateral body. The electric currents needed to evoke movements were lowest in a narrow strip along the rostral bank of the central sulcus.

Their experiments demonstrated that, even within this strip of tissue, discrete sites contained neurons with distinctive functions. Stimulation of adjacent sites evoked movements in adjacent body parts, starting with the foot, leg, and tail medially, and proceeding to the trunk, arm, hand, face, mouth, and tongue more laterally. When they lesioned a cortical site at which stimulation had evoked movements of a part of the body, motor control of that body part was perturbed or lost after the animal recovered from surgery. These early experiments showed that the motor strip contains an orderly motor map of the contralateral body and that the integrity of the motor map is necessary for voluntary control of the corresponding body parts.

In the first half of the 20th century more focal electrical stimulation allowed the motor map to be defined in greater detail. Clinton Woolsey and his colleagues tested the functional organization of the motor cortex in several species of mammals, whereas Wilder Penfield and co-workers tested discrete sites in human neurosurgical patients (Figure 37–1). Their findings demonstrated that the same general topographic organization is conserved across many species. One important discovery was that the motor map is not a point-to-point representation of the body. Instead, the

most finely controlled body parts, such as the fingers, face, and mouth, are represented in the motor map by disproportionately large areas, reflecting the larger number of neurons needed for fine motor control.
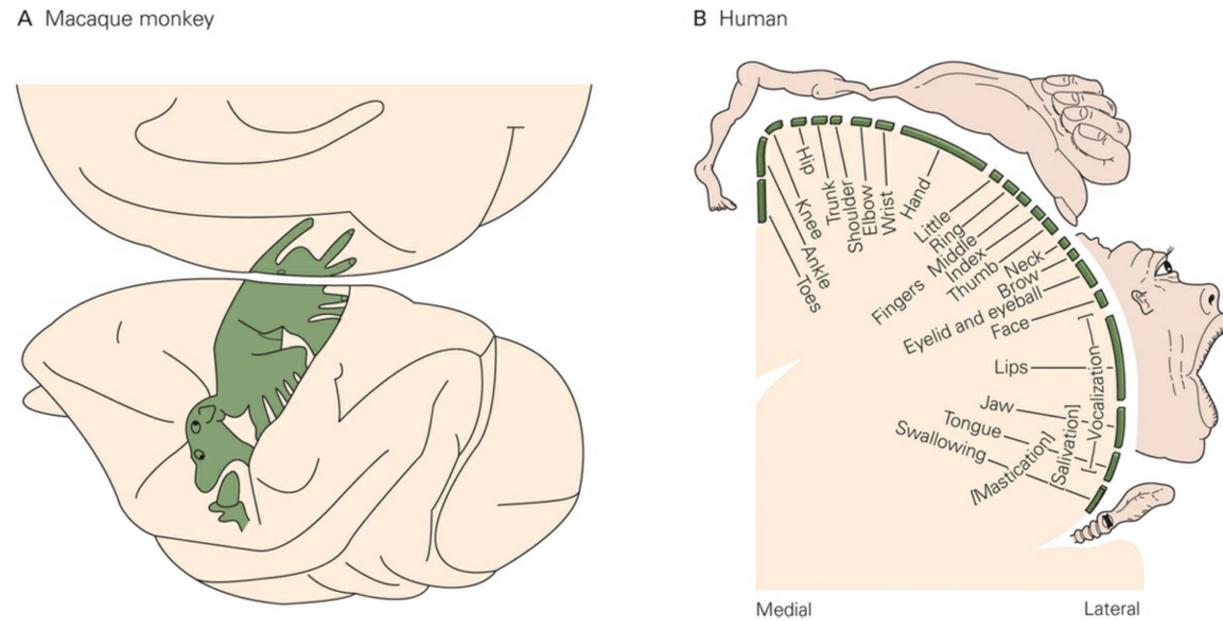

Figure 37–1 The motor cortex contains a topographic map of motor output to different parts of the body.

A. Studies by Clinton Woolsey and colleagues confirmed that the representation of different body parts in the monkey follows an orderly plan: Motor output to the foot and leg is medial, whereas the arm, face, and mouth areas are more lateral. The areas of cortex controlling the foot, hand, and mouth are much larger than the regions controlling other parts of the body.

B. Wilder Penfield and colleagues showed that the human motor cortex motor map has the same general mediolateral organization as in the monkey. However, the areas controlling the hand and mouth are even larger than in monkeys, whereas the area controlling the foot is much smaller. Penfield emphasized that this cartoon illustrated the relative size of the representation of each body part in the motor map; he did not claim that each body part was controlled by a single separate part of the motor map.

Woolsey and Penfield both recognized, however, that their simple motor map masked a deeper complexity. Today the best-studied regions of the map are those parts controlling the arm and hand. Recent map-

ping studies have revealed that the neurons controlling the muscles of the digits, hand, and distal arm tend to be concentrated within a central zone, whereas those controlling more proximal arm muscles are located in a horseshoe-shaped ring around the central core (Figure 37–2A). Furthermore, across the concentrically organized areas of the arm motor map there is extensive overlap of stimulation sites that causes contractions of muscles acting across different joints; conversely, each muscle can be activated by stimulating many widely dispersed sites (Figure 37–2B). Moreover, different combinations of muscle contractions and joint motions can be evoked by stimulating different sites. Finally, local horizontal axonal connections link different sites, allowing neural activity at multiple output sites in the map to be coordinated during the formation of motor commands.
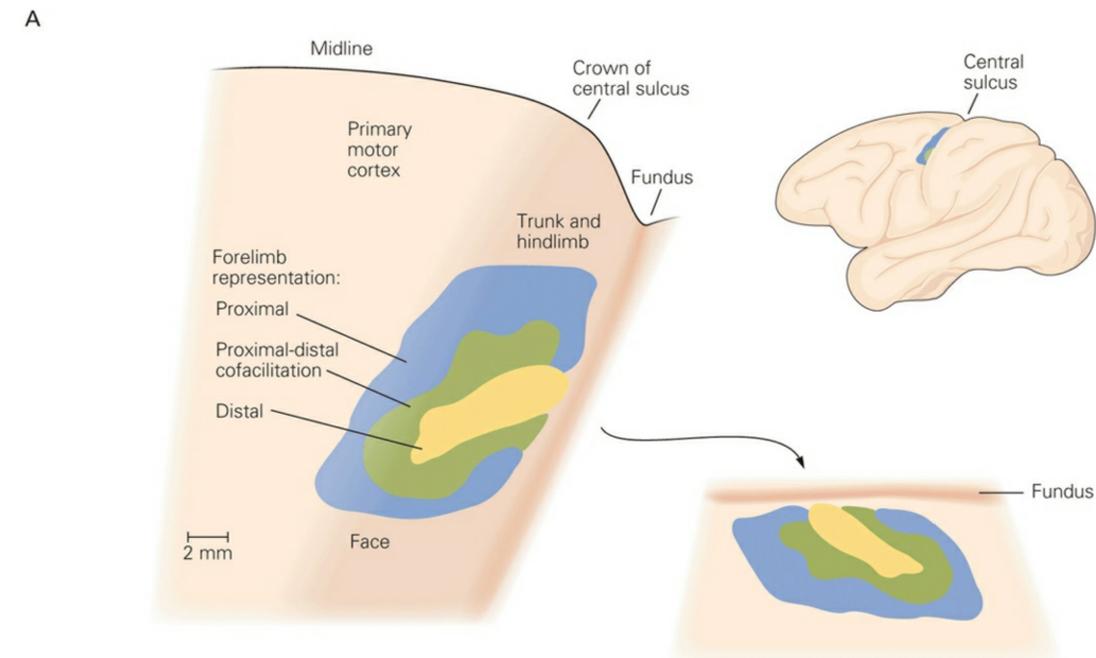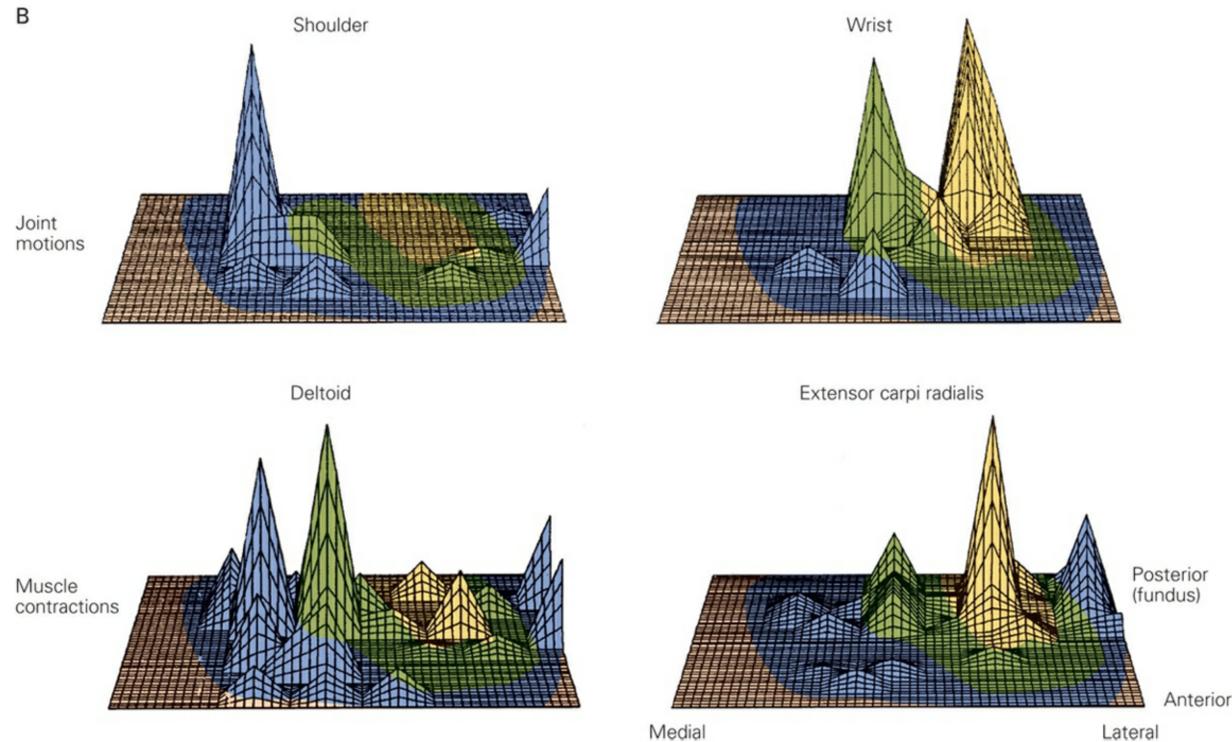
Figure 37–2 Internal organization of the motor map of the arm in the motor cortex.

A. The arm motor map in monkeys has a concentric, horseshoe-shaped organization: Neurons that control the distal arm (digits and wrist) are concentrated in a central core (yellow) surrounded by neurons that control the proximal arm (elbow and shoulder; blue). The neuron populations that control the distal and proximal parts of the arm overlap extensively in a zone of proximal-distal cofacilitation (green). The arm motor representation is seen in its normal anatomical location in the anterior bank of the central sulcus (left), and also after flattening and rotation to bring it into approximate alignment with the microstimulation maps in part B. (Reproduced, with permission, from Park et al. 2001.)

B. Microstimulation of several sites in the arm motor map can produce rotations of the same joint. Neurons that control wrist movements are concentrated in the central core whereas those that regulate shoulder movements are distributed around the core, with some overlap between the two populations. In these maps, the height of each peak is scaled to the inverse of the stimulation current: the higher the peak,

the lower the current necessary to produce a response. The distribution and overlap of stimulation sites that evoke contractions of muscles in the shoulder (deltoid) and wrist (extensor carpi radialis) are even more extensive than that of sites for joint rotations. The yellow, green, and blue color zones on these maps correspond only approximately to the functional zones identified in the motor map of part **A**. (Reproduced, with permission, from Humphrey and Tanji 1991.)

To date, studies have not revealed any repeating functional elements in the fine details of the motor map for the arm and hand analogous to the ocular-dominance bands and orientation pinwheels in the visual cortex. However, the complex, extensively overlapped organization of the arm motor map and the network of local horizontal connections likely provide a mechanism to coordinate whole-limb actions such as reaching to grasp and manipulate an object.

Many Cortical Areas Contribute to the Control of Voluntary Movements

Voluntary Motor Control Appears to Require Serial Processing

Much of what we do in everyday life involves a sequence of actions. One normally does not take a shower after getting dressed or put cake ingredients into the oven to bake before blending them into a batter. It seems logical that most brain functions are also serial.

Largely on the basis of indirect psychological studies, the neural processes by which the brain controls voluntary behavior are commonly divided into three sequential stages. First, perceptual mechanisms generate a unified sensory representation of the external world and the individual within it. Next, cognitive processes use this internal replica of the world to decide on a course of action. Finally, the selected motor plan is relayed to action systems for implementation (Figure 37–3A).
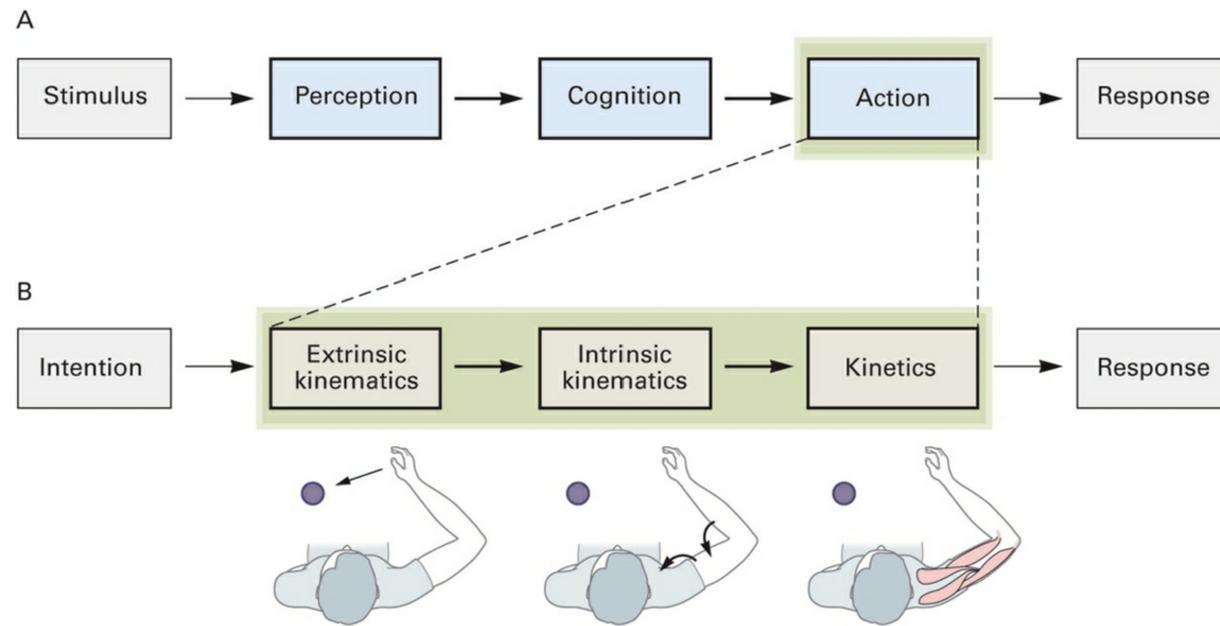
Figure 37–3 Cortical control of voluntary behavior appears to be organized in a hierarchical series of operations.

A. The brain's control of voluntary behavior has often been divided into three main operational stages, in which perception generates an internal neuronal image of the world, cognition analyzes and reflects on this image to decide what to do, and the final decision is relayed to action systems for execution. However, this three-stage serial organization was largely based on introspective psychological studies rather than on direct neurophysiological study of neural mechanisms.

B. Each of the three main operational stages is presumed to involve its own serial processes. For example, the "action" stage that converts an intention into a physical movement is often presumed to involve a hierarchy of operations that transform a general plan into progressively more detailed instructions about its implementation. The model shown here, inspired by early controller designs for multijoint robots, suggests that the brain plans a chosen reaching movement by first calculating the extrinsic kinematics of the movement (eg, target location, trajectory of hand displacement from the starting location to the target location), then calculating the required intrinsic kinematics (eg, joint rotations) and finally the causal kinetics or dynamics of movement (eg, forces, torques, and muscle activity). (See also Figure 33–2.)

The final stage, execution of the chosen motor plan, also appears to be serial in nature. It has often been modeled as a series of sensorimotor transformations of representations of a movement into different coordinate frameworks, progressing from a general description of the overall form of the movement to increasingly specific details, culminating in patterns of muscle activity (Figure 37–3B).

According to this serial scheme, each sequential operation is encoded by a different neuronal population. Each population encodes specific features or parameters of the intended movement in a particular coordinate system, such as the direction of movement of the hand through space or the patterns of muscle contractions and forces. These several populations are connected serially and only the last population in the chain projects to the spinal cord.

As we shall see in this and the next chapter, this model has some heuristic value for describing how the brain is organized to control voluntary movement, but direct neurophysiological studies of neural mechanisms show that a strict adherence to serial processing is simplistic and incorrect. We know now for instance that the brain does not have a single, unified perceptual representation of the world (see Chapter 38). The serial scheme also wrongly implies that the only role of the motor system is to determine which muscles to contract, when, and by how much. We now know that several cortical motor areas also play a critical role in the actual choice of what action to take, a process that is usually considered more "cognitive" than "motor." This is described in more detail in Chapter 38.

The Functional Anatomy of Precentral Motor Areas is Complex

In the early 20th century Alfred Campbell and Korbinian Brodmann divided the human cerebral cortex into a large number of cytoarchitectonic areas with distinct anatomical features. They noted that the *precentral cortex* in the gyri immediately rostral to the central sulcus lacks the six layers characteristic of most cerebral cortex. It lacks a distinct internal granule cell layer and thus is often called *agranular cortex*. Campbell and Brodmann subdivided the precentral cortex into caudal and rostral parts, which Brodmann designated cytoarchitectonic areas 4 and 6 (Figure 37–4).
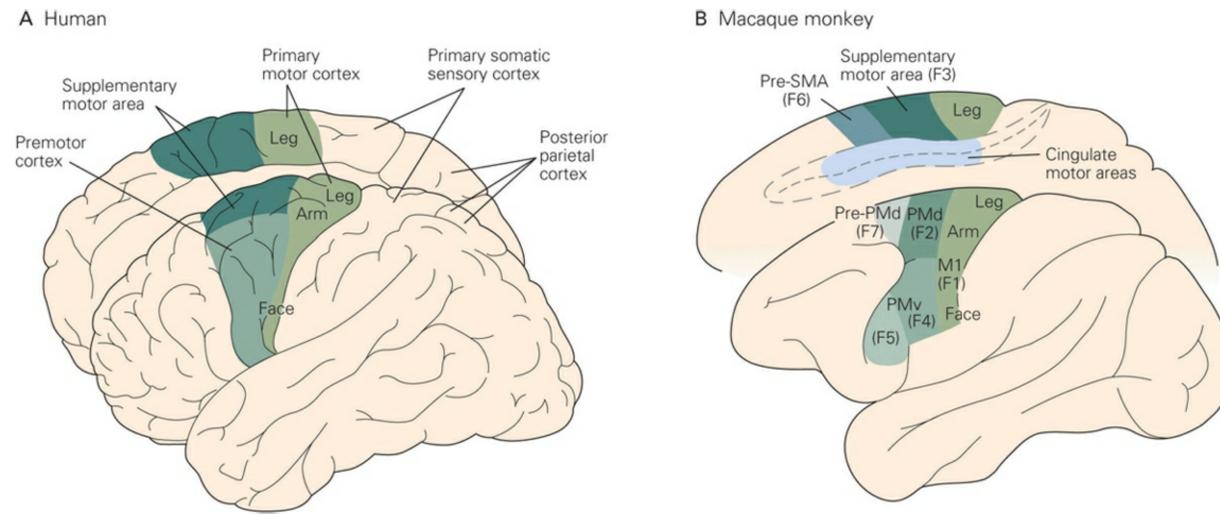
Figure 37–4 Multiple areas of the cerebral cortex are devoted to motor control and many are somatotopically organized.

A. Based on their histological studies at the beginning of the 20th century, Korbinian Brodmann and Alfred Campbell each divided the precentral cortex in humans into two anatomically distinct cytoarchitectonic areas: the primary motor cortex (Brodmann's area 4) and premotor cortex (Brodmann's area 6). Subsequent studies by Woolsey and colleagues led to subdivision of the premotor cortex into medial and lateral halves, the supplementary motor area and lateral premotor cortex, respectively. Since those pioneering studies the human premotor cortex and supplementary motor area have been subdivided into several smaller functional areas whose homologs can be seen in nonhuman primates. The medial surface of the hemisphere is shown in this and other similar figures as if reflected in a mirror.

B. More recent studies have subdivided the premotor cortex of macaque monkeys into several more functional zones with different patterns of cortical and subcortical anatomical connections and different neuronal responses during various motor tasks. A similarly detailed functional subdivision of the parietal cortex has also been made (not illustrated). (M1, primary motor cortex; Pre-SMA, pre-supplementary motor area; PMd, dorsal premotor cortex; Pre-PMd, pre-dorsal premotor cortex; PMv, ventral premotor cortex.)

Campbell proposed that these two regions were functionally distinct motor areas. He thought that the caudal region, or *primary motor cortex*,

controlled the motor apparatus in the spinal cord and generated simple movements. The rostral region, he argued, was specialized for higher-order aspects of motor control and for movements that are more complex, conditional, and voluntary in nature. He thought that these areas influenced movement indirectly by projecting to the primary motor cortex and so he named them the *premotor cortex*.

Some years later, while mapping motor areas of cortex with electrical stimuli, Clinton Woolsey and his colleagues discovered that movements of the contralateral body can be evoked not only by electrical stimulation of the primary motor cortex, but also by stimulating a second region in a part of the premotor cortex on the medial surface of the cerebral hemisphere now known as the *supplementary motor area* ([Figure 37–4B](#)). The motor map of different body parts evoked by stimulation of the supplementary motor area is less detailed than that of the primary motor cortex and lacks the enlarged distal arm and hand representation seen in the primary motor cortex. Stimulation of the supplementary motor area can evoke movements on both sides of the body or halt ongoing voluntary movements, effects that rarely result from stimulation of the primary motor cortex.

Anatomical and functional studies in humans and nonhuman primates over the past 25 years have radically changed the view of how the precentral cortex is organized functionally. First, architectonic studies demonstrated that Brodmann's area 6 is not homogeneous but consists of several distinct subareas. Second, these subareas have specific connections among themselves and with the rest of the cerebral cortex. Third, functional studies found that each subarea separately controls movements of some or all parts of the body and that the properties of neurons in each subarea differ in important ways. These areas are identified by two different nomenclatures in the literature.

As a result, in current maps of the precentral cortex Brodmann's area 6 is usually divided into five or six functional areas in addition to the *primary motor cortex* (or area F1) in Brodmann's area 4 ([Figure 37–4B](#)). The classical supplementary motor area originally identified by Woolsey on the medial cortical surface is now split into two functional regions. The more caudal part is called the *supplementary motor area proper* (area F3), whereas the more rostral part is the *pre-supplementary motor area* (F6). The caudal and rostral parts of the dorsal convexity of area 6 are called the

dorsal premotor cortex (F2) and *predorsal premotor cortex* (F7), respectively. The ventral convexity of Brodmann's area 6 has also been identified as a separate functional area called the *ventral premotor cortex*, and has been further subdivided into two subareas called F4 and F5 ([Figure 37–4B](#)). Finally, three additional motor areas outside Brodmann's area 6, in the rostral cingulate cortex, have been delineated recently.

The multiplicity of cortical motor areas would seem redundant if their only role was to initiate or coordinate muscle activity. However, we now know that neurons in these areas have unique properties and interact to perform diverse operations that select, plan, and generate actions appropriate to external and internal needs and context.

The Anatomical Connections of the Precentral Motor Areas Do Not Validate a Strictly Serial Organization

To understand the roles of these multiple precentral motor areas in voluntary motor control, it is important to know their connections with one another, their connections with other cortical areas, and their descending projections.

The cortical motor areas are interconnected by complex patterns of reciprocal, convergent, and divergent projections rather than simple serial pathways. The supplementary motor area, dorsal premotor cortex, and ventral premotor cortex have somatotopically organized reciprocal connections not only with the primary motor cortex but also with each other. The primary motor cortex and supplementary motor area receive somatotopically organized input from the primary somatosensory cortex and the rostral parietal cortex, whereas the dorsal and ventral premotor areas are reciprocally connected with progressively more caudal, medial, and lateral parts of the parietal cortex. These somatosensory and parietal inputs provide the primary motor cortex and caudal premotor regions with sensory information to organize and guide motor acts.

In contrast, the pre-supplementary and pre-dorsal premotor areas do not project to the primary motor cortex and are only weakly connected with the parietal lobe. They receive higher-order cognitive information through reciprocal connections with the pre-frontal cortex and so may impose more arbitrary context-dependent control over voluntary behav-ior.

Several cortical motor regions project in multiple parallel tracts to subcortical areas of the brain as well as the spinal cord. The best studied output path is the *pyramidal tract*, which originates in cortical layer V in a number of precentral and parietal cortical areas. Precentral areas include not only primary motor cortex but also the supplementary motor and dorsal and ventral premotor areas. The pre-supplementary motor and pre-dorsal premotor areas do not send axons to the spinal cord; their descending output reaches the spinal cord indirectly through projections to other subcortical structures. Parietal areas that contribute descending axons to the pyramidal tract include the primary somatosensory cortex and adjacent rostral parts of the superior and inferior parietal lobules.

Many pyramidal tract axons decussate at the pyramid and project to the spinal cord itself, forming the *corticospinal tract* ([Figure 37–5A](#)). Because several cortical areas contribute axons to the corticospinal tract, the traditional view that the primary motor cortex is the spinal cord is incorrect. Instead, several premotor and parietal areas of cortex can also influence spinal motor function through their own corticospinal projections.
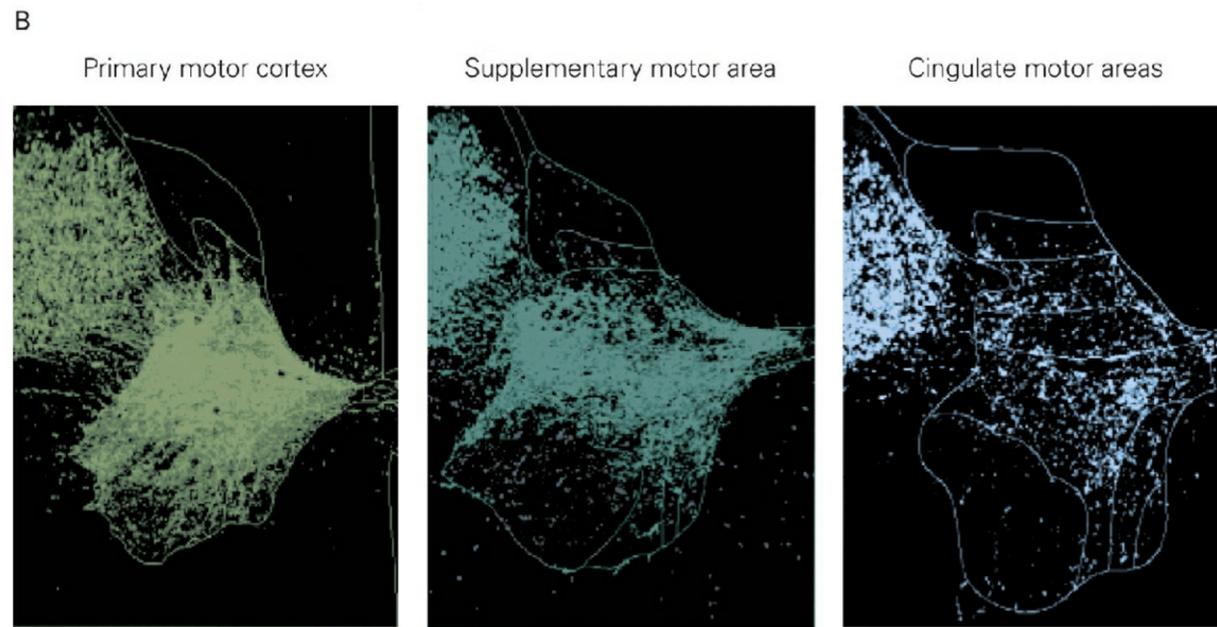
A

B

Primary motor cortex   Supplementary motor area   Cingulate motor areas
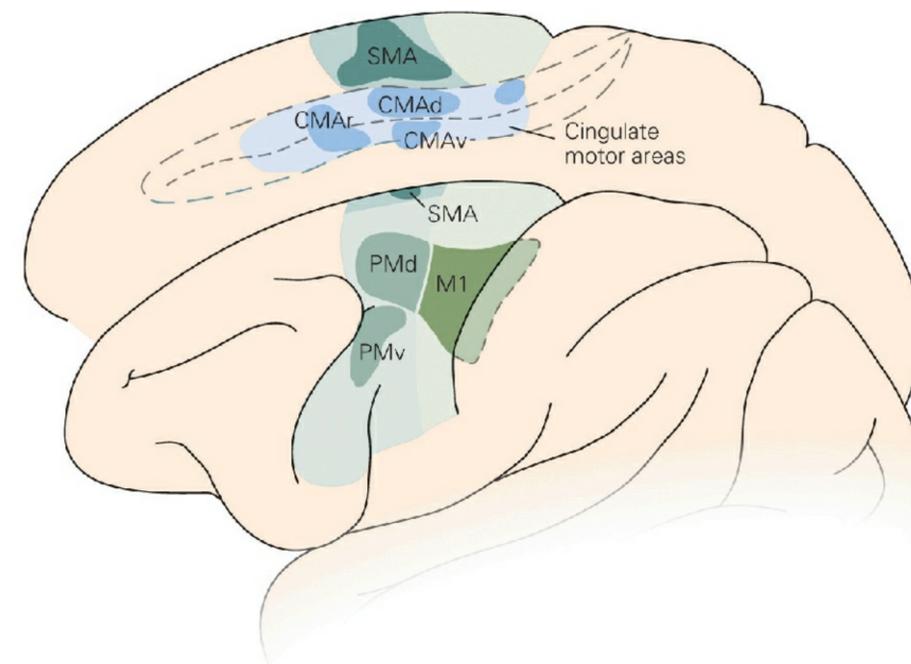
Figure 37–5 Cortical origins of the corticospinal tract. (Reproduced, with permission, from Dum and Strick 2002.)

A. Neurons that modulate muscle activity in the contralateral arm and hand originate in the primary motor cortex (M1) and many subdivisions of the premotor cortex (PMd, PMv, SMA) and project their axons into the spinal cord cervical enlargement. Corticospinal fibers projecting to the leg, trunk, and other somatotopic parts of the brain stem and spinal motor system originate in the other parts of the motor and premotor cortex. (M1, primary motor cortex; SMA, supplementary motor area; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; CMAd, dorsal cingulate motor area; CMAv, ventral cingulate motor area; CMAr, rostral cingulate motor area.)

B. The axons of corticospinal fibers from the primary motor cortex, supplementary motor area, and cingulate motor areas terminate on interneuronal networks in the intermediate laminae (VI, VII, and VIII) of the spinal cord. Only the primary motor cortex contains neurons whose axons terminate directly on spinal motor neurons in the most ventral and lateral part of the spinal ventral horn. Rexed's laminae I to IX of the dorsal and ventral horns are shown in faint outline. The dense cluster of labeled axons adjacent to the dorsal horn (upper left) in each section are the corticospinal axons descending in the dorsolateral funiculus, before entering the spinal intermediate and ventral laminae.

Many corticospinal axons from the primary motor cortex and premotor areas in primates, and virtually all corticospinal axons in other mammals, terminate on spinal interneurons in the intermediate region of the spinal cord (Figure 37–5B). These interneurons are components of reflex and pattern-generating circuits that produce stereotypical motor synergies and locomotor rhythms (see Chapter 36). In primates much of the control exerted by the primary motor cortex on spinal motor circuits and all of the control from premotor areas is mediated indirectly through these descending cortical projections to spinal interneurons.

In primates the terminals of some corticospinal axons also extend into the ventral horn of the spinal cord (lamina IX) where they arborize and contact the dendrites of spinal motor neurons (Figure 37–6B; Figure 37–5B). These monosynaptically projecting cortical neurons are called *corticomotoneurons*. The axons of these neurons become a progressively larger component of the corticospinal tract in primate phylogeny from prosimians to monkeys, great apes, and humans.
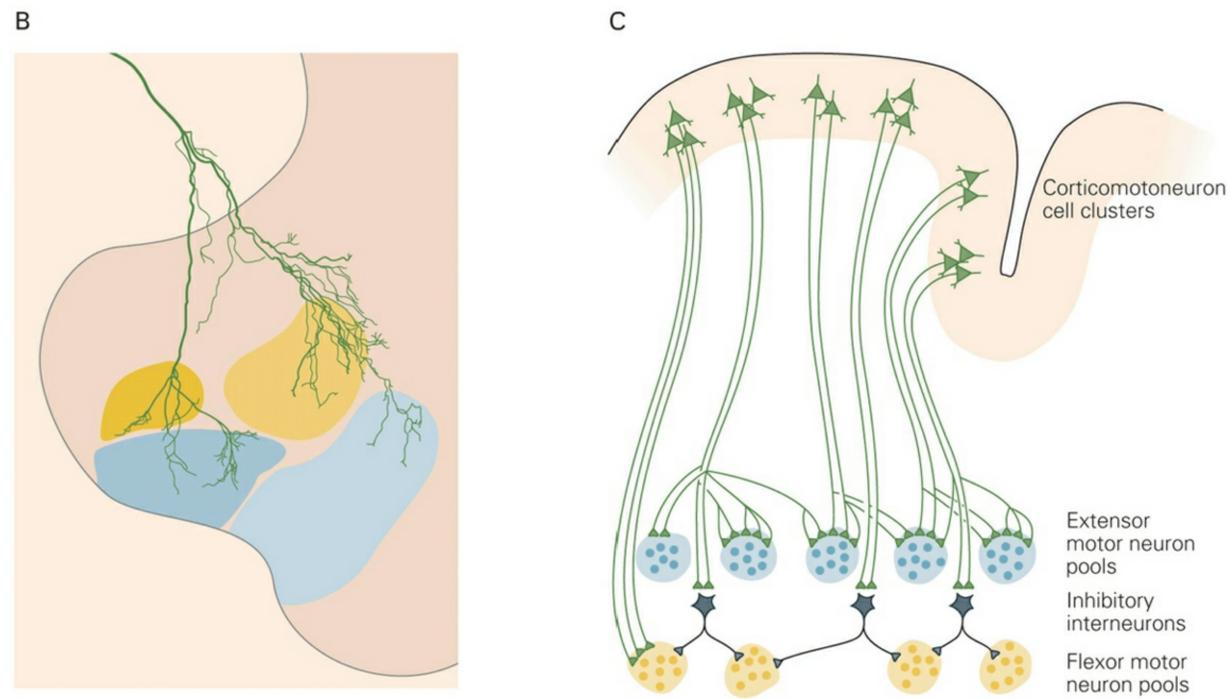
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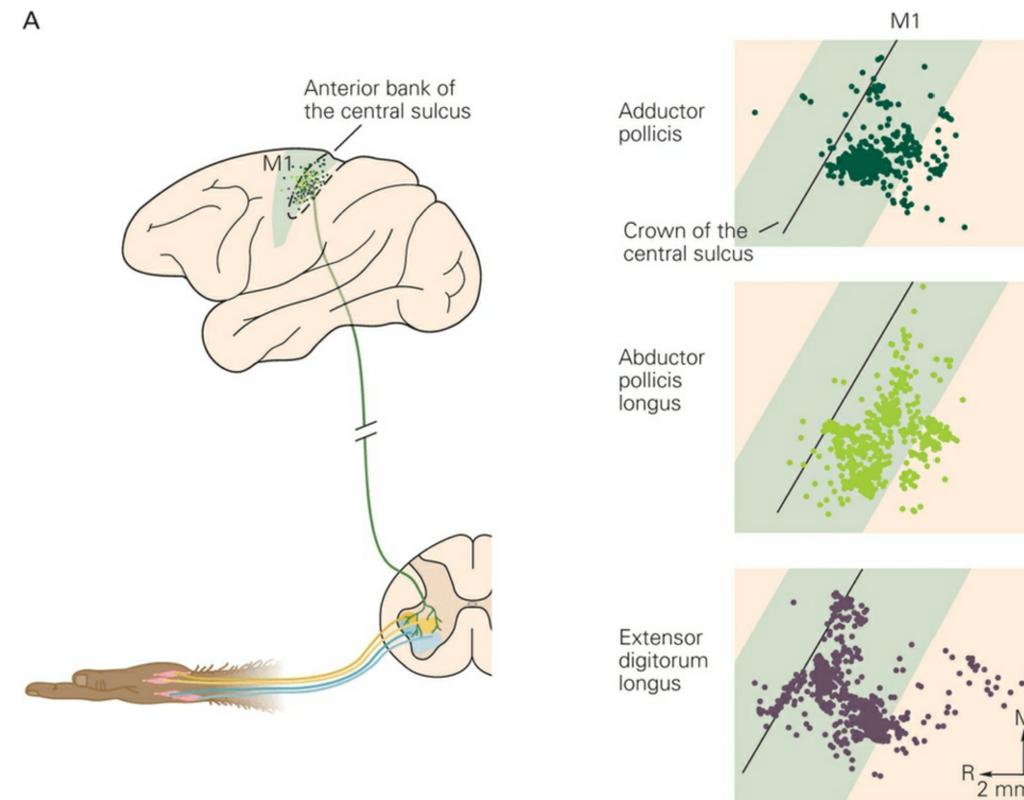
Figure 37–6 Corticomotoneurons activate complex muscle patterns through divergent connections with spinal motor neurons that innervate different arm muscles.

A. Corticomotoneurons, which project monosynaptically to spinal motor neurons, are located almost exclusively in the caudal part of the primary motor cortex (M1), within the anterior bank of the central sulcus. The corticomotoneurons that control a single hand muscle are widely distributed throughout the arm motor map, and there is extensive overlap of the distribution of neurons projecting to different hand muscles. The distributions of the cell bodies of corticomotoneurons that project to the spinal motor neuron pools that innervate the adductor pollicis, abductor pollicis longus, and extensor digitorum communis (shown on the right), illustrate this pattern. (R, rostral; M medial.) (Reproduced, with permission, from Rathelot and Strick 2006.)

B. A single corticomotoneuron axon terminal is shown arborized in the ventral horn of one segment of the spinal cord.

It forms synapses with the spinal motor neuron pools of four different intrinsic hand muscles (yellow and blue zones) as well as with surrounding interneuronal networks. Each axon has several such terminal arborizations distributed along several spinal segments. (Reproduced, with permission, from Shinoda, Yokata, and Futami 1981.)

C. Different colonies of corticomotoneurons in the primary motor cortex terminate on different combinations of spinal interneuron networks and spinal motor neuron pools, thus activating different combinations of agonist and antagonist muscles. Many other corticospinal axons terminate only on spinal interneurons (not shown). The figure shows corticomotoneuronal projections largely onto extensor motor neuron pools. Flexor motor pools receive similar complex projections (not shown). (Modified, with permission, from Cheney, Fetz, and Palmer 1985.)

In monkeys corticomotoneurons are found only in the most caudal part of the primary motor cortex that lies within the anterior bank of the central sulcus. There is extensive overlap in the distribution of the corticomotoneurons that project to the spinal motor neuron pools innervating different muscles (Figure 37–6A). In monkeys more corticomotoneurons project to the motor neuron pools for muscles of the digits, hand, and wrist than to those for more proximal parts of the arm.

The terminal of a single corticomotoneuron axon often branches and terminates on spinal motor neurons for several different agonist muscles, and can also influence the contractile activity of still more muscles through synapses on spinal interneurons (Figure 37–6B, C). This termination pattern is functionally organized to produce coordinated patterns of activity in a *muscle field* of agonist and antagonist muscles. Most frequently, a single corticomotoneuron axon directly excites the spinal motor neurons for several agonist muscles and indirectly suppresses the activity of some antagonist muscles through local inhibitory interneurons (Figure 37–6C). The fact that corticomotoneurons are more prominent in humans than in monkeys may be one of the reasons why lesions of the primary motor cortex have such a devastating effect on motor control in humans compared to lower mammals (Box 37–1).

Although neurons in several motor-cortical areas send axons into the corticospinal tract, the primary motor cortex has the most direct access to spinal motor neurons, including the monosynaptic projections of corticomotoneurons. However, the corticospinal tract is not the only pathway for descending control signals to spinal motor circuits. The spinal cord

also receives inputs from the rubrospinal, reticulospinal, and vestibulospinal tracts. These pathways influence movement through monosynaptic terminations onto spinal interneurons and spinal motor neurons.

In summary, a strictly serial organization of voluntary movement would require a pattern of serial connections between cortical areas, ending at the primary motor cortex, which then projects to the spinal cord. In reality, however, the multiple precentral and parietal cortical motor areas are interconnected by a complex network of reciprocal, divergent, and convergent axonal projections. Moreover, several cortical areas project to the spinal cord in parallel with projections from the primary motor cortex. Finally, the spinal motor circuits receive inputs from several subcortical motor centers in addition to those from the cerebral cortex.

The Primary Motor Cortex Plays an Important Role in the Generation of Motor Commands

In the 1950s Herbert Jasper and colleagues pioneered chronic microelectrode recordings from alert animals engaged in natural behaviors. This approach, which allows researchers to study the activity of single neurons while animals perform a controlled behavioral task, has made enormous contributions to our knowledge of the neuronal mechanisms underlying many brain functions. A microelectrode can also be used to deliver weak electrical currents to a small volume of tissue around its tip. When used in the cerebral cortex, this technique is called *intracortical microstimulation*.

These methods have been complemented more recently by techniques that can be used in human subjects, such as functional imaging and transcranial magnetic stimulation. Nearly every insight that will be described in the rest of this chapter and in Chapter 38 has been derived from these techniques.

Edward Evarts, the first to use chronic microelectrode recordings to study the primary motor cortex in behaving monkeys, made several discoveries of fundamental importance. He found that single neurons in this area discharge during movements of a limited part of the contralateral body, such as one or two adjacent joints in the hand, arm, or leg (Figure 37–9). Some neurons discharge during flexion of a particular joint and are reciprocally suppressed during extension, whereas other cells display the

opposite pattern. This movement-related activity typically begins 50 to 150 ms before the onset of agonist muscle activity. These pioneering studies suggested that single neurons in primary motor cortex generate signals that provide specific information about movements of specific parts of the body before those movements are executed.
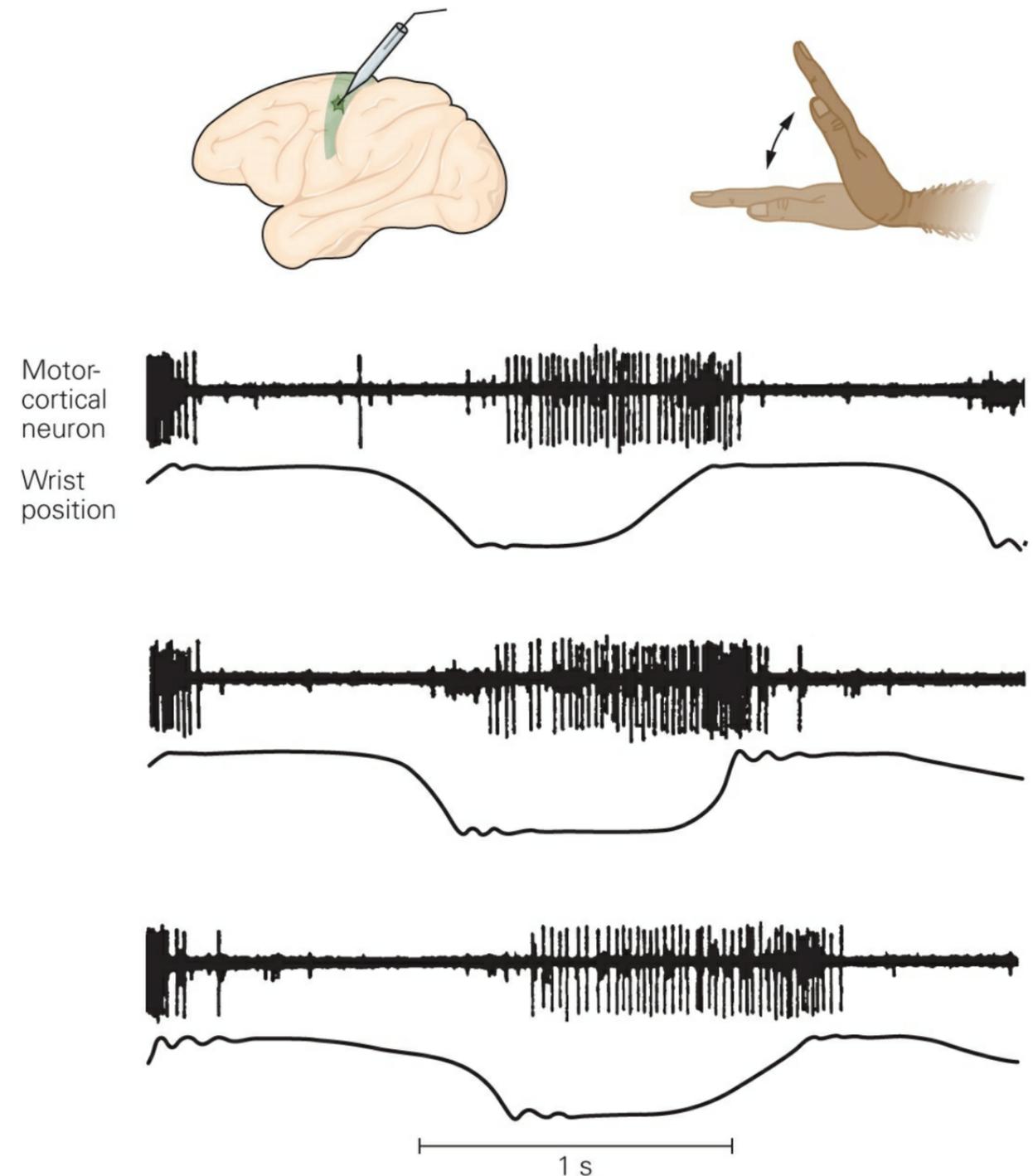

**Figure 37–9** The discharge of individual pyramidal tract neurons varies

with particular movements of specific parts of the body. The discharge of a motor cortex neuron with an axon that projects down the pyramidal tract is recorded while a monkey makes a sequence of flexion and extension movements of the wrist. The three parts of the figure show three consecutive flexion-extension cycles, proceeding from top to bottom. In the trace showing wrist position the direction of flexion is down and extension up. The pyramidal tract neuron discharges before and during extensions and is reciprocally silent during flexion movements. It does not discharge during movements of other body parts. Other motor cortex neurons show the opposite pattern of activity, discharging before and during flexion movements. (Reproduced, with permission, from Evarts 1968.)

Box 37–1 Lesion Studies of Voluntary Motor Control

Naturally occurring or experimentally induced lesions have long been used to infer the roles of different neural structures in motor control. However, the effects of lesions must always be interpreted with caution.

It is often incorrect to conclude that the function perturbed by an insult to a part of the motor system resides uniquely in the damaged structure, or that the injured neurons explicitly perform that function. Furthermore, the effects of lesions can be masked or altered by compensatory mechanisms in remaining, intact structures. Nevertheless, lesion experiments have been fundamental in differentiating the functional roles of cortical motor areas as well as the pyramidal tract.

Focal lesions of the primary motor cortex typically result in such symptoms as muscle weakness, slowing and imprecision of movements, and discoordination of multijoint motions, perhaps as a result of selective perturbations of the control circuitry for specific muscles (Figure 37–7). Larger lesions lead to temporary or permanent paralysis.
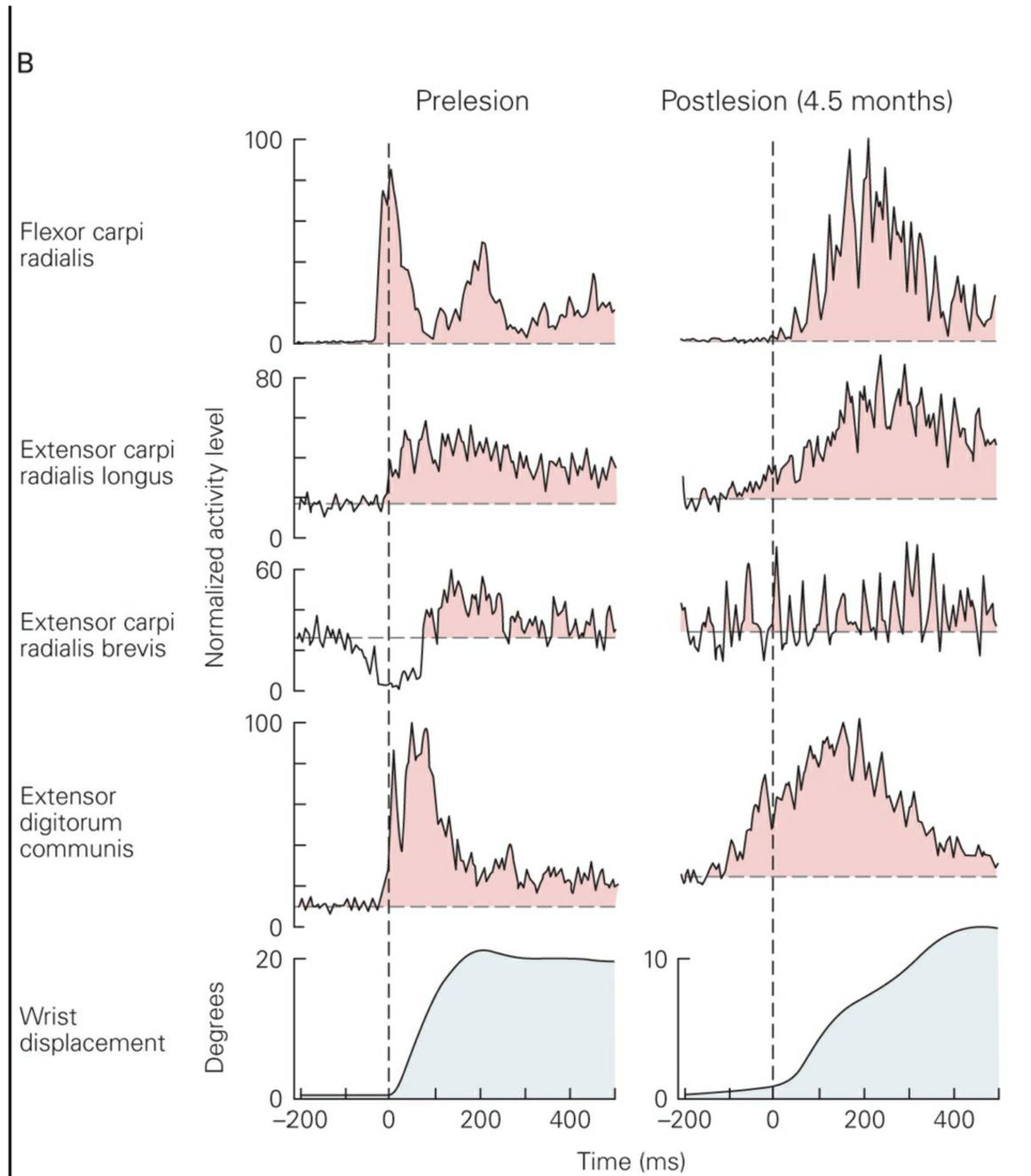

A

Postlesion

Target area

Lesion in arm region
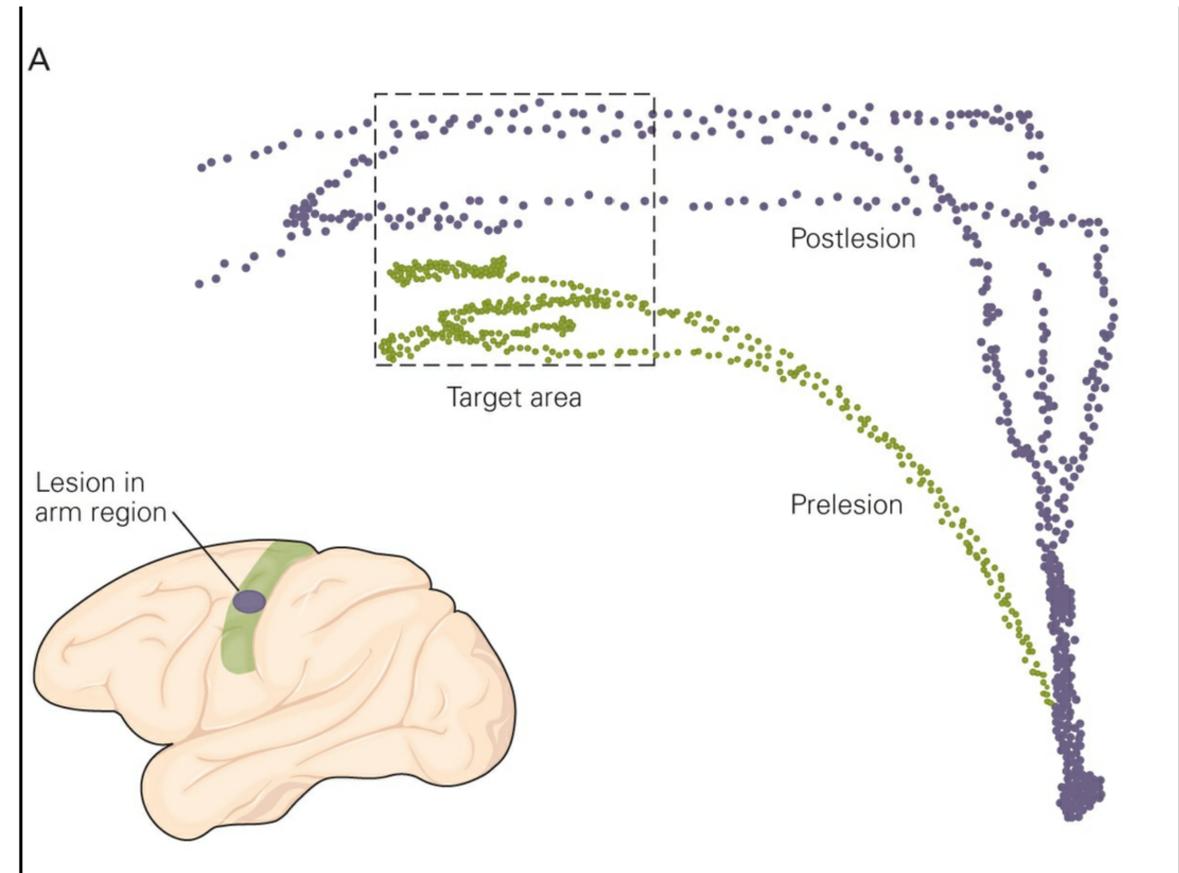
Prelesion

Figure 37–7 Fractionated control of muscle activity patterns requires cortical input.

A. A monkey can readily make diagonal movements of the wrist that require complex coordinated muscle patterns before a motor cortical lesion ("prelesion"). After a large lesion of the arm region of the motor cortex, the monkey shows major deficits in the ability to make diagonal movements even after lengthy rehabilitation.

B. The movement deficit is accompanied by a severe loss of the

ability to make precisely timed fractionated muscle contractions of different agonist and antagonist muscles. (Reproduced, with permission, from Hoffman and Strick 1995.)

If the lesion is limited to a part of the motor map, the paralysis affects primarily the movements represented in that sector, such as the contralateral arm, leg, or face. There is diminished use of the affected body parts, and movements of the distal extremities are much more affected than those of the proximal arm and trunk.

The severity of the deficit as a result of focal lesions also depends on the degree of required skill. Control of fine motor skills, such as independent movements of the fingers and hand and precision grip, is abolished. Any residual control of the fingers and the hand is usually reduced to clumsy, claw-like, synchronous flexion and extension motions of all fingers, not unlike the unskilled grasps of young infants. Even remaining motor functions, such as postural activity, locomotion, reaching, and grasping objects with the whole hand, are often clumsy and lack refinement.

Large lesions of the motor cortex or its descending pathways (for example the internal capsule) often produce a suite of symptoms known as the pyramidal syndrome (Figure 37–8). This condition is characterized by contralateral paralysis; increase of muscular tone (spasticity), often preceded by a transient phase of flaccid paralysis with decreased muscle tone; increase of deep reflexes (such as the patellar reflex); disappearance of superficial reflexes (such as the abdominal reflex); and appearance of the Babinski reflex (dorsiflexion of the great toe and fanning of the other toes when a blunt needle is drawn along the lateral edge of the sole). The increase in muscle tone alters the patient's posture, such that the arm contralateral to the lesion is flexed and adducted whereas the leg is extended.

The term "pyramidal syndrome" is a misnomer. In fact, the symptoms result from lesions of descending cortical projections to several subcortical sites, not just the pyramidal tract. Spasticity, for instance, results from damage to nonpyramidal fibers, specifically those that innervate the brain stem centers involved in the control of muscular tone. Clear evidence for this comes from observation of the behavior of monkeys following surgical transection of the

medullary pyramid, an anatomical structure that contains only pyramidal tract fibers. Transection at this level produces contralateral hypotonia rather than spasticity.

Lesions of the primary motor cortex in humans perturb the dexterous execution of movements, with deficits ranging from weakness and discoordination to complete paralysis. Lesions of other cortical regions, in contrast, do not result in paralysis and have less impact on the execution of movements than on the organization of action. One effect is difficulty in suppressing the natural motor response to a stimulus in favor of other actions that would be more appropriate to accomplish a goal.

For example, when a normal monkey sees a tasty food treat behind a small transparent barrier, it readily reaches around the barrier to grasp it. However, after a large premotor cortex lesion the monkey persistently tries to reach directly toward the treat rather than making a detour around the barrier, and thus repeatedly strikes the barrier with its hand.

Focal lesions of premotor areas cause a variety of more selective deficits that do not result from an inability to perform individual actions but rather an inability to choose the appropriate course of action. Lesions or inactivation of the ventral premotor cortex perturb the ability to use visual information about an object to shape the hand appropriately for the object's size, shape, and orientation before grasping it. Lesions of the dorsal premotor cortex or supplementary motor area impact the ability to learn and recall arbitrary sensorimotor mappings such as visuomotor rotations, conditional stimulus-response associations, and temporal sequences of movement.

The effects of motor cortex lesions also differ across species. Large lesions in cats do not cause paralysis; the animals can move and walk on a flat surface. However, they have severe difficulties using visual information to navigate within a complex environment, avoid obstacles, or climb the rungs of a ladder. Trevor Drew and colleagues have shown that pyramidal tract neurons in the motor cortex of cats are much more strongly activated when the cats must modify their normal stepping to clear an obstacle under visual guidance

than during normal, unimpeded locomotion over a flat, featureless surface.

Similar lesions of motor cortex in monkeys have more drastic consequences, including initial paralysis and usually the permanent loss of independent, fractionated movements of the thumb and fingers. Monkeys nevertheless recover some ability to make clumsy movements of the hands and arms and to walk and climb, even after large lesions (Figure 37–8). In humans large lesions of the motor cortex are particularly devastating, often resulting in flaccid or spastic paralysis with a limited potential for recovery.
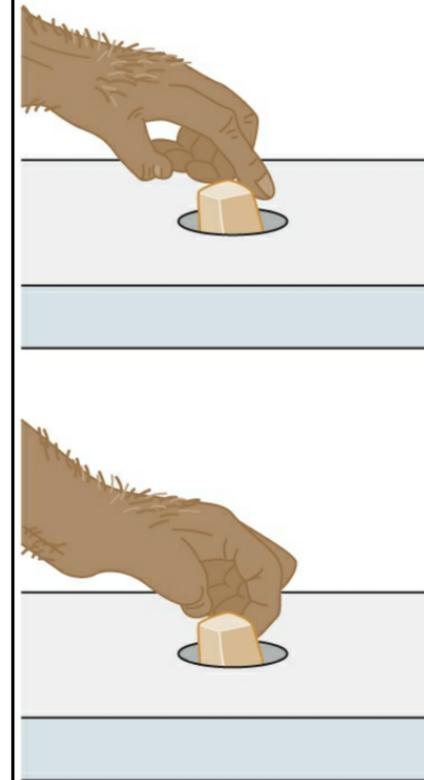
A Normal **B** After sectioning of pyramidal tract fibers
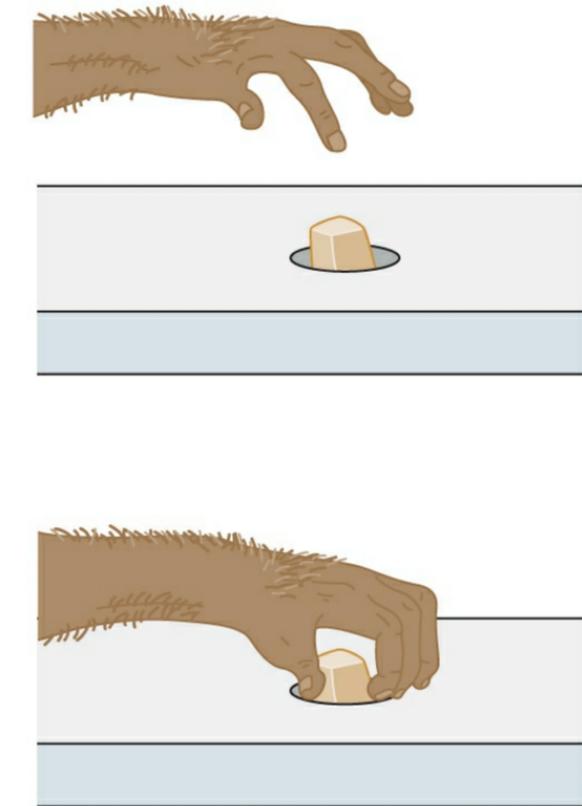
Figure 37–8 A lesion of the pyramidal tract abolishes fine grasping movements.

A. A monkey is normally able to make individuated movements of the wrist, fingers, and thumb in order to pick up food in a small well.
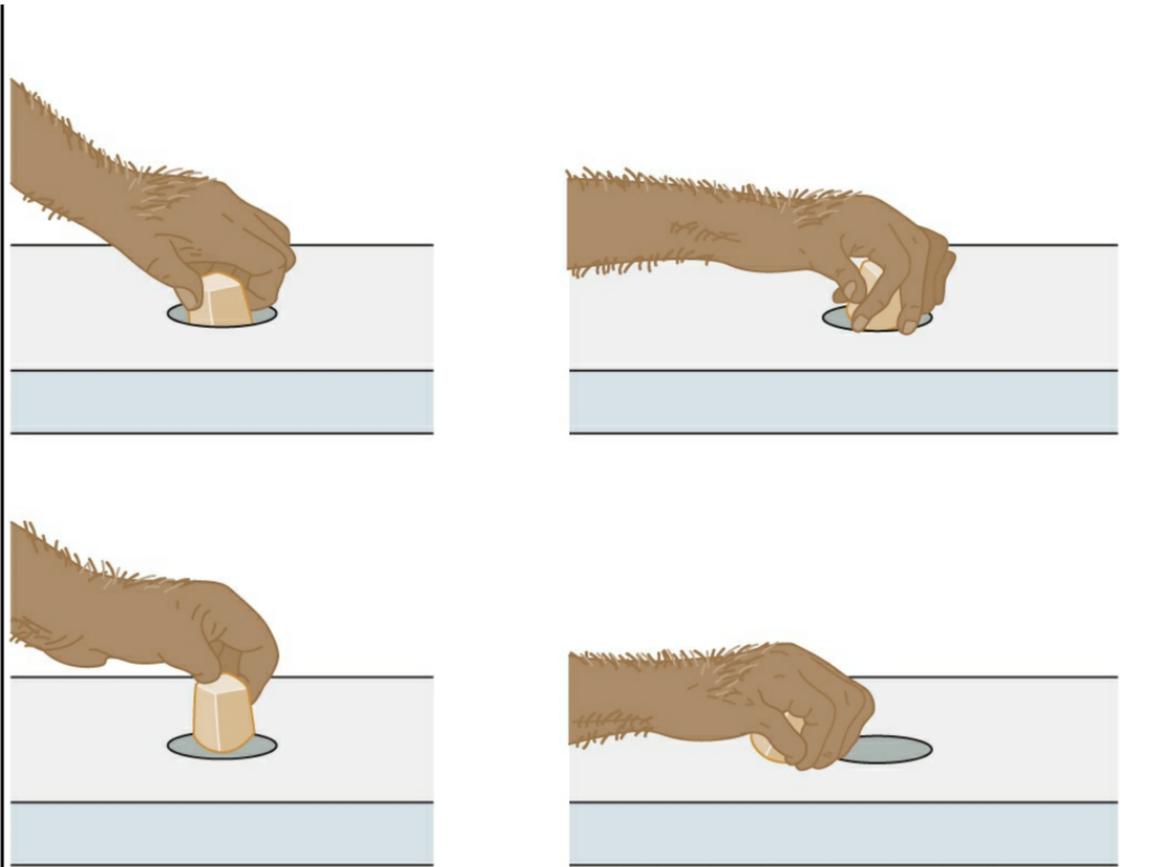
B. After bilateral sectioning of the pyramidal tract the monkey can remove the food only by grabbing it clumsily with the whole hand. This change results mainly from the loss of direct inputs from corticomotoneurons onto spinal motor neurons. A pyramidal tract transection is not equivalent to a motor cortex lesion, however, because not all pyramidal tract axons terminate in the spinal cord. The axons that do project to the spinal cord originate in several cortical areas, including the motor cortex, and the corticospinal tract is only one of several parallel output pathways of the motor cortex. (Reproduced, with permission, from Lawrence and Kuypers 1968.)

These differences in primates and man presumably reflect the increased importance in man of descending signals from motor cortex and a correspondingly diminished capacity of subcortical motor structures to compensate for the loss of those descending signals.

Many subsequent studies have provided further insight into the contribution of different cortical motor areas to the control of voluntary movements. In general, the output signals from premotor areas are strongly dependent on the context in which the action is performed, such as the stimulus-response associations and the rules that guide which movement to make. In contrast, the commands generated by the primary motor cortex are more closely related to the mechanical details of the movement and are usually less influenced by the behavioral context. However, the relative role of these different areas to voluntary motor control, including the primary motor cortex itself, continues to be an area of active research and controversy. The rest of this chapter and Chapter 38 describe our current understanding of the different roles of cortical motor areas.

Columnar arrays of neurons with similar response properties are a prominent feature of many sensory areas of cortex. It is surprising therefore that there is only weak evidence for such functional columns in the primary motor cortex. The cell bodies and apical dendrites of primary motor cortex neurons tend to form radially oriented columns. The terminal arbors of thalamocortical and corticocortical axons form localized columns or bands and corticomotoneurons tend to cluster in small groups with similar muscle fields. Motor cortex neurons recorded successively as a microelectrode descends perpendicularly through the neuronal layers between the pial surface and the white matter typically discharge during movements of the same part of body and can have similar preferred movement directions. Nevertheless, adjacent cells often show very different response patterns.

Motor Commands Are Population Codes

The complex overlapping organization of the motor map for the arm and hand suggests at least two different ways to generate the motor command for a given movement. The map could function as a *look-up table* within which a desired movement is generated by selective activation of a few sites whose combined output produces all the required muscle activity

and joint motions. Or it could be a distributed *functional map* in which many sites contribute to each motor command.

Apostolos Georgopoulos and colleagues recorded from the primary motor cortex while a monkey reached in different directions from a central starting position toward targets arrayed on a circle in the horizontal plane. Individual neurons responded during many movements, not just a single one ([Figure 37–10A](#)). Each neuron's activity was strongest for a *preferred* direction and often weakest for the opposite direction, as Evarts had found for single-joint movements. However, each cell also responded in a graded fashion to directions of movement between the preferred and the opposite directions. Its activity pattern thus formed a broad directional tuning curve, maximal at the preferred direction and decreasing gradually with increasing difference between the preferred direction and the target direction.
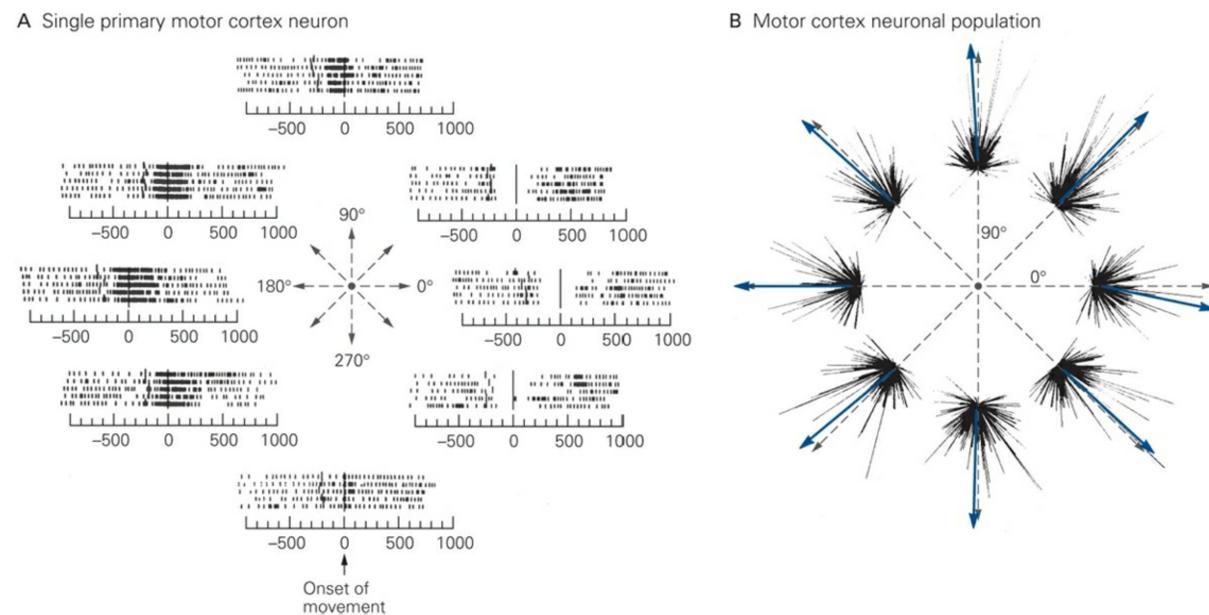

Figure 37–10 A reaching movement is coded by a population of neurons in the arm motor map.

A. Raster plots show the firing pattern of a single primary motor cortex neuron during movements in eight directions. The neuron discharges at the maximal rate for movements near 135 degrees and 180 degrees and at lesser intensities for movements in other directions. The cell's lowest firing rate is for movements opposite the cell's preferred direction. Different cells have different preferred directions, and their broad directional tuning curves overlap extensively. The plots are from a study in which a monkey was trained to move a handle to eight targets arranged radially on a horizontal plane around a central starting position. Each row of tics in each raster plot represents the activity in a single trial, aligned at the time of movement onset (time zero). (Reproduced, with permission, from Georgopoulos et al. 1982.)

B. Many primary motor cortex neurons with a broad range of preferred movement directions respond at different intensities during reaching movements in a particular direction. The overall directional bias of the activity within the population of neurons shifts systematically with movement direction so that the vectorial sum of the activity of all cells is a population vector that closely matches that of the direction of movement. This shows that the motor command for a movement is generated by a widely distributed population of cells throughout the arm motor map, each of which fires at a different intensity for movement in a particular direction.

The eight single-neuron vector clusters and the population vectors shown here represent the activity of the same population of cells during reaching movements in eight different directions. The activity of each neuron during each reaching movement is represented by a thin black vector that points in the neuron's preferred movement direction and whose length is proportional to the discharge of the neuron during that movement. Blue arrows are the population vectors, calculated by vectorial addition of all the single-cell vectors in each cluster; dashed arrows represent the direction of movement of the arm. (Reproduced, with permission, from Georgopoulos et al. 1983.)

Different cells had different preferred directions, and their tuning curves overlapped extensively. All directions were represented in the neuronal population. Cells with similar preferred directions were located at several different sites in the arm motor map, and nearby cells often had different preferred directions. As a result, many cells with a broad range of preferred directions discharged at different intensities at many locations across the arm motor map during each reaching movement.

Despite the apparent complexity of the response properties of single neurons, Georgopoulos found that the global pattern of activity of the entire population provided a clear signal for each movement. He represented

each cell's activity by a vector pointing in the cell's preferred direction. The vector's length for each direction of movement was proportional to the mean level of activity of that cell averaged over the duration of the movement (Figure 37–10B). This vectorial representation implied that an increase of activity of a given cell is a signal that the arm should move in the cell's preferred direction, and that the strength of this directional influence varies continuously for different reach directions as a function of the neuron's directional tuning.

Vectorial addition of all of the single-cell contributions to each output command produces a *population vector* that corresponds closely to the actual movement direction. That is, an unambiguous signal about the desired motor output is encoded by the summed activity of a large population of active neurons throughout the arm motor map in the primary motor cortex. As a result, neurons in all parts of the arm motor map contribute to the motor command for each reaching movement, and the pattern of activity across the motor map changes continuously as a function of the intended direction of the reaching movement.

Andrew Schwartz and colleagues used the same population-vector analysis to represent temporal variations in the activity of populations of primary motor cortex neurons every 25 ms while monkeys performed continuous arm movements. In the resulting time sequence of population vectors, each vector predicts the instantaneous direction and speed of the motion of the monkey's arm approximately 100 ms later (Figure 37–11). These results show that the pattern of neural activity distributed across the arm motor map varies continuously in time during complex arm movements, signaling the moment-to-moment details of the desired movement.

A Finger trajectories
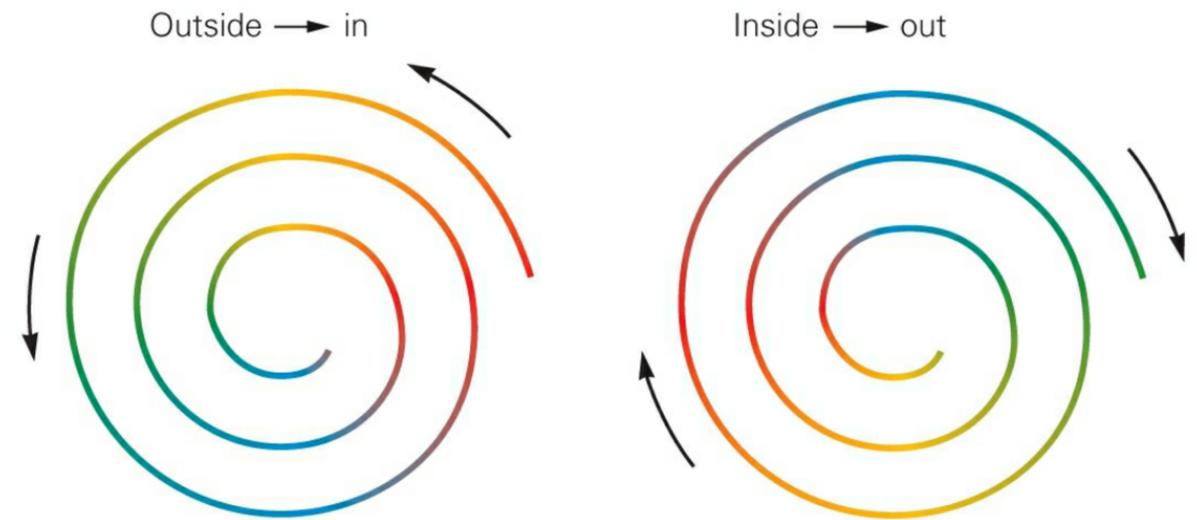
B Temporal sequence of movement vectors
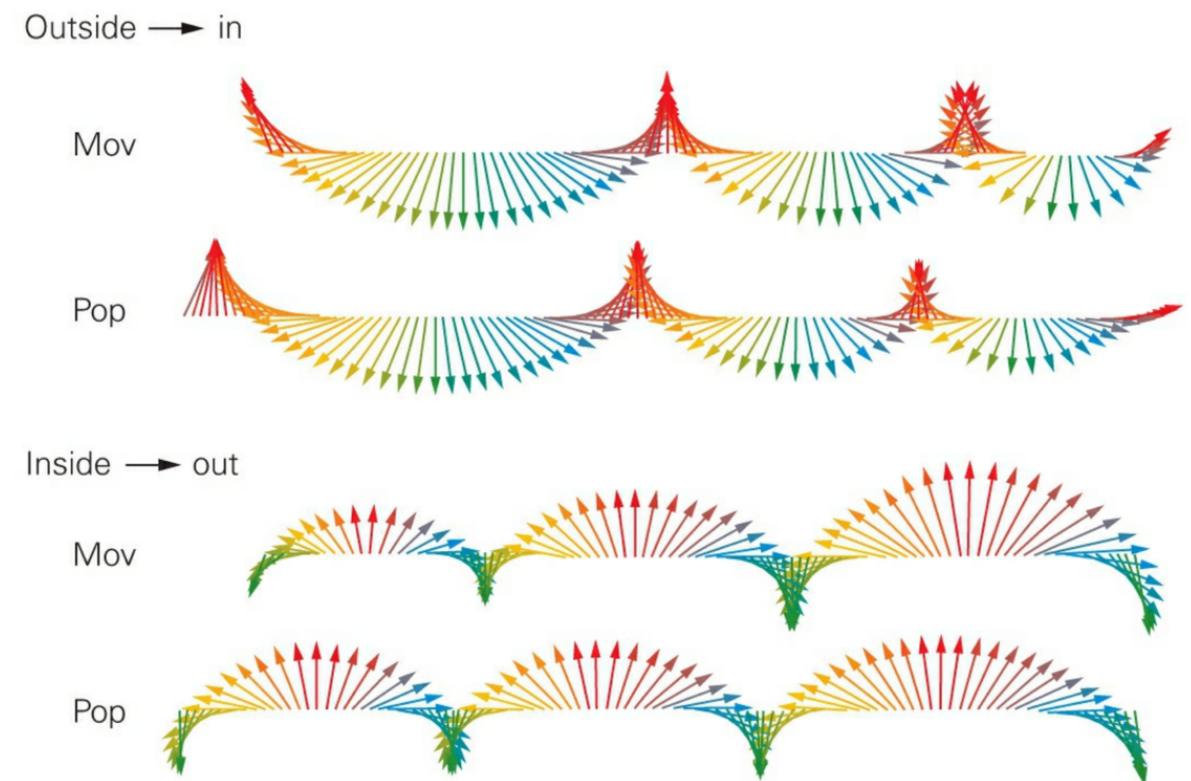
C Predicted trajectories made by joining instantaneous population vectors from part B tip to tail

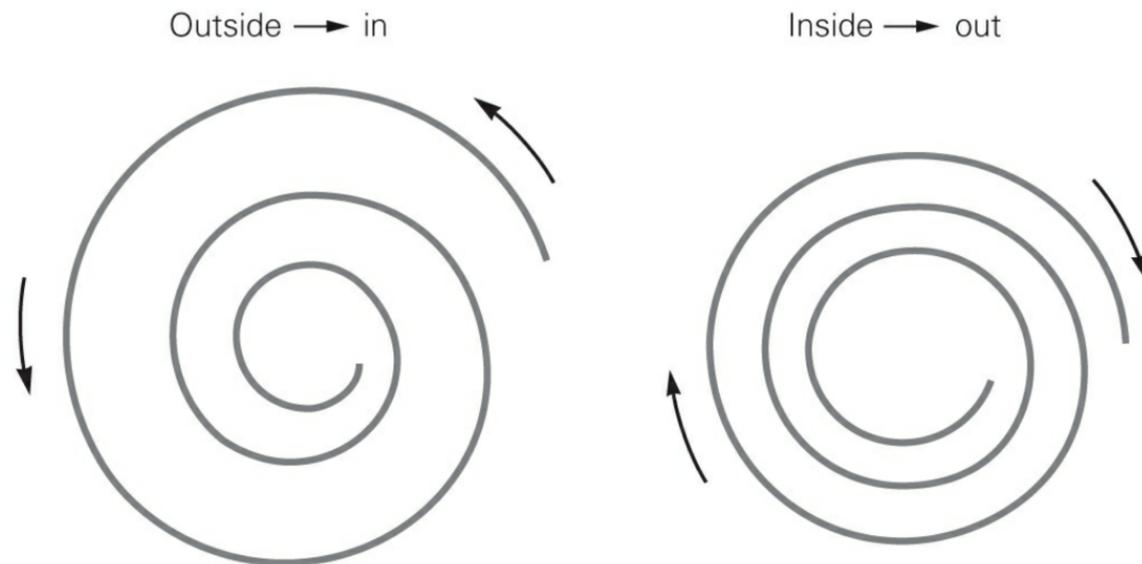Outside ⟶ in   Inside ⟶ out

Figure 37–11 The moment-to-moment activity of a population of motor cortex neurons predicts arm movements over time. (Reproduced, with permission, from Moran and Schwartz 1999.)

A. A monkey uses its arm to trace spirals with its finger.

B. Temporal sequences of vectors, reading left to right, illustrate the instantaneous direction and speed of movement of the finger (**Mov**) and the net population vector signal (**Pop**) of the activity of 241 motor cortex neurons every 25 ms during the drawing movements. The population vectors precede the hand displacement vectors by approximately 100 ms.

C. Joining the instantaneous population vectors tip to tail produces "neural trajectories" that predict the spatial trajectory of movement of the finger along the spiral path approximately 100 ms in the future.

Further studies have confirmed that similar population-coding mechanisms are used in all cortical motor areas. This common coding mechanism undoubtedly facilitates the communication of movement-related information between the multiple areas of motor cortex during voluntary behavior.

The Motor Cortex Encodes Both the Kinematics and Kinetics of Movement

Population-vector analyses show that neural activity in the primary motor cortex contains information about the trajectory of hand motions during reaching and drawing movements. However, to execute those movements the motor system must implement the desired motions by generating particular patterns of muscle activity.

Electrical stimulation of the primary motor cortex readily evokes muscle contractions, and some cells in this region have direct access to spinal motor neurons. Indeed, it was long assumed that the major role of the primary motor cortex was to specify the muscle activity that generates voluntary movements. Because muscle contractions generate the forces that displace a joint or limb in a particular direction, a critical question is whether primary motor cortex neurons signal the desired spatiotemporal form of a behavior or the forces and muscle activity required to generate the movement. That is, do these neurons encode the kinematics or the kinetics of an intended movement (Box 37–2)?

Kinematics refers to the parameters that describe the spatiotemporal form of movement, such as direction, amplitude, speed, and path. *Kinetics* concerns the causal forces and muscle activity. It is also useful to distinguish the *dynamic* forces that cause movements from the *static* forces required to maintain a given posture against constant external forces such as gravity.

Evarts was the first to address this question with single-neuron recordings. Using a system of pulleys and weights, he applied a load to the wrist of a monkey to pull the wrist in the direction of flexion or extension. To make a particular movement the animal had to alter its level of muscle activity to compensate for the load. As a result, the kinematics (direction and amplitude) of wrist movements remained constant but the kinetics (forces and muscle activity) changed with the load. The activity of many primary motor cortex neurons associated with movements of the hand and wrist increased during movements in their preferred direction when the load opposed that movement but decreased when the load assisted it (Figure 37–12). These changes in neural activity paralleled the changes in muscle activity required to compensate for the external loads. This was

the first study to show that the activity of many primary motor cortex neurons is more closely related to *how* a movement is performed, the kinetics of motion, than to *what* movement is performed, the corresponding kinematics.
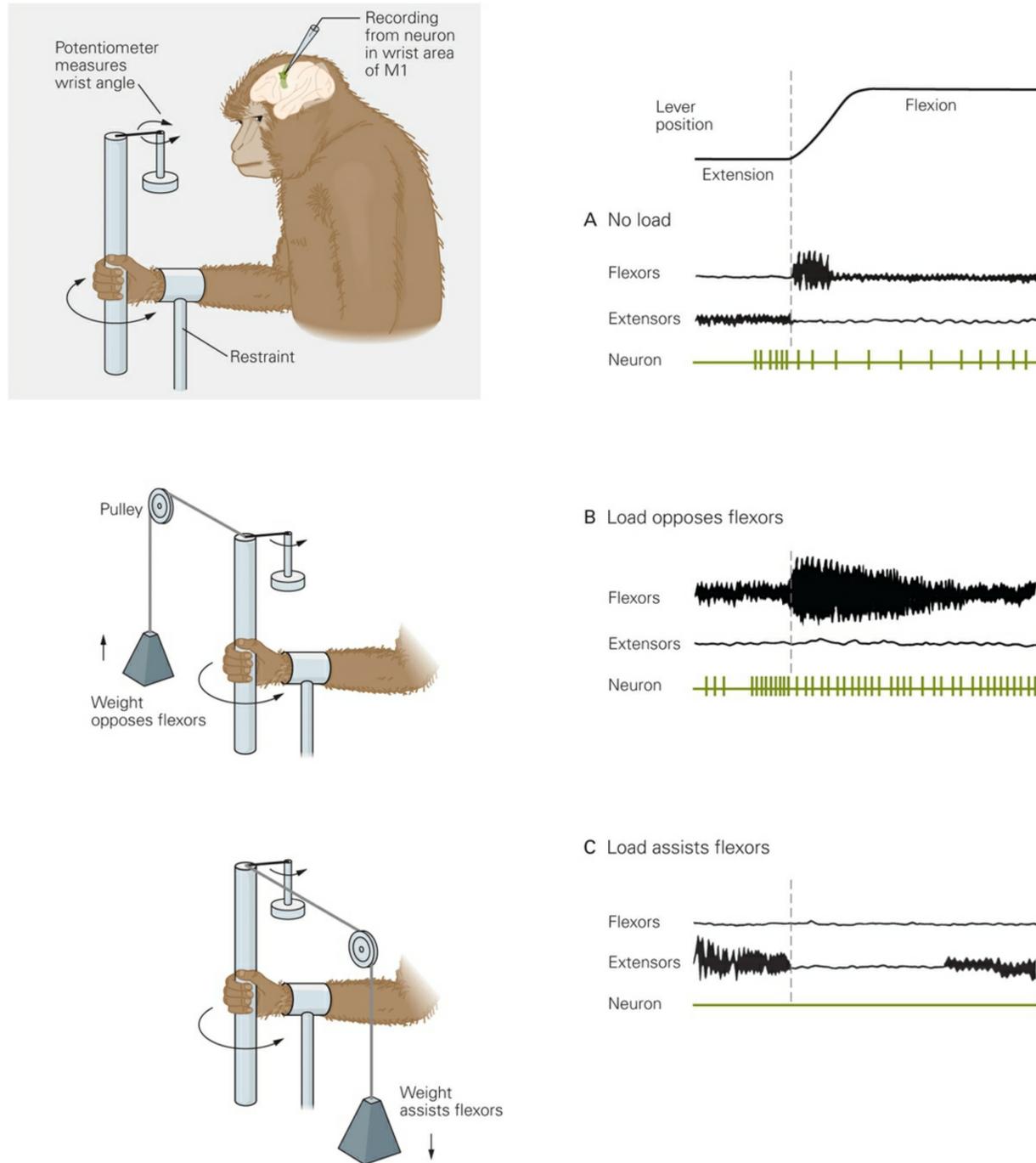

Figure 37–12 Activity of a motor cortex neuron correlates with changes in the direction and amplitude of muscle forces during wrist movements. The records are from a primary motor cortex (**M1**) neuron with an axon

that projected down the pyramidal tract. The monkey flexes its wrist under three load conditions. When no load is applied to the wrist, the neuron fires before and during flexion (A). When a load opposing flexion is applied, the activity of the flexor muscles and the neuron increases (B). When a load assisting wrist flexion is applied, the flexor muscles and neuron fall silent (C). In all three conditions the wrist displacement is the same, but the neuronal activity changes as the loads and compensatory muscle activity change. Thus the activity of this motor cortex neuron is better related to the direction and level of forces and muscle activity exerted during the movement than to the direction of wrist displacement. (Reproduced, with permission, from Evarts 1968.)

A later study confirmed this property of motor cortex activity during whole-arm reaching movements. A monkey made arm movements exactly as in the task used by Georgopoulos (Figure 37–10), but additional external loads pulled the arm in different directions. To continue to move the arm along the same path, the monkey had to change the activity of its arm muscles to counteract the external loads. The level of activity of many motor cortex neurons changed systematically with the direction of the external load even though the movement path did not change. When the load opposed the direction of reach, the single-cell and total population activity increased. When the load assisted the reaching direction, the neural activity decreased in a manner that signaled the change in muscle activity and output forces required to make the movement (Figure 37–13).
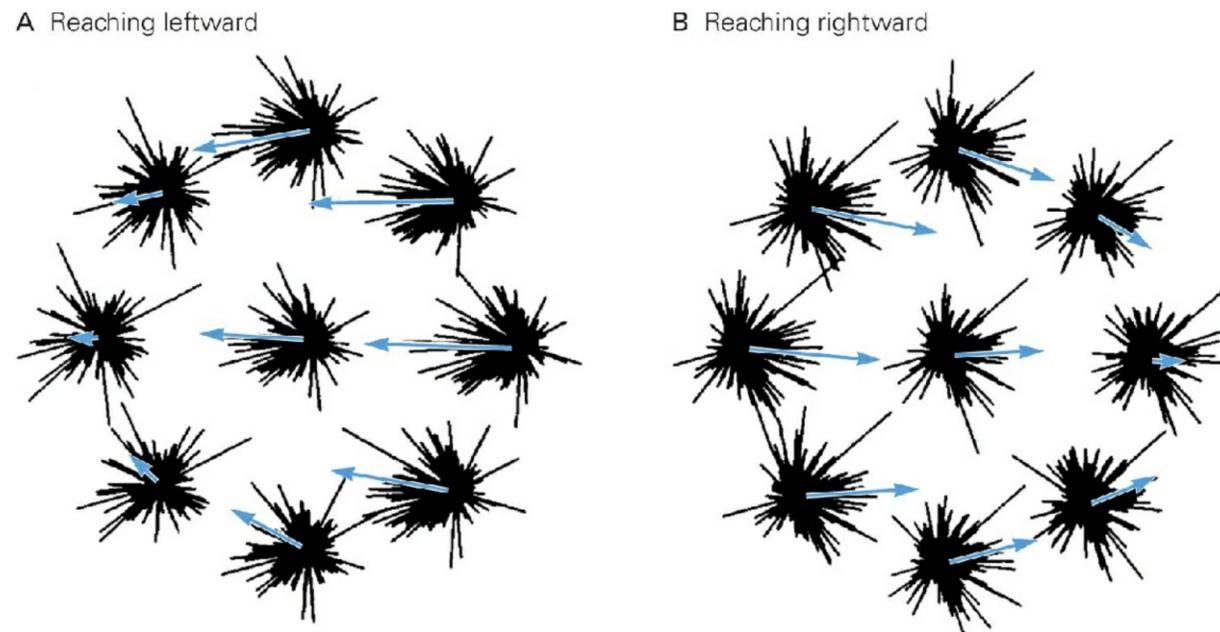
A Reaching leftward   B Reaching rightward

Figure 37–13 Activity of primary motor cortex neurons varies with the forces required to maintain the direction of reaching movements against external loads. A vectorial representation of the directional activity of approximately 260 motor cortex neurons (**black lines**) when a monkey makes reaching movements to the left and right. The vectors in the center represent activity when no external load is applied to the arm, whereas the vector clusters around the center represent the activity of the same 260 neurons when an external load pulls the arm in different directions. The location of each vector cluster relative to the central cluster corresponds to the direction in which the external load pulls on the arm. The change in population vectors (**blue arrows**) for the vector clusters around the center indicates that the strength and overall directional bias of the activity of the neural population vary systematically with the direction of the external load, in order to counteract its effect, even though the trajectory of the movement does not change. (Reproduced, with permission, from Kalaska et al. 1989.)

Box 37–2 The Equilibrium-Point Hypothesis of Movement

Most theoretical and neurophysiological studies of neural control of movement are based on variants of the force-control hypothesis, which states that the motor system controls a movement by planning and controlling its causal dynamic forces or muscle activity.

The *position-control* or *equilibrium-point hypothesis*, however, argues that cortical motor centers do not compute inverse kinematics or dynamics to specify the necessary muscle activity. Instead, this model proposes that the output from the motor cortex signals the desired spatial endpoints and equilibrium configurations of the arm and body, that is, the posture in which all external and internal (muscular) forces are at balance and no further movement occurs.

According to the equilibrium-point hypothesis, the motor cortex causes a movement of part or all of the body by generating a signal specifying a particular equilibrium or *referent configuration*. This descending signal exploits spinal reflex circuits and the spring-like biomechanical properties of muscles to change muscle activity and create an imbalance between external and internal forces, causing the limb to move until equilibrium is restored.

If no external force is applied to the limb, the desired, signaled, and actual equilibrium configurations should all correspond. If the motor system is confronted with an external force, however, it must signal a different referent configuration whose internal forces compensate for the external forces. Thus, according to the equilibrium-point hypothesis, the motor cortex commands the desired movement without computing the complex transformations required to encode the required forces and muscle activities. According to the hypothesis, the inverse-kinematics and inverse-dynamics transformations occur implicitly at the local spinal cord circuits and in the motor periphery itself.

Other studies have examined the issue whether the primary motor cortex organizes the kinematics or kinetics of movement by using tasks in which subjects generate isometric forces against immovable objects rather than moving the arm. The activity of many primary motor cortex neurons varies with the direction and level of static isometric output forces generated across a single joint, such as the wrist or elbow, as well as during precise pinches with the thumb and index finger (Figure 37–14A). At least over part of the tested range these responses vary linearly with the level of static force. When a monkey uses its whole arm to exert isometric force in different directions, the activity of many motor cortex neurons varies systematically with force direction, and the directional

tuning curves resemble those for activity associated with reaching movements (Figure 37–14B). Because no movement is intended or produced in isometric tasks, this strongly suggests that the primary motor cortex contributes to the control of static and dynamic output forces during many motor actions.
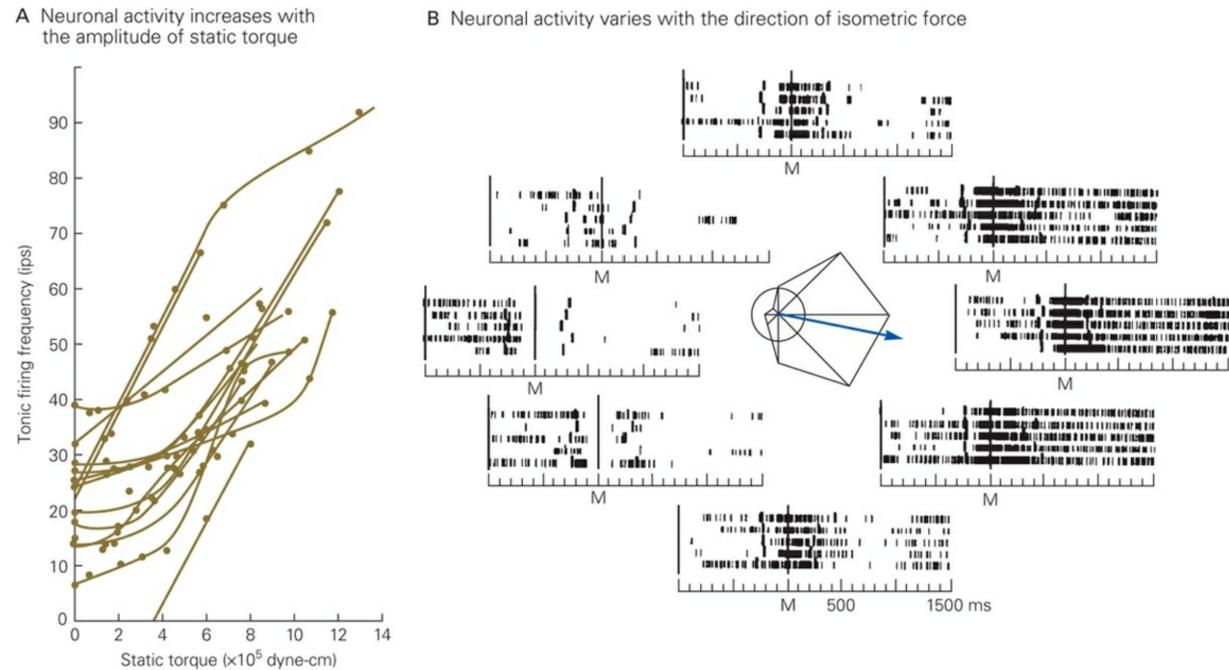

A Neuronal activity increases with the amplitude of static torque

B Neuronal activity varies with the direction of isometric force

Figure 37–14 The firing rates of many primary motor cortex neurons correlate with the level and direction of force exerted in an isometric task.

A. The activity of many primary motor cortex neurons increases with the amplitude of static torque generated across a single joint. The plot shows the tonic firing rates of several different corticomotoneurons at different levels of static torque exerted in the direction of wrist extension. Other motor cortex neurons show increasing activity with torque exerted in the direction of wrist flexion, and so would show response functions with the opposite slope (not shown). (Reproduced, with permission, from Fetz and Cheney 1980.)

B. When a monkey uses its whole arm to push on an immovable handle in its hand, the activity of some primary motor cortex neurons varies with the direction of isometric forces. Each of the eight raster plots shows the activity of the same primary motor cortex neuron during five repeated force ramps in one direction. Each row shows the pattern of spikes during a single trial of the task. The position of each raster of

activity corresponds to the direction in which the monkey is generating isometric forces on the handle. The onset of the force ramp is indicated by the vertical line labeled M. The thick ticks to the left of that line in each row indicate when the target appeared on a computer monitor, telling the monkey the direction in which it should push on the handle. The central polar plot illustrates the directional tuning function of the neuron as a function of the direction of isometric forces. Note the similarity of the shapes of the tuning function for the direction of whole-arm isometric forces here and for whole-arm reaching movements in Figure 37–10A. (Reproduced, with permission, from Sergio and Kalaska 2003.)

Finally, several studies have found that the activity of some motor cortex neurons can be correlated with the detailed contraction patterns of specific muscles during such diverse tasks as isometric force generation, precision pinching of objects between the thumb and index finger, and complex reaching and grasping actions (Figure 37–15).
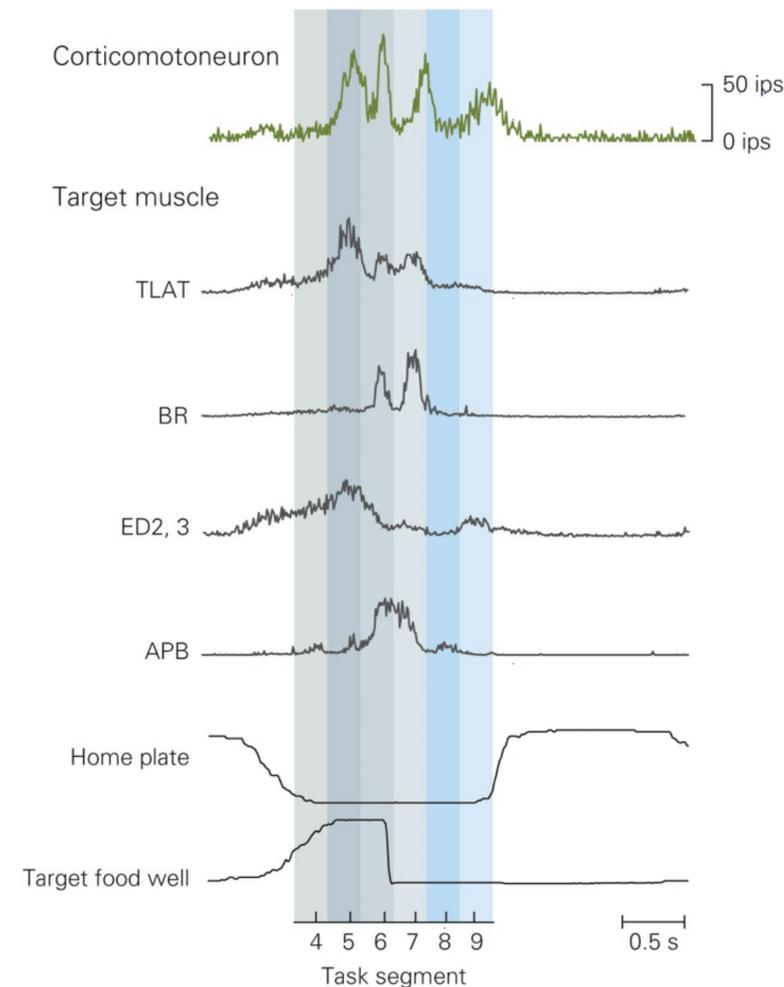
Figure 37–15 The activity of some primary motor cortex neurons can be correlated with particular patterns of muscle activity. The bursts of activity in a single corticomotoneuron during a reach-and-grasp movement to retrieve food pellets from a small well are correlated with bursts of contractile activity in several of its target muscles at different times during the movement. (**APB**, abductor pollicis brevis; **BR**, brachioradialis; **ED2, 3**, extensor digitorum 2, 3; **TLAT**, lateral triceps.) (Reproduced, with permission, from Griffin et al. 2008.)

These findings show that some neurons in the primary motor cortex can provide information about the causal forces and muscle activity of motor outputs. Nevertheless, the activity of other neurons in the primary motor cortex appears to signal the desired kinematics of arm and hand movements rather than their kinetics, or the desired direction of isometric force but not its magnitude. Perhaps most surprisingly, the activity of some corticomotoneurons does not always correlate with the contraction of their target muscles. For instance, some corticomotoneurons discharge strongly while a monkey generates weak contractions of the target muscles to make carefully controlled delicate movements of the hand and fingers, but are nearly silent when the monkey generates powerful contractions of the same muscles to make brisk, forceful movements.

How can we reconcile these apparently contradictory findings about the role of the primary motor cortex in the control of movement? According to the serial model of motor control all of the neurons in the primary motor cortex should have similar properties and so should represent either the kinematics or kinetics of the desired movement, but not both. However, the experimental evidence suggests that a strictly serial model is too simplistic. The response properties of primary motor cortex neurons are not homogeneous. Signals about both the desired kinematics and required kinetics of movements may be generated simultaneously in different, or possibly even overlapping, populations of primary motor cortex neurons. Rather than representing only what movement to make (kinematics) or how to make it (kinetics), the true role of the motor cortex may be to perform the transformation between these two representations of voluntary movements.

Delineating the movement-related information encoded in motor cortex activity is increasingly important for the development of brain-controlled interfaces and neuroprosthetic controllers that allow patients with severe motor deficits to control remote devices such as a computer cursor, a wheelchair, or a robotic limb by neural activity alone (Box 37–3).

Hand and Finger Movements Are Directly Controlled by the Motor Cortex

The monosynaptic projection from the primary motor cortex onto spinal motor neurons is most dense for muscles of the distal arm, hand, and fingers. This arrangement allows the primary motor cortex to regulate the activity of those muscles directly, in contrast to its indirect regulation of muscles through the reflex and pattern-generating functions of the spinal circuits. It also provides primates and humans with a greatly enhanced capacity for individuated control of hand and finger movements. Large lesions of the primary motor cortex permanently destroy this capacity.

Although monkeys and humans can make isolated movements of the thumb and fingers, most hand and finger actions involve combinations of stereotypical hand and finger configurations and coordinated wrist and digit movements. This has led to the hypothesis that separate cortical circuits selectively control these different stereotypical hand actions, and that the primary motor cortex converts these signals into more specific motor commands (see Chapter 38).

The anatomy of the muscles of the wrist and fingers further complicates the commands for individuated finger and hand movements. Several muscles have long, bifurcating tendons that act across several joints and even act on several fingers rather than just one. As a consequence, individuated control of hand and finger movements requires highly specific patterns of activation and inhibition of multiple muscles.

Cortical neurons controlling the hand and digits occupy the large central core of the primary motor cortex motor map but also overlap extensively with populations of neurons controlling more proximal parts of the arm (see Figure 37-2A). Some neurons within the central core discharge preferentially during movements of a single digit, but many discharge during coordinated movements of several digits, and even of the wrist and more proximal joints. Neurons that discharge during movements of different digits are distributed throughout the motor map in an exten-

sively overlapping fashion. As a result, neural activity required to generate an individuated action of the hand and digits is distributed broadly across the distal arm and hand areas of the motor map, as is also the case for the output to more proximal parts of the arm.

This highly intermixed organization of the hand and digit motor map stands in striking contrast to the much more highly ordered representation of tactile sensory inputs from different parts of the hand and digits in the primary somatosensory cortex. This difference likely reflects differences in the cortical mechanisms required to analyze the spatiotemporal distribution of tactile input on the hand and digits versus those needed to coordinate individuated movements of the digits and hand.

Sensory Inputs from Somatic Mechanoreceptors Have Feedback, Feed-Forward, and Adaptive Learning Roles

Many primary motor cortex neurons receive sensory input from proprioceptors or cutaneous mechanoreceptors. The tactile input is particularly prominent on neurons implicated in the control of hand and digit movements. These inputs inform the motor system about the current state of the body, such as the position, posture, and movement of the arm and hand and their interactions with the environment. This information can play at least three functional roles: in feedback control of ongoing movements, in feed-forward control of intended movements, and as a teaching signal during motor learning.

Sensory feedback from the arm provides information about both the progress of an ongoing arm movement and deviations from the intended path that should be corrected. Feedback corrections during movement are implemented by neural circuits at many levels of the motor system, ranging from reflex responses in the spinal cord to corrective adjustments of voluntary motor commands from the motor cortex. Similarly, the activity of many neurons in the primary motor cortex that control hand movements is strongly influenced by tactile stimuli on the glabrous surface of the digits and palm of the hand. This tactile input helps adjust the output signal from hand-related neurons to ensure that the subject applies enough force to the surface of an object to grasp and manipulate it, but not to crush it or let it slip.

Sensory feed-forward control involves continuously adjusting the level and distribution of neuronal activity throughout the cortical motor map to reflect the limb's current state of posture and movement. By pretuning the pattern of activity in the motor-cortical map and spinal motor apparatus as a function of the limb's motor state before the onset of a movement, somatic sensory input helps to assure that the appropriate motor command is generated in the motor cortex and converted into the appropriate patterns of muscle activity at the spinal level.

Finally, sensory input can provide information about errors experienced during movement that could be used by adaptive motor circuits to make changes to future motor commands, thus facilitating motor learning.

The Motor Map Is Dynamic and Adaptable

The mediolateral sequence of major body segments in the motor map is highly consistent across individuals, but the details in each functional subregion can vary. This suggests that the motor map is continually shaped by an individual's motor experience. The dynamic nature of the map has been demonstrated in several ways. For instance, functional reorganization often occurs after a focal lesion so that some of the movements that had been evoked by the injured tissue are now generated by the adjacent cortex. This reorganization likely contributes to the recovery of function after local infarcts.

Learning a motor skill can also induce reorganization. Randy Nudo and colleagues trained monkeys to use precise movements of the thumb, index finger, and wrist to extract treats from a small well. After a monkey had become adept at the task, the area of its motor map in which intracortical microstimulation could evoke the skilled movements was larger than before training (Figure 37–16). If the monkey did not practice the task for a lengthy period, its skill level decreased, as did the cortical area from which the relevant movements could be elicited. Similar modifications of the representation of practiced actions have also been demonstrated in human motor cortex by functional imaging and transcranial magnetic stimulation.
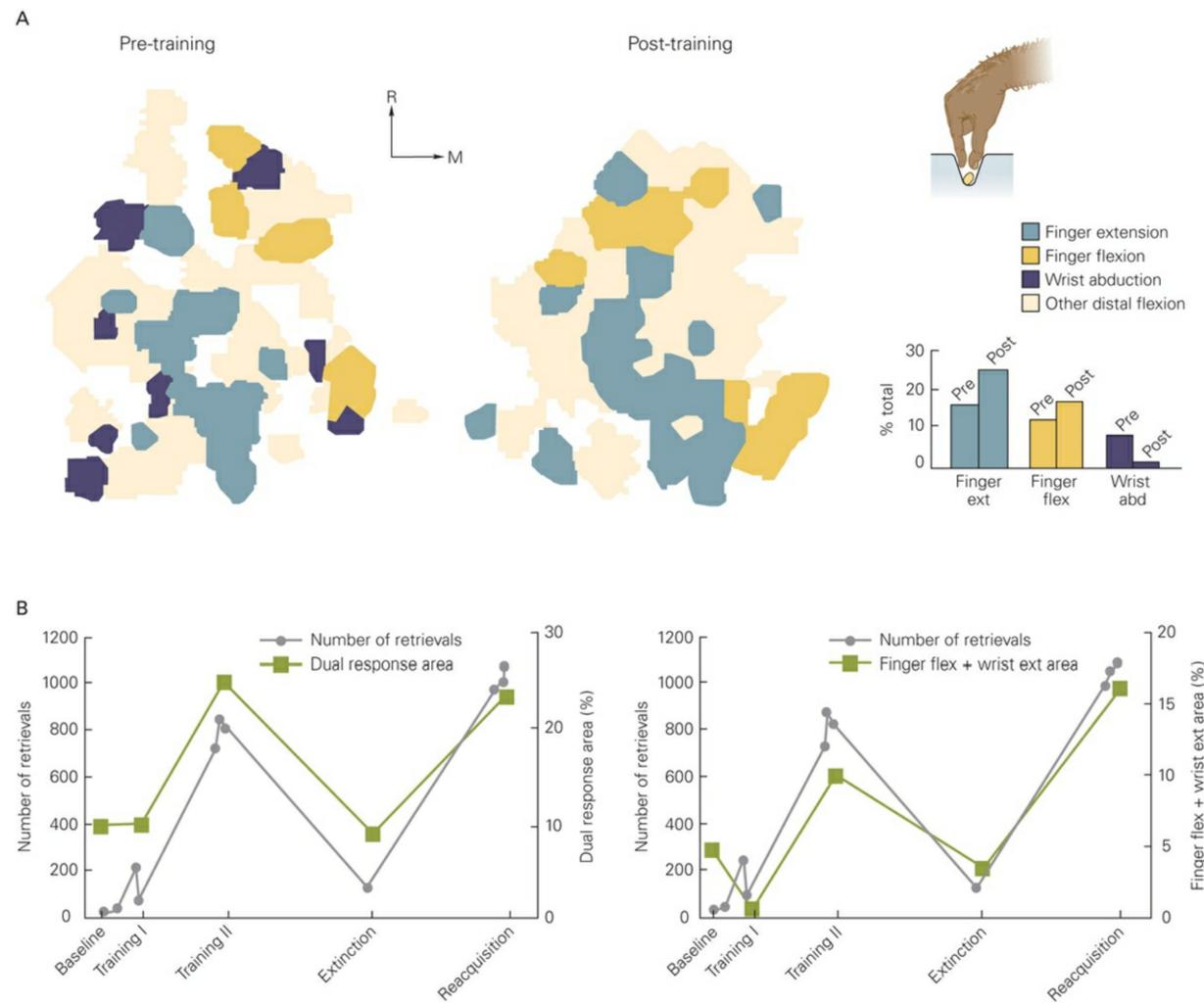
Figure 37–16 Learning a motor skill changes the organization of the motor map. (Reproduced, with permission, from Nudo et al. 1996.)

A. Motor maps for the hand in a monkey before and after training on retrieval of treats from a small well. Before training output sites that generate index finger and wrist movements occupy less than half of a monkey's motor map. After training the area from which those trained movements can be evoked by intracortical microstimulation expands substantially. The area of the map from which one could elicit individuated movements such as finger extension and flexion has expanded considerably, while the areas controlling wrist abduction, which this monkey used less in the new skill, became less prominent. (R, rostral; M, medial.)

B. The areas of the motor output map from which the trained movements can be evoked parallel the level of performance (number of successful pellet retrievals) during acquisition of the motor skill and extinction (due to lack of practice). Two areas were tested: a "dual response" area (**left plot**), from which any combination of finger and wrist motions could be evoked, and an area from which the specific combination of finger flexion and wrist extension could be evoked (**right plot**). Both areas increased as the monkey's skill improved with practice and decreased as the monkey's skill was extinguished through lack of practice. These data are from a different monkey than the one in part A but one that was trained in the same task.

> **Box 37–3 Enhancing the Quality of Life of Neurological Patients: Brain-Machine Interfaces**
>
> Every year thousands of people suffer severe spinal cord trauma, subcortical strokes, or degenerative neuromuscular diseases such as multiple sclerosis and amyotrophic lateral sclerosis. Although their cortical motor systems remain largely intact and they try strenuously to move, they cannot convert their willful intentions into physical action.
>
> These patients must depend on caregivers to attend to even their most basic needs. One of the greatest quality-of-life issues for these patients is the loss of autonomy resulting from the inability to move and sometimes even to communicate. Several technological solutions have been sought to enhance the autonomy of such patients.
>
> One approach has been to use electroencephalographic activity recorded by scalp electrodes as a control signal for remote devices such as computer cursors or robotic tools. An alternative approach has been to record the eye movements of subjects and to use them as the control signals.
>
> However, both methods have significant limitations. Electroencephalographic control often takes months to master because the subjects must learn how to synchronize the activity of large populations of neurons within a cortical region to generate an electrical signal that is recordable and discriminable in real time and without extensive averaging of multiple repetitions.
>
> Eye-movement methods are much easier to implement and learn,

but they prevent subjects from looking toward other objects of interest while attempting to perform a task. Moreover, both approaches require intense concentration and the focused attention of the subjects to the virtual exclusion of all other activities.

A major recent advance has been the development of brain-machine interfaces (also often called brain-computer, brain-controlled, or neuroprosthetic interfaces). This technology records neural activity reflecting the motor intentions of the individual and converts this activity into control signals for external devices. It exploits the discovery that information about static arm postures and the direction and velocity of arm movements can be extracted from the activity patterns of neuronal populations in the primary motor cortex and other arm movement-related areas of the cerebral cortex.

Brain-machine interfaces include four basic components:

1. Implantable electrode arrays and associated hardware to record the activity of neuronal populations in a cortical area.

2. Computer algorithms to extract signals about the motor intentions of the individual.

3. Interfaces to convert the extracted signals into control signals to generate the desired action by an external effector.

4. Sensory feedback signals to improve performance.

Originally tested in experimental animals, brain-machine interfaces are now undergoing clinical trials in human neurological patients. Severely paralyzed patients with multi-electrode arrays in the primary motor cortex are quickly able to learn to control a cursor on a computer monitor so as to operate computer programs, compose messages, track the random motions of a moving target, and control a simple robotic arm. The subjects are able to control the remote effectors merely by thinking about making the corresponding movements.

The centrally generated intentions activate motor cortex neurons in a manner similar to that during normal movements. The subjects can control the devices while at the same time engaged in other activities such as looking around the laboratory or even engaging in conversations. This ability dramatically illustrates the fact that much of the cortical activity that converts a motor intention into overt action occurs in the subconscious.

The initial studies using this technology demonstrated that electrodes implanted in different cortical areas yield different types of neural signals. Electrodes in the primary motor cortex provide the best signals for continuous control of the time-varying details of the kinematics and kinetics of the trajectory of a robotic device. Such control is particularly useful for tasks like manipulating objects and for making complex movements as in drawing or writing.

In contrast, signals from the premotor cortex and posterior parietal cortex may be more appropriate for specifying the overall goals and desired outcome of an action, such as the final target location, without elaborating the details of how to accomplish the goal.

A brain-controlled interface that uses a combination of signals from different cortical areas might afford a level of context-dependent control that resembles the normal voluntary control of behavior.

John Donoghue and colleagues demonstrated that these adaptive changes depend on horizontal connections and local inhibitory circuits. They found two adjacent sites in the rat's motor map at which intracortical microstimulation caused contractions of muscles in the upper lips or forearm (Figure 37–17A). Within minutes after transection of the facial nerve innervating the lip muscles, stimulation of the lip-muscle site began to evoke contractions of forearm muscles.
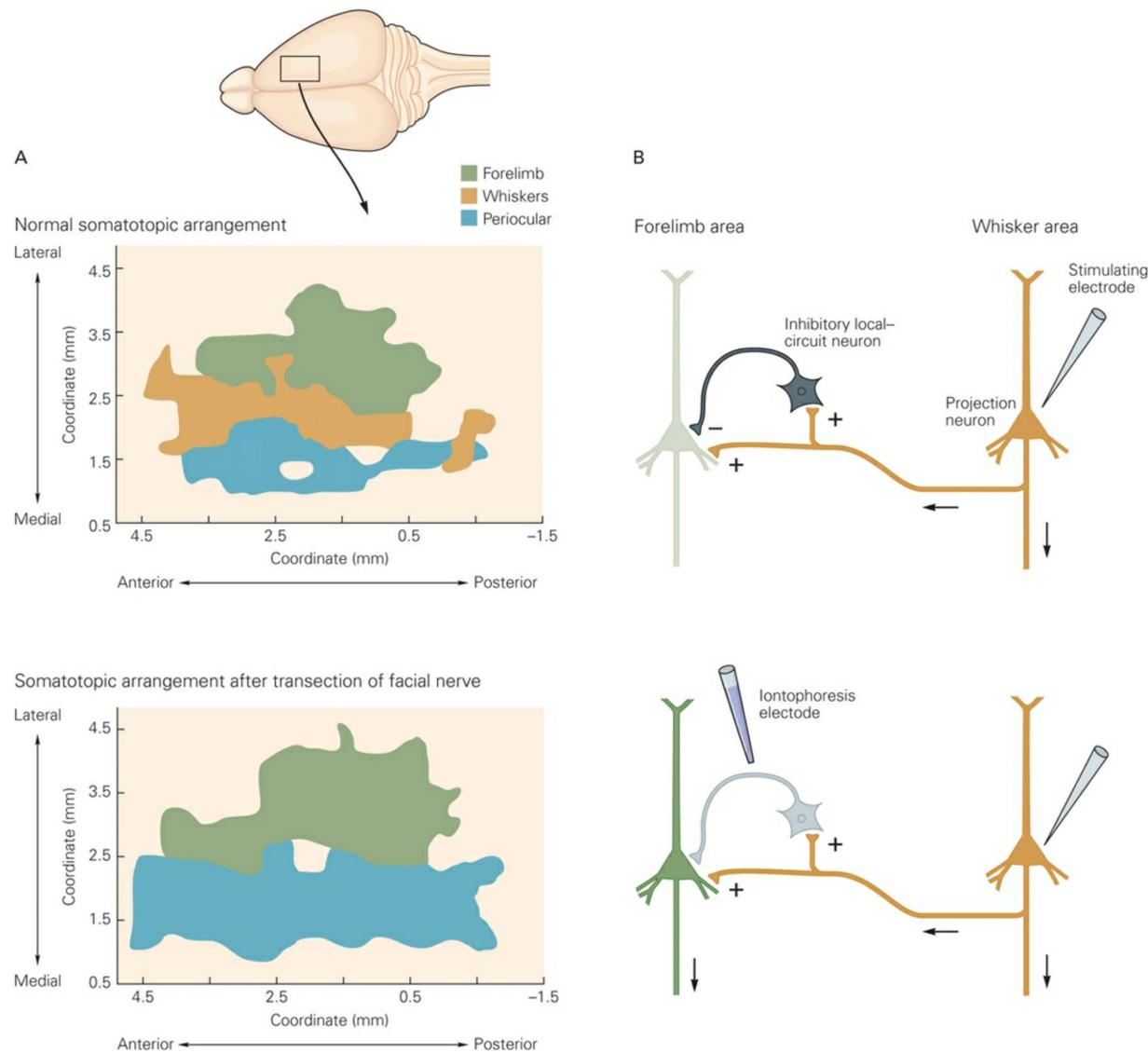
Figure 37–17 The functional organization of the motor map of a rat changes rapidly after transection of the facial nerve. (Reproduced, with permission, from Sanes et al. 1988 and from Jacobs and Donoghue 1991.)

A. A surface view of the rat's frontal cortex shows the normal somatotopic arrangement of areas representing forelimb, whisker, and periocular muscles. Within minutes after transection of the branches of the facial nerve that innervate whiskers, stimulation of cortical sites that formerly activated whisker muscles causes contraction of forelimb and periocular muscles.

B. Elimination of the sensory inputs after transection of the facial nerve may lead to rapid changes in the balance of local inhibitory circuits in the motor cortex. Under normal conditions (**top**) the excitatory effect of horizontal axonal projections between different parts of the motor map is subject to inhibition mediated by local inhibitory interneurons, so that electrical stimulation of a whisker site evokes contractions of only whisker muscles and not forelimb muscles. Iontophoretic injection of bicuculline into a forelimb site in the motor map blocks local GABA-mediated inhibition (**bottom**). As a result, stimulation of whisker sites can excite output neurons in forelimb and periocular sites through horizontal axonal collaterals whose influence is normally restricted by inhibitory interneurons.

In a related experiment they injected bicuculline into a forearm-muscle site in the motor cortex of an intact rat without a facial nerve transection to block the neurotransmitter GABA (ɣ-aminobutyric acid). Within minutes stimulation of the lip-muscle site evoked contractions of both lip and forearm muscles. They concluded that stimulation of the lip-muscle site activated local horizontal axons that projected into the forearm-muscle site, activity that was normally suppressed by GABAergic inhibitory interneurons (Figure 37–17B).

The Motor Cortex Contributes to Motor Skill Learning

One of the most remarkable properties of the brain is the adaptability of its circuitry to changes in the environment—the capacity to learn from experience and store the acquired knowledge as memories. When human subjects practice a motor skill their performance improves. Important advances have been made in understanding the mechanisms underlying the learning of motor skills, also known as procedural learning (see Chapter 66). For instance, Donoghue and colleagues found an increase in the synaptic strength of local horizontal connections between different parts of the arm motor map in rats that became increasingly skilled at reaching through a small hole in a transparent barrier to grasp, retrieve, and eat small food pellets.

Adaptation to perturbations of movement caused by external forces has been studied extensively in human subjects. One type of force field pushes on the arm in a direction perpendicular to the direction of the arm's movement; the strength of this force increases with movement

speed. Although such *viscous curl* fields may seem odd, they are exactly the kind of forces that act on an arm when a person reaches out while simultaneously turning his or her body. Normally, these coriolis forces do not deflect the arm movement from its intended path because your motor system has learned to predict that these forces will arise during this natural behavior and generates a motor command that corrects for them in advance.

However, when a subject is stationary and unexpectedly encounters an experimentally generated viscous curl field for the first time during an arm movement, the arm is deflected sideways from its usual, nearly straight path and the hand path becomes curved. When the subject makes repeated movements in the same field, the movement paths become incrementally straighter until they are indistinguishable from movements without the curl field. If the force field is then unexpectedly turned off, the path of movement curves strongly in the opposite direction (Figure 37–18A). This *after-effect* demonstrates that the subject has changed the motor command required to produce the desired straight movement in anticipation of the perturbing effect of the force field.
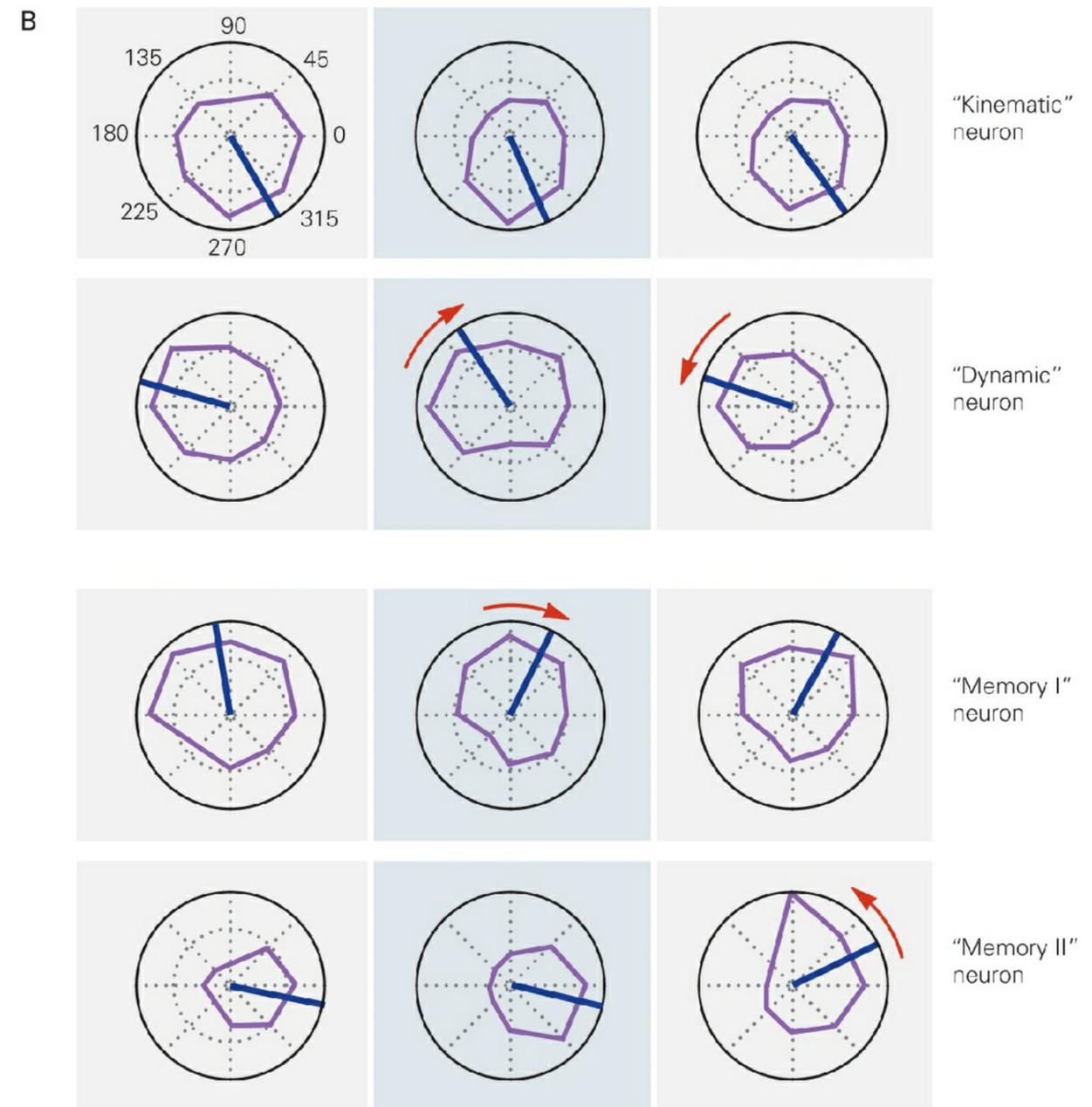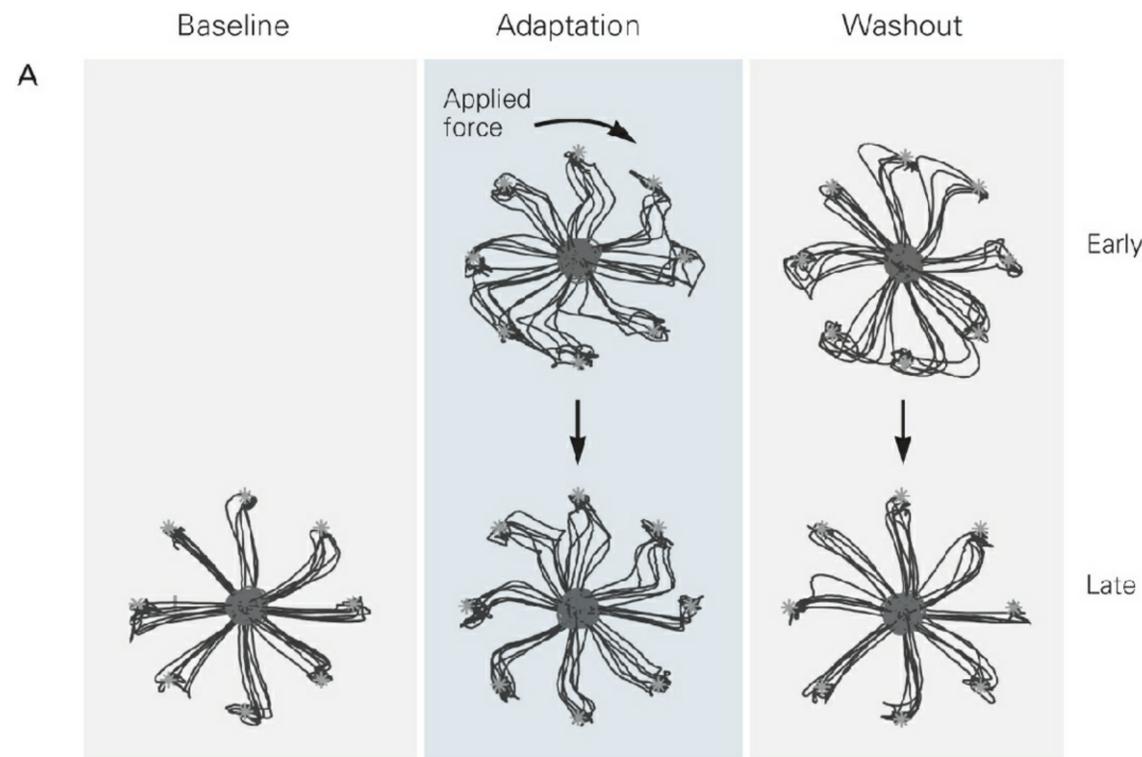

Figure 37–18 Different motor cortex neurons may contribute to different aspects of adaptation to an external force field.

A. The records depict the hand paths of reaching movements from a central position to eight peripheral targets prior to and during adaptation to an external force field and then during the return to original baseline conditions. Paths are generally straight when no external force field is applied during reaching to the targets (**late baseline**). When a viscous curl field pushes the arm in the clockwise direction (**arrow**) hand paths are initially curved in the clockwise direction (**early**

adaptation). After approximately 150 trials the paths become much straighter, indicating that the subject has learned to correct for the perturbing effect of the external force field (**late adaptation**). When the external field is abruptly removed, the paths in the first few trials are curved in the opposite direction (**early washout**), indicating that the exposure to the force field had led to a change in the subject's internal model of the environment to reflect the presence of the field. It takes several trials in the original conditions before the after-effect of the learning episode is no longer evident in hand kinematics (**late washout**). (Adapted, with permission, from Padoa-Schioppa, Li, and Bizzi 2004.)

B. Response patterns of four motor cortex neurons during and after adaptation to arm movement in a viscous curl field. All four neurons were directionally tuned in the baseline conditions (**left column**). The tuning of some neurons changed only during adaptation ("memory I" neuron); only during washout, that is, readaptation to the baseline conditions ("memory II" neuron); or both ("dynamic" neuron). Muscles showed the same pattern of responses as the "dynamic" neuron, implicating this neuron in the control of the forces needed to compensate for the field. (Adapted, with permission, from Li, Padoa-Schioppa, and Bizzi 2001.)

As a subject adapts to the force field, motor behavior changes from feedback correction for actual perturbations to predictive feed-forward compensation for expected perturbation. Motor-learning theory suggests that this adaptive process may involve at least two distinct learning mechanisms, known as feedback-error learning and supervised learning.

In *feedback-error learning* sensory signals about the experienced error both guide the correction for the immediate perturbation and alter adaptive feedback control circuits to permit more efficient compensation for expected perturbation. In *supervised learning* the motor system gradually adapts internal models, neural circuits that learn the relationship between desired movements and required motor commands in that environment (see Chapter 33). An internal *forward model* estimates the state of the limb in the near future based on an efference copy of the motor command and sensory feedback of the ongoing movement, and uses this estimate to generate an error signal proportional to the deviation of the estimated movement from its desired kinematics. An internal *inverse model* uses this and other error signals to learn how to generate the motor command that will produce a desired movement by compensating in a predictive manner for the anticipated perturbation. Neural circuits that constitute these internal forward and inverse models are thought to be located in several brain structures, including the cerebellum, superior parietal cortex, premotor cortex, and primary motor cortex.

Emilio Bizzi and colleagues recorded the activity of the same primary motor cortex neurons over several hours in monkeys as the animals first made arm movements without an external force field, then while they made many movements to adapt to a viscous curl field, and finally while they readapted to the baseline condition (the "washout" period). As the monkeys adapted to the force field the directional tuning of many neurons gradually changed by 15 to 20 degrees from what it was before exposure to the viscous curl field, and then rotated back to the baseline during the washout period (Figure 37–18B). Arm muscles showed similar changes during adaptation and washout, implicating those neurons in the incremental adaptation of the motor command to the external curl field. Other neurons did not change directionality during either adaptation or washout, as if their signals communicated the desired movement kinematics across all force-field conditions.

Two other groups of neurons showed special properties. The directional tuning of one group changed when the monkeys switched from the null field to the curl field but did not return to baseline during washout (Figure 37–18B). The other group did not change during the original adaptation from null field to curl field but changed during washout. Bizzi proposed that these two groups of neurons retain the memory of one or the other of the successive learning episodes—adaptation and washout—in the task. That is, even though the motor performance of the monkeys returned to baseline, the functional state of the primary motor cortex did not revert to its original condition—a trace of the recent learning history persisted in the altered tuning properties of some neurons.

These and similar findings from other studies suggest that the motor map of the primary motor cortex is not static. Instead, the neuronal circuitry creates a dynamic, adaptive map that generates the motor commands required to accomplish desired actions under different conditions. This strongly implicates the primary motor cortex in the acquisition, re-

tention, and recall of procedural skills, but does not clarify whether it functions primarily as part of a feedback controller, as an inverse internal model for task dynamics, or both.

Furthermore, recent studies have found that adaptive changes in motor cortex activity lag the improvement in motor performance by several trials during adaptation. This suggests that learning-related adjustments to motor commands are initially made elsewhere, with the cerebellum as one strong candidate. The primary motor cortex may thus be more strongly involved in the slower processes of long-term retention and recall of motor skills rather than the initial phase of learning a new skill.

An Overall View

The discovery of a topographically organized map of motor outputs to different parts of the body within a limited area of the cerebral cortex provided the first compelling experimental evidence for the cortical localization of motor function. For many years thereafter the role of the motor cortex was relegated to that of a simple map of muscles and muscle activity patterns by which the rest of the cerebral cortex controlled spinal motor neurons. Terms such as "upper-motor-neuron disease" were common in the clinical literature of an earlier era, but this view of motor cortex function is simplistic and incorrect.

Although the motor cortex does play a critical role in the control of voluntary movements, its neurons do not function like spinal motor neurons whose sole role is to encode muscle activity patterns. Instead, the motor cortex contains a heterogeneous population of neurons that contribute to the several operations required to convert a plan of action into the motor commands that execute the plan. The novel evolutionary development in primates of a direct, monosynaptic projection onto spinal motor neurons enables the primary motor cortex to control movements of the hand and fingers in a uniquely skillful way. This feature has been critical in the acquisition of dexterous hand movements that only higher primates and especially humans possess.

The primary motor cortex is part of a distributed network of cortical motor areas, each with its own role in voluntary motor control. The primary motor cortex should be regarded as a dynamic computational map whose internal organization and spinal connections convert central signals about motor intentions and sensory feedback about the current state of the limb into motor output commands, rather than as a static map of specific muscles or movements of body parts. The motor cortex also provides a substrate for adaptive alterations during the acquisition of motor skills and the recovery of function after lesions.

John F. Kalaska Giacomo Rizzolatti

Selected Readings

Ashe J. 1997. Force and the motor cortex. Behav Brain Res 87:255–269.

Dum RP, Strick PL. 2002. Motor areas in the frontal lobe of the primate. Physiol Behav 77:677–682.

Kalaska JF. 2009. From intention to action: motor cortex and the control of reaching movements. Adv Exp Med Biol 629:139–178.

Lemon RN. 2008. Descending pathways in motor control. Annu Rev Neurosci 31:195–218.

Porter R, Lemon R. 1993. *Corticospinal Function and Voluntary Movement*. Oxford: Clarendon.

Rizzolatti G, Luppino G. 2001. The cortical motor system. Neuron 31:889–901.

Schieber M. 2001. Constraints on somatotopic organization in the primary motor cortex. J Neurophysiol 86:2125–2143.

Taylor CSR, Gross CG. 2003. Twitches versus movements: a story of motor cortex. Neuroscientist 9:332–342.

References

Arce F, Novick I, Mandelblat-Cerf Y, Israel Z, Ghez C, Vaadia E. 2010. Combined adaptiveness of specific motor cortical ensembles underlies learning. J Neurosci 30:5415–5525.

Asanuma H, Rosén I. 1972. Topographical organization of cortical effer-

ent zones projecting to distal forelimb muscles in the monkey. Exp Brain Res 14:243–256.

Ashe J, Georgopoulos AP. 1994. Movement parameters and neural activity in motor cortex and area 5. Cereb Cortex 4:590–600.

Caminiti R, Johnson PB, Urbana A. 1990. Making arm movements within different parts of space: dynamic aspects in the primate motor cortex. J Neurosci 10:2039–2058.

Carmena JM, Lebedev MA, Crist RE, O'Doherty JE, Santucci DM, Dimitrov D, Patti PG, Henriquez CS, Nicolelis MA. 2003. Learning to control a brain-machine interface for reaching and grasping by primates. PLoS Biol 1:193–208.

Cheney PD, Fetz EE. 1980. Functional classes of primate corticomotoneuronal cells and their relation to active force. J Neurophysiol 44:773–791.

Cheney PD, Fetz EE. 1985. Comparable patterns of muscle facilitation evoked by individual corticomotoneuronal (CM) cells and by single intracortical microstimuli in primates: evidence of functional groups of CM cells. J Neurophysiol 53:786–804.

Cheney PD, Fetz EE, Palmer SS. 1985. Patterns of facilitation and suppression of antagonist forelimb muscles from motor cortex sites in the awake monkey. J Neurophysiol 53:805–820.

Evarts EV. 1968. Relation of pyramidal tract activity to force exerted during voluntary movement. J Neurophysiol 31:14–27.

Evarts EV, Fromm C, Kröller J, Jennings VA. 1983. Motor cortex and control of finely graded forces. J Neurophysiol 49:1199–1215.

Fetz EE, Cheney PD. 1980. Postspike facilitation of forelimb muscle activity by primate corticomotoneuronal cells. J Neurophysiol 44:751–772.

Fetz EE, Finocchio DV. 1975. Correlations between activity of motor cortex neurons and arm muscles during operantly conditioned response patterns. Exp Brain Res 23:217–240.

Georgopoulos AP, Ashe J, Smyrnis N, Taira M. 1992. The motor cortex and the coding of force. Science 256:1692–1695.

Georgopoulos AP, Caminiti R, Kalaska JF, Massey JT. 1983. Spatial coding of movement: A hypothesis concerning the coding of movement direction by motor cortical populations. Exp Brain Res Suppl 7:327–336.

Georgopoulos AP, Kalaska JF, Caminiti R, Massey JT. 1982. On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. J Neurosci 2:1527–1537.

Georgopoulos PA, Merchant H, Naselaris T, Amirikian B. 2007. Mapping of the preferred direction in the motor cortex. Proc Natl Acad Sci USA 104:11068–11072.

Gribble PL, Scott SH. 2002. Overlap of internal models in motor cortex for mechanical loads during reaching. Nature 417:938–941.

Griffin DM, Hudson HM, Belhaj-Saïf A, Cheney PD. 2009. Stability of output effects from motor cortex to forelimb muscles in primates. J Neurosci 29:1915–1927.

Griffin DM, Hudson HM, Belhaj-Saïf A, McKiernan BJ, Cheney PD. 2008. Do corticomotoneuronal cells predict target muscle EMG activity? J Neurophysiol 99:1169–1186.

He SQ, Dum RP, Strick PL. 1993. Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere. J Neurosci 13:952–980.

Hochberg, LR, Serruya, MD, Friehs GM, Mukand JA, Saleh M, Caplan AH, Branner A, Chen D, Penn RD, Donohgue JP. 2006 Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature 442:164–171.

Hoffman DS, Strick PL. 1995. Effects of a primary motor cortex lesion on step-tracking movements of the wrist. J Neurophysiol 73:891–895.

Humphrey DR, Schmidt EM, Thompson WD. 1970. Predicting measures of motor performance from multiple cortical spike trains. Science 170:758–762.

Humphrey DR, Tanji J. 1991. What features of voluntary motor control are encoded in the neuronal discharge of different cortical areas? In: DR Humphrey, H-J Freund (eds). *Motor Control: Concepts and Issues*, pp 413–443. New York: Wiley.

Jackson A, Mavoori J, Fetz EE. 2007. Correlations between the same motor

cortex cells and arm muscles during a trained task, free behavior, and natural sleep in the macaque monkey. J Neurophysiol 97:360–374.

Jacobs KM, Donoghue JP. 1991. Reshaping the cortical motor map by unmasking latent intracortical connections. Science 251:944–947.

Kakei S, Hoffman DS, Strick PL. 1999. Muscle and movement representations in the primary motor cortex. Science 285:2136–2139.

Kalaska JF, Cohen DA, Hyde ML, Prud'Homme M. 1989. A comparison of movement direction-related versus load direction-related activity in primate motor cortex, using a two-dimensional reaching task. J Neurosci 9:2080–2102.

Lawrence DG, Kuypers HG. 1968. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. Brain 91:1–14.

Lemon RN. 1981. Functional properties of monkey motor cortex neurones receiving afferent input from the hand and fingers. J Physiol 311:497–519.

Li CS, Padoa-Schioppa C, Bizzi E. 2001. Neuronal correlates of motor performance and motor learning in the primary motor cortex of monkeys adapting to an external force field. Neuron 30:593–607.

Maier MA, Bennett KM, Hepp-Reymond MC, Lemon RN. 1993. Contribution of the monkey corticomotoneuronal system to the control of force in precision grip. J Neurophysiol 69:772–785.

McKiernan BJ, Marcario JK, Kerrer JH, Cheney PD. 2000. Correlations between corticomotoneuronal (CM) cell postspike effects and cell-target muscle covariation. J Neurophysiol 83:99–115.

Moran DW, Schwartz AB. 1999. Motor cortical activity during drawing movements: population representation during spiral tracing. J Neurophysiol 82:2693–2704.

Morrow MM, Jordan LR, Miller LE. 2007. Direct comparison of the task-dependent discharge of M1 in hand space and muscle space. J Neurophysiol 97:1786–1798.

Muir RB, Lemon RN. 1983. Corticospinal neurons with a special role in precision grip. Brain Res 261:312–316.

Murphy JT, Kwan MC, MacKay WA, Wong YC. 1978. Spatial organization of precentral cortex in awake primates. III. Input-output coupling. J Neurophysiol 41:1132–1139.

Musallam S, Corneil BD, Greger B, Scherberger H, Andersen RA. 2004. Cognitive control signals for neural prosthetics. Science 305:258–262.

Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. 1996. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. J Neurosci 16:785–807.

Li C-SR, Padoa-Schioppa C, Bizzi E. 2001. Neuronal correlates of motor performance and motor learning in the primary motor cortex of monkeys adapting to an external force field. Neuron 30:593–607.

Padoa-Schioppa C, Li CS, Bizzi E. 2004. Neuronal activity in the supplementary motor area of monkeys adapting to a new dynamic environment. J Neurophysiol 91:449–473.

Paninski L, Fellows MR, Hatsopoulos NG, Donoghue JP. 2004. Spatiotemporal tuning of motor cortical neurons for hand position and velocity. J Neurophysiol 91:515–532.

Park MC, Belhaj- Saïf A, Cheney PD. 2004. Properties of primary motor cortex output to forelimb muscles in rhesus macaques. J Neurophysiol 92:2968–2984.

Park MC, Belhaj-Saïf A, Gordon M, Cheney PD. 2001. Consistent features in the forelimb representation of primary motor cortex in rhesus macaques. J Neurosci 21: 2784–2792.

Paz R, Boraud T, Natan, Bergman H, Vaadia E. 2003. Preparatory activity in motor cortex reflects learning of local visuomotor skills. Nat Neurosci 6:882–890.

Rathelot JA, Strick PL. 2006. Muscle representation in the macaque motor cortex: an anatomical perspective. Proc Natl Acad Sci USA 103:8257–8262.

Rioult-Pedotti MS, Friedman D, Hess G, Donoghue JP. 1998. Strengthening of horizontal cortical connections following skill learning. Nat Neurosci 1:230–234.

Rosén I, Asanuma H. 1972. Peripheral afferent inputs to the forelimb area

of the monkey motor cortex: input-output relations. Exp Brain Res 14:257–273.

Sanes JN, Suner S, Lando JF, Donoghue JP. 1988. Rapid reorganization of adult rat motor cortex somatic representation patterns after motor nerve injury. Proc Natl Acad Sci USA 85:2003–2007.

Schwartz AB. 1993. Motor cortical activity during drawing movements: population representation during sinusoidal tracing. J Neurophysiol 70:28–36.

Schwartz AB, Kettner RE, Georgopoulos AP. 1988. Primate motor cortex and free arm movements to visual targets in three-dimensional space. I. Relations between single cell discharge and direction of movement. J Neurosci 8:2928–2937.

Scott SH, Kalaska JF. 1997. Reaching movements with similar hand paths but different arm orientations. I. Activity of individual cells in motor cortex. J Neurophysiol 77: 826–852.

Sergio LE, Kalaska JF. 2003. Systematic changes in motor cortex cell activity with arm posture during directional isometric force generation. J Neurophysiol 89:212–228.

Sergio LE, Hamel-Pâquet C, Kalaska JF. 2005. Motor cortex neural correlates of output kinematics and kinetics during isometric-force and arm-reaching tasks. J Neurophysiol 94:2353–2378.

Shen L, Alexander GE. 1997. Neural correlates of a spatial sensory-to-motor transformation in primary motor cortex. J Neurophysiol 77:1171–1194.

Shinoda Y, Yokota J, Futami T. 1981. Divergent projections of individual corticospinal axons to motoneurons of multiple muscles in the monkey. Neurosci Lett 23:7–12.

Smith AM, Hepp-Reymond MC, Wyss UR. 1975. Relation of activity in precentral cortical neurons to force and rate of force change during isometric contractions of finger muscles. Exp Brain Res 23:315–332.

Thach WT. 1978. Correlation of neural discharge with pattern and force of muscular activity, joint position, and direction of intended next arm movement in motor cortex and cerebellum. J Neurophysiol 41:654–476.

Townsend BR, Paninski L, Lemon RN. 2006. Linear coding of muscle activity in primary motor cortex and cerebellum. J Neurophysiol. 96:2578–2592.

Velliste M, Perel S, Spalding MC, Whitford AS, Schwartz AB. 2008. Cortical control of a prosthetic arm for self-feeding. Nature 453:1098–1101.

Wise SP, Moody SL, Blomstrom KJ, Mitz AR. 1998. Changes in motor cortical activity during visuomotor adaptation. Exp Brain Res 121:285–299.