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The Organization of Movement

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IN THE PRECEDING PART of this book we considered how the brain constructs internal representations of the world by integrating information from the different sensory systems. These sensory representations are the framework in which the motor systems plan, coordinate, and execute the motor programs responsible for purposeful movement. In this part of the book we shall learn how the motor systems of the brain and spinal cord allow us to maintain balance and posture, to move our body, limbs, and eyes, and to communicate through speech and gesture. In contrast to sensory systems, which transform physical energy into neural signals, motor systems produce movement by translating neural signals into contractile force in muscles.

Just as our perceptual skills reflect the capabilities of the sensory systems to detect, analyze, and estimate the significance of physical stimuli, our motor agility and dexterity reflect the capabilities of the motor systems to plan, coordinate, and execute movements. The accomplished pirouette of a ballet dancer, the powered backhand of a tennis player, the fingering technique of a pianist, and the coordinated eye movements of a reader all require a remarkable degree of motor skill that no robot approaches. Yet, once trained, the motor systems execute the motor programs for each of these skills with ease, for the most part automatically.

The ability of humans to carry out skilled movements while still performing cognitive tasks—such as thinking while using tools or speaking while walking—requires flexibility and skills no other animal has. A striking aspect of motor function is the effortlessness with which we carry out the most complicated motor tasks without a thought given to the actual joint motions

or muscle contractions required. Although we are consciously aware of the intent to perform a task, such as driving a car, and planning certain sequences of actions, and at times we are aware of deciding to move at a particular moment, the details of our movements generally seem to occur automatically. The tennis player need not consciously decide which muscles to contract to return a serve with a backhand or which head motions and body parts must be moved to intercept the ball. In fact, thinking about each body movement before it takes place would disrupt the player's performance. Thus, conscious processes are not necessary for the moment-to-moment control of movement.

The graceful and effortless quality of normal movement carried out automatically depends on a continuous flow of visual, somatosensory and postural information to the motor systems. The “effortless” quality of normal motor control is frequently lost if the motor systems are deprived of a continuous flow of sensory information, from vision, somatic sensation, and vestibular inputs. Vision is particularly important to guiding movement and provides critical cognitive information about the location and shape of objects. The blind must explore space using tactile and kinesthetic cues, a more lengthy process, and they need to rely more on memorized representations of the locations of objects than do sighted persons. Similarly, movements become inaccurate and posture unstable when somatic sensation is lost from the limbs and posture changes. Loss of vestibular input also impairs ability to maintain balance and orientation.

Successively higher levels of the motor hierarchy specify increasingly more complex aspects of a motor task. This hierarchy of motor representations depends on a parallel hierarchy of sensory input; more complex sensory information is extracted, at each level, from the spinal cord to the motor cortex. The crucial insight that the components of the motor systems are organized hierarchically was first obtained in the eighteenth century in studies that showed the spinal cord severed from the brain stem and forebrain is capable of organized behaviors. These relatively automatic behaviors include rhythmic behaviors, such as breathing or running as well as reflexes, such as the knee jerk or coughing. These patterned responses to sensory stimuli differ according to the level at which the neuraxis is transected. These differences therefore provide useful clinical indicators of the level of a lesion and of the integrity of afferent and efferent pathways.

Because these movements are so stereotyped, in contrast to the endless variety of voluntary movements, reflex and voluntary movements were originally thought to be controlled by qualitatively different neuronal mechanisms. At the beginning of the twentieth century, however, Charles Sherrington in England proposed that voluntary movements represent chains of reflex responses linked together by the brain. Although this is not correct, the spinal cord does contain local circuits that coordinate reflexes, and these same circuits participate in more complex voluntary movements governed by higher brain centers.

In this chapter we first review the principles that govern various classes of movement and action. We shall learn how motor psychophysical studies of movement describe the relationships between intended actions and performance, just as sensory psychophysical studies relate physical stimuli to sensory experience in a quantitative way (Chapter 2). The lawful relationships emerging from these studies provide critical insights into how motor systems operate. Finally, we review the overall anatomical organization of the motor systems, from local spinal reflex circuits to the systems of the brain stem and the cerebral cortex that coordinate simple muscle contractions into elaborate purposeful actions.

The Motor Systems Generate Reflexive, Rhythmic, and Voluntary Movements

Just as there are distinct modalities of sensation, there are three distinct categories of movement: reflexive, rhythmic, and voluntary.

Reflexive and Rhythmic Movements Are Produced by Stereotyped Patterns of Muscle Contraction

Reflexes are *involuntary* coordinated patterns of muscle contraction and relaxation elicited by peripheral stimuli. They are typically isolated in animals in which motor pathways from higher brain centers to the spinal cord have been cut (such animals are called *decerebrate* or *spinal* animals depending on the level of the cut). The spatial and temporal patterns of muscle contraction vary in different reflexes, depending on the type of sensory receptors that are stimulated. Receptors in muscles produce stretch reflexes whereas cutaneous receptors produce withdrawal reflexes. In reflexes the particular muscles that contract in response to a stimulus vary with the site of stimulation, a phenomenon termed *local sign.* If external conditions remain the same, a given stimulus will elicit the same response time after time. However, both the intensity of the response and the local sign of reflexes can be modulated by mechanisms that switch the patterns of connections of afferent fibers to spinal interneurons

and motor neurons depending on the context of the behavior. We consider reflexes in greater detail in Chapter 36.

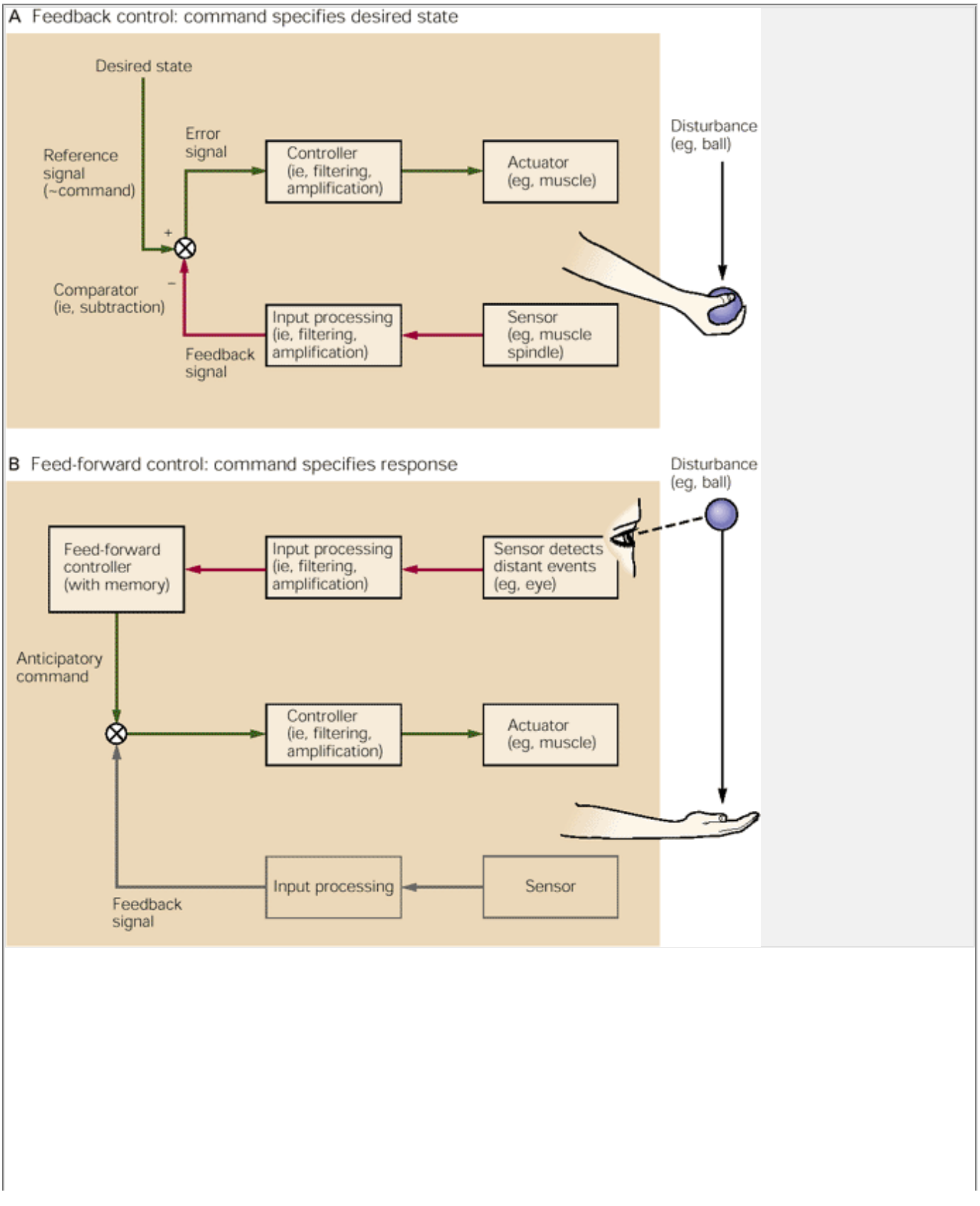

Figure 33-1 Feed-forward and feedback control circuits.

A. In a feedback system a signal from a sensor is compared with a reference signal by a comparator. The difference, the error signal, is sent to a controller and causes a proportional change in output to the actuator. For example, if the task is to maintain the elbow at a given angle, the muscles are the actuators and the controlled system is the elbow. The reference signal specifies the muscle contraction required to maintain the joint at the required angle. Proprioceptive or visual information about the current elbow angle provides the feedback. The difference between the current and the reference angle determines the degree to which extensor and flexor muscles are activated.

B. Feed-forward control relies on information acquired before the feedback sensor is activated; this mechanism is essential for rapid movements. For example, a person catching a ball uses visual information about the ball's initial direction to anticipate the path of the ball in order to initiate the correct response to intercept it. Accuracy requires prior knowledge of the trajectories of thrown balls and the factors that might influence trajectory, such as the spin placed on the ball by the thrower. In the diagram a feedback response directly influences the very disturbance picked up by the sensor. This is not always the case with feed-forward control.

Understanding how input connects to output in spinal reflexes is important because the motor systems make use of this circuitry to coordinate muscles in complex purposeful movements. Also, different spinal reflexes are tested clinically to diagnose the integrity of afferent and efferent pathways and to locate the level of a lesion.

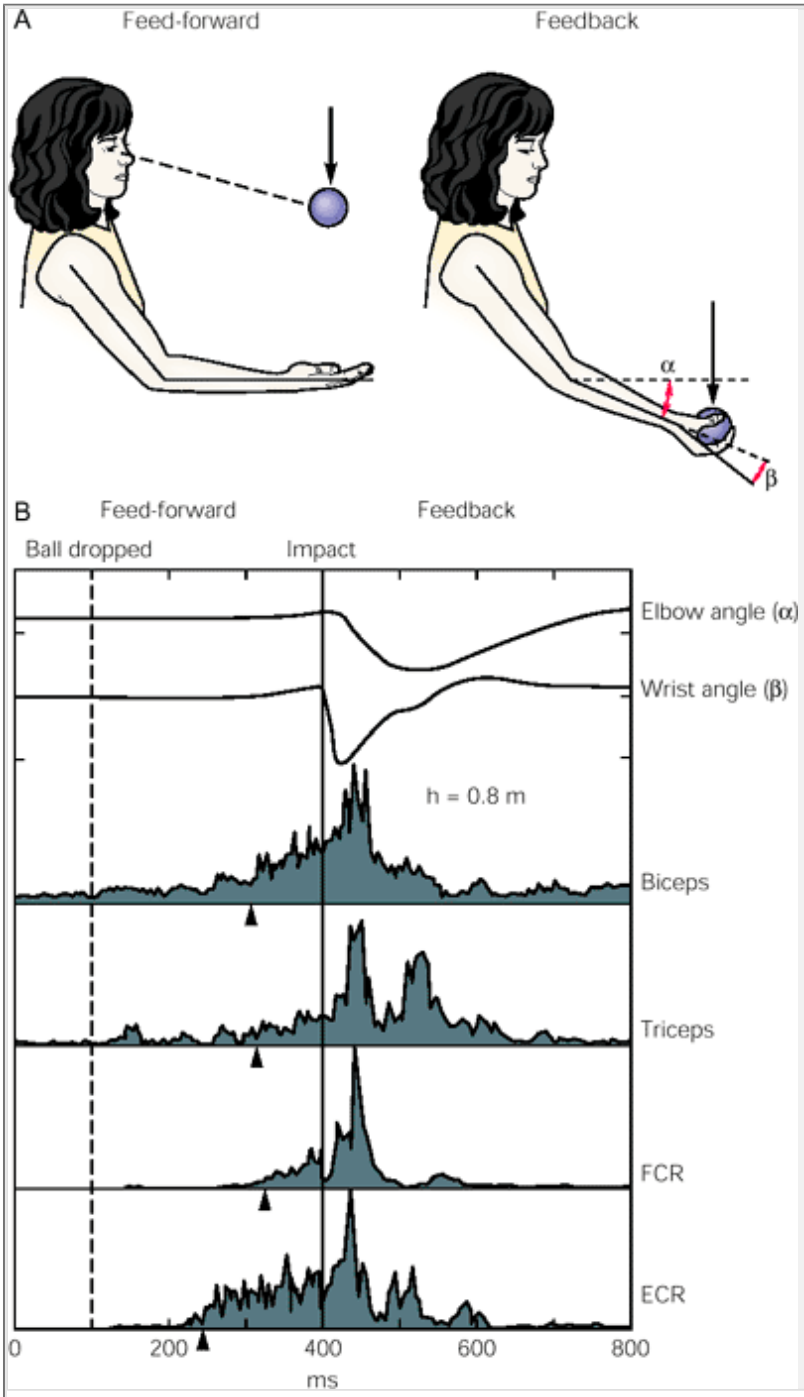

Figure 33-2 Catching a ball requires feed-forward and feedback controls.

A. Setup for ball-catching experiment. The ball can be dropped from any height set by the investigator.

B. The averaged responses of a subject catching a ball falling from a height of 0.8 m. The traces from top to bottom correspond to elbow angle (α), wrist angle (β), and rectified EMG activity of the biceps, triceps, flexor carpi radialis (FCR), and extensor carpi radialis (ECR). The anticipatory responses, before the impact of the ball, consist of coactivation of biceps and triceps muscles (**arrow heads**). After impact there is transient modification of the stretch reflex with further coactivation of flexor and extensors (rather than reciprocal inhibition).

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Repetitive rhythmic motor patterns include chewing, swallowing, and scratching, as well as the alternating contractions of flexors and extensors on either side of the body during quadrupedal locomotion. The circuits for these repetitive rhythmic motor patterns lie in the spinal cord and brain stem. Although these patterns may occur spontaneously, they are more commonly triggered by peripheral stimuli that activate the underlying circuits.

Voluntary Movements Are Goal-Directed and Improve With Practice as a Result of Feedback and Feed-Forward Mechanisms

In contrast to reflexes, voluntary movements are initiated to accomplish a specific goal. Voluntary movements may, of course, be triggered by external events—we put on the brakes when we see the traffic light turn red or rush to catch a ball in flight. Voluntary movements improve with practice as one learns to anticipate and correct for environmental obstacles that perturb the body.

The nervous system learns to correct for such external perturbations in two ways. First, it monitors sensory signals and uses this information to act directly on the limb itself. This moment-to-moment control is called *feedback.* Second, the nervous system uses the same or different senses—for example, vision, hearing, and touch—to detect imminent perturbations and initiate proactive strategies based on experience. This anticipatory mode is called *feed-forward* control. Understanding the computations needed for these two forms of control is central to understanding how the motor systems control posture and movement.

In feedback control (also called *servo-control*) signals from sensors are compared with a desired state, represented by a *reference signal.* The difference, or *error signal*, is used to adjust the output (Figure 33-1A). In a negative or proportional feedback system the computed error immediately produces a compensatory change in output. Because the system forms a closed loop, the output of the feedback system itself can be altered by changing the reference signal. For example, in automatic regulation of room temperature a gauge monitors the ambient temperature and compares it with the desired value set on a thermostat. If the temperature is below the value desired, a heater is turned on; if it is too high, the heater is turned off.

Feedback systems are characterized by their *gain.* A high-gain system acts vigorously to minimize deviations from the optimal target state. However, high-gain systems may be unstable if there are large delays across the loop, for example from sensory neurons to interneuron(s)

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to motor neurons to muscle to a change in contractility. The delay between the input and output of a system is called the *phase lag.* If lags are long and external conditions change rapidly, specific feedback corrections may not be appropriate by the time they are implemented. In many feedback systems the gain is kept relatively low so that corrections do not produce large errors if conditions have changed. In low-gain systems, however, disturbances are corrected slowly, because the small corrections have to be repeated.

Feedback is especially important in maintaining the position of our limbs or the forces we apply to objects that we are holding. Very sensitive mechanoreceptors in muscles (the muscle spindles we shall consider in Chapter 36) and cutaneous afferents in the finger tips provide critical feedback signals for these tasks. Remarkable disorders of posture and movement occur in patients who lack this information. This information is disrupted when the large-diameter fibers that carry the signals from the mechanoreceptors are damaged. Affected patients can neither sense the motions of their joints nor detect objects touching their fingers. They cannot maintain their hand in one position or grasp an object steadily; after a few seconds the force and position of the limb begin to "drift" as fatigue in local groups of muscle fibers goes undetected.

Unlike feedback systems, feed-forward control acts in advance of certain perturbations. When we enter a house we can immediately light a fire or close the windows to prevent becoming cold. This form of control is often referred to as *open loop* control to emphasize that feedback sensory signals do not directly affect the timing of the response. The term is somewhat misleading, however, because it suggests that actions controlled in this way are independent of sensory signals. In fact, feed-forward control must rely on a great deal of information—from sensors as well as experience—to operate correctly (Figure 33-1B). *Anticipatory* control is therefore the more appropriate term.

Feed-forward control is widely used by motor systems to control posture and movement. When we lift an arm while standing, we contract the muscles of our legs before those of the arm so that the shift in center of mass will not cause us to fall over. Even without any movement of the limbs, the contraction of our leg muscles is continuously being adjusted to compensate for the changes in the center of mass that occur during breathing

Experience is important in feed-forward control. Catching a ball is a visually triggered feed-forward response. We use visual information about the initial part of the ball's trajectory to predict the ball's path. Only after the ball hits the hand and displaces it can feedback begin to adjust the hand's position. Feed-forward mechanisms allow us to compute the time of the ball's impact and to contract the opposing arm muscles just before the ball reaches the hand (Figure 33-2). Interestingly, this anticipatory contraction

always precedes impact by the same amount of time, regardless of the height from which the ball is seen to fall. This demonstrates that catchers use experience (knowledge that the ball is constantly accelerated by gravity) to time their muscle contractions accurately.

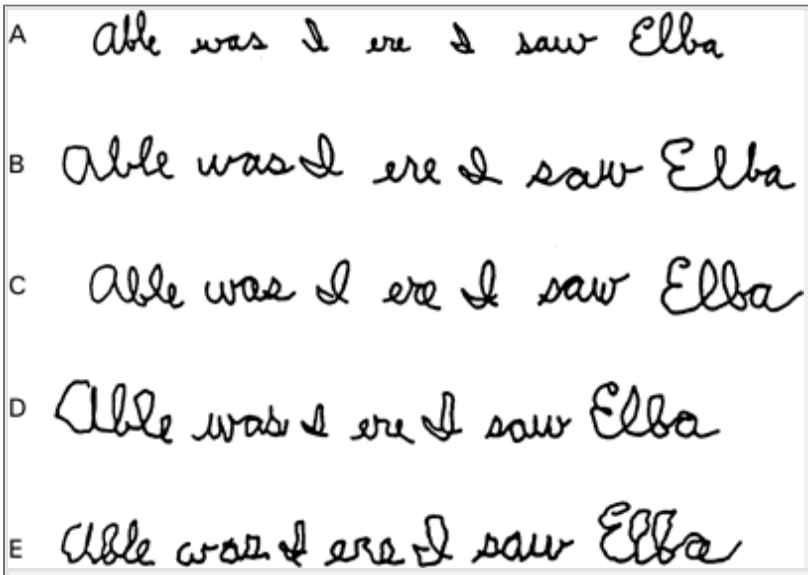
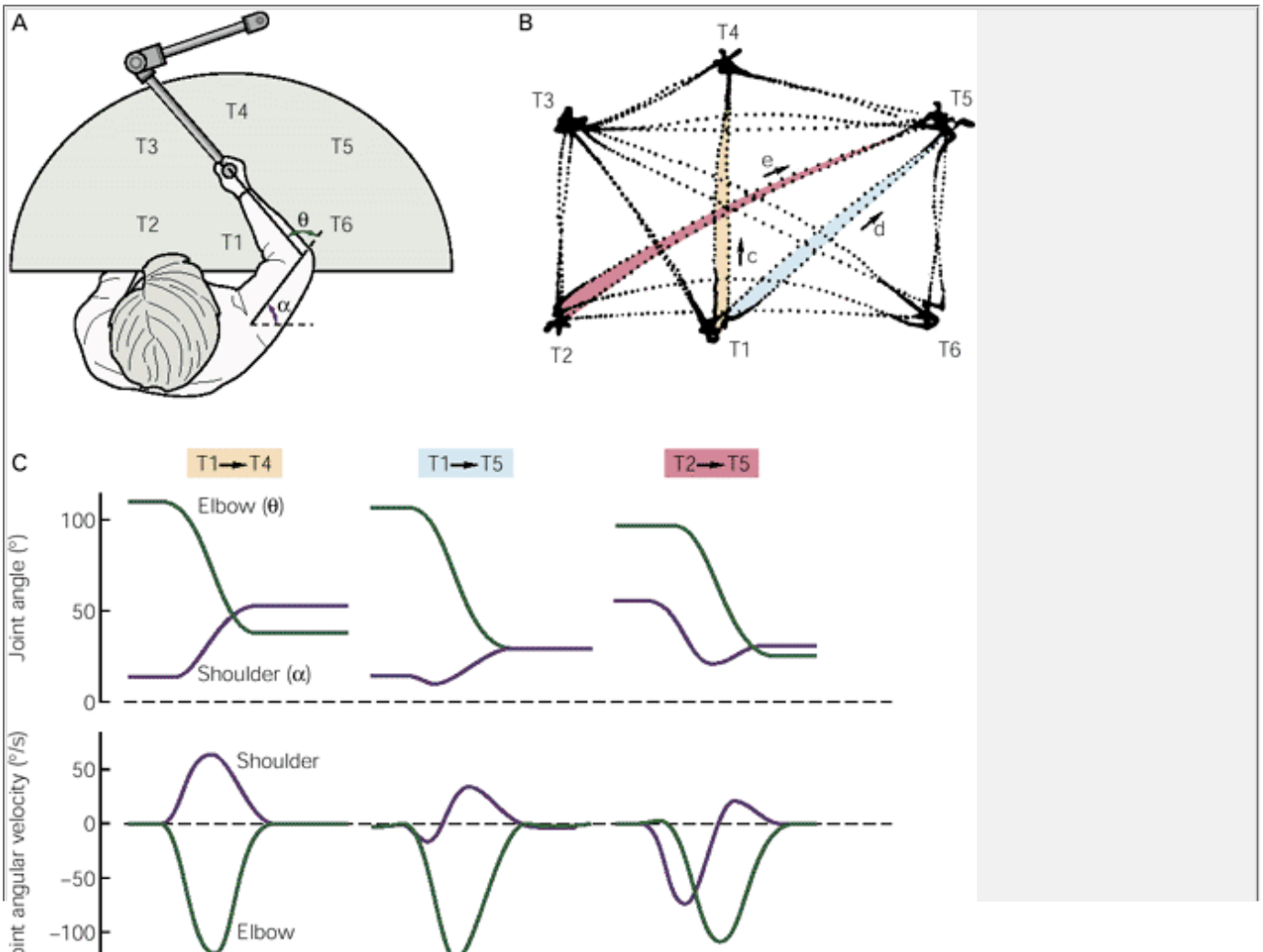


Figure 33-3 Writing can be performed using different parts of the body. The examples here were written with the right (dominant) hand (**A**), with the right arm but with the wrist immobilized (**B**), with the left hand (**C**), with the pen gripped between the teeth (**D**), and with the pen attached to the foot (**E**), The ability of different motor sets to achieve the same behavior is called motor equivalence. (From Raibert 1977.)

What happens after impact? Normally the rapid stretch of a muscle evokes a reflex controlled by spinal circuits: the stretched muscle contracts and its antagonist relaxes. But when people expect to catch a falling ball, the sudden muscle stretch produced by the ball's impact evokes the contraction of *both* the agonist and antagonist muscles. These contractions stiffen the elbow joint and transiently dampen the motions of the joint. Only spinal circuits can mediate such rapid feedback adjustments.

Catching a ball illustrates three key principles in the feed-forward control of movement. First, feed-forward control is essential for rapid action. Second, it depends on the ability of the nervous system to predict the consequences of sensory events, such as where a falling ball will drop. Third, feed-forward mechanisms can modify the operation of feedback mechanisms in the spinal cord.



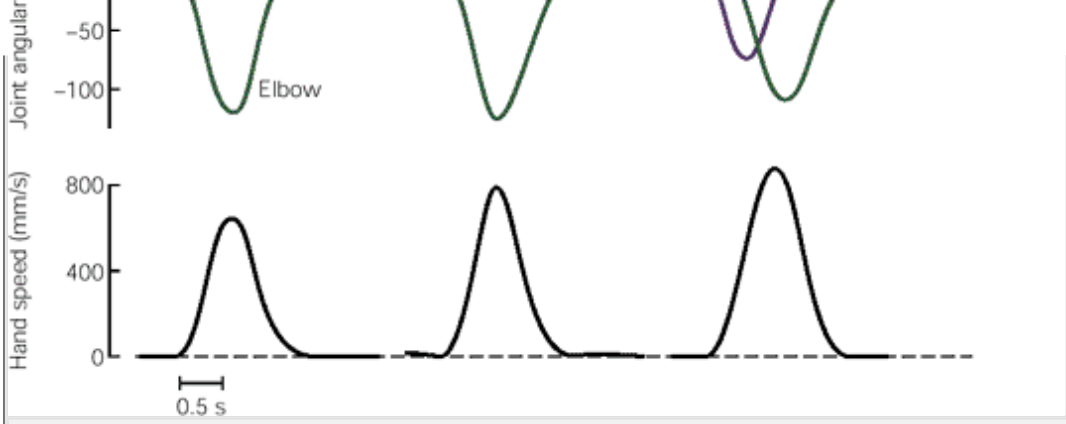


Figure 33-4 The brain plans reaching movements as hand trajectories.

A. Experimental setup. The subject sits in front of a semicircular plate and grasps the handle of a two-jointed apparatus that moves in one plane and records hand position. The subject is instructed to move the hand to various targets (T1-T6).

B. The paths traced by one subject while moving his hand to a series of targets.

C. Kinematic data for hand paths **c, d**, and **e** shown in part B. All paths are roughly straight and all hand speed profiles have the same shape and scale in proportion to the distance covered. In contrast, the profiles for the elbow and shoulder angles for the three hand paths differ. The straight hand paths and common profiles for speed suggest that planning is done with reference to the hand because these parameters can be linearly scaled. Planning with reference to joints would require computing nonlinear combinations of joint angles.

Voluntary Movements Obey Psychophysical Principles

The task of the motor systems is the reverse of the task of the sensory systems. Sensory processing generates an internal representation of the world or the state of the body, but motor processing *begins* with an internal representation, namely the desired result of movement. Nevertheless, just as psychophysical analysis of sensory processing tells us about the capabilities and limitations of the sensory systems, psychophysical analysis of motor performance provides crucial information about how the brain produces voluntary movements.

Psychophysical studies typically involve a subject performing a specific task (pushing a button, pointing, or reaching for an object) on signal. Light or sound cues may be used to instruct the subjects to delay a response or to vary it. The physiological circuits mediating behavior can be understood by combining pychophysical studies with neuroimaging or intracellular recording from single neurons ("single unit") in awake, behaving primates.

Psychophysical studies reveal that voluntary movements are governed by certain laws, which can be modified by learning. Three of these laws have been extensively studied because they have particular, practical significance. First, the brain represents the outcome of motor actions independently of the specific effector used or the specific way the action is achieved. Second, the time taken to respond to a stimulus depends on the amount of information that needs to be processed to accomplish the task. Third, there is a trade-off between the speed of a movement and its accuracy. We shall discuss each of these laws of voluntary movement in turn.

Voluntary Movements Have Certain Invariant Features and Are Governed by Motor Programs

In the early 1950s the psychologist Donald Hebb observed that individual motor actions share important characteristics even when performed in different ways. For example, our handwriting appears about the same regardless of the size of the letters or of the limb or body segment used to produce them (Figure 33-3). Hebb called this *motor equivalence.*

Motor equivalence suggests that a purposeful movement is represented in the brain in some abstract form rather than as a series of joint motions or muscle contractions. The path of the hand on its way to the target is always relatively straight, regardless of its starting or final position. As the target is approached, the speed of the hand at first increases and then declines to zero. In contrast, the motions of the joints in series (shoulder, elbow, and wrist) are complicated and vary greatly with different initial and final positions. Since rotation at a single joint would produce an arc at the hand, both elbow and shoulder joints have to be rotated concurrently to produce a straight path. In some directions the elbow moves more than the shoulder; in others the reverse occurs. When the hand is moved from one side of the body to the other, one or both joints may have to reverse direction in mid course (Figure 33-4).

If the brain forms a representation of a movement before its execution, does it plan the extent of the movement or does it continuously assess the distance between the hand and the target and use visual information to stop movement once the target is reached? If the brain relied primarily on vision to stop, the initial speed of the hand might be relatively similar in movements of different extents. Instead, both the speed and the acceleration of the hand movement are scaled proportionately to the distance of the target (Figure 33-5). This means that the extent of a movement is planned before the movement is initiated. The representation of this plan for movement is called a *motor program.* The motor program specifies the spatial features of the movement and the

angles through which the joints will move. These are colectively known as *movement kinematics.* The program must also specify the forces required to rotate the joints (torques) to produce the desired movement. This is known as *movement dynamics.*

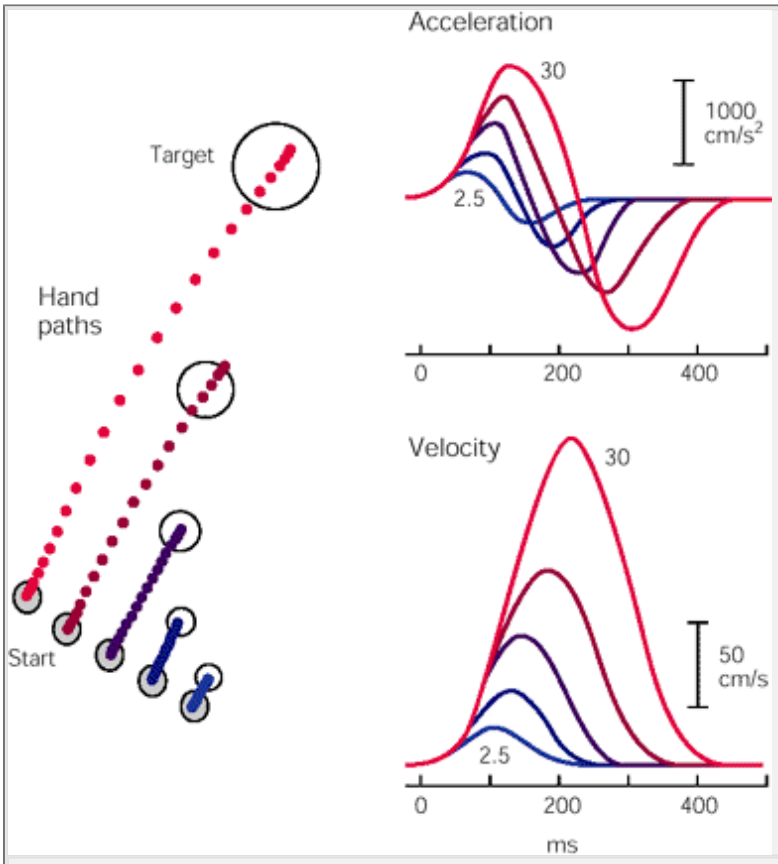


Figure 33-5 Acceleration and velocity scale with movement extent. Hand paths of a subject reaching for targets located 2.5, 5, 10, 20, and 30 cm from the starting position (dots are hand positions at 20 ms intervals) are presented at random. The subject could not see his hand during movement. The average acceleration and velocity profiles are scaled linearly as a function of the extent of movement to the target. The single peaks indicate that the extent of movement is specified prior to actual movement as a scaled impulse of force accelerating the limb.

Motor programs not only specify the kinematic and dynamic features of the movement, they also tell the nervous system how to respond to certain patterns of sensory information. In lifting an object between thumb and

index finger we set our grip force and the acceleration of our hand in accordance with the expected slipperiness of the object and its weight using feed-forward control. If the activation of cutaneous receptors indicates that slippage is occurring, our grip force is increased immediately through rapid feedback control via a spinal cord circuit. This circuit is said to be "gated" during lifting as no such response occurs if the same receptors are stimulated when the hand is at rest (Figure 33-6).

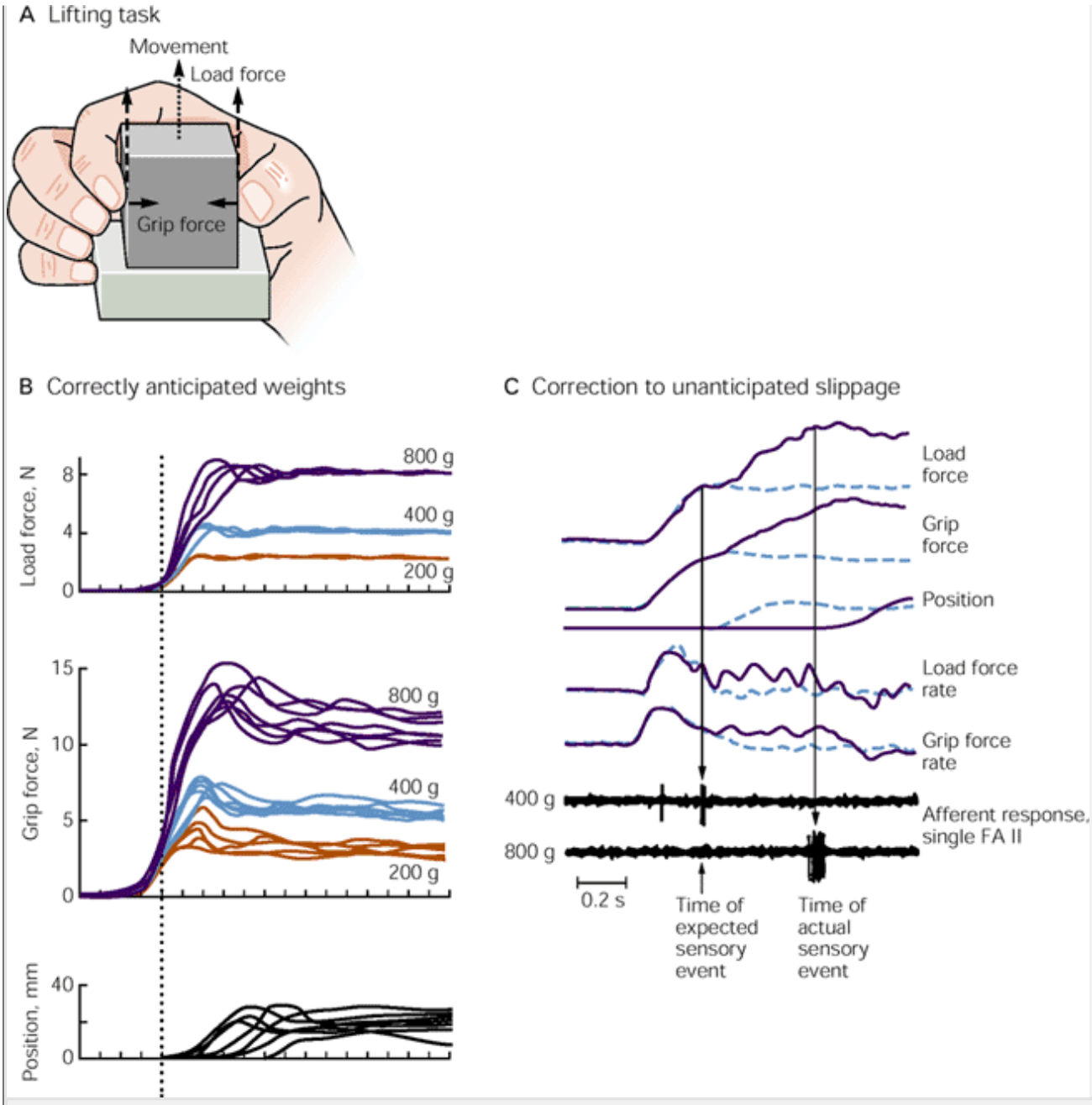


Figure 33-6 Both feedback and feed-forward controls are used when lifting a slippery object.

A. The subject lifts a test object from the table. Sensory receptors measure the load force applied to the object to overcome gravity and inertia, the grip force, and vertical motion. The discharge of different sensory receptors is recorded by microelectrodes inserted within identified sensory axons of the peripheral nerve, a procedure called microneuronography.

B. When the subject knows the weight of the object in advance the applied forces are adequate to lift the object. Three sets of traces (24 trials superimposed) show load force, grip force, and position as subjects lifted three objects of different weights (200, 400, and 800 g). The grip force increases in proportion to the weight of the object. This is done by scaling a preprogrammed force profile. (Notice that the profiles have the same shape but different amplitudes.)

C. When the weight is larger than expected the subject responds to slippage of the object. After being presented with a 400 g object for several trials (**dashed lines**), the subject was given an 800 g object (**solid lines**). On each trial with the 400 g object a burst of action potentials occurs in the afferent axon due to activation of a Pacinian corpuscle, triggering the beginning of the hold phase during which the grip force is constant. When the 800 g object is presented, the absence of burst responses, because of slippage, triggers a slow increase in force that is terminated when movement (the lifting) begins.

The nervous system deconstructs complex actions into elemental movements that have highly stereotyped spatial and temporal characteristics. For example, the

seemingly continuous motion of drawing a figure eight actually consists of discrete movement segments that are constant in duration, regardless of their size (Figure 33-7). The simple spatiotemporal elements of a movement are called *movement primitives* or *movement schemas.* Like the simple lines, ovals, or squares in computer graphics programs, movement primitives can be scaled in size or in time. The neural representations of complex actions, such as prehension, writing, typing, or drawing, are thought to be stored sets of these simple spatiotemporal elements.

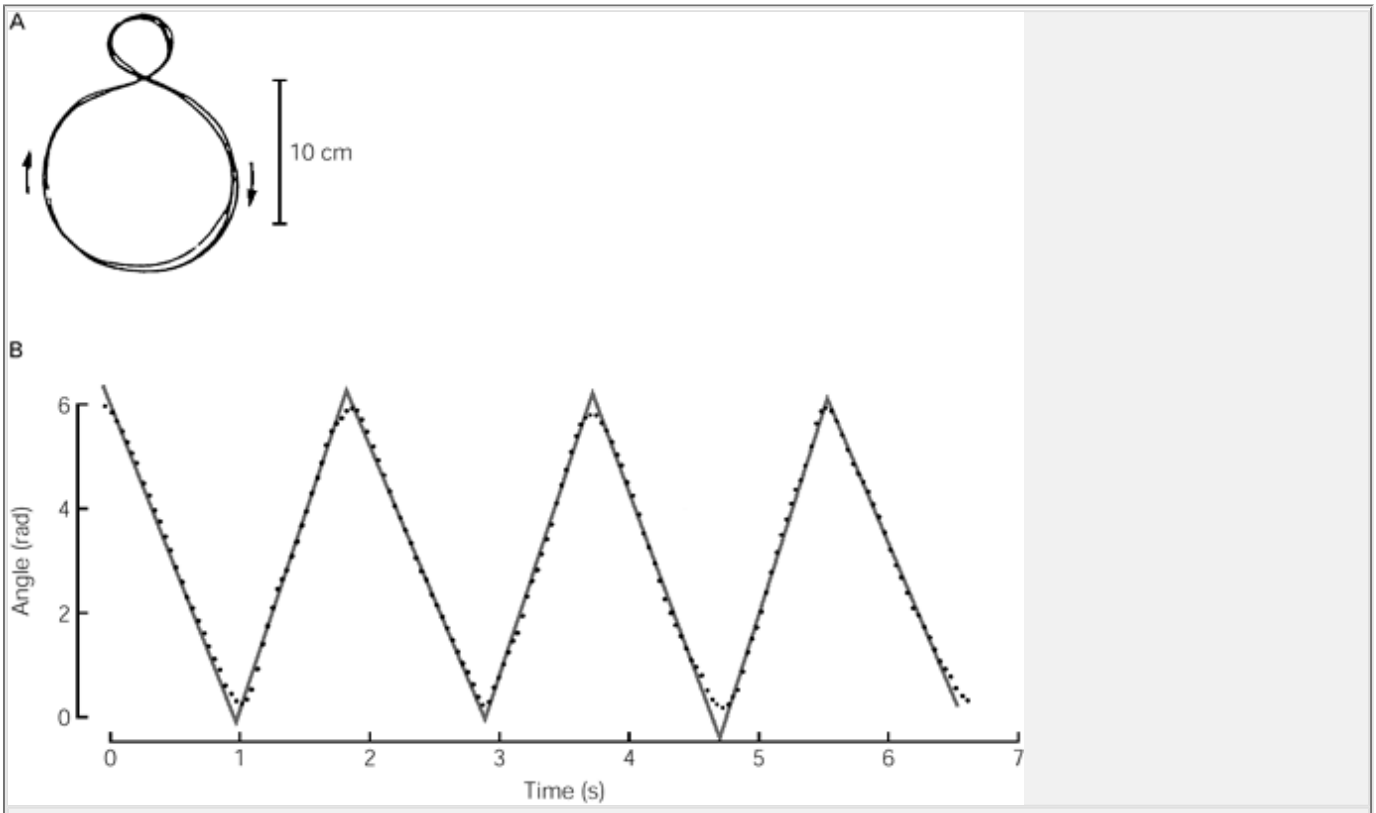


Figure 33-7 Complex movements are made up of discrete segments. (From Lacquaniti, Terzuolo, and Viviani, 1983.)

A. Figure eight drawn by a subject.

B. The continuous motion of drawing a figure eight consists of regular increases and decreases in the angular motion of the hand. These changes in angular motion occur at regular intervals during which the hand describes approximately equal angles, a feature termed *isogony.* The duration of each hand movement is the same regardless of the length of the hand path, a feature termed *isochrony.* Studies of more complex movements, such as those made during random continuous scribbling, show a similar segmentation. Such studies also reveal a consistent relationship between the speed of hand motion and the degree of curvature of the hand path: Velocity varies as a continuous function of the curvature raised to the 2/3 power. This two-thirds power law governs virtually all movements and expresses an obligatory slowing of the hand during movement segments that are more curved and a speeding up during segments that are straight.

Reaction Time Varies With the Amount of Information Processed

Reaction time, the time between the presentation of a stimulus and the initiation of a voluntary response, is an indication of the amount of neural processing taking place between a stimulus and the response. Reaction times also vary with several factors, including the neural conduction distance and the modality of the stimulus.

Voluntary reaction times are significantly longer than the latencies of reflex responses elicited by comparable stimuli. For example, the reaction times for voluntary responses to proprioceptive stimuli range from 80 to 120 ms. In contrast, the shortest latency for a monosynaptic reflex response to comparable muscle stretches is only around 40 ms. The longer time for the voluntary response results from the additional synapses interposed between afferent input and motor output. Thus, reactions to visual stimuli require still more time (150-180 ms) because of the larger number of synaptic relays in the retina. Unfortunately, one cannot compute the number of synapses involved in triggering a movement from the reaction time because the summation time of synapses is highly variable.

Reaction time is shortest if subjects know which response they will have to make when a stimulus is presented and is prolonged when they must choose among different responses. For example, if a subject may be presented with one of several cues signifying different movements. The added time needed to select a particular response is called the *choice effect.* Reaction time increases systematically with the number of choices available (Figure 33-8A). For complex tasks, reaction times are half a second to a second. Analyses of the effect of choice on reaction time gave rise to the idea that voluntary responses are processed in stages, including a step in which an appropriate response is selected from among alternatives (Figure 36-8B). Efforts at quantifying the rate of information processing

have yielded delays of 100-150 ms per information bit, a rate much slower than that of even small personal computers.

However, it is now known that multiple stimuli and responses can be processed in parallel pathways (Box 33-1). Parallel processing overcomes the slowness of serial neural processing. Learning continually improves the efficiency of this parallel processing.

Voluntary Movements Trade Speed for Accuracy

In the 1890s the psychologist Robert Woodworth showed that fast movements are less accurate than slow ones. This is in part

because fast movements leave less time for feedback corrections. In fact, the fastest movements are shorter than the reaction time itself. But lack of time for correction does not explain fully why fast movements are less accurate and more variable than slow ones; faster movements made without visual feedback are also more variable in both extent and speed.

Several factors contribute to the increase in variability with speed. One of these is the recruitment of additional motor neurons to produce rapid increases in force, since the excitability of motor neurons is subject to random variations. We shall see in the next chapter that a constant incremental increase in force is produced by progressively smaller numbers of motor neurons. Therefore, as force increases, fluctuations in the number of motor neurons lead to proportionately greater fluctuations in force and thus velocity. This proportional relationship is maintained over most of the range of contractile force and corresponds to the proportional increase in variability with the speed of movement (Figure 33-10) and the distance of the target. The slope of the speed-accuracy trade-off is seen in Figure 33-10 and is analogous to the Weber-Fechner law, which characterizes sensory discriminations.

Variability also arises because subjects may be uncertain about the forces and loads that are needed to oppose movement. This uncertainty decreases with practice, however, so that both the accuracy and the speed of movement increase. For example, a monkey that is trained to grasp a handle and move it to a series of targets learns to anticipate opposing forces and to program its movements accurately before initiating a movement. With time, movement paths to each target become straighter and less variable (Figure 33-11).

In competitive sports and other tasks requiring skill the brain eventually learns to take account of even subtle changes in posture, external loads, and other factors that might influence the trajectory of movement.

This principle is beautifully illustrated by expert pistol shooters, who achieve accuracy by synchronizing trigger actions with their involuntary tremors. Only beginners seek to immobilize themselves when pulling the trigger.

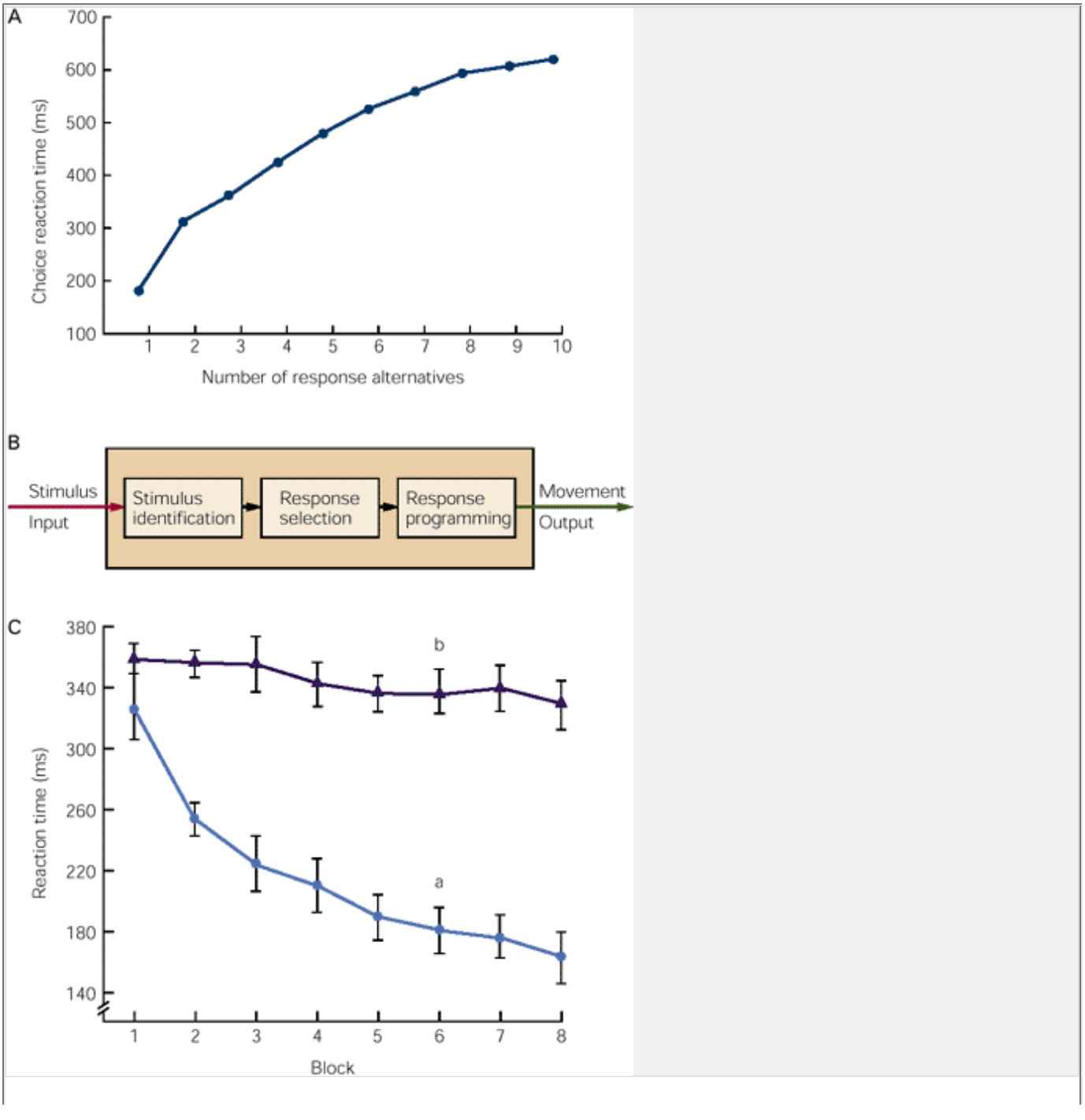


Figure 33-8 Reaction time increases with choice and decreases with learning.

A. Reaction time increases nonlinearly with the number of response alternatives available to the subject.

B. In this outdated but still useful model of information processing three stages intervene between stimulus presentation and the motor response: stimulus identification, choice of response to the stimulus, and programming of the chosen response.

C. Reaction time decreases with learning as stimuli become predictable. In the plot each block represents 10 repetitions of a 10-trial sequence. On each trial a light appeared at one of four locations and subjects were instructed to press a key under the light. For one group of subjects (**a**) the same 10-trial sequence was repeated in a single block; the reaction time of this group decreased dramatically. For the other group (**b**) the position of the light in each trial was random; there was no significant decrease in reaction time for this group.

The Motor Systems Are Organized Hierarchicaly

The Spinal Cord, Brain Stem, and Forebrain Contain Successively More Complex Motor Circuits

The motor systems can perform so many different motor tasks—reflex, rhythmic, and voluntary—with speed and accuracy because of two features of their functional organization. First, the processing of sensory inputs and commands to motor neurons and muscles is distributed in hierarchically interconnected areas of the spinal cord, brain stem, and forebrain. Each level has circuits that can, through their input and output connections, organize or regulate complex motor responses. Second, sensory information relating to movement is processed in different systems that operate in parallel. The hierarchical organization of the motor systems is illustrated in Figure 33-12.

The spinal cord is the lowest level of this hierarchical organization. It contains the neuronal circuits that mediate a variety of reflexes and rhythmic automatisms such as locomotion and scratching. Similar circuits governing reflex movements of the face and mouth are located in the brain stem. The simplest neural circuit is monosynaptic; it includes only the primary sensory neuron and the motor neuron. However, most reflexes are mediated by polysynaptic circuits, where one or more interneurons are interposed between the primary sensory neuron and the motor neuron.

Interneurons and motor neurons also receive input from axons descending from higher centers. These supraspinal signals can modify reflex responses to peripheral stimuli by facilitating or inhibiting different populations of interneurons. They also coordinate motor actions through these interneurons. For example, when we flex a joint the descending commands that drive the flexor muscle also inhibit the opposing extensor muscle through the same inhibitory interneuron that is activated during the stretch reflex. Nevertheless, all motor commands eventually converge on motor neurons, whose axons exit the spinal cord or brain stem to innervate skeletal muscles. Thus in Sherrington's words, motor neurons are the “final common pathway” for all motor action.

The next level of the motor hierarchy is in the brain stem. Two systems of brain stem neurons, the medial and lateral, receive input from the cerebral cortex and subcortical nuclei and project to the spinal cord. The *medial descending systems* of the brain stem contribute to the control of posture by integrating visual, vestibular, and somatosensory information. The *lateral descending systems* control more distal limb muscles and are thus important for goal-directed movements, especially of the arm and hand. Other brain stem circuits control movements of the eyes and head.

The cortex is the highest level of motor control. The primary motor cortex and several premotor areas project directly to the spinal cord through the corticospinal tract and also regulate motor tracts that originate in the brain stem. The premotor areas are important for coordinating and planning complex sequences of movement. They receive information from the posterior parietal and prefrontal association cortices (see Chapter 19) and project to the primary motor cortex as well as to the spinal cord.

The variety of reflex circuits in the spinal cord and brain stem simplifies the instructions the cortex must send to lower levels. By facilitating some circuits and inhibiting others, higher levels can let sensory inputs at lower levels govern the temporal details of an evolving movement. The timing of activation of agonists and antagonist muscles is intrinsic to the spinal circuit and thus the descending signals themselves need not be timed as precisely. The patterns of coordination in spinal circuits are relatively stereotyped. A cat with its cervical cord transected can, if provided with body support, walk on a moving treadmill and bring its paw around an obstacle after hitting it. But the spinal cat cannot lift its forelimb *before* impact with an obstacle, as an intact animal does, because this movement requires control of the limbs using visual information. This anticipatory control, in turn, requires intervention by the motor cortex to suppress the oscillatory circuit that coordinates normal stepping.

The Cerebellum and Basal Ganglia Influence Cortical and Brain Stem Motor Systems

In addition to the three hierarchical levels—spinal cord, brain stem, and cortex—two other parts of the brain also regulate the planning and execution of movement. The cerebellum and basal ganglia provide feedback circuits that regulate cortical and brain stem motor areas: They receive inputs from various areas of cortex and project to motor areas of the cortex via the thalamus. The loop circuits of these two structures flow through separate regions of the thalamus and to different cortical areas.

Likewise, the inputs to them from the cortex are also separate. The cerebellum and basal ganglia do not send significant output to the spinal cord, but they do act directly on motor neurons in the brain stem.

Box 33-1 Parallel Processing in Movement

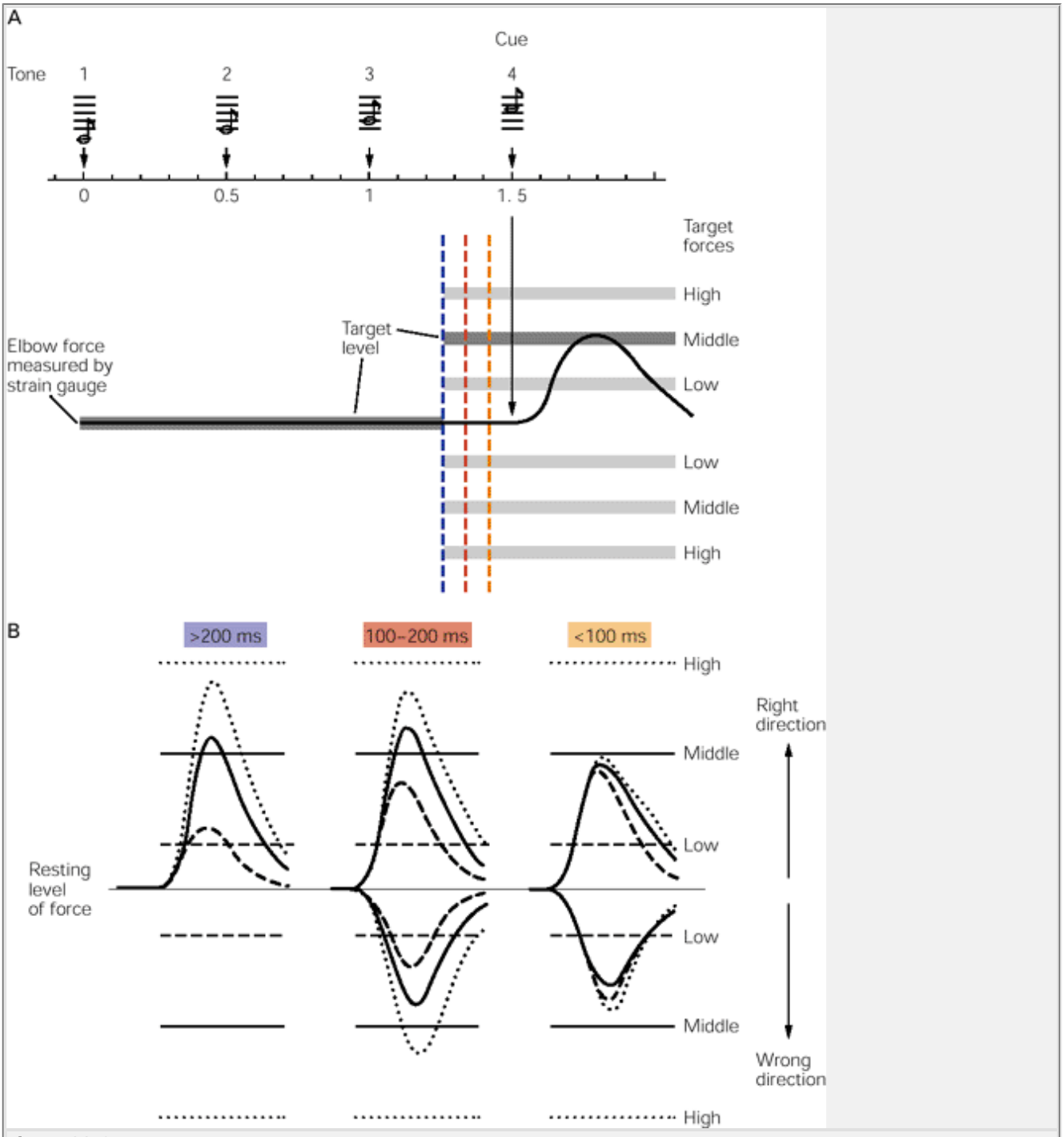


Figure 33-9

A. The timed response paradigm. In each trial four successive tones of increasing pitch are presented to a subject at 0.5-s intervals. The subject, whose arm is immobilized, is instructed to produce a pulse of elbow force (a brief isometric elbow flexion or extension) in synchrony with the fourth tone. The subject is also instructed to attempt to match the peak of the force pulse to a level specified at an unpredictable time between the third and fourth tone but not to correct their response if they were unable to match the target level. There were six possible target levels: three up (flexion) and three down (extension).

B. Average force trajectories of responses. The traces on the **left** are for responses initiated 200 ms or more after the target force was specified. Such responses were fully preprogrammed before execution. The shapes of the trajectories are highly stereotyped and match the target amplitude, and none of the responses is in the wrong direction (up rather than down). The traces on the right are for responses initiated 0-100 ms after the target was presented, ie, before information about the extent or direction of the movement could be processed. Half are in the right direction and half are wrong. Nevertheless, the shapes of these "default" trajectories are similar to those of fully preprogrammed responses, and their amplitudes are all clustered at the center of the range. The traces in the center are for responses initiated 100-200 ms after the target was presented. Responses in the correct direction begin to show some degree of scaling: Responses to small- and large-amplitude target forces are smaller or larger than responses to the middle target. A second point of interest, however, is that this scaling is equally evident for responses in the wrong direction. This demonstrates that amplitude and direction are specified independently. (From Hening

et al. 1988.)

How long does it take for a motor program (eg, direction or extent) to be fully specified? The answer depends on whether individual parameters are specified in successive stages of processing or in parallel pathways. This issue was first addressed by David Rosenbaum in an experiment to determine whether the delay in choice reaction time can be shortened by providing subjects with partial information about an expected response.

In this experiment the choices available to subjects were which hand to move, the direction to move in, and the distance to move. As expected, reaction time is longest when subjects have no advance information and becomes progressively shorter as more information is provided. This indicates that the brain can program individual features of a movement before executing the movement.

Such experiments do not, however, address the question of whether individual features of a movement can be programmed in separate but parallel pathways while the action is underway. Can subjects initiate a response before its features are fully specified, ie, can they adopt different strategies when one or another parameter is uncertain? To determine whether the extent and direction of a movement can be programmed in separate but parallel pathways and how long it takes to program these features, it is necessary to examine how responses change as a function of the time available to specify a given feature. This was done using the *timed response paradigm* (Figure 33-9A). Subjects were trained to initiate a simple response in synchrony with a predictable auditory cue (as occurs in dancing). They were also given visual cues about the amplitude and direction of each response. Training the subjects to begin their response with the auditory cue ensured that the visual cue did not initiate the response but only provided information about amplitude and direction.

The influence of processing time on the characteristics of the trajectory of a movement was assessed by systematically varying the time between presentation of the information on the expected amplitude and direction of movement and the onset of movement. When subjects have to act before knowing which response to make, they set *default values* for amplitude and direction based on their expectation. When two directions are equally probable, responses are equally distributed in both directions. After the visual cues are presented and information on the extent and direction of movement can be processed, specification occurs over about 200 ms. Interestingly, amplitude is specified progressively for movements in both the correct and wrong directions. Thus, specifications of the extent and direction of movement are processed in parallel. Since the bell-shaped speed profiles, straightness, and movement time are the same for default responses, partially specified responses, and fully specified responses (Figure 33-9B), these movements are not substantially adjusted during execution. Similar results have been obtained for hand movements in space.

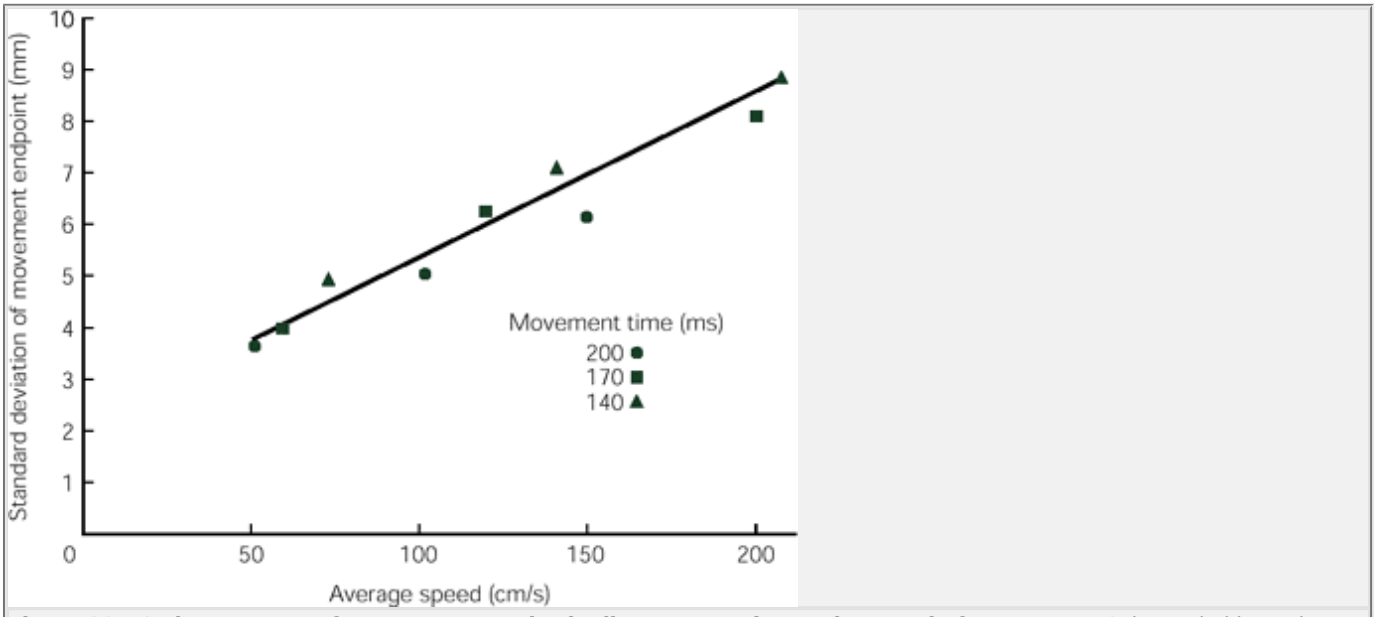


Figure 33-10 The accuracy of a movement varies in direct proportion to the speed of movement. Subjects held a stylus and had to hit a straight line lying perpendicular to the direction in which they moved the stylus. Subjects could not see their hand and thus were unable to correct their movement. The variability in the motion of the subjects' arm movements is shown here as the standard deviation of the extent of movement plotted against average speed (for three different movement times). The variability in movement increases in proportion to the speed and therefore to the force producing the movement. (From Schmidt et al. 1979.)

Although the precise contribution of the cerebellum and basal ganglia to motor action is still not clear, both are necessary for smooth movement and posture. Damage to either structure has significant clinical effects. Degenerative diseases of the basal ganglia, such as Parkinson or Huntington disease, produce involuntary movements, abnormalities in posture, and, as recent studies have shown, major impairment in cognitive processing. Thus the basal ganglia have increasingly been implicated in motivation and the selection of adaptive behavioral plans (Chapter 43). Damage to the cerebellum by vascular lesions and certain familial degenerative conditions produces cerebellar ataxia, a characteristic loss of coordination and accuracy of limb movement. Cerebellar circuits are involved with the timing and coordination of movements in progress and with the learning of motor skills (Chapter 42).

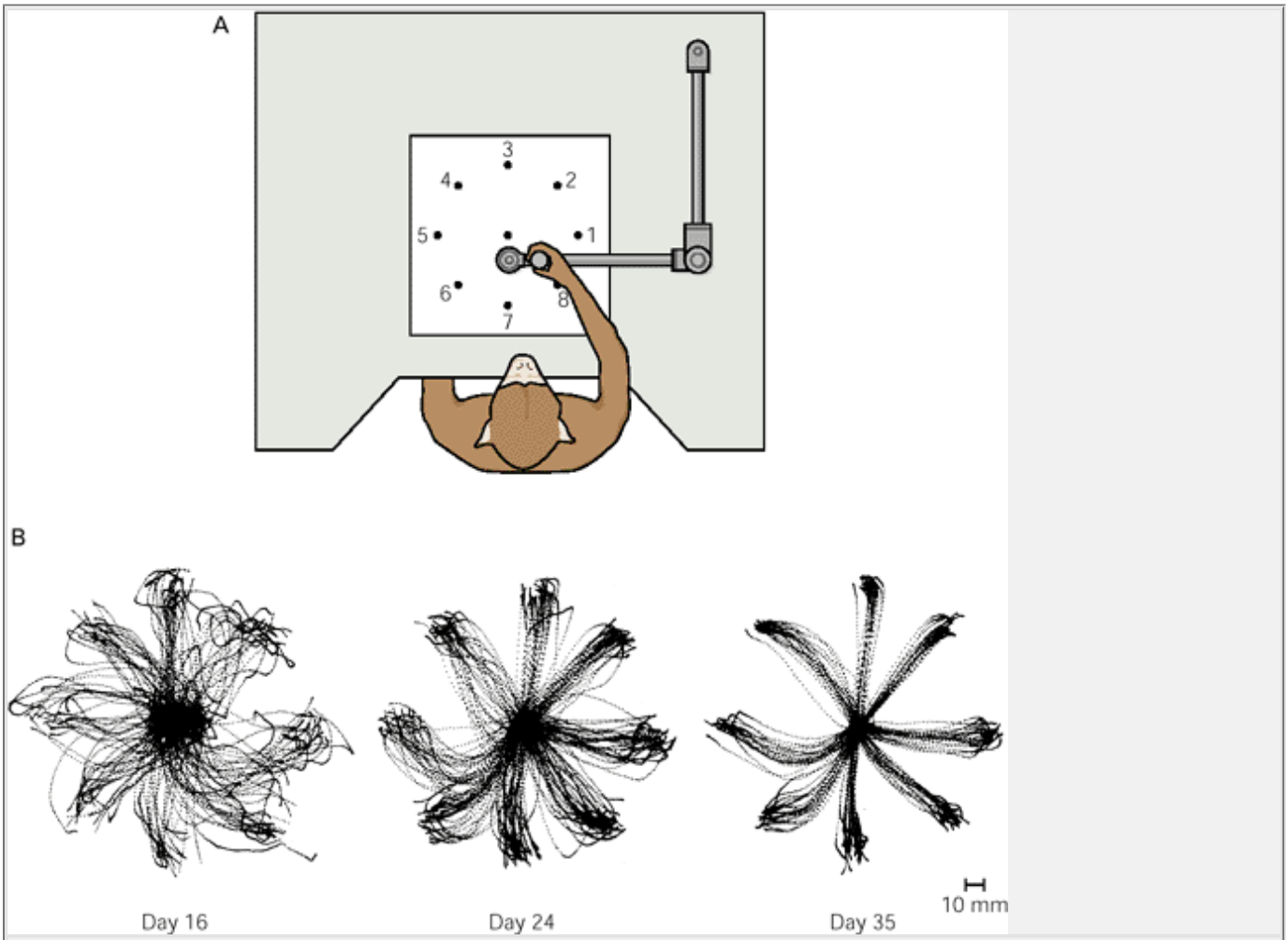


Figure 33-11 Learning improves the accuracy of reaching.

A. A monkey was made to sit at a table and move a handle at the end of a manipulandum (starting from the position shown) over the surface toward targets arranged in a circular array (numbered 1-8). The monkey was required to move the handle from the center of the array to whichever one of the targets lit up, covering the target with a clear plexiglass circle on the end of the manipulandum.

B. Records of movement trajectories for a monkey are shown at successive stages of training. The trajectories become straighter with practice, and increasing accuracy is reflected in the decreased dispersion (variability) of the trajectories. (The persistent curvature of the trajectories to targets 4, 5, and 6 is a result of mechanical constraints of the apparatus.)

Lesions of the Motor Pathways Produce Positive and Negative Signs

The nineteenth-century neurologist John Hughlings Jackson, whose clinical insights were so informative for the early understanding of different regions of cortex (Chapter 19), was also the first to recognize that lesions of the nervous system result in both negative and positive signs. Negative signs reflect the loss of particular capacities normally controlled by the damaged system, for example loss of strength. Positive signs, also called *release phenomena*, are abnormal and stereotyped responses that are explained by the withdrawal of tonic inhibition from neuronal circuits mediating a behavior. When cerebral control of the brain stem is disconnected in the cat, ordinary head and neck movements produce postural reflexes that otherwise do not occur in the intact animal.

In humans, lesions that interrupt the descending pathways from the cortex or brain stem produce weakness in voluntary movements (a negative sign) and, at the same time, increase muscle tone, a key feature of the clinical picture of *spasticity.* In this condition, as in decerebrate rigidity, stretch reflexes are abnormally active. Clinicians often must decide if a patient's weakness arises from a disease that affects systems descending from the cortex and brain stem to motor neurons or from a disease that directly affects the motor neurons or their axons. Although both conditions produce weakness by diminishing neural input to muscle, three important differences distinguish them. First, diseases affecting the descending pathways give rise to spasticity whereas diseases of motor neurons do not. Second, diseases affecting motor neurons directly result in denervation atrophy and reduced muscle volume, whereas this does not occur with damage to the descending pathway. Third, damage to descending systems tends to be distributed more diffusely in limb or face muscles and often affects large groups of muscles, for example the flexors. In contrast, degeneration in local groups of motor neurons tends to affect muscles in a patchy way and may even be limited to single muscles. Nerve lesions result in weakness that reflects the known distribution of individual nerves.

We now consider the organization of the three levels of the motor hierarchy—the spinal cord, brain stem, and cerebral cortex—and how they control proximal and distal muscles.

Spinal Motor Neurons Execute Movement

Primary afferent fibers from cutaneous and deep peripheral receptors (Chapter 22) branch profusely before terminating in the various laminae of the spinal gray matter, where they form connections with four types of neurons: (1) local interneurons, whose axons are confined to the same or adjacent spinal segments; (2) propriospinal neurons, whose axon terminals reach distant spinal segments; (3) projection neurons, whose axons ascend to higher brain centers; and (4) motor neurons, whose axons exit the nervous system to innervate muscles. We first consider the motor neurons and then the interneurons and propriospinal neurons that are important in motor control.

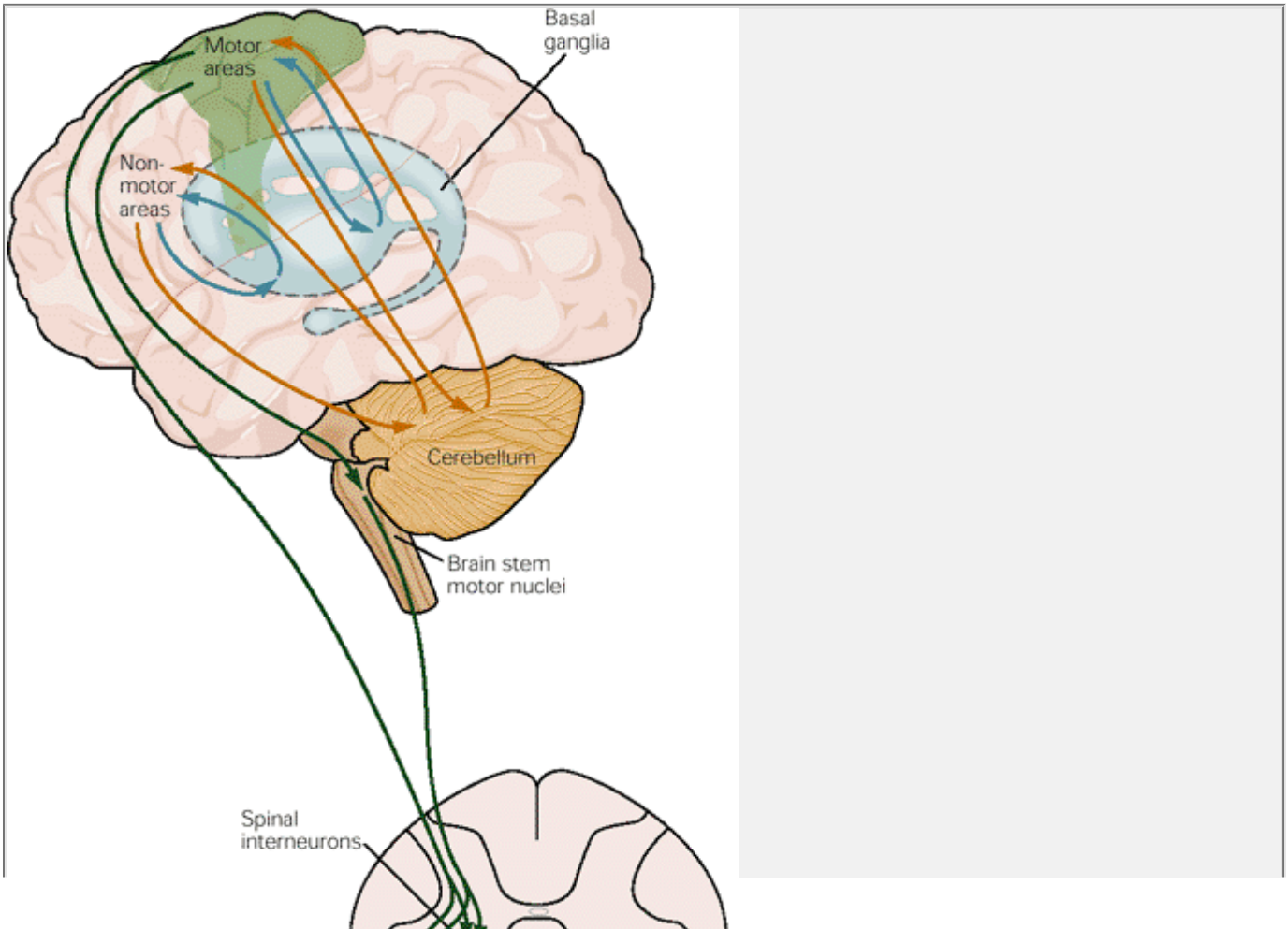
The cell bodies of motor neurons that innervate individual muscles are clustered in motor neuron pools, or *motor nuclei*, which form longitudinal columns extending over one to four spinal segments. The spatial organization of the different motor nuclei follows a *proximaldistal rule.* According to this rule, motor nuclei innervating the most proximal muscles lie most medially within the spinal cord while those innervating more distal muscles are located progressively more laterally. Thus, for the arm, the motor nuclei innervating the axial, shoulder girdle, elbow, wrist, and digit muscles are arrayed from medial to lateral positions (Figure 33-13). The separation of motor neurons innervating axial and proximal muscles from those innervating distal muscles is maintained throughout the spinal cord.

The functional specialization of medial and lateral motor nuclei is also reflected in the organization of the local interneurons of the spinal cord. Interneurons in the most medial parts of the intermediate zone of the spinal cord project to the medial motor nuclei that control axial muscles on both sides of the body. More laterally located interneurons project only to the motor neurons that innervate ipsilateral girdle muscles, while the most lateral ones synapse on motor neurons that innervate the most distal ipsilateral muscles (Figure 33-13).

The axons of propriospinal neurons course up and down the white matter of the spinal cord and terminate on interneurons and motor neurons located several segments away from the cell bodies (Figure 33-13). Axons of medial propriospinal neurons run in the ventral and medial columns. They have long axons that branch extensively; some axons extend through the entire length of the spinal cord to coordinate movements of the neck and pelvis. This organization allows the axial muscles, which are innervated from many spinal segments, to be coordinated easily during postural adjustments.

More laterally placed propriospinal neurons interconnect smaller numbers of segments and have less diffuse terminations. This explains the greater independence of action of more distal muscles, allowing a larger variety of muscle activation patterns. Although shoulder and elbow muscles are used to direct the hand in reaching for objects in different directions, shoulder and elbow motions are more stereotyped and less varied than those of the wrist and the elbow. Control of the digits requires the greatest degree of differentiation. Even the movements of a single digit require highly differentiated

and coordinated contraction of many different muscles (Chapter 38).



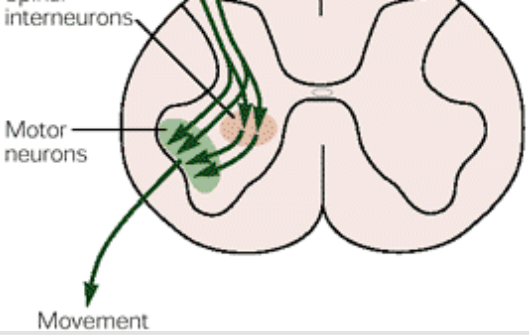


Figure 33-12 The motor systems have three levels of control—the spinal cord, brain stem, and forebrain—organized both serially and in parallel. The motor areas of the cerebral cortex can influence the spinal cord either directly or through the descending systems of the brain stem. All three levels of the motor systems receive sensory inputs and are also under the influence of two independent subcortical systems: the basal ganglia and the cerebellum. (The basal ganglia and cerebellum act on the cerebral cortex through relay nuclei in the thalamus, which are omitted from the diagram for clarity.)

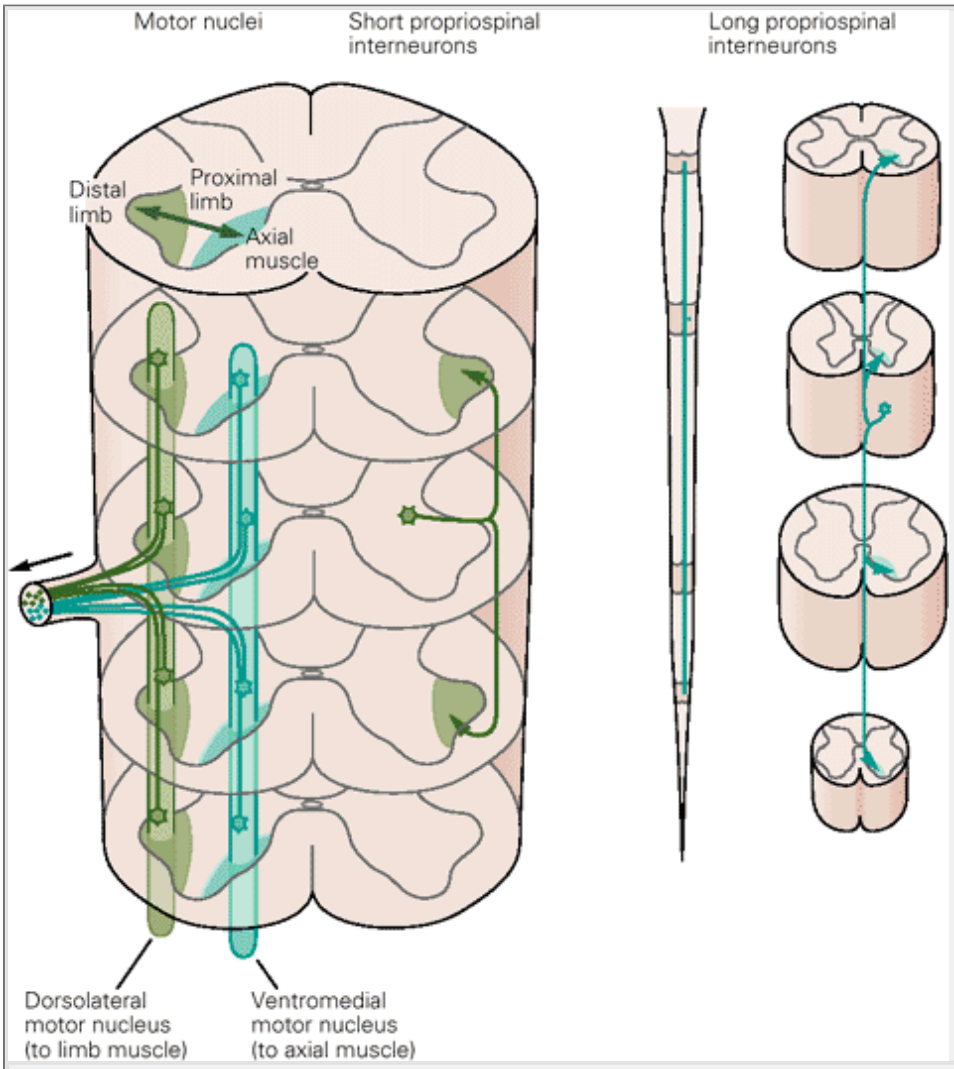


Figure 33-13 The motor nuclei of the spinal cord are arranged along a medial-lateral axis according to function. The medial nuclei contain the motor neurons innervating axial muscles of the neck and back; among the lateral nuclei the most medial motor neurons innervate proximal muscles while the most lateral innervate distal muscles. The medial motor nuclei are interconnected across several segments of the spinal cord by propriospinal neurons with long axons, whereas the lateral nuclei are interconnected across fewer segments by propriospinal neurons with shorter axons.

The Brain Stem Modulates the Action of Spinal Motor Circuits

The brain stem contains, in addition to the motor nuclei that regulate the facial muscles, many groups of neurons that project to the spinal gray matter. These projections were classified by the Dutch neuroanatomist Hans Kuypers into two main systems: the medial and the lateral brain stem pathways.

The medial pathways provide the basic postural control system upon which the cortical motor areas can organize more highly differentiated movement. They are phylogenetically the oldest component of the descending motor systems and consist of three major tracts: the vestibulospinal (medial and lateral), reticulospinal (medial and lateral), and tectospinal tracts. These pathways descend in the ipsilateral ventral columns of the spinal cord and terminate predominantly on interneurons and long propriospinal neurons in the ventromedial part of the intermediate zone (Figure 33-14A), thus influencing motor neurons that innervate axial and

proximal muscles. They also terminate directly on some motor neurons, particularly those of the medial cell group that innervate axial muscles. The wide area of termination of individual axons is important in distributing control to a variety of functionally related motor nuclei.

The lateral brain stem pathways are more concerned with goal-directed limb movements such as reaching and manipulating; they terminate on interneurons in the dorsolateral part of the spinal gray matter and thus influence motor neurons that control distal muscles of the limbs. The main lateral descending pathway from the brain stem is the *rubrospinal tract*, which originates in the magnocellular portion of the red nucleus in the midbrain. Rubrospinal fibers descend through the medulla to the dorsal part of the lateral column of the spinal cord (Figure 33-14B). In

cats and monkeys the rubrospinal tract is important in the control of distal limb muscles used for manipulating objects. In anthropoid apes and humans this function is largely assumed by the corticospinal system.

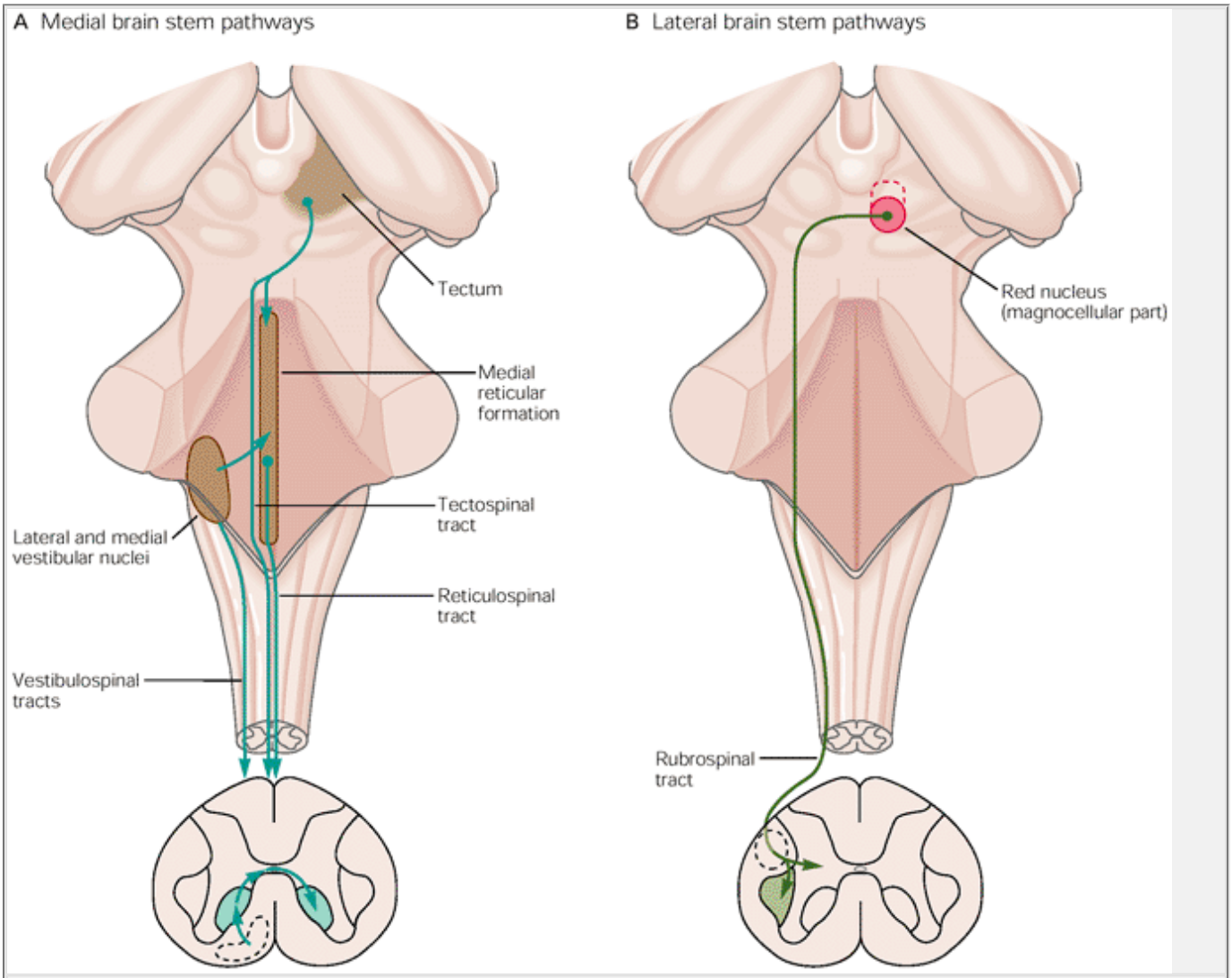


Figure 33-14 Medial and lateral descending pathways from the brain stem control different groups of neurons and different groups of muscles.

A. The main components of the medial pathways are the reticulospinal, medial and lateral vestibulospinal, and tectospinal tracts that descend in the ventral column. These tracts terminate in the ventromedial area of the spinal gray matter.

B. The main lateral pathway is the rubrospinal tract, which originates in the magnocellular portion of the red nucleus. The rubrospinal tract descends in the contralateral dorsolateral column and terminates in the dorsolateral area of the spinal gray matter.

The Cerebral Cortex Modulates the Action of Motor Neurons in the Brain Stem and Spinal Cord

The ability to organize complex motor acts and execute fine movements with precision depends on control signals from the motor areas in the cerebral cortex. Cortical motor commands descend in two tracts. The corticobulbar fibers control the motor nuclei in the brain stem that move facial muscles, while the corticospinal fibers control the spinal motor neurons that innervate the trunk and limb muscles. In addition, the cerebral cortex indirectly influences spinal motor activity by acting on the descending brain stem pathways.

The Cerebral Cortex Acts on Spinal Motor Neurons Both Directly and Indirectly

At the end of the nineteenth century Gustav Fritsch and Eduard Hitzig discovered that electrical stimulation of the cortex produces movements on the contralateral side

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of the body. Systematic stimulation of the surface of the cortex in primates revealed somatotopic maps of the body in frontal areas. In addition, lesions of the arm or leg area of motor cortex led to axonal degeneration at cervical and lumbar levels of the spinal cord, respectively. This demonstrated that somatotopic areas project to their expected targets in the spinal cord. The primary motor cortex lies along the precentral gyrus in Brodmann's area 4. Several other motor maps can also be defined in area 6, the premotor cortex. (These maps and their contributions to motor control are described in Chapter 38 in the context of voluntary movement.) The axons of cortical neurons that project to the spinal cord run together in the corticospinal tract, a massive bundle of fibers containing about 1 million axons. About a third of these originate from the precentral gyrus of the frontal lobe. Another third originate from area 6. The rest originate in areas 3, 2, and 1 in the somatic sensory cortex and regulate transmission of afferent input through the dorsal horn.

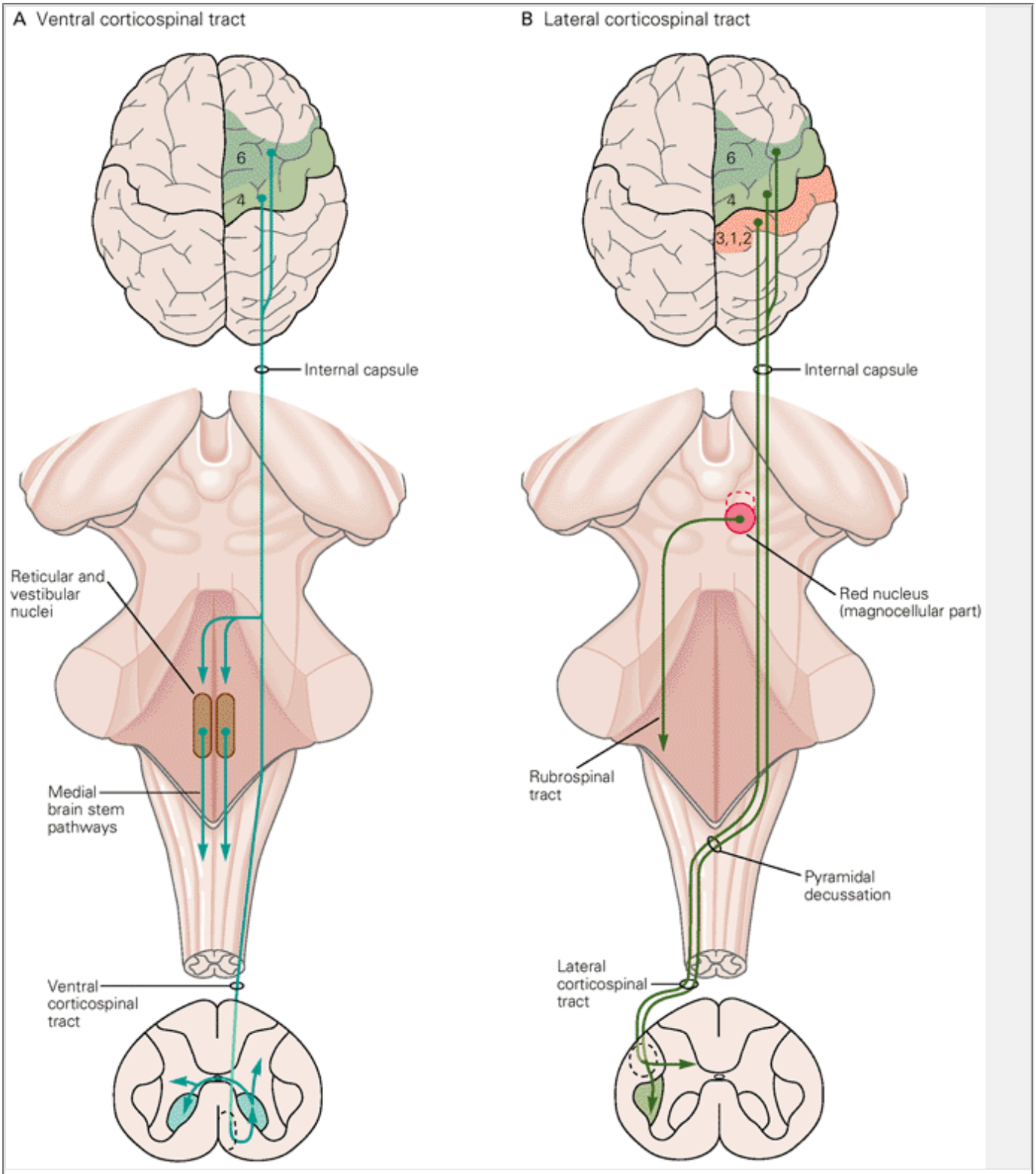

Figure 33-15 The cortex directly controls motor neurons in the spinal cord through two descending pathways.

A. The ventral corticospinal tract originates principally from premotor neurons in Brodmann's area 6 and in zones in area 4 controlling the neck and trunk. The descending fibers terminate bilaterally and send collaterals to the medial pathways from the brain stem.

B. The lateral corticospinal tract originates in two motor areas (Brodmann's areas 4 and 6) and three sensory areas (3, 2, and 1). It crosses at the pyramidal decussation, descends in the dorsolateral column, and terminates in the spinal gray matter. The fibers from the sensory cortex terminate primarily in the medial portion of the dorsal horn. However, collateral fibers project to dorsal column nuclei. These terminations allow the brain to actively modify sensory signals.

The corticospinal fibers run together with corticobulbar fibers through the posterior limb of the internal capsule to reach the ventral portion of the midbrain. In the pons they separate into small bundles of fibers that course between the pontine nuclei. They then regroup in the medulla to form the medullary pyramid, a conspicuous landmark on the ventral surface of the medulla. About three-quarters of the corticospinal fibers cross the midline in the pyramidal decussation at the junction of the medulla and spinal cord. The crossed fibers descend in the dorsal part of the lateral columns (dorsolateral column) of the spinal cord, forming the lateral corticospinal tract. The uncrossed fibers descend in the ventral columns as the ventral corticospinal tract (Figure 33-15).

The lateral and ventral divisions of the corticospinal tract terminate in approximately the same regions of spinal gray matter as do the lateral and medial systems from the brain stem. The lateral corticospinal tract projects primarily to motor nuclei in the lateral part of the ventral horn and to interneurons in the intermediate zone. The ventral corticospinal tract projects bilaterally to the ventromedial cell column and to adjoining portions of the intermediate zone that contain the motor neurons that innervate axial muscles.

The Cerebral Cortex Acts on Brain Stem Motor Neurons Through the Corticobulbar Tract

The corticobulbar fibers that control muscles of the head and face terminate in motor and sensory (cranial nerve) nuclei in the brain stem. In humans the corticobulbar fibers form monosynaptic connections with motor neurons in the trigeminal, facial, and hypoglossal nuclei. The trigeminal motor nuclei and facial nuclei receive cortical projections from both hemispheres. The motor neurons innervating muscles of the upper part of the face receive approximately an equal number of axons from both hemispheres, whereas those innervating the lower face receive predominantly contralateral fibers. As a result, damage to corticobulbar fibers on one side produces weakness only of the muscles of the contralateral lower part of the face. Movements of the eyes are controlled by a different system (Chapter 41).

The Motor Cortex Is Influenced by Both Cortical and Subcortical Inputs

The major cortical inputs to the motor areas of cortex are from the prefrontal, parietal, and temporal association areas. These are mainly focused on the premotor cortex and supplementary motor area. There are, however, connections from the primary sensory cortex to the primary motor cortex. Other corticocortical inputs arise from the opposite hemisphere and course through the corpus callosum. Callosal fibers interconnect homologous areas in the two hemispheres. The left and right finger representations, however, do not receive callosal fibers and are thus functionally independent of one another. As we shall see in Chapters 41, 42, and 43, the major subcortical input to the motor cortical areas comes from the thalamus, where separate nuclei convey inputs from the basal ganglia and the cerebellum.

An Overall View

The primary purpose of the elaborate information processing and storage that takes place in the brain is to enable us to interact with our environment. Our infinitely varied and purposeful motor behaviors are governed by the integrated actions of the brain's several motor systems. Nevertheless, the first insight into the neural mechanisms of motor action came from analyses of the motor capabilities remaining when the spinal cord or brain stem is disconnected from the brain or after local damage. The discovery of spinal reflexes showed that the spinal cord contains the neural circuits for generating simple and coordinated movements.

Reflexes do not differ from voluntary movements as fundamentally as was once thought. Reflexes are organized by specific sensory inputs such that the locus and magnitude of the response are appropriate for the site and the intensity of the stimulus. These sensorimotor relationships are not, however, immutable and, as we will see in Chapter 36, the reflex patterns produced through

spinal circuits can be converted from one set of movements to another by signals from higher levels of the nervous system. While voluntary movements are strikingly adaptable, they too are governed by well-defined rules.

Motor commands are organized hierarchically. The brain stem integrates spinal reflexes into a variety of automated movements that control posture and locomotion. Several interconnected areas of cortex that project to the descending systems of the brain stem and to the spinal cord itself initiate and control our more complex voluntary movements. Unlike motor systems at lower levels, cortical motor areas are not influenced only by peripheral sensory input; they also receive crucial information from sensory association and prefrontal areas that integrate current sensory information with stored knowledge. In addition, motor areas in the cortex are modulated by two subcortical structures, the basal ganglia and cerebellum.

The corticospinal and corticobulbar pathways are the most direct and powerful route by which the cerebral cortex can control the motor neurons that innervate muscles. The cortex also regulates spinal motor neurons indirectly through its influence on the brain's

various descending systems. This redundancy allows for significant recovery of function in cases of injury. In contrast, the only route by which the cortex can control the muscles of our hands and fingers is through the direct projection from the primary motor cortex to distal motor neurons. Therefore, injury to these fibers results in permanent loss of all the skilled movements that we use to manipulate small objects.

Three features of the motor hierarchy are particularly important. First, the inputs to each component create a rough somatotopic map of the body, and this somatotopic organization is preserved in the outputs of each component. For example, regions of primary motor cortex that control the hand receive input from hand control areas in the premotor cortex and influence fibers of the descending brain stem pathways that affect hand movement. Second, each level of motor control receives peripheral sensory information that is used to modify the motor output at that level. At the same time, each level contains distinct populations of neurons that project in parallel to sensory relay nuclei and other structures, including the thalamus and cerebellum. These recurrent pathways provide the sensory systems and other processing systems with information about ongoing motor commands and allow higher motor centers to control the information that reaches them, conveying only such information as may be relevant to a given task.

Third, motor programs are refined continuously by learning. Functional imaging and physiological studies have shown that there are changes and shifts in the anatomical location of representations of motor programs as a motor behavior progresses, through learning, from being novel to being automatic. Even though motor learning is acquired primarily through practice, skilled performers are often unable to express what it is they have learned. Motor learning is thus referred to as "implicit" learning, in contrast to the "explicit" acquisition of knowledge that is typically expressed in statements about the world.

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34

The Motor Unit and Muscle Action

Gerald E. Loeb

Claude Ghez

> … to move things is all that mankind can do, for such the sole executant is muscle, whether in whispering a syllable or in felling a forest.
>
> --Charles Sherrington, 1924

THE MAJOR CONSEQUENCE of the elaborate information processing that takes place in the brain is the contraction of skeletal muscles. Indeed, animals are distinguishable from plants by their ability to make precise, goal-directed movements of their body parts. The problem of deciding when and how to move is, to a large degree, the driving force behind the evolution of the nervous system. In this chapter we examine how the electrical and chemical signals used to convey information in the nervous system are ultimately converted into the forces and displacements that make up movement.

In all but the most primitive animals movement is generated by specialized muscle cells. There are three general types of muscles: smooth muscle, used primarily for internal actions such as peristalsis and control of blood flow; cardiac muscle, used exclusively for pumping blood; and skeletal muscle, used primarily for moving bones. In this chapter we deal exclusively with the organization and neural control of mammalian skeletal muscles.

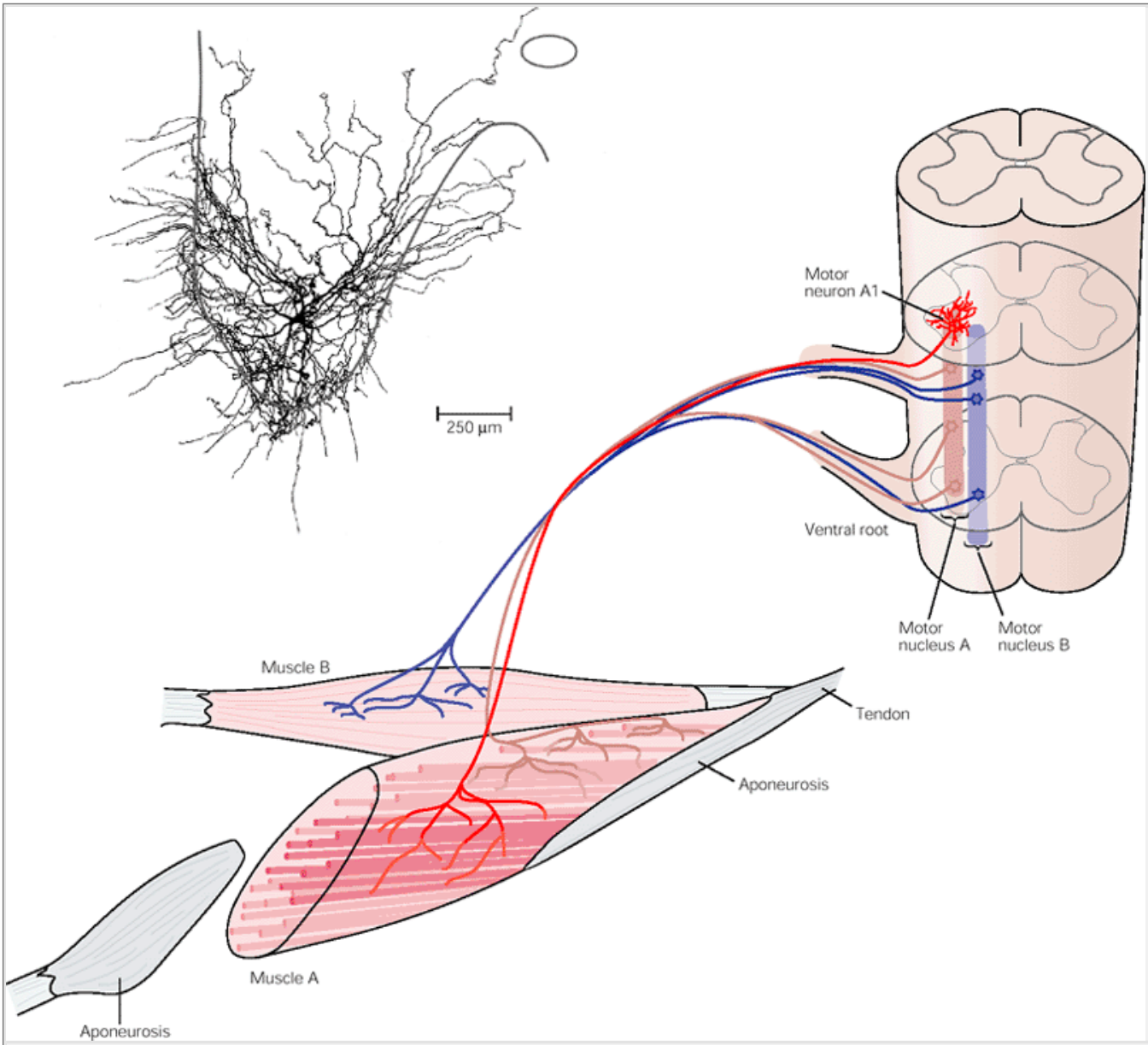

Figure 34-1 A typical muscle consists of many thousands of muscle fibers working in parallel and organized into a smaller number of motor units. A motor unit consists of a motor neuron and the muscle fibers that it innervates. The motor neurons innervating one muscle are usually clustered into an elongated motor nucleus within the ventral spinal cord that may extend over 1-4 segments. In the example shown here the motor neuron A1 plus other motor neurons innervating muscle A form motor nucleus A. Muscle B is innervated by motor neurons lying in a separate motor nucleus B. Note that the extensively branched dendrites of a typical motor neuron (shown for A1 only) tend to intermingle with those from other motor nuclei. The axons from the various motor nuclei are intermingled in the ventral roots and peripheral nerves, but they resegregate to emerge as individual muscle nerves. (Reconstructed motor neuron courtesy of P. K. Rose.)

Much of this chapter concerns the mechanical properties of muscles, tendons, and joints and the laws of physics that govern the motion of limbs. In order to

perform a task the brain must solve a control problem that depends on these properties and laws. The difficulty of controlling a system with multiple linked segments can be appreciated by considering that, despite substantial computing power, industrial robots are relatively poor at compensating for unexpected perturbations that would pose no problem even for a simple animal. At

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least a part of the solution to the control problem resides in the muscles themselves. Our skeletal muscles are endowed with mechanical properties that contribute importantly to the grace, speed, efficiency, and robustness of our movements.

Motor Neurons Convey Commands to Muscle Fibers

Skeletal muscle is subdivided into parallel bundles of stringlike fascicles, which themselves are bundles of even smaller stringlike multinucleated cells called *muscle fibers.* A typical mammalian muscle fiber has a diameter of 50-100 μm and a length of 2-6 cm. Thus a typical muscle is composed of hundreds of thousands, even millions, of independent contractile elements arranged in parallel and, in longer muscles, in series. The main job of the motor nervous system is to control these elements in all of the muscles simultaneously so that the correct tension is applied to the skeleton to produce the desired movement.

A typical muscle is controlled by about a hundred large motor neurons whose cell bodies lie in a distinct cluster called a motor nucleus in the spinal cord or brain stem (Figure 34-1). The axon of each motor neuron exits the spinal cord through a ventral root (or through a cranial nerve from the brain stem) and traverses progressively smaller branches of peripheral nerves until it enters the muscle it controls. There it branches widely to innervate anywhere from 100 to 1000 muscle fibers scattered over a substantial part of the muscle. Except during development, each muscle fiber is normally innervated by only one motor neuron in only one place, usually near its midpoint. The ensemble of muscle fibers innervated by a single motor neuron is called a *muscle unit*, and that ensemble together with its motor neuron is called a *motor unit.* The number of muscle fibers constituting a single motor unit varies greatly in muscles in different parts of the body (see Chapter 35).

The functional connection between a motor neuron and a target muscle fiber is a chemical synapse called the end-plate (Chapter 11). End-plates are usually clustered into bands that extend across some or all of the muscle. The neuromuscular synapse formed by a motor neuron on a muscle fiber is large and filled with many vesicles containing the neurotransmitter acetylcholine. This synapse is constructed so that each action potential in the motor neuron releases sufficient transmitter to depolarize the postsynaptic membrane of the muscle fiber to its threshold for an action potential. The acetylcholine released from the presynaptic terminals is rapidly hydrolyzed by acetylcholinesterase, leaving the muscle fiber ready to respond again in an all-or-none manner to the next action potential. All of the muscle fibers innervated by the same motor neuron respond faithfully and synchronously to each action potential of the motor neuron.

Once the postsynaptic membrane of the neuromuscular junction is depolarized to its threshold, an action potential propagates along the membrane of the muscle fiber (the sarcolemma). The action potential propagates relatively slowly (3-5 m/s) in both directions away from the end-plate region. A muscle fiber is electrically similar to a large-diameter, unmyelinated axon in that high transmembrane currents are required to propagate the action potential. These currents give rise to relatively large potential gradients in the extracellular fluid around the muscle fiber.

Because a single action potential in a motor neuron can activate hundreds of muscle fibers in synchrony, the resulting currents sum to generate an electrical signal that is readily detectable outside the muscle itself. Furthermore, when more than minimal force is required, many motor neurons generate an asynchronous barrage of action potentials with overlapping action potentials arising in each muscle unit. The result is a complex pattern of electrical potentials (typically on the order of 100 μV in amplitude) that can be recorded as an *electromyogram* (EMG) using simple electrodes on the surface of the overlying skin. The relative timing and amplitude of these patterns recorded over particular muscles reflect closely the aggregate activity of motor neurons that innervate each muscle. Electromyographic signals are valuable for studying motor control and for diagnosing pathology in the motor systems and in the muscles themselves (see Chapter 35).

The Contractile Machinery of Muscle Fibers Is Organized Into Sarcomeres and Cross Bridges

When viewed through the light microscope a single skeletal muscle fiber can be seen to contain many *myofibrils*, each of which has a longitudinally repeating pattern of dark and light bands called *striations.* The dark bands are constant in length, but the light bands tend to become longer or shorter as the muscle lengthens or shortens, respectively.

Sarcomeres Are Composed of Interdigitated Thick and Thin Filaments

Under the electron microscope individual myofibrils can be seen to consist of longitudinally repeated cylindrical units, called *sarcomeres.* Each sarcomere contains contractile

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proteins, organized into a regular interdigitated matrix of thick and thin filaments, and is bounded by Z disks (Figure 34-2). The changing banding pattern with muscle contraction evident in the light microscope results from the changing overlap between these filaments. The sarcomere is the functional unit of length in skeletal muscle. All myofibrils in all muscle fibers of a muscle tend to change length in concert as a result of the various noncontractile components that link them mechanically. The physiological range of length of each sarcomere is 1.5-3.5 μm. A muscle fiber with a 4-cm resting length would have about 20,000 sarcomeres in series.

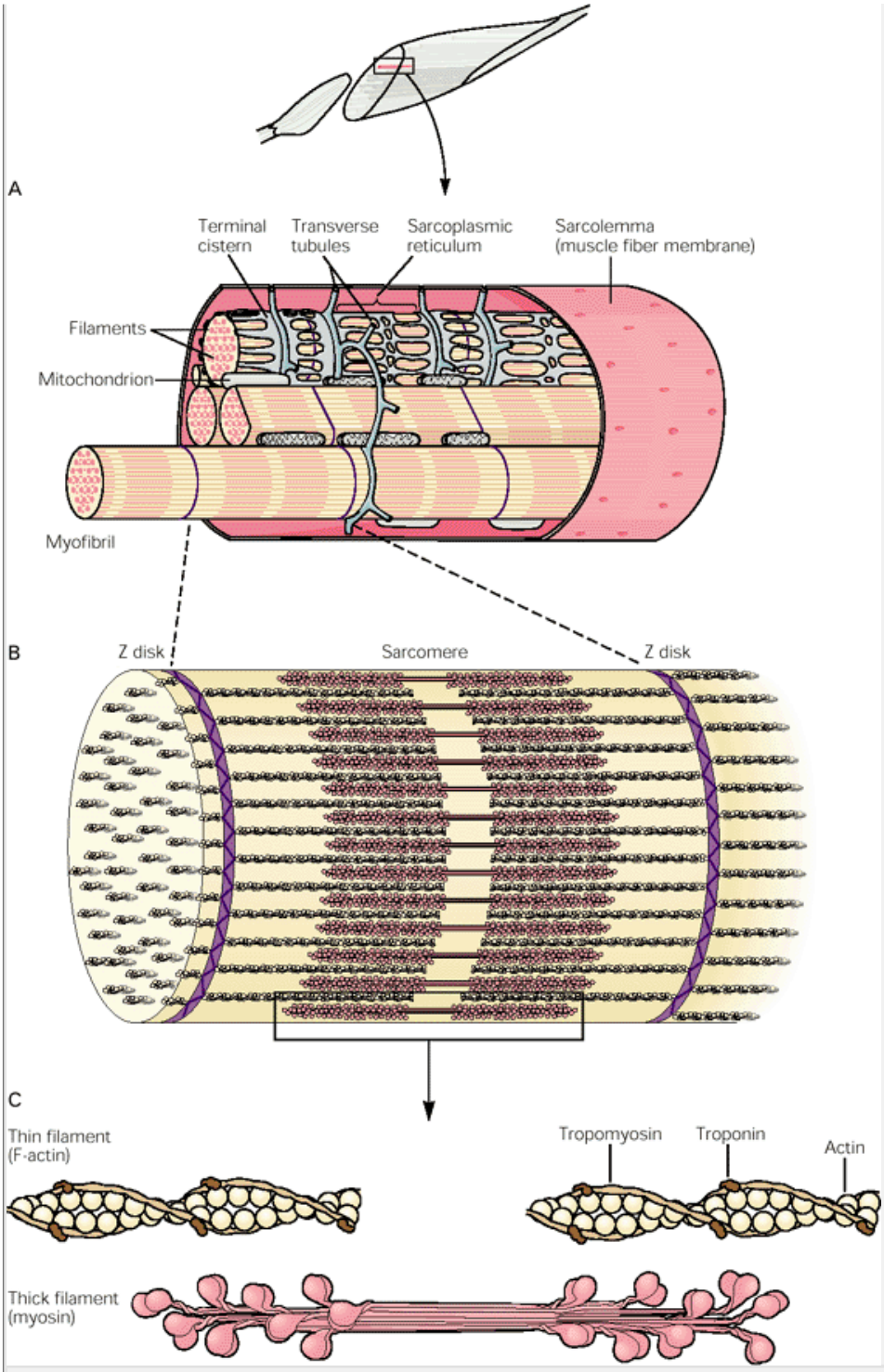


Figure 34-2 A single muscle fiber contains several myofibrils. (Adapted from Bloom and Fawcett, 1975; Loeb and Gans, 1986.)

A. This three-dimensional reconstruction of a section of muscle fiber shows the relationship of the myofibrils to the membrane, transverse tubule system, and sarcoplasmic reticulum.

B. The sarcomere is the functional unit of the muscle. It contains contractile proteins, the thick and thin filaments, bounded by thin Z disks, from which the thin filaments arise. Thick and thin filaments overlap, creating alternating dark bands that give skeletal muscle its characteristic striated appearance. This banded pattern changes as the overlap between the thin and thick filaments changes during shortening or lengthening of the muscle fiber.

C. Detail of the contractile proteins (myofilaments). The thin filaments are composed principally of polymerized actin but also include tropomyosin and troponin. The thick filaments consist of arrays of entwined pairs of myosin molecules; each molecule includes a stem and a double globular head that protrudes from the stem.

The thin filaments project in both directions from the Z disks, whereas the thick filaments are discontinuous and float in the middle of the sarcomere. The main constituent of each thin filament is a pair of polymerized actin monomers (F actin) arranged as a helix (Figure 34-2C). The thin filament also contains tropomyosin (a long filamentous protein that lies in the grooves formed by the paired strands of actin) and troponin (small molecular complexes that are attached to the tropomyosin filament at regular intervals).

The thick filament is made up of about 250 myosin molecules entwined together along most of their lengths. The myosin molecules have globular heads on short stems that stick out from the sides of the thick filament in a staggered array, pointing away from a bare region in the middle of the filament where there are no heads (Figure 34-2C).

Contractile Force Is Produced by Cross Bridges

The thick and thin filaments comprise the contractile machinery of the muscle. In a contracting muscle adjacent thick and thin filaments slide past each other, propelled by cyclical interactions between the myosin heads of the thick filaments and binding sites on the actin of the adjacent thin filaments. This is the "sliding

filament hypothesis" developed by A.F. Huxley and colleagues starting in the 1950s.

Each globular myosin head contains an ATPase that converts the chemical energy of adenosine triphosphate (ATP) into mechanical energy, resulting in a "cocked" deformation of the myosin head (Figure 34-3). This stored mechanical energy can be released only after the myosin head attaches to a binding site on one of the adjacent thin filaments that has been activated by Ca^{2+} (a process described later). The attached head, or *cross bridge*, then acts like an oar, pulling the thin filament longitudinally in a direction that increases the overlap between the thick and thin filaments and shortening the muscle fiber.

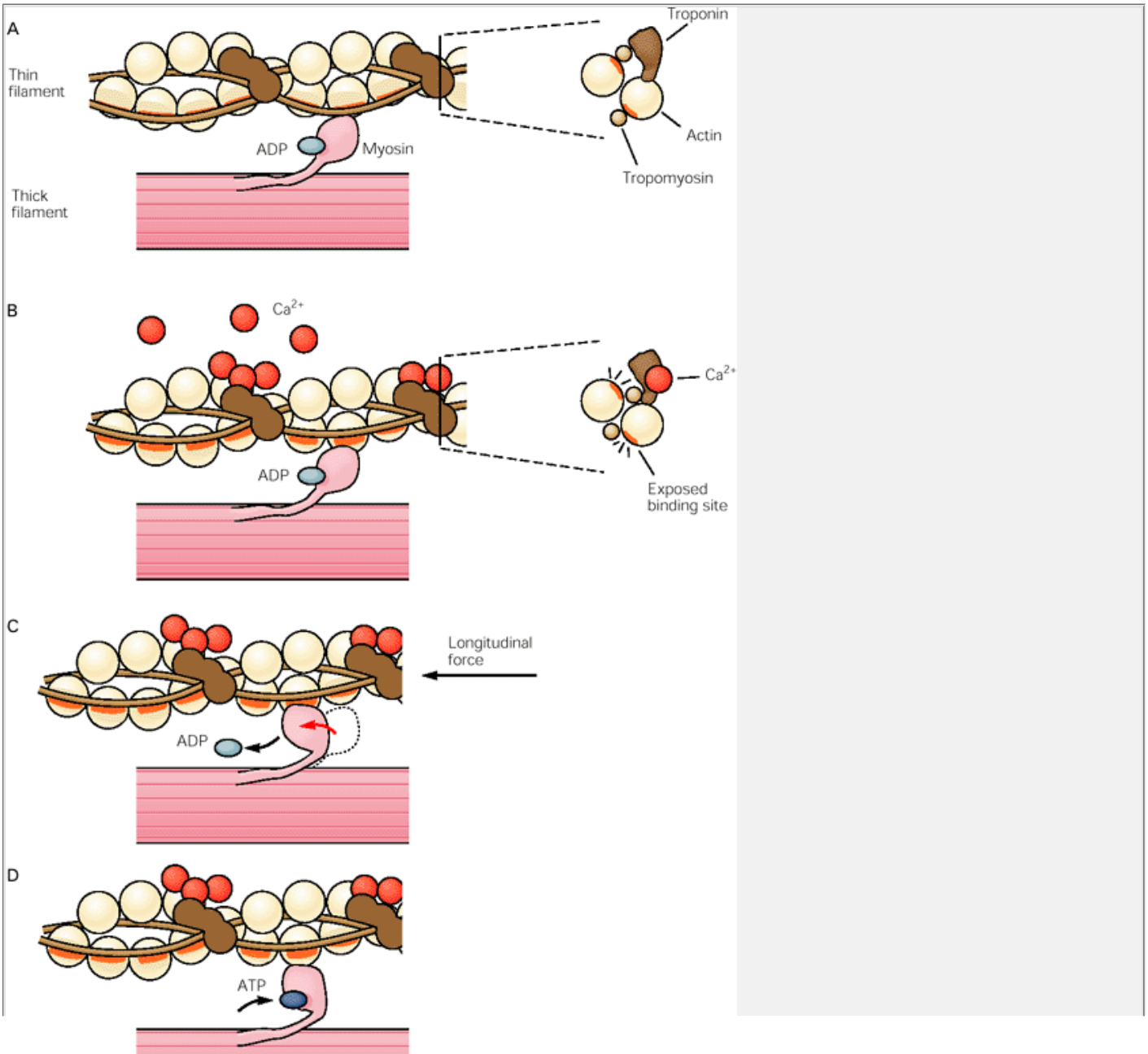
After a sliding motion of about 0.06 μm, the stress in the cross bridge is completely relieved and it can detach. Detachment is accompanied by recocking the head for reattachment to another binding site. The detachment of the myosin head from the actin molecule is an active process that uses energy derived from the hydrolysis of ATP into adenosine diphosphate (ADP) and phosphate in the presence of Ca^{2+}. The process of attachment, rotation, and detachment therefore continues as long as Ca^{2+} and ATP are present in the cell in sufficient amounts. The stiff state of muscles after death known as *rigor mortis* results from cross bridges that cannot detach because ADP is not phosphorylated to replenish the ATP supply.

Noncontractile Components in Muscle Fibers Provide Stability for the Contractile Elements

Muscle fibers contain several structural elements whose mechanical properties ensure stable and efficient production and transmission of the active force generated by the contractile apparatus of the thin and thick filaments. In addition to the contractile myofilaments described above, a set of very thin and highly elastic filaments, the connecting filaments or *connectins*, extend from the ends of the thick filaments and attach on both flanking Z disks (see Figure 34-5 below). These connectins form a continuous elastic structure along the entire length of the muscle fiber, accounting for at least some of the springlike restoring force that can be measured when an inactive muscle is stretched passively (see below). The connecting filaments keep the thick and thin filaments aligned with respect to each other if the muscle is stretched past the overlap of the filaments. The remainder of the passive force is provided by endomysial connective tissue, a loose matrix of collagen that surrounds each muscle fiber and helps to distribute tension and sarcomere length changes evenly. Any active force generated by the contractile mechanism is independent of and additional to the passive force generated by these parallel elastic elements.

At the ends of muscle fibers that insert onto connective tissue the last set of actin filaments attaches to specialized sites on the muscle fiber membrane where the tension is conveyed to invaginated strands of extracellular collagen in the connective tissue. Tendons and aponeuroses (see below) can stretch and store mechanical energy during muscle contraction, particularly if these in-series elastic elements are relatively long compared with the muscle fibers. Some muscles have long fascicles that are staggered bundles of shorter muscle fibers. The intrafascicular ends of these muscle fibers have a long tapered shape that provides a large surface area over which tensile force can be

passed as shear force into the surrounding connective tissue. Some of the myopathies described in Chapter 35 may be related to failures of the noncontractile components of muscle.



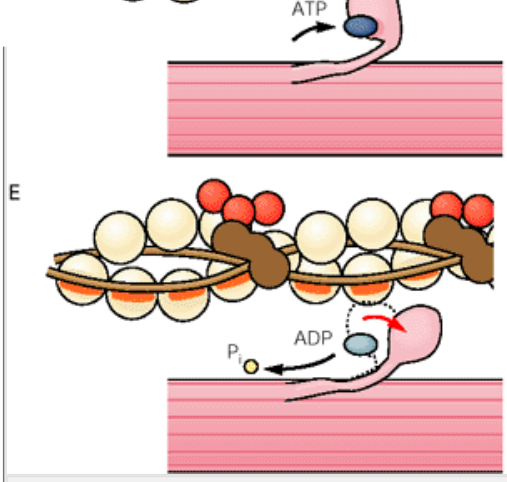


Figure 34-3 Contraction is produced by cyclical attachment and detachment of myosin heads on adjacent thin filaments. (Based on Huxley and Simmons, 1971; Squire, 1983.)

A. In a muscle fiber at rest the myosin heads of the thick filaments are all in a "cocked" position with bound adenosine diphosphate (ADP). The troponin-tropomyosin complexes on the thin filaments have no bound Ca^{2+} and are positioned so as to block the binding sites on the actin (**orange**).

B. When the muscle fiber is activated, Ca^{2+} is released from the cisternae of the sacroplasmic reticulum (see Figure 34-2) and binds to at least some of the tropomyosin sites. This action causes a conformational change in the thin filament that exposes actin-binding sites, allowing the myosin heads to attach and form cross bridges between the thick and thin filaments.

C. Attached myosin heads rotate, exerting longitudinal forces that pull the thick and thin filaments into greater overlap, shortening the muscle fiber.

D. At the end of the cross-bridge power stroke fresh adenosine triphosphate (ATP) binds to the myosin head, which then detaches.

E. Chemical energy released by dephosphorylation of the ATP to bound ADP is used to recock the myosin head for attachment to another binding site and thus another power stroke. $\mathbf{P}_i$ = phosphate.

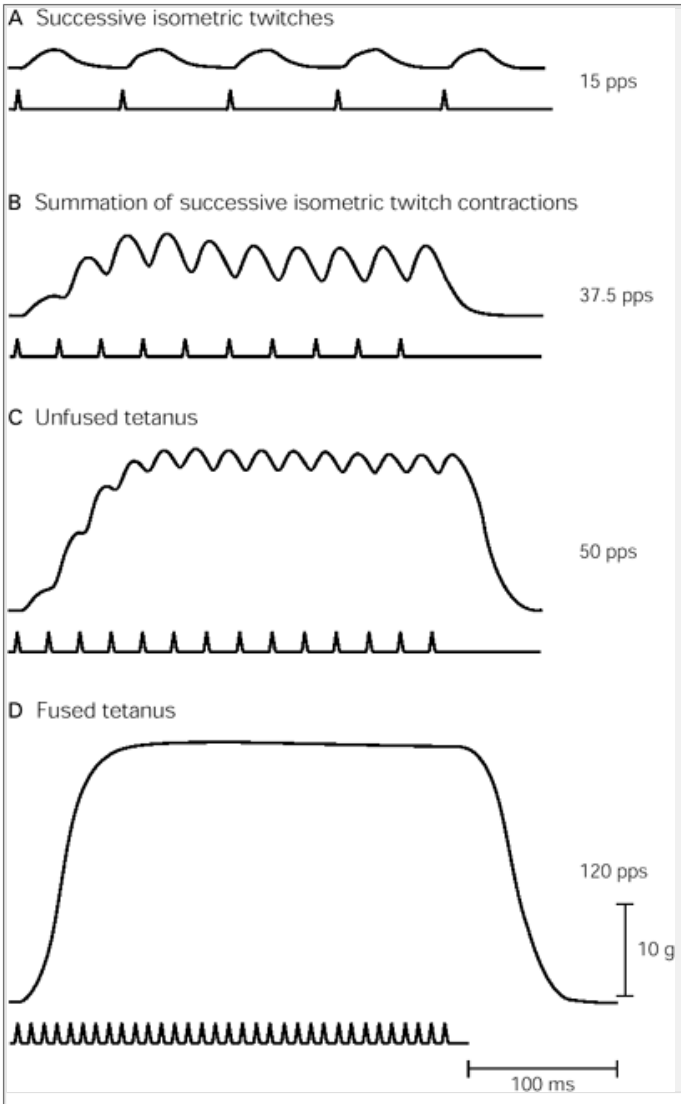


Figure 34-4 The active tension in a muscle varies with the rate of stimulation of the muscle nerve. The muscle nerve is stimulated electrically while the muscle is held at a constant length. The example is from the caudofemoralis, a very fast cat muscle. (All parts are scaled identically to the maximal specific force per unit cross-sectional area shown in D.) The comparable stimulus range for human muscle would be about 5-60 pps. (Courtesy of I. E. Brown and G. E. Loeb).

A. Successive stimuli at a low frequency evoke discrete and separate twitches characterized by a rapid rise in force and a slower decay.

B. If the force produced by a given twitch has not returned to baseline by the time the next is evoked, the contractile force of successive twitches increases at first, but a stable mean level is achieved after a few stimuli, resulting in a ripple of force.

C. Increasing the rate of stimulation produces a higher mean force. However, distinct ripples corresponding to individual stimuli can still be seen.

D. At high rates of stimulation individual stimuli do not produce discrete force fluctuations and the mean force is somewhat greater than during the unfused contraction. Note the delay before force decays back to baseline after the cessation of stimulation. The frequency of action potentials needed to produce a fused tetanic contraction is higher than that occurring during physiological recruitment.

Contractile Force Depends on the Level of Activation of Each Muscle Fiber and Its Length and Velocity

The total force output that can be measured at the tendon of a muscle reflects the sum of its passive tension plus the instantaneous active tension generated by cross bridges. Three physically independent processes affect active tension: the number of cross bridges formed, the force produced by each cross bridge, and the velocity of cross-bridge motion.

Formation of Cross Bridges Depends on Calcium

The actin-binding sites for the myosin heads are normally covered by troponin-tropomyosin complexes (Figure 34-3A). When a troponin molecule binds with Ca^{2+}, the troponin-tropomyosin complex undergoes a conformational change that exposes local actin-binding sites, permitting a cocked myosin head to attach and exert contractile force as a cross bridge.

Muscle fibers contain an extensive network of longitudinally oriented tubules and chambers called the *sarcoplasmic reticulum* (Figure 34-2) that sequester and release Ca^{2+}. Under resting conditions the amount of intracellular Ca^{2+} is kept very low by active pumping into the sarcoplasmic reticulum. The Ca^{2+} is transported through the tubules to terminal cisternae distributed throughout the cross section of the muscle fiber. These cisternae are tightly bound to the transverse

tubules, which are actually invaginations of the sarcolemma (Figure 34-2).

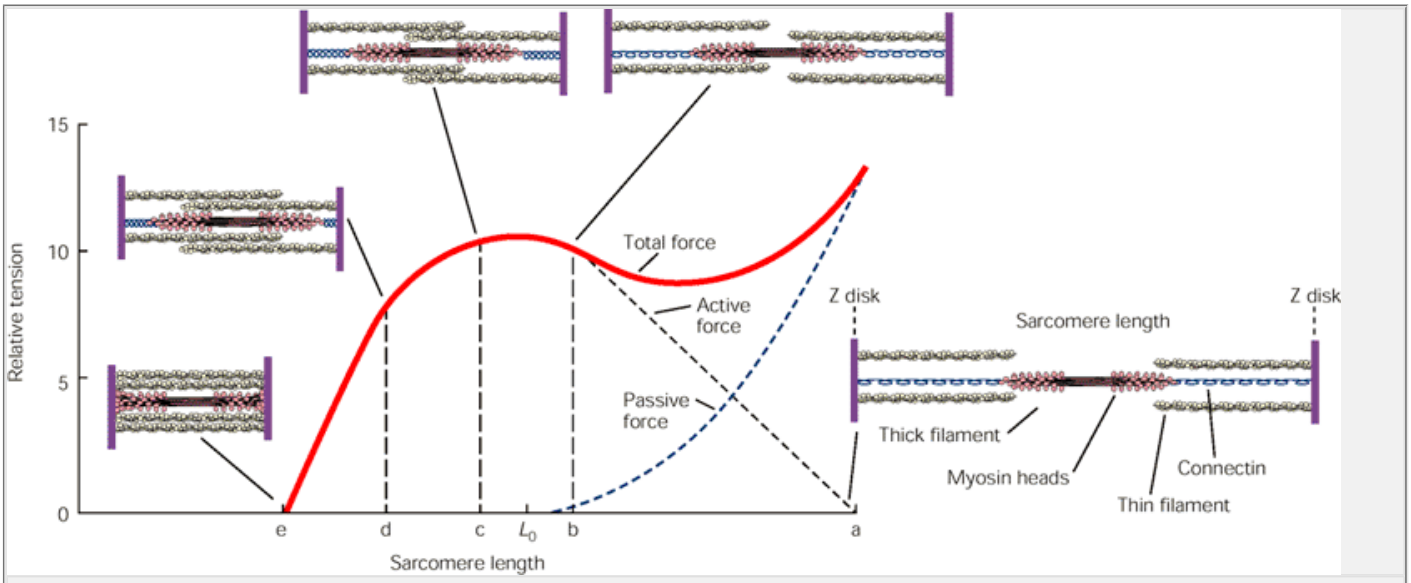


Figure 34-5 The amount of active contractile force developed during contraction depends on the degree of overlap of thick and thin filaments. When the sarcomere is stretched beyond the length at which the thick and thin filaments overlap (length **a**), no active force develops because the myosin heads are not near any binding sites and thus cross bridges cannot form. As the filaments overlap (lengths **a-b**) the force that can develop increases linearly as length decreases because of the progressive increase in the number of binding sites for myosin heads. Around the muscle's optimal length (L_0, between lengths **b-c**) the level of force remains constant because the central portion of the thick filaments is devoid of myosin heads. With further reductions in length (lengths **c-d**) the progressive overlap of thin filaments with each other occludes potential attachment sites and the force begins to fall. Once the thick filaments abut the Z disks (lengths **d-e**), they act like compression springs opposing the active force generated by the cross bridges. Passive force exists in muscle regardless of activation, starting at about L_0 and rising at first exponentially and then linearly as progressive lengthening of the muscle stretches the connectin filaments that tether the thick filaments between the Z disks. Total force is the sum of active and passive force.

When an action potential propagates along the surface of the muscle fiber, it actively depolarizes the transverse tubules within the muscle fiber. Changes in the transmembrane charge in the transverse tubules are coupled to the terminal cisternae by processes that are not yet fully understood. The end result is that Ca^{2+} is released through transmembrane channels in the cisternae, diffuses passively among the myofilaments, and binds reversibly to troponin, thus enabling cross bridges to form (ie, the myosin heads are able to bind to actin).

The release of Ca^{2+} is very rapid, but it may take 20-50 ms to activate the thin filaments fully and for cross bridges to form. Meanwhile, the total amount of free Ca^{2+} is rapidly reduced by reuptake, causing a decrease in cross bridges and a fall in contractile force over a period of 80-200 ms. Activation and calcium reuptake—two competing, time-dependent processes—account for the different time courses of the rise and fall of active tension in a *twitch contraction*, the muscle's response to a single action potential (Figure 34-4A).

The contractile force produced by a single action potential is relatively small because the amount and persistence of released Ca^{2+} is considerably less than that required to activate all of the actin-binding sites (ie, relatively few cross bridges form during a twitch). If another action potential occurs before all the Ca^{2+} released by the first action potential has been resequestered, more cross bridges form, resulting in a greater output of force (Figure 34-4B). The higher the

frequency of action potentials, the higher the amount of force up to the point at which all cross bridge binding sites are continuously activated and force output no longer shows any ripples (Figure 34-4D). This smoothly fused contraction is called a *fused tetanus*, or *maximal tetanic contraction.*

The Number of Cross Bridges Depends on the Degree of Overlap Between Actin and Myosin Filaments

Cross bridges can form only in regions of the sarcomere where myosin heads lie adjacent to actin filaments. As

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the muscle fiber and its sarcomeres are stretched, the region of overlap decreases until at zero overlap no active force can be generated (although there is usually considerable passive force at this length). Thus the amount of active force depends on both the frequency of action potentials in the muscle fiber and the fiber's length.

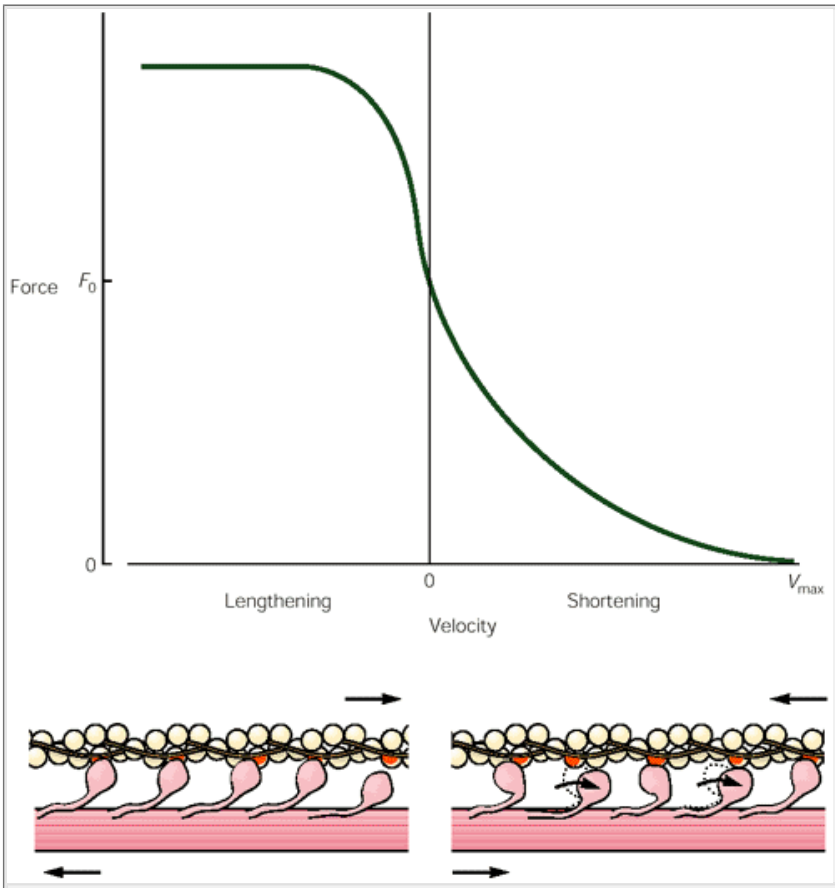

Figure 34-6 The active force produced by muscle depends on the velocity at which it is changing length. Starting from the isometric point (zero velocity), increasing rates of shortening result in decreasing ability to generate force until contractile force drops to zero at V_{max}. As shown in the drawing below, shortening causes the myosin heads to spend more time near the end of their power stroke, when they produce less contractile force, and in detaching, recocking, and reattaching, when they produce no force. When muscle is actively lengthened, contractile force rises rapidly and tends to stay high. The myosin heads spend more time stretched past their angle of attachment and little time in the unattached state because they do not need to be recocked after being pulled away from the actin in this manner (see Figure 34-3).

As the sarcomeres shorten, the actin filaments from each end of the sarcomere overlap with a longer portion of the thick filaments (Figure 34-5), thus increasing the ability to generate contractile force. There is a plateau in the force-length relationship, however, because the mid region of the thick filament does not contain myosin heads. With further shortening the actin filaments interdigitate with each other. This interferes with the ability of the myosin heads to find binding sites, decreasing force generation. The thick filaments eventually collide with and crumple against the Z disks, producing a pushing force that increasingly counteracts the contractile force. The force-length relationship thus has an inverted U shape, meaning that the muscle cannot produce active force at either extreme of length and produces maximal force at an intermediate length, usually called L_0 (Figure 34-5).

If the fibers of a muscle extended from the bony origin to the bony insertion of the muscle, the relationship between muscle length and fiber and sarcomere length would be a simple matter, and we could compute the total force output as the sum of the force produced by all active fibers at that length. In many muscles, however, the muscle fibers are arranged obliquely to the long axis of the muscle and are attached to plates of connective tissue that extend over the surface and sometimes into the body of the muscle (see muscle A in Figure 34-1). These *aponeuroses* gather and transmit the force of muscle fibers to a band of connective tissue, the tendon, which typically inserts on the bone. This pennate (feather-like) architecture enhances the total force that can be generated by a given volume of muscle because there are more fibers working in parallel. There is a cost, however, to this mechanical advantage: a change in length of the whole muscle results in a proportionately larger length change in each contractile unit. As we have seen, force generation depends on muscle length; if the muscle fibers start at their optimal length, a large change in length will shift them to a suboptimal point in their force-length relationship (see Figure 34-5).

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The Force Produced by Cross Bridges Depends on the Velocity of the Sarcomere

The force-length relationship reflects the ability of cross bridges to produce force when length remains unchanged, that is, when the muscle is isometric. Muscles are rarely isometric, however; they usually work to change the motion of loads. If the load is less than the contractile force, the muscle shortens (sometimes called concentric work). The faster the sarcomeres are shortening and the cross bridges are cycling, the less force they produce (Figure 34-6). The shortening velocity at which active force output goes to zero is called V_{max}. If the load is greater than the contractile force, the muscle will lengthen (active lengthening or eccentric work). In this case, the muscle is absorbing rather than generating mechanical energy, such as is required to decelerate a heavy object when catching it. Lengthening muscles actually produce more force than isometric muscles at the same level of activation.

The rate of energy consumption by the cross bridges is proportional to their velocity, not to the force they produce. During rapid shortening when the muscle produces little force, the rate of energy consumption is very high, because each cross bridge dephosphorylates one ATP molecule in the process of detaching at the end of the power stroke. In contrast, during active lengthening the rate of energy consumption is much lower because the cross bridges are pulled apart without ATP binding. During lengthening, cross bridges that have been ripped away from their actin attachments remain cocked and immediately find another actin-binding site, so they continue to contribute to the force-resisting stretch of the muscle regardless of stretch velocity. The force-velocity relationship modifies force output simultaneously with, and more or less independently of, the force-length relationship (Figure 34-7).

Repeated Activation of Muscle Causes Fatigue

When muscle fibers are repeatedly activated, energy supplies are depleted and the muscles fatigue: they produce less force and the rate of rise of force is reduced. When fatigued, muscle fibers also take longer to relax (ie, to slacken when activation ceases) because relaxation is an active process that requires ATP. This prolongation in relaxation time has the paradoxical effect of allowing the force produced by successive nerve impulses to summate at lower frequencies (longer interspike intervals) than when the muscle is rested. As a result, early during fatigue the summed force produced by unfused tetanic stimulation decreases more slowly than the force of individual twitches. As fatigue develops, the firing frequency of motor neurons is decreased to compensate for the summed force. In the next chapter we shall see how receptors in the muscles sense changes in tension and length and can compensate for them through reflex actions on motor neurons.

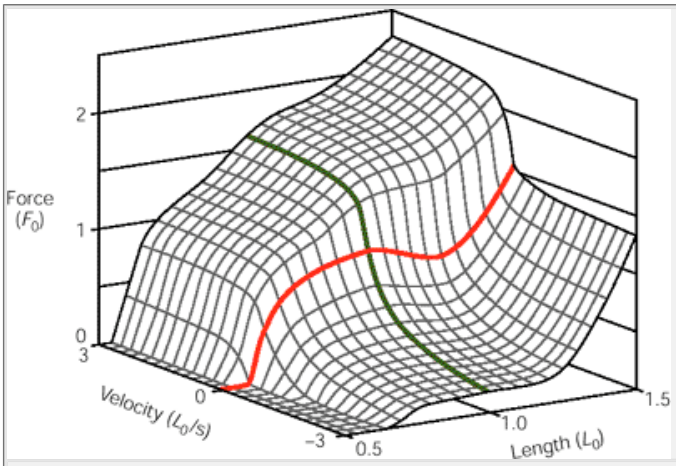

Figure 34-7 The total force (active plus passive) produced by a muscle fiber at a given level of activation depends on both its instantaneous length and velocity, which are independent kinematic variables. Figure 34-5 shows the mechanisms responsible for the effects of length alone and Figure 34-6 the mechanisms responsible for the effects of velocity alone.

This surface plot was generated from a mathematical model that captures the behavior of the slow-twitch soleus muscle of the cat during maximal tetanic activation. It incorporates additional interrelations between length and velocity that occur at nonoptimal lengths. For muscle fibers activated at less than tetanic levels the height of the surface scales downward (lower force), but additional dependencies between activation, length, and velocity change the shape of the surface somewhat. (Adapted from Brown et al. 1996.)

During a natural movement both the length and the velocity of active muscle fibers are likely to change as a result of skeletal motion and stretching of the elastic connective tissues that are in series between the muscle fibers and the bones. Such changes in the kinematic conditions of the muscle fibers alter the force output of the muscle, even if the neural activation of the muscle does not change. In the plot the direction and steepness of the slope of the surface in a particular region represent changes in force output due to small perturbations in the kinematic state of the muscle. Small changes in velocity around zero create particularly large changes in force. These intrinsic changes in force are instantaneous and generally tend to oppose the perturbations, helping to stabilize the muscle in a given kinematic state.

Three Types of Motor Units Differ in Speed, Strength of Contraction, and Fatigability

Anyone who has carved a roasted chicken knows that its muscles are either light colored ("white" muscle) or

dark colored ("red" muscle). The red muscles of the legs are specialized for standing and walking, while the white muscles that operate the wings of this flightless bird are used only occasionally in a vigorous escape maneuver. The distinctive appearance and specialized mechanical capabilities of each type of muscle stem from structural specializations and different metabolic properties of the muscle fibers. Most mammalian muscles are composed of a mix of three fiber types: slow-twitch fibers and two types of fast-twitch fibers. All of the muscle fibers innervated by a single motor neuron are of the same type.

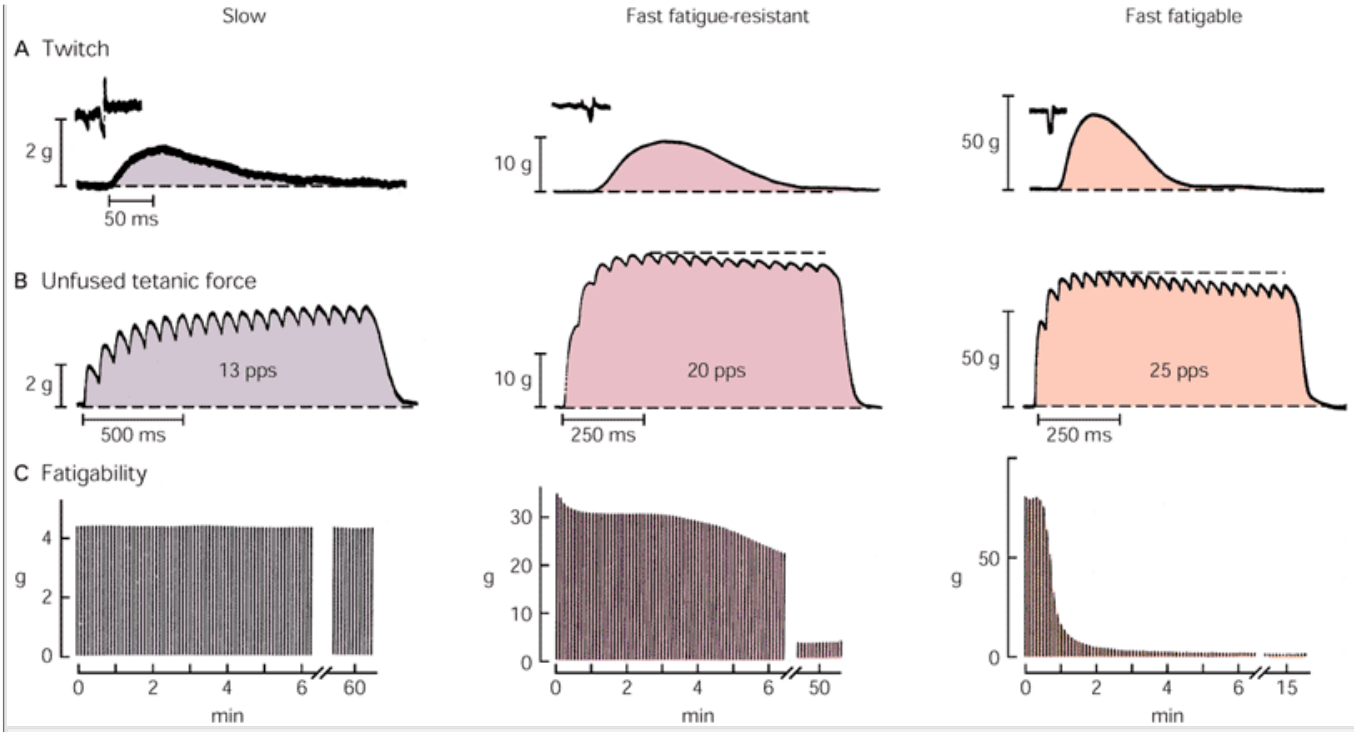

Figure 34-8 Slow, fast fatigue-resistant, and fast fatigable motor units vary in twitch, tetanic force, and fatigability. (From Burke et al. 1973.)

A. Traces show the twitches of the three motor units.

B. Unfused contractions produced by a train of stimuli at a rate typical for each type of motor unit. Fast units produce much larger twitch and tetanic forces than do slow units (vertical scale changed for each).

C. Fatigability can be seen in records of the force produced by sustained activation. The motor units were activated by stimulus trains (40 pps) lasting 0.33 s and repeated every second. In the records shown here a single vertical line represents the force produced by one contraction, recorded at slow speed. In the slow unit the force remained essentially constant for over an hour of repeated stimulation. In the fast fatigable unit the force dropped abruptly after only a minute. The fast fatigue-resistant unit had substantial resistance to fatigue and the force declined slowly over many minutes; some residual force remained after 50 min.

Red muscles are composed mostly of slow-twitch fibers, also called type I fibers. The force produced by type I fibers rises and falls relatively slowly in response to an action potential (Figures 34-8A and 34-9). Muscles composed of type I fibers can produce relatively small amounts of tension for long periods without running down their energy stores. This fatigue resistance results from their reliance on oxidative catabolism, by which glucose and oxygen from the bloodstream can be used almost indefinitely to regenerate the ATP that fuels the contractile apparatus. To support this aerobic metabolism, slow-twitch muscle fibers are surrounded by an extensive network of capillaries. They also are provided with large numbers of mitochondria and oxidative enzymes as well as with myoglobin, a heme protein that helps bind and store oxygen from the blood stream. Individual red muscle fibers produce less contractile force than fast-twitch fibers because they are smaller and have fewer contractile filaments.

White muscles are composed mostly of fast-twitch fibers, also called type II. The force produced by type II fibers rises and falls rapidly (Figure 34-8). These fibers also have a different form of myosin; the cross bridges produce force more effectively at rapid shortening velocities. Fast-twitch fibers are generally categorized into two subtypes depending on their metabolic processes

and fatigue resistance. The *fast fatigable* (type IIB) fibers rely on anaerobic catabolism to sustain force output. They have relatively large stores of glycogen that provide energy to phosphorylate ADP rapidly as the glycogen is converted into lactic acid. However, the rapid depletion of glycogen stores and accumulation of lactic acid limit these fibers to brief bursts of force, after which they take many hours to recover fully. The other fast-twitch subgroup, *fast fatigue-resistant* (type IIA) fibers, combine relatively fast twitch dynamics and contractile velocity with enough aerobic capacity to resist fatigue for several minutes.

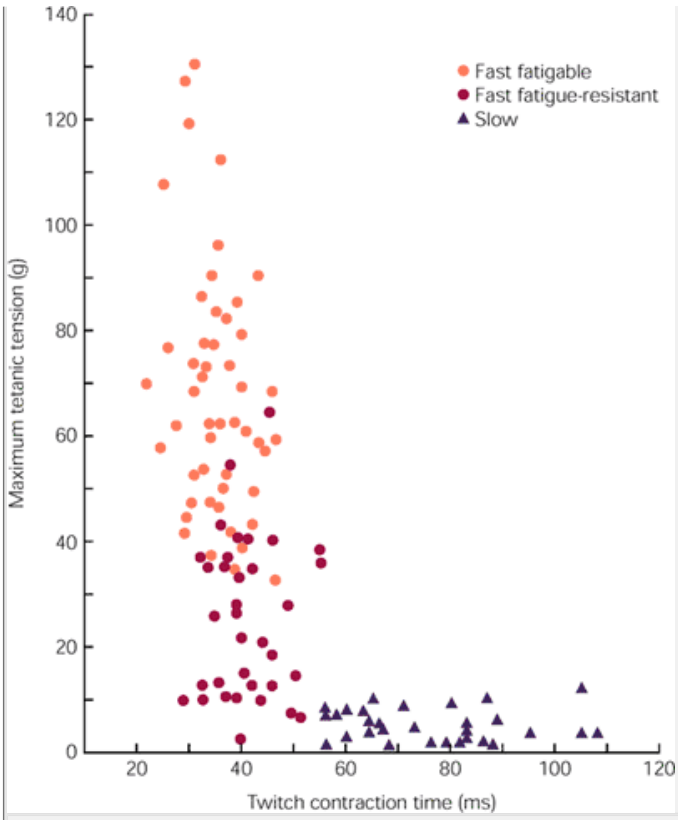

Figure 34-9 This physiological profile of motor units in the gastrocnemius muscle of the cat shows the distinctive actions of slow-twitch and fast-twitch motor units. The fast fatigable units produce larger force than the fast fatigue-resistant units. The slow units have very long twitch-contraction times and generate very low force. (From Burke et al. 1973.)

The contractile force of a motor unit depends on the force-generating capabilities of its fiber type multiplied by the number of muscle fibers innervated by the motor neuron. The motor neurons that control the fast-twitch (type II) muscle fibers usually innervate many large fibers, thus enhancing their ability to produce large forces rapidly (Figure 34-9). These motor neurons have

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relatively large cell bodies and large-diameter axons that conduct action potentials at high velocities.

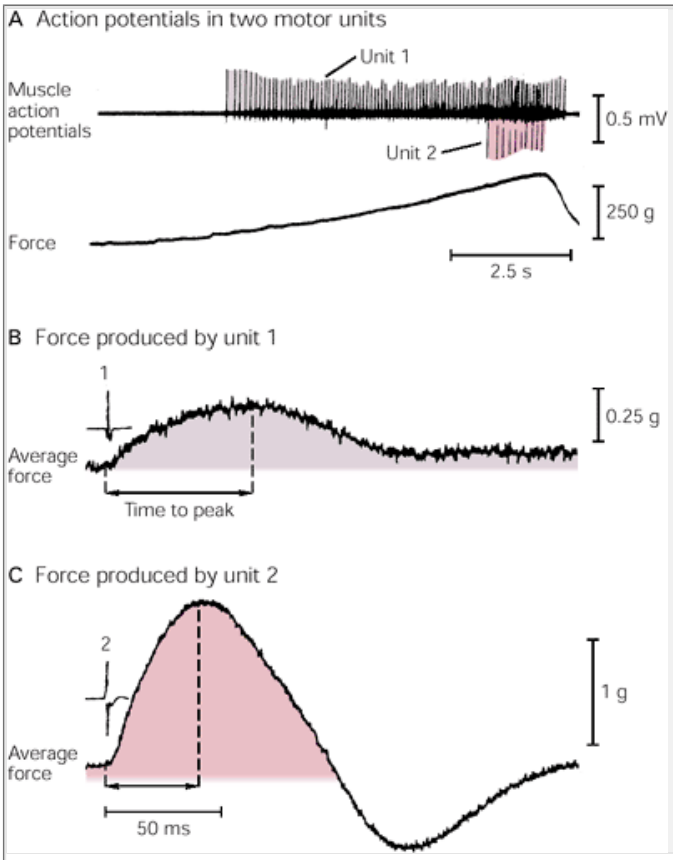

Figure 34-10 Motor units that produce a small amount of force are recruited before motor units that produce larger forces. (Adapted from Desmedt and Godaux, 1977.)

A. Action potentials from two motor units were recorded simultaneously through a single intramuscular microelectrode (**upper trace**) while the subject gradually increased the force produced by the muscle (**lower trace**). The motor neuron labeled unit 1 starts firing near the beginning of the voluntary contraction and increases its firing rate steadily as the force increases. Motor unit 2 starts firing only near the peak of the voluntary contraction and turns off as soon as the force declines.

B-C. Average twitch forces produced by motor units 1 and 2. Because many unrecorded motor units fire asynchronously but more or less at the same time, there is no recognizable deflection in the force trace associated with each of the spikes. To assess the force of a single recorded motor unit, brief segments of the recorded force are aligned with the time of occurrence of each spike and summed. The changes in force that are uncorrelated with a particular action potential, representing noise, will cancel each other out, while the forces that result specifically from this action potential are time locked with it and sum constructively with each added spike. With enough spikes (typically several hundred) the time course of the twitch becomes evident, as in the traces here. Following the size principle of recruitment, the average force produced by unit 1, recruited first, is less than one-quarter that produced by unit 2, while the time from onset to peak force is roughly double.

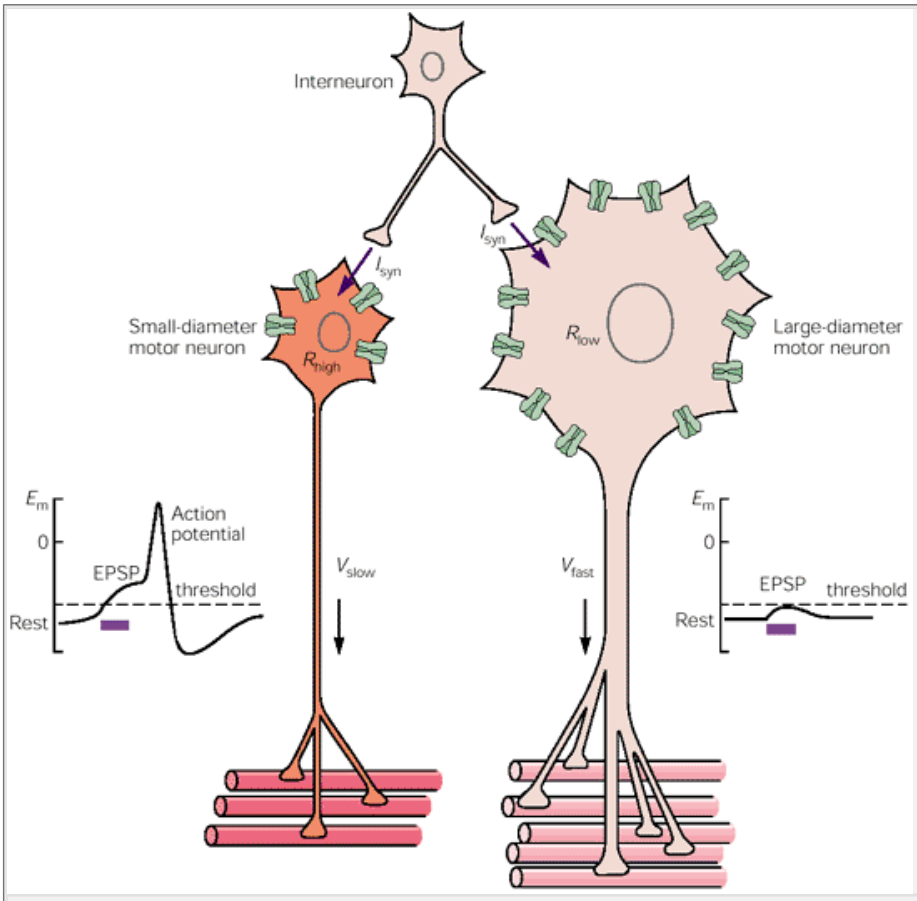

Figure 34-11 Two motor neurons of different sizes have the same resting membrane potential (E_m starts at the resting level in both plots) and receive the same excitatory synaptic current (I_{syn}) from a spinal interneuron. Because the small motor neuron has a small surface area, it has fewer parallel ion channels and therefore a higher overall resistance (R_{high}). According to Ohm's Law ($E = IR$) the synaptic current in the small neuron produces a large excitatory postsynaptic potential (**EPSP**) that reaches threshold, resulting in an action potential. The small motor neuron also has a small-diameter axon that conducts the action potential relatively slowly to the few small muscle fibers that comprise its muscle unit. In contrast, the large motor neuron has a larger surface area, resulting in a lower overall transmembrane resistance (R_{low}) and a smaller, subthreshold EPSP in response to I_{syn}. As a result, its many muscle fibers are not recruited.

The motor neurons that control the slow-twitch (type I) muscle fibers have smaller cell bodies and innervate fewer, thinner fibers, resulting in much smaller force output (as little as 1% of the force produced by fast fatigable units). As might be expected, motor neurons innervating fast fatigue-resistant fibers tend to be intermediate in size and speed.

Motor Units Are Recruited in Fixed Order

In both reflexive and voluntary contractions motor units are recruited in a fixed order from weakest to strongest. Thus when only a small amount of force is required from a muscle innervated by more than one type of motor unit, this force is provided exclusively by the slow-twitch units (Figure 34-10). As more force is required, fast fatigue-resistant and then fast fatigable units are recruited in remarkably precise order according to the magnitude of the force each unit produces. As muscle force is decreased, motor units drop out in the order opposite from their recruitment: the largest are the first to cease activity.

The Electrical Properties of Motor Neurons Determine Their Responses to Synaptic Input

The order of recruitment is highly correlated with the diameter and conduction velocity of the axons and the size of the motor neuron cell bodies, as well as the size and strength of their muscle units. A cell's threshold for firing depends on its electrical resistance, which is inversely related to its surface area. The same synaptic input will produce larger changes in membrane potential in small-diameter cells, which have high electrical resistance, than in large-diameter cells (Figure 34-11). Thus, as the net amount of excitatory synaptic input to a motor nucleus increases, individual motor neurons reach threshold levels of depolarization in the order of their size: The smallest fire first and the largest fire last. This is the size principle of motor neuron recruitment.

Size-ordered recruitment serves two important purposes. First, it minimizes the development of fatigue by allowing the most fatigue-resistant muscle fibers to be

used most of the time, holding the more fatigable fibers in reserve until needed to achieve higher forces. A cat uses half the motor units in an ankle extensor for standing and walking, activities that require about 20% of the maximal force of the muscle. Only during powerful and rapid movements such as jumping are the rest of the units recruited. Thus, about 80% of the total muscle force is held in reserve for transient use during predatory or escape behaviors. Second, size-ordered recruitment ensures that the increment of force generated by successively activated motor units will be roughly proportional to the level of force at which each individual unit is recruited. In natural conditions spinal motor neurons receive synaptic inputs from many sources (eg, sensory afferents, spinal interneurons, descending projections), causing their membrane potentials to fluctuate somewhat randomly. During a fine motor task requiring only small amounts of force by a few slow-twitch motor units, random recruitment of a fast fatigable motor unit, whose twitch contraction might be larger than all slow-twitch units combined, would seriously disrupt the task.

The Force of Contraction Depends on the Number of Recruited Motor Neurons and Their Individual Firing Rates

When a motor nucleus begins to be activated by peripheral or descending inputs, individual motor neurons begin firing at a slow regular rate (5-10 impulses per second in humans). This results in a partially fused train of contractions in the target muscle fibers. As the net excitatory synaptic input in the nucleus increases, the firing rate of the cells increases and other, slightly larger motor neurons reach their threshold for firing, adding their force as well. In this way the mean level of force produced in the muscle gradually increases (Figure 34-12). The overall force of a contraction depends on both the number and size of active motor units and their individual firing rates (see Figure 34-4D). Because the relative timing of the individual action potentials in the various motor units is asynchronous, the various unfused contractions produced by all active motor units blend together into a smooth contraction.

Movements Are Produced by the Coordinated Work of Many Muscles Acting on Skeletal Joints

The human body has over 250 muscles, each with a distinct mechanical action at one or more joints. The nervous system could, in principle, be wired up to control each muscle independently, producing any combination of achievable forces in each. However, this would make for a great deal of neural redundancy. In fact, the nervous system must learn which muscles to use to perform a movement, primarily by trial and error exploration of the mechanical advantages of various combinations of muscles. The suitability of particular muscles depends on the distribution of fiber types as well as the mechanical arrangement of fibers (muscle architecture). The choice of a particular combination of muscles influences the efficiency of performance and the ability to recover gracefully from an unexpected perturbation. The spatial and temporal control of different combinations of muscles is mediated by the divergent and convergent patterns of connections of primary afferents, interneurons, and descending axons within the spinal cord.

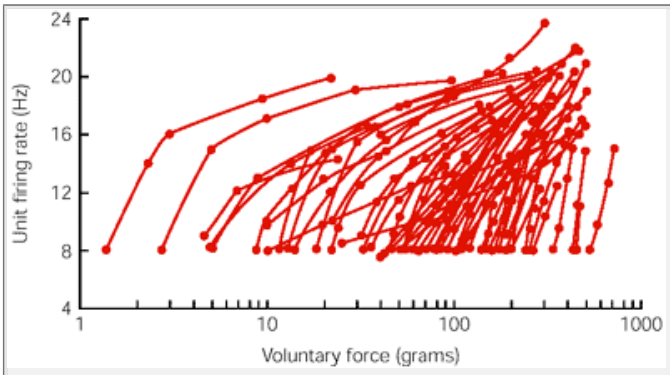

Figure 34-12 For motor tasks that require a slow increase in force, motor units are gradually recruited one at a time and their firing frequency is increased progressively. Units fire at about 8 Hz when first recruited and their firing rate increases as the load on the muscle increases. The record here is from the extensor digitorum communis of a human subject. (Adapted from Monster and Chan 1977.)

Muscles Have Different Actions at Individual Joints

The simplest joint is a hinge, like the elbow and interphalangeal joints. These joints allow movement back and forth in only one plane. Because muscles pull but cannot push, hinge joints require at least two muscles pulling in opposite directions, so called *antagonist* muscles. Most joints are not as simple and have at least a limited range of motion in more than one plane. For example, the ankle permits a large range of extension and flexion together with modest amounts of axial rotation and inversion-eversion. Ball joints, such as the shoulder and hip, permit wide ranges of motion in all three possible

axes of rotation. A few joints move primarily in translation, rather than rotation, such as the sliding of the scapula on the trunk. The number of different, independently controllable axes of motion possible at a joint is called its degree of freedom and ranges from one, for a simple hinge joint, up to a maximum of six (three rotational and three translational). In a multiarticular limb the degree of freedom is the sum of the degrees of freedom of all of its joints. Thus the arm (not counting the digits) has seven degrees of freedom: three at the shoulder, one at the elbow, and three at the wrist.

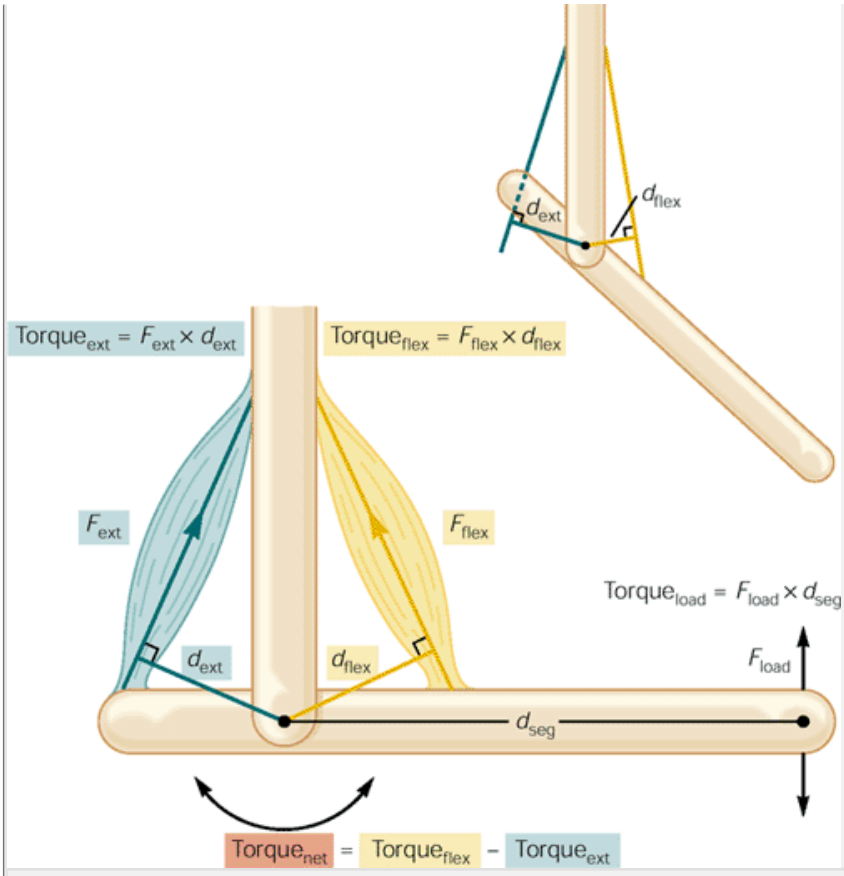

Figure 34-13 Each muscle produces a torque at a joint that is the product of its contractile force (*F*) and its moment arm at that joint *(d)*. The moment arm of a muscle is defined as the length of a perpendicular from the line of pull of the muscle to the center of rotation of the joint (it may be necessary to extend the line of pull past the end of the muscle to construct such a perpendicular, as done for d_{ext} in the inset). Note that the moment arm changes when the angle of the joint changes if the distance between the tendon and the joint changes (as in the inset). The moment arm at a given angular position is often determined experimentally by measuring the change of length of the muscle produced by a small change in angular position and computing the effective moment arm trigonometrically.

The net torque at a joint is the sum of the torques of all of the muscles crossing the joint. The antagonistic muscles shown here (ext = extensor; flex = flexor) produce torque in opposite directions, so the net torque is the difference between the torques produced by each. If the limb is at rest, the net torque produced by the muscles must be opposed by another equal but opposite torque, such as would be caused by a force from a load at the end of the limb segment. If that external force (F_{load}) is measured perpendicular to the long axis of the limb segment (as depicted here), then this external torque ($Torque_{load}$) is the product F_{load} times the length of the segment (d_{seg}, which is the moment arm for F_{load}).

The action of a muscle on a simple hinge joint depends on its anatomical orientation with respect to the center of rotation of the joint. The muscle plus any tendon in series acts like a rope pulling on a lever or passing around a pulley, so its action can be described as a *torque* (a force that rotates a joint) according to the laws of physical mechanics. The shortest distance from the muscle's line of pull to the center of the joint is called its *moment arm*, measured in a plane perpendicular to the axis of rotation of the joint (Figure 34-13). This distance can change as the angle of the joint changes; for example, elbow flexor muscles pass closer to the center of rotation when the elbow joint is fully extended rather than in mid position. A muscle with a large moment arm can generate a lot of torque but only at the expense of large changes in length and velocity. The action of a muscle on a joint with several degrees of freedom can be computed for each axis of rotation from the same geometrical principles. In more complex joints the moment arms of muscles often change in complicated ways as a result of shifts in the centers of rotation and the routing of tendons around bony protuberances and through connective tissue sheaths.

Rapid Changes in Joint Torque Involve Sequential Activation of Agonist and Antagonist Muscles

The nervous system controls the torques at joints by varying the frequency of action potentials in motor units. Because the build-up of force at the onset of neural activity and its decay when neural activity ceases are both slow, muscle force cannot follow rapid fluctuations in neural discharge (Figure 34-14A). Yet for many tasks it is necessary to produce rapidly rising and falling torques. The nervous system accomplishes this by activating the agonist muscle more vigorously and then activating an antagonist muscle with a slight delay so that the excess agonist torque is opposed by the antagonist torque (Figure 34-14B).

Muscle Force Is Required to Overcome Inertia

Movement of the body depends on more than just the contractile properties of agonist and antagonist muscles. It also depends on the interplay of external forces such as gravity, the mechanical constraints of joints and ligaments, and the laws of physics governing the movement of mass.

Newton's Laws of mechanics dictate that the velocity of an object will change if and only if acted upon by an external force. For the body to stay motionless in the face of an external force such as gravity, an equal and opposite force must be applied by the muscles. Conversely, muscle force is required to accelerate a limb from rest and then to decelerate it back to rest when the desired new position is attained. This explains why rapid movements are often accompanied by sequences of activity in agonist and antagonist muscles (Figure 34-15).

Muscle Force May Be Used to Create Stiffness at Joints

Movement of any joint crossed by a muscle tends to change the length and velocity of that muscle, whether the movement is caused by the action of the muscle itself, the action of other muscles, or by external forces. Because the force produced by a muscle depends on its length and on the velocity at which its length is changing, joint movement produces an instantaneous change in the muscle's force without any change in its state of activation. At first this might seem like an unfortunate complication, requiring yet more compensatory computations by the nervous system. In fact, the nervous system uses these properties to great advantage in coping with unanticipated perturbations.

When standing still, little or no ankle muscle activity is required to stabilize your body over your ankle joints. But consider the problem of trying to stand on the deck of a small boat pitching back and forth in the water. Now you must apply large forces rapidly in order to pull the center of mass back from any direction. By cocontracting the ankle muscles before these perturbations occur, you increase the stiffness at the joint (ie, the force produced by a given change in length in both directions increases). When the body is rapidly thrown in one direction, the muscles that normally pull in that direction suddenly shorten and their tension drops abruptly, while those that pull one back suddenly lengthen and their force increases. Additionally, because the muscle is active, you can take advantage of the force-velocity relationship of the co-contracting muscles. The resulting changes in force are quite large in precisely the direction required to keep your balance (Figure 34-16). Furthermore, these intrinsic changes in active force are instantaneous. Even the fastest reflex response to the sensory information about the perturbation requires about 50 ms to travel from the sensors to the spinal cord and out along the motor axons, followed by another 50 ms delay for the processes involved in excitation-contraction coupling to change the force output of the muscle. One disadvantage of co-contraction is that

it must be initiated and maintained before a perturbation occurs, which increases metabolic cost and risks fatiguing the muscles.

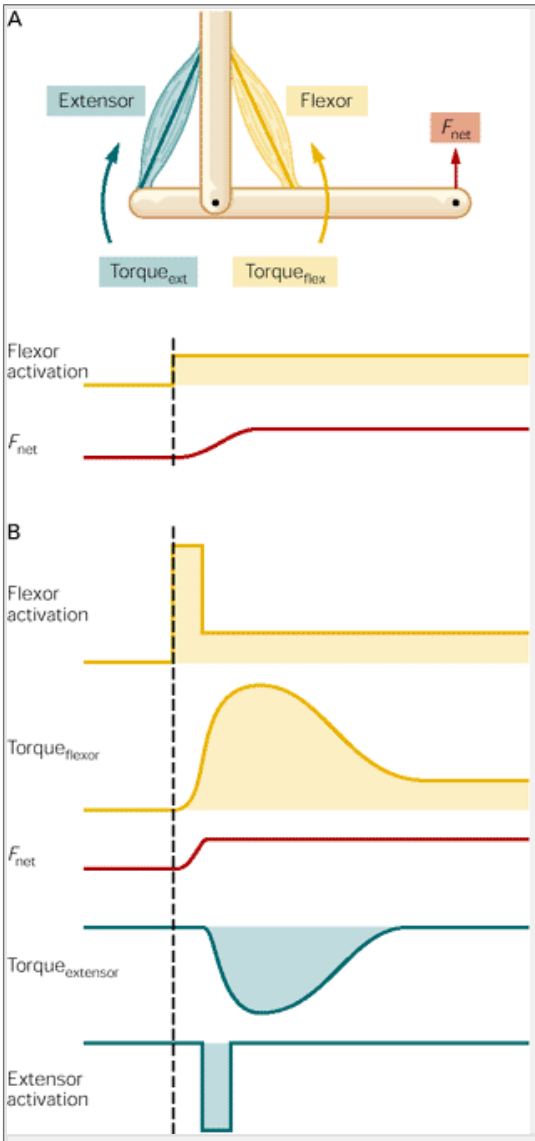

Figure 34-14

A. The ability of a muscle to rapidly exert a force is limited by the relatively slow rate of rise of its contractile force following electrical activation by its motor neurons.

B. The nervous system can increase torque more rapidly by using a larger initial burst of motor neuronal activity, but it must then prevent the net torque from overshooting the desired level. It cannot turn off the agonist muscle quickly enough because the fall time of its contractile force is even slower than the rise time. The nervous system solves this problem by briefly activating the antagonist muscle shortly after activating the agonist, so that the negative torque of the antagonist counteracts the anticipated overshoot from the agonist muscle. In this and the following figures muscle activation and torque are shown as positive for the agonist and negative for the antagonist. In experimental work electrical activation is often estimated by rectifying and smoothing the recorded EMG signal, an amplitude-modulated, broadband AC waveform whose amplitude is highly correlated with the aggregate activation of the muscle fibers in the whole muscle.

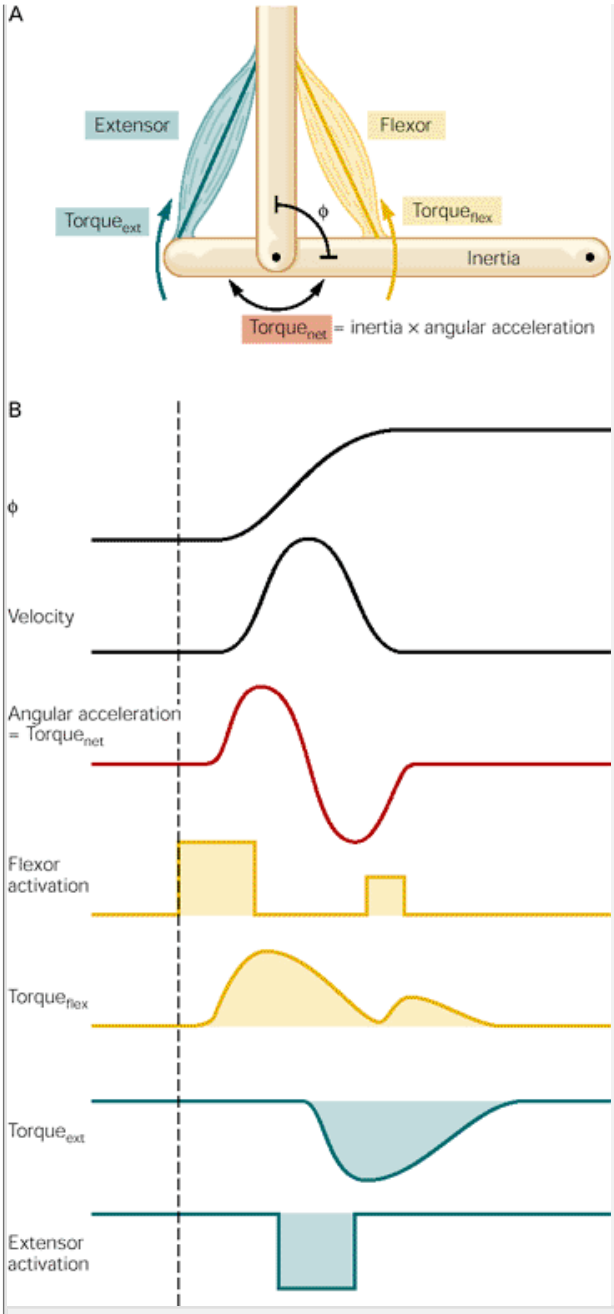

Figure 34-15 Muscle torques are required to overcome inertia when movements are started and stopped.

A. According to Newton's Law, force is required to change the velocity of a mass. The common form of the relationship for linear translation is force = mass × acceleration. Muscles produce torque to rotate the inertial mass of the skeletal segment around a joint. For torque, the equivalent form of Newton's Law is torque = rotational inertia × angular acceleration, where the inertia depends on the mass of the limb segment as well as its distribution over the length of the segment.

B. When humans move their limbs from one position to another they generally change joint angles in a smooth manner, such that angular velocity follows a symmetrical, bell-shaped profile. According to Newton's Law, this requires equal and opposite net torque pulses to produce the corresponding acceleration and deceleration phases. The flexor and extensor muscles are activated in succession, as shown by their activation levels and individual torque contributions. Because the relatively slow fall time of contractile force would tend to cause the decelerating torque from the extensor muscle to overshoot, a small, third phase of activity (from the flexor muscle) is often included to stop the limb exactly on target, particularly for fast movements. (Joint angle Φ graphed inverted so that flexion is upward.)

Muscles Act on More Than One Joint

More than half of the muscles of the body cross more than one joint. The ability of a multiarticular muscle to produce force at one joint depends on movement of the other joints that it crosses. For example, the grip strength of the finger flexor muscles in the forearm is greatly reduced when they are shortened by flexion of the wrist joint, because their sarcomere lengths become disadvantageously short (see Figure 34-5).

In physical mechanics work is performed when a force acts over a distance. If the motions at two joints result in offsetting lengthening and shortening effects in a multiarticular muscle, the muscle cannot perform much mechanical work itself because it exerts force over a length change of zero. Nevertheless, it may be useful to activate the muscle so that it acts like a stiff strut in a pantograph (Figure 34-17A). In this case the muscle exerts force over a

period of time, which represents momentum in physical mechanics. Such a linkage economically transfers mechanical momentum from one body segment to another. This can greatly improve the overall efficiency of a rhythmic task such as walking, in which individual limb segments must be alternately accelerated and decelerated with each step

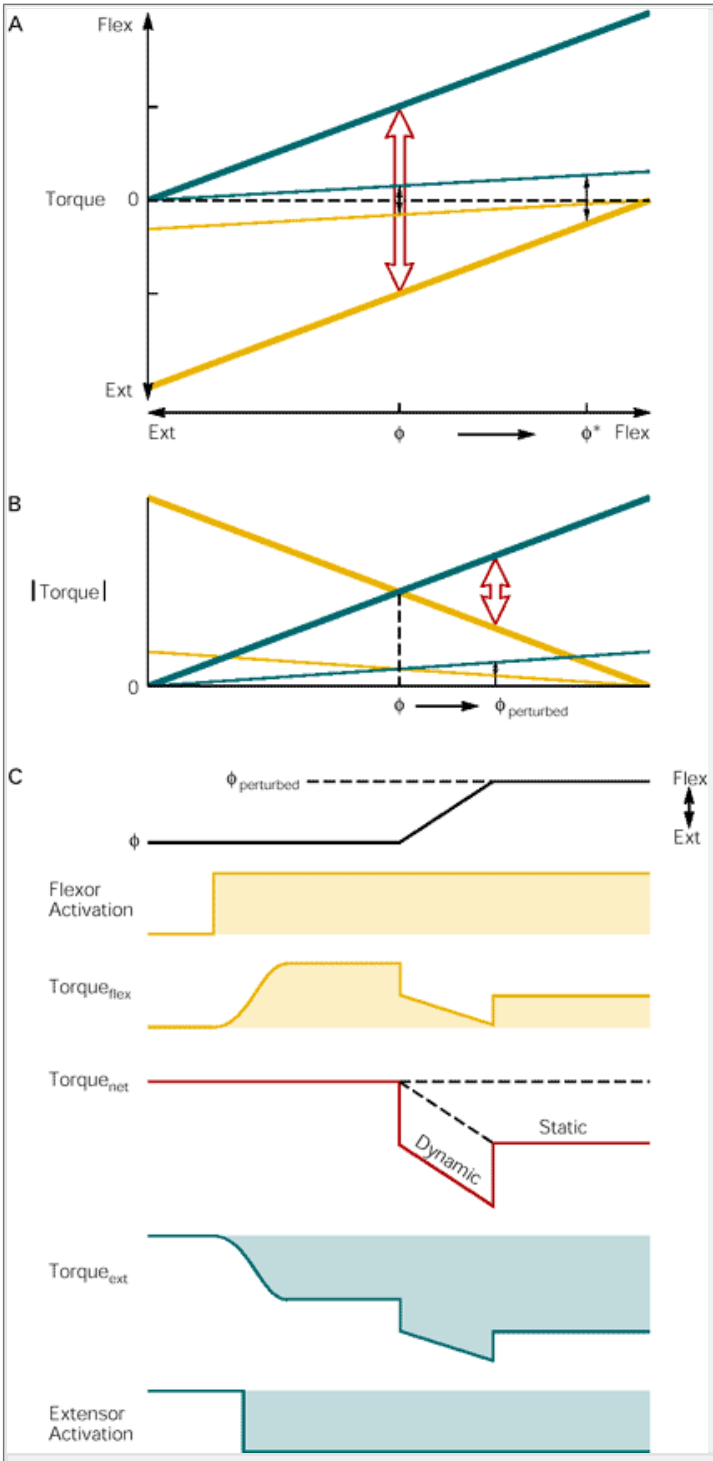

Figure 34-16 The intrinsic mechanical properties of muscles restore forces when a limb is perturbed.

A. Because of the shapes of the active and passive force-length relationships (see Figure 34-5), muscles are springlike, increasing their total force output as they are lengthened. The slope of the relationship (the ratio of force to length) is equivalent to the stiffness of the spring. This ratio can be varied according to the level of activation of the muscle. For an antagonist pair of muscles as shown, the force-length relationships can be graphed as torque versus joint angle (Φ) relationships with opposite signs. When the torque amplitudes are equal and opposite, the limb will be at rest at an equilibrium position. A given equilibrium position (Φ) can be achieved with different degrees of coactivation of the antagonist muscles, as long as their torques are equal and opposite. If the relative activation of the two muscles changes, the limb will move to a new equilibrium position, Φ^*.

B. It is easier to see how the opposing torques interact with each other by inverting one and seeing where they intersect. If the joint is shifted from an equilibrium angle, Φ, to a new angle, $\Phi_{perturbed}$, while the activation levels of the muscles remain constant, there will be a net torque that resists the shift and that is equal to the difference between the two torques at the new angle (**red arrows**). The resisting net torque is much higher when the same joint angles are achieved with higher levels of muscle coactivation (**thick, steep lines**).

C. The nervous system takes advantage of the intrinsic force-length and force-velocity relationships in muscle to produce a resistive force against sudden perturbations. By co-contracting the flexor and extensor muscles as shown in the activation traces, the net torque before the perturbation does not change and the joint angle stays the same but the stiffness increases. When a perturbation in joint angle occurs, the stretch of the extensor muscle and the shortening of the flexor muscle result in a large resisting net torque that occurs before any reflexes could produce a change in muscle activation. This torque has two components: a large dynamic change produced by the force-velocity relationship of the two active muscles and a smaller static force due to the force-length relationship. This intrinsic response is usually supplemented by subsequent reflex effects on muscle activation mediated by stretch receptors in the muscles and their projections onto spinal interneurons and motor neurons (see subsequent chapters).

Although a muscle produces torque only at the joint it crosses, this torque may well affect the movement of other joints throughout the body because of mechanical interactions through the skeletal linkage (Figure 34-17B, C). For example, the soleus muscle crosses only the ankle joint and produces only an extensor torque at

the ankle. However, when standing with the weight of the body on the foot, soleus contraction produces a backward rotation of the shank, which pulls the knee and hip joints into extension.

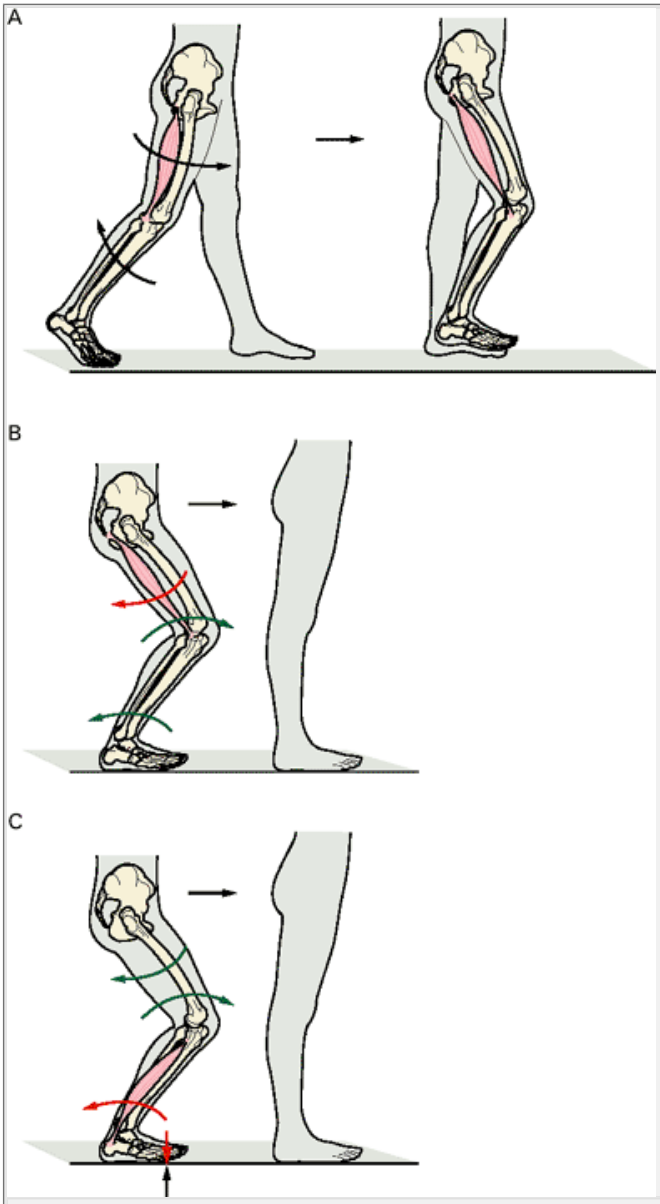

Figure 34-17 A single muscle can affect the motion of many joints.

A. Many muscles cross more than one joint. For example, the hamstring muscles of the leg extend the hip and flex the knee. During the swing phase of walking the knee is flexed, which tends to shorten the hamstrings, while the hip is also flexed, which tends to lengthen the hamstrings (**black arrows**). If the flexion of the knee were accomplished by a monoarticular knee flexor, the muscle would have to work hard and consume much energy to achieve the necessary force while shortening rapidly. The same knee flexion torque is much more easily obtained by the biarticular hamstring muscle, which is working under isometric or even active lengthening conditions. The hip extension torque produced by the hamstrings is also desirable because it helps to decelerate the forward velocity of the leg in preparation for placing the foot on the ground. The stiffened biarticular muscle acts like a strut to convey momentum from one body segment to another without itself doing much mechanical work.

B-C. Muscles produce torques directly on the joints they cross (**red arrows**) but also cause widespread and sometimes counterintuitive accelerations at remote joints (**green arrows**). When standing still, the hip and ankle extensor muscles each cause similar changes in position at three joints (hip, knee, and ankle). The large rotational inertia of the trunk resists tilting backward, so the monoarticular hip extensors tend to pull the thigh into extension (**B**). The weight of the body keeps the foot from sliding backward, so the knee and ankle must extend, even though the hip muscle has no direct action on these joints. The ankle extensors affect acceleration of the knee and hip when the foot is planted on the ground because they can only pull the shank back, not plantarflex the foot down (**C**). If left on indefinitely, the hip, knee, and ankle extensors each would eventually result in different postural results, but the short-term accelerations are similar in their ability to keep the leg extended. When standing quietly, humans naturally rotate the activation of hip, knee, and ankle extensors to minimize fatigue.

Contracting a muscle to accelerate one body segment causes mechanical effects that propagate backward and forward through the linkages of the skeleton. For example, if the elbow is flexed with the hand in the prone (palm down) position, the wrist and fingers will tend to lag behind and become flexed unless their extensor muscles are activated at the same time as the elbow flexors. Similarly, the trunk will also be thrown forward unless stiffened by contracting the axial and leg muscles.

While we may describe and plan movements in relatively simple terms (eg, "bend the elbow"), execution of movements by the motor systems must anticipate and correct for these and many other consequences of physical dynamics. In fact, the first muscles recruited when one tries to move the arm as quickly as possible are in the legs, despite their greater distance from the brain. The nervous system normally learns to program its muscle commands in this way through lengthy practice in infancy and early childhood. Nevertheless, changes in body mass and muscle strength throughout life require continuous adjustments in motor programs, and these in turn depend on a steady stream of sensory

feedback from muscles that is provided by receptors in muscles and joints (Chapter 36).

An Overall View

The musculoskeletal system is the mechanical apparatus by which our nervous system interacts with the outside world. The mechanical properties of muscles have been largely conserved throughout vertebrate phylogeny and these properties have been a primary determinant in shaping and adapting the neural mechanisms of movement. For an engineer, muscles may appear to be highly imperfect transducers of electrical and chemical energy to mechanical energy. They respond quite slowly to variations in the frequency of action potentials reaching them, and the force they generate in response to neural input varies in a nonlinear fashion with their length, velocity, and activation history. Nevertheless, many of these properties help to make the musculoskeletal system mechanically robust and tolerant of computational noise and delays in the nervous system.

Motor performance improves as we learn to deal appropriately with the many perturbations of the musculoskeletal machinery that occur during skilled movement. These perturbations may be external, such as those produced by unpredictable loads or footing. They may also be internal, due to the nervous system itself; for example, membrane noise affects the recruitment of individual motor units, resulting in some unpredictability in the force produced by the muscles. When the brain decides on a motor program to perform a task it takes into account its stored experience with these various perturbations. It also weighs the importance of speed versus accuracy, the willingness to expend energy, and the ability to tolerate transmission delays in neural circuits.

The brain implements a motor program for limb movement by sending signals to the spinal cord. Some of the signals are transmitted directly to motor neurons, but most are relayed through a variety of interneurons. Most spinal interneurons also receive convergent input from many somatosensory modalities. In turn, they project directly and indirectly to many different motor nuclei. A single motor neuron is thus bombarded with synaptic inputs, and the net result determines whether it reaches threshold and hence whether the muscle fibers it controls will participate in a motor program.

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38

Voluntary Movement

John Krakauer

Claude Ghez

*I*N PREVIOUS CHAPTERS WE saw how spinal and brain stem circuits can organize elementary movement patterns in response to somatosensory, vestibular, and other stimuli. However such reflex actions are relatively stereotyped and the repertory of movements is limited. In this chapter we shall see how the motor areas of the cerebral cortex integrate visual, proprioceptive, and other information to produce the more elaborate voluntary movements that require planning.

Voluntary movements differ from reflexes in several important ways. First, voluntary movements are organized around the performance of a purposeful task. Thus the selection of which joints and body segments will be used for a movement depends on the goal of the movement, whether it is designed to reach for and lift a glass of water or to return a tennis serve. In contrast to the stereotyped relation between response and stimulus, characteristic of reflexes, voluntary movements vary in response to the same stimulus depending on the behavioral task. Second, the effectiveness of voluntary movements improves with experience and learning. Finally, unlike reflexes, voluntary movements are not mere responses to environmental stimuli but can be generated internally. The higher levels of our motor systems can therefore dissociate two aspects of a stimulus—its informational content and its capacity to trigger a movement. In the cortex the information content of a stimulus signals where to move or what to do, but the occurrence of the stimulus may or may not actually initiate the appropriate movement. In reflexes these aspects of the stimulus are linked.

The motor areas of the cerebral cortex are subdivided into a primary motor area and several premotor areas. Each area contains populations of neurons that

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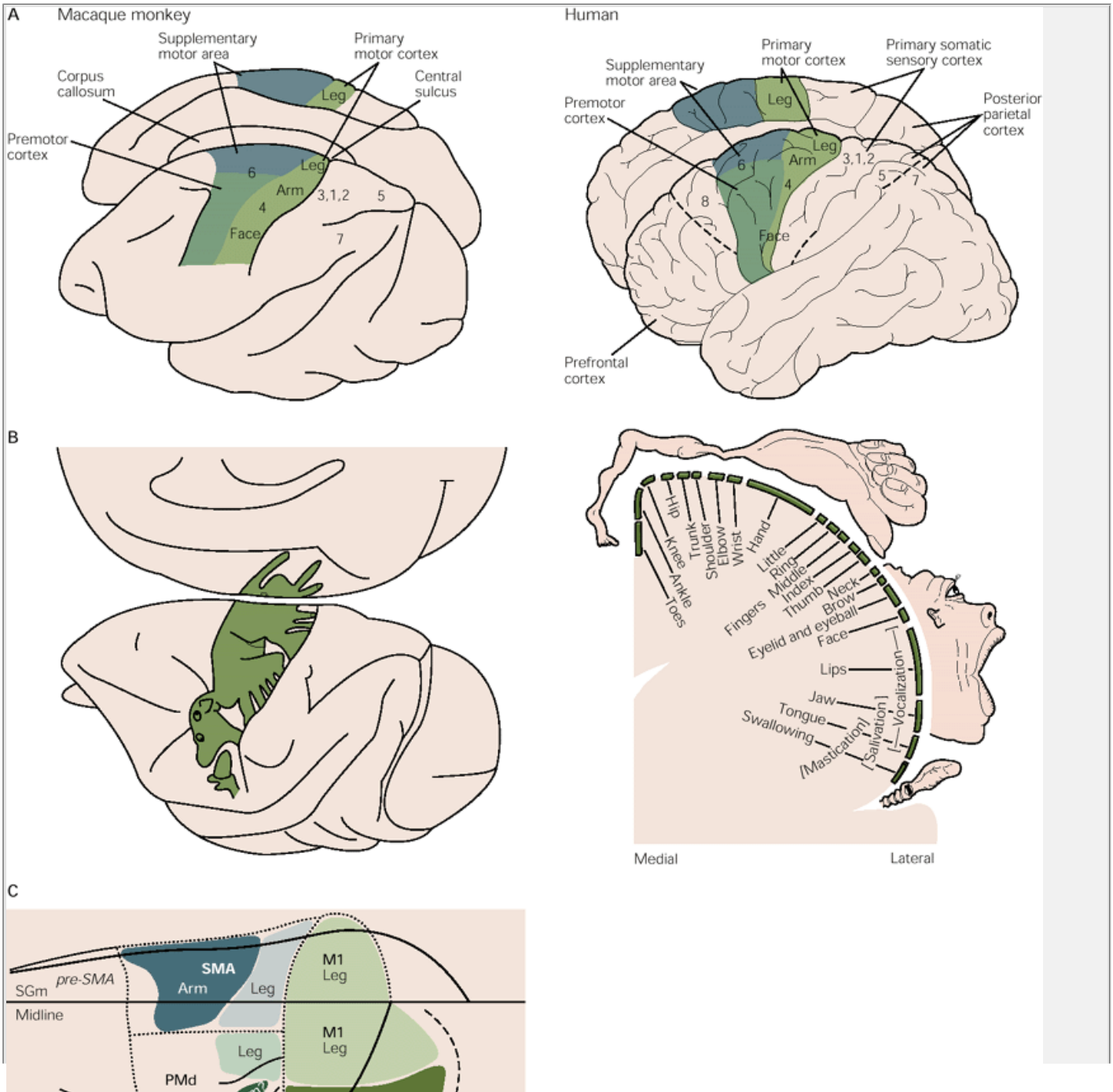
project from the cortex to the brain stem and spinal cord. In this chapter we first describe the organization of the motor areas of the cerebral cortex, showing how they communicate with each other and with primary sensory and association areas. We then examine how these different motor areas control simple and complex aspects of movement.



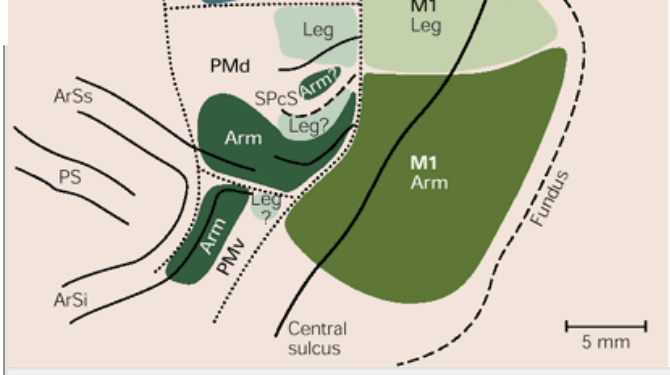


Figure 38-1 Motor cortical areas are organized somato-topically.

A. Brodmann's cytoarchitectural areas in monkeys and humans.

B. Comparison of the somatotopic organization of the primary motor cortex in monkeys and humans. The sequence of representation of body parts is similar. The ankle control area is medial while the face, mouth, and mastication control areas are lateral. The face and fingers in the human motor cortex have much larger representations because of the greater degree of cortical control of these areas. (Left: from Woolsey 1958; right: adapted from Penfield and Rasmussen 1950.)

C. Somatotopic organization of the medial and lateral motor cortex in the monkey, showing the arm and leg representations. (**ArSi**, arcuate sulcus, inferior limb; **ArSs** = arcuate sulcus, superior limb; **CS** = central sulcus; **M1** = primary motor cortex; **PMd** = dorsal premotor area; **PMv** = ventral premotor area; **PS** = precentral sulcus; **SGm** = superior frontal gyrus, medial wall; **SMA** = supplementary motor area; **pre-SMA** = presupplementary motor area; **SPcS** = superior precentral sulcus.) (From Dum and Strick 1996.)

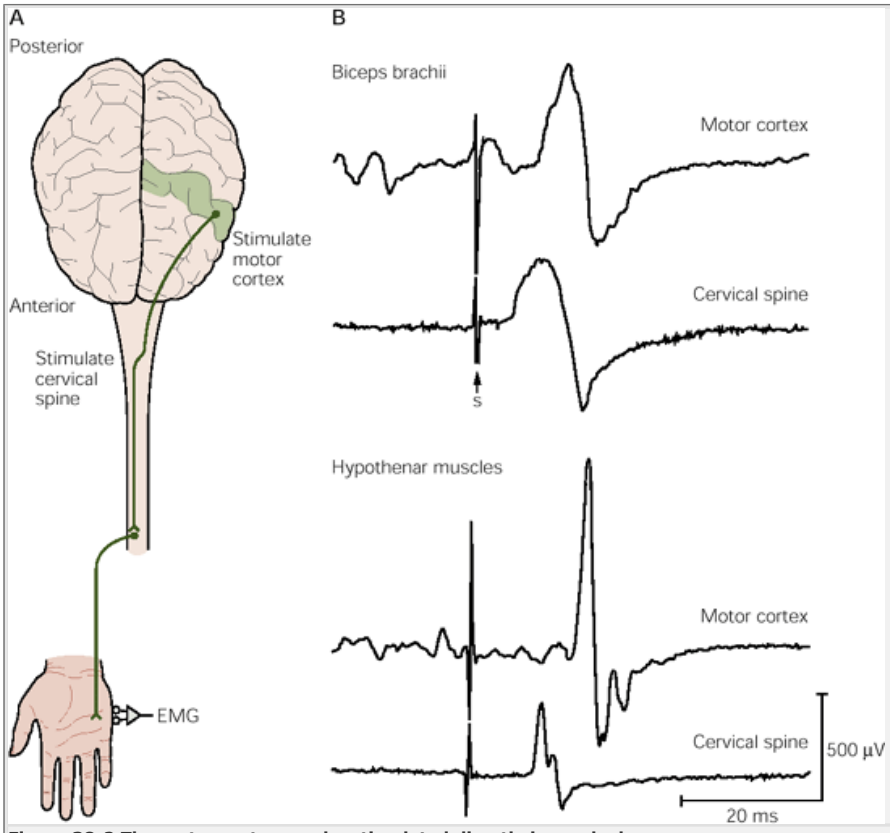


Figure 38-2 The motor cortex can be stimulated directly in awake humans.

A. Magnetic stimulation of the motor cortex or cervical spine produces muscle contraction painlessly. Stimulation of the motor cortex activates the corticospinal fibers and produces a short-latency electromyographic (EMG) response in contralateral muscles.

B. The traces show activation of arm and hand muscles (biceps brachii and hypothenar) when stimulation is applied over the cortex or the cervical spine. The peaks occur earlier from cervical stimulation because the corticospinal impulse has less distance to travel. The point marked **s** is a stimulus artifact, reflecting the application of the magnetic field pulse. (From Rothwell 1994.)

Voluntary Movement Is Organized in the Cortex

The Primary Motor Cortex Controls Simple Features of Movement

The discovery in 1870 that electrical stimulation of different parts of the frontal lobe produces movements of muscles on the opposite side of the body had a major impact on neurological thinking. In the early twentieth century electrical stimulation was used to identify the specific motor effects of discrete sites in the frontal lobe in different species—including primates and humans—and the resulting *motor maps* were correlated with anatomical and clinical observations on the effects of local lesions. The contralateral precentral gyrus (Brodmann's area 4), the region now called the *primary motor cortex*, proved to be the area in which the lowest-intensity stimulation elicited movements. At low intensities the effects of stimuli can be attributed to the activation of neurons near the electrode that are connected to the spinal cord either directly or via only a small number of synapses.

The motor maps produced by these experiments show an orderly arrangement along the gyrus of control areas for the face, digits, hand, arm, trunk, leg, and foot. However, the fingers, hands, and face—which are used in tasks requiring the greatest precision and finest control—have disproportionately large representations in the motor areas of cortex (Figure 38-1), much as the inputs from regions of the body that have important roles in perception predominate in the sensory areas of the cortex. Consistent with the overall somatotopic organization, lesions in arm representation lead to degeneration of myelinated fibers in the cevical cord, while lesions in the leg representation produced degeneration extending all the way to the lumbar spinal cord. These axons arise from specialized large pyramidal neurons in lamina V

named Betz cells after their discoverer.

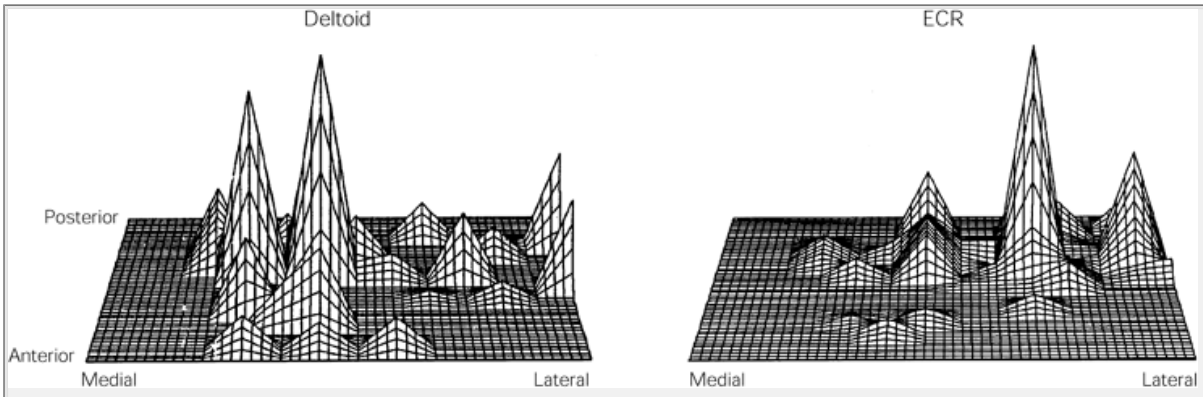


Figure 38-3 Sites controlling an individual muscle are not located together but are distributed over a wide area of motor cortex. Intracortical microstimulation was used to identify sites in monkey primary motor cortex at which low-threshold stimulation evoked electromyographic activity (indicating monosynaptic connections) in a shoulder abduction muscle (middle head of deltoid muscle) and a wrist extensor muscle (extensor carpi radialis; **ECR**). Topographic maps of the identified sites, reveal overlap between shoulder and wrist representations. The maps were constructed based on the inverse of the threshold (1/threshold) in microamperes, with the peaks representing approximately 1/3 μA and the valleys 1/40 μA. (From Humphrey DR, Tanji J. 1991. In: DR Humphrey, HJ Freund (eds.). *Motor Control: Concepts and Issues*, pp 413-443. New York: Wiley.)

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The results of animal experiments done in the early 1900s helped explain the clinical signs in patients produced by traumatic, vascular, and other forms of local damage to the contralateral frontal lobe. They also explained focal epilepsy, which can develop as a result of traumatic injury or tumors. The abrupt rhythmic flexion-extension movements seen in focal seizures resemble the movements produced by electrical stimulation of the primary motor cortex. Indeed, in the nineteenth century, before electroencephalographic recordings were available, John Hughlings Jackson had already pro-posed that seizure activity resulted from paroxysmal increases in local neuronal activity in a limited area of cerebral cortex that corresponds to the primary motor cortex. Focal seizures often start in the fingers and spread proximally down the limb as the focus of discharges spreads from the hand area to adjacent sites controlling more proximal muscles. Clinically this is known as the *Jacksonian march.*

In the past decade it has become possible to stimulate motor cortical areas in alert humans by inducing electrical fields in the brain using rapidly alternating magnetic fields produced by wire coils applied to the scalp. The responses in muscles (eg, of the hand) are recorded with surface electrodes. The motor action potentials are large and have a short latency, consistent with the fact that they are conducted by corticospinal fibers (Figure 38-2). Magnetic stimulation can be used to map the body representation in the primary motor cortex or to perturb processing in other cortical motor areas.

The early mapping experiments stimulating the cortical surface electrically (and more recently magnetically) initially led to the simplistic idea that the primary motor cortex acts as a massive switchboard with a switch controlling individual muscles or small groups of adjacent muscles. More detailed studies, however, using microelectrodes inserted into the depths of the cortex (intracortical microstimulation or ICMS) to stimulate small groups of output neurons indicate that this simple view is incorrect. Whereas the weakest stimuli may evoke the contraction of individual muscles, the same muscles are invariably activated from several separate sites as well, indicating that neurons in several cortical sites project axons to the same target (Figure 38-3).

In addition, most stimuli activate several muscles, with muscles rarely being activated individually. This is corroborated by recent anatomical and physiological experiments showing that the terminal distributions of individual corticospinal axons diverge to motor neurons innervating more than one muscle. Instead of a simple switchboard of muscle representations, detailed maps of monkey motor cortex suggest a concentric organization: sites influencing distal muscles are contained at the center of a wider area containing sites that also influence more proximal muscles, while sites in the peripheral ring around this central area influence proximal muscles alone. An implication of this redundancy in muscle representation is that inputs to motor cortex from other cortical areas can combine proximal and distal muscles in different ways in different tasks.

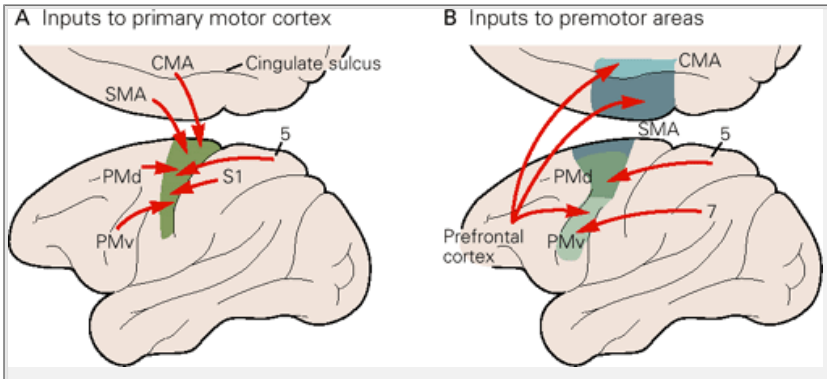

Figure 38-4 The major inputs to the motor cortex in monkeys.

A. The major inputs to the primary motor cortex. (**PMd** = dorsal premotor area; **PMv** = ventral premotor area; **S1** = primary sensory cortex; **SMA** = supplementary motor area.)

B. The major inputs to the premotor areas. Dense interconnections between the premotor areas are not shown here.

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Premotor Cortical Areas Project to the Primary Motor Cortex and Spinal Cord

In the late 1930s it was discovered that movements can also be elicited by direct electrical stimulation of the *premotor areas*, Brodmann's area 6, although the intensity of stimulation necessary to produce movement is greater here than in the primary motor cortex. Brodmann's area 6 lies anterior to the precentral gyrus, on the lateral and medial surfaces of the cortex. Like the primary motor cortex, the premotor areas contain pyramidal (output) neurons in layer V that project to the spinal cord, although the cell bodies are smaller than those in the primary motor cortex.

Recent anatomical studies indicate there are four main premotor areas in primates—two on the lateral convexity and two on the medial convexity. The two on the lateral convexity are the *lateral ventral* and *lateral dorsal premotor areas.* The two in the medial wall of the hemisphere are the *supplementary motor area* and the *cingulate motor areas*, located in the banks of the cingulate sulcus. Similar premotor areas exist in humans, but differences in size and sulcal patterns make it difficult to identify homologous areas with precision.

Motor maps of the face and extremities can be delineated in each premotor area (Figure 38-1C). However, unlike the primary motor cortex, where stimulation typically evokes simple movements of single joints, stimulation of the premotor areas often evokes more complex movements involving multiple joints and resembling natural coordinated hand shaping or reaching movements. Stimulation of the medial parts of area 6, the supplementary motor area, can give rise to bilateral movements, suggesting that this area has a role in coordinating movements on the two sides of the body.

All the premotor areas project to both the primary motor cortex and the spinal cord, although there are fewer projections from the premotor areas to the spinal cord than from the primary motor cortex. In the spinal cord the areas of termination of the premotor and primary motor projections overlap. For example, the corticospinal axons of neurons in the supplementary motor area terminate in motor nuclei innervating digit and hand muscles, as do those of neurons in the hand area in the primary motor cortex. The corticospinal projections from the dorsal premotor area terminate mainly in motor nuclei innervating proximal limb musculature. The existence of these direct mono-synaptic connections suggests that the premotor neurons can control hand movements independently of the primary motor cortex.

Each Cortical Motor Area Receives Unique Cortical and Subcortical Inputs

The primary motor cortex receives somatotopically organized inputs directly from two sources. First, it receives inputs from the primary somatosensory cortex (areas 1, 2, and 3). This means that, like neurons in somatosensory cortex, neurons in the motor cortex have receptive fields in the periphery. For example, some neurons in the motor cortex receive proprioceptive input from the muscles to which they project and many neurons in the hand region of the motor map respond to

tactile stimuli applied to specific regions of the digits and palms. These so-called *transcortical* circuits are discussed later. Second, the primary motor cortex receives inputs from posterior parietal area 5. Posterior parietal areas 5 and 7 are involved in integrating multiple sensory modalities for motor planning (Figure 38-4A).

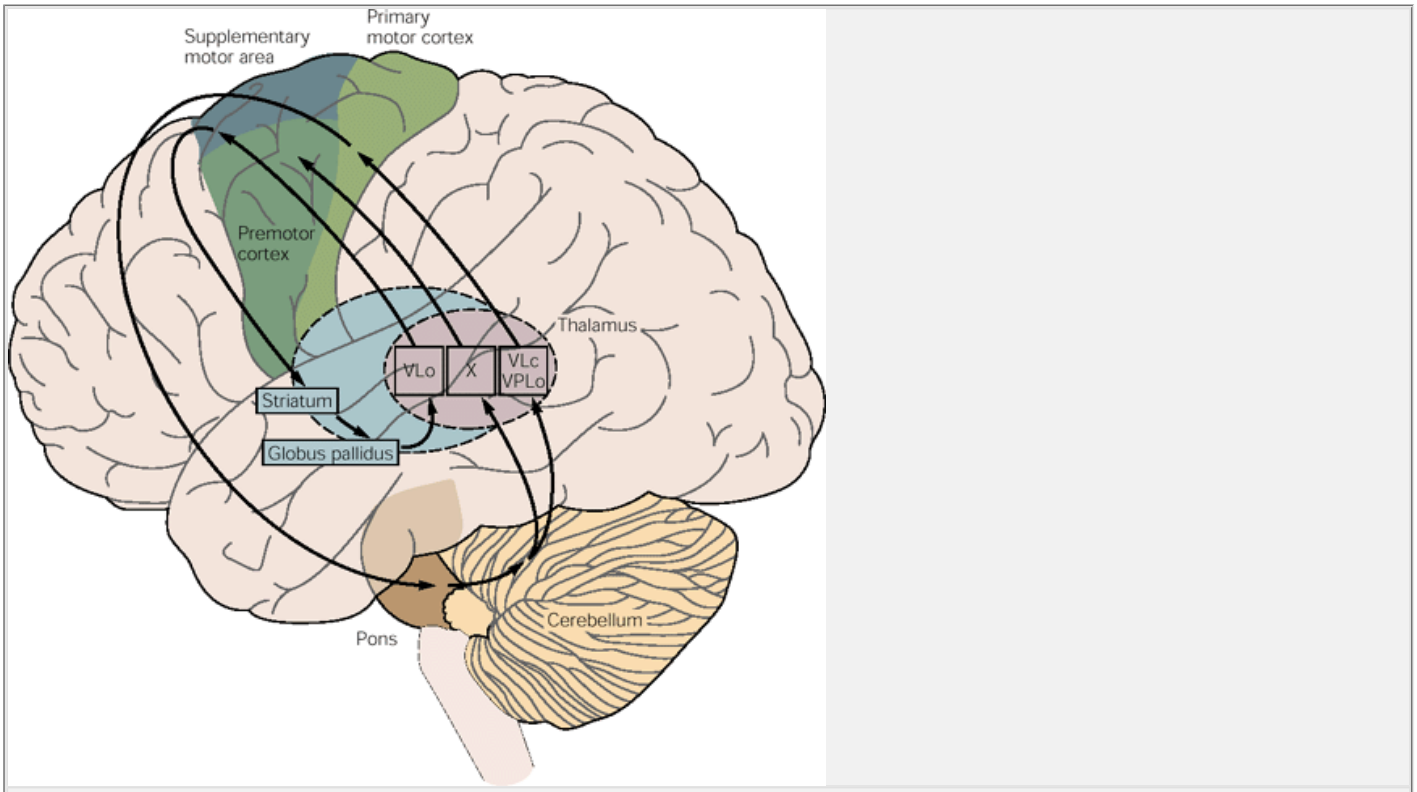

Figure 38-5 The motor cortex receives inputs from the cerebellum via the thalamus. VLo and **VLc** = oral (rostral) and caudal portions of the ventrolateral nucleus; **VPLo** = oral portion of the ventral posterolateral nucleus; **X** = nucleus X.

The premotor areas receive major inputs from areas 5 and 7 as well as from area 46 in the prefrontal cortex (Figure 38-4B). Each premotor area has its own pattern of inputs from distinct locations in areas 5 and 7. Area 46 projects mainly to the ventral premotor area and is important in working memory; it is thought to store information about the location of objects in space only long enough to guide a movement. There are also dense connections between the premotor areas themselves. These connections are thought to allow working memory to influence specific aspects of motor planning that are mediated by the different premotor subregions.

The premotor areas and primary motor cortex also receive input from the basal ganglia and cerebellum via different sets of nuclei in the ventrolateral thalamus (Figure 38-5). The basal ganglia and cerebellum do not project directly to the spinal cord.

An important feature of the relationship between cortical areas and subcortical structures is the reciprocal nature of their connections. Each cortical motor area appears to have a unique pattern of cortical and subcortical input. Thus there are many cortico-subcortical loops, each one making a different contribution to a motor behavior (Chapter 43).

The Somatotopic Organization of the Motor Cortex Is Plastic

The somatotopic organization of the motor cortex is not fixed but can be altered during motor learning and following injury. This plasticity has been demonstrated in many experiments and clinical studies. In one study using mature rats the representation of the whiskers in the primary motor cortex was first mapped using intracortical microstimulation. The whiskers were then denervated. Electrical stimulation of the cortical region that had caused whisker movement subsequently produced forelimb movement (Figure 38-6). This shift in functionality may be due to facilitation of preexisting circuits in the whisker region that are connected to the forelimb. The change can take place in just a few hours. The loss of sensory inputs from the whiskers into the motor area is thought to trigger the reorganization. This indicates that neurons influencing facial musculature are more widely distributed than is revealed by local electrical stimulation at any given point in time.

The idea that the organization of at least some mature

motor circuits in the cortex can change depending on sensory or motor activity holds important promise for the rehabilitation of patients who have had strokes and other

forms of brain injury. Evidence in favor of this possibility has recently been obtained in animal experiments. In one such experiment, a small cortical artery was occluded in squirrel monkeys to destroy a portion of the population of cells in the primary motor cortex controlling the hand and digits. The animals lost the ability to retrieve food pellets from the smallest of a series of wells, and with time the area of hand representation around the lesion shrank.

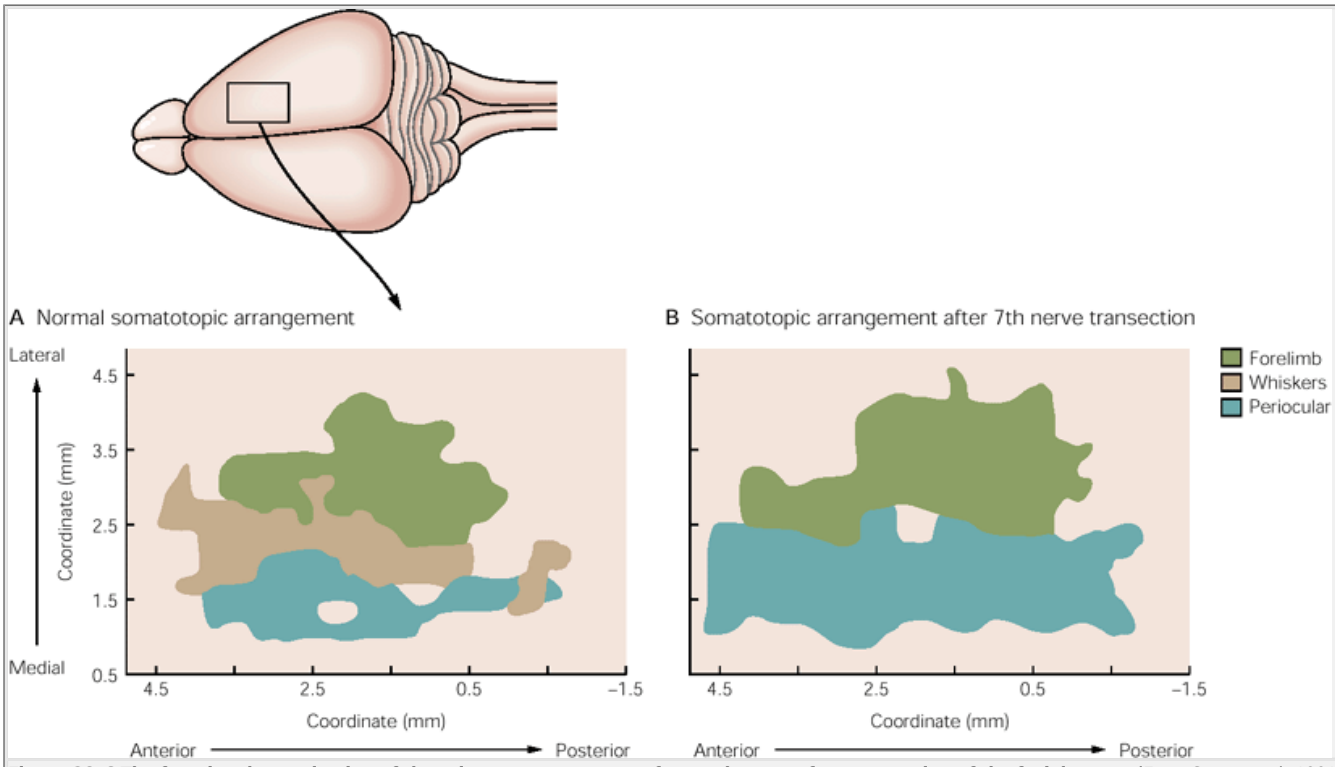

Figure 38-6 The functional organization of the primary motor cortex of a rat changes after transection of the facial nerve. (From Sanes et al. 1991.)

A. Surface view of the rat frontal cortex shows the normal somatotopic arrangement of areas representing forelimb, whisker, and periocular muscles.

B. Same view after transection of branches of the facial nerve. Areas of cortex devoted to forelimb and periocular control have increased, extending into the area previously devoted to whisker control.

Some animals were retrained and others not. The changes in the cortical maps of hand and forearm representation were strikingly different in the two groups. In animals that had not practiced using the hand and relied only on proximal muscle control, all areas of hand and forearm representation were lost. The neurons outside the lesion did not die but elbow and shoulder areas expanded into the remaining (undamaged) hand area. In animals that practiced using their hand daily, the undamaged cortex controlling the hand and digit expanded into adjacent undamaged cortex previously occupied by neurons controlling the elbow and shoulder. These animals fully recovered the ability to retrieve pellets after 3 or 4 weeks. This result emphasizes the importance of practice in sensorimotor tasks for rehabilitation following stroke and other focal brain damage.

As noted in the introduction, a characteristic feature of voluntary movements is that they improve with practice. This may be associated with cortical reorganization. In one study striking changes were found in the motor cortex in human subjects after practice of a single motor task. Subjects were asked to practice a finger opposition task for about 20 minutes every day, touching the thumb to the tip of each finger in a specific repeating sequence. As one can readily appreciate, at first this task was performed slowly and hesitatingly. However, as with typing or playing the piano, speed and accuracy increased with each successive day of practice until the performance learning curve reached asymptote in about 3 weeks. Functional magnetic resonance imaging (MRI) scans revealed that the area of cortex activated during performance of the trained sequence was larger than that activated during a novel untrained sequence (Figure 38-7)

It is important to emphasize that subjects performed both the novel and learned sequences at the same rate. This is crucial in order to exclude the possibility that the differences in activation are simply due to differences in the speed of finger movements. Moreover,

practice with one finger sequence did not facilitate performance of a new sequence nor did it transfer to the untrained hand. (Hand areas are unique in that they are not connected across the corpus callosum.) Such experience-dependent change in the primary motor cortex is likely to be important for the acquisition and retention of other motor skills.

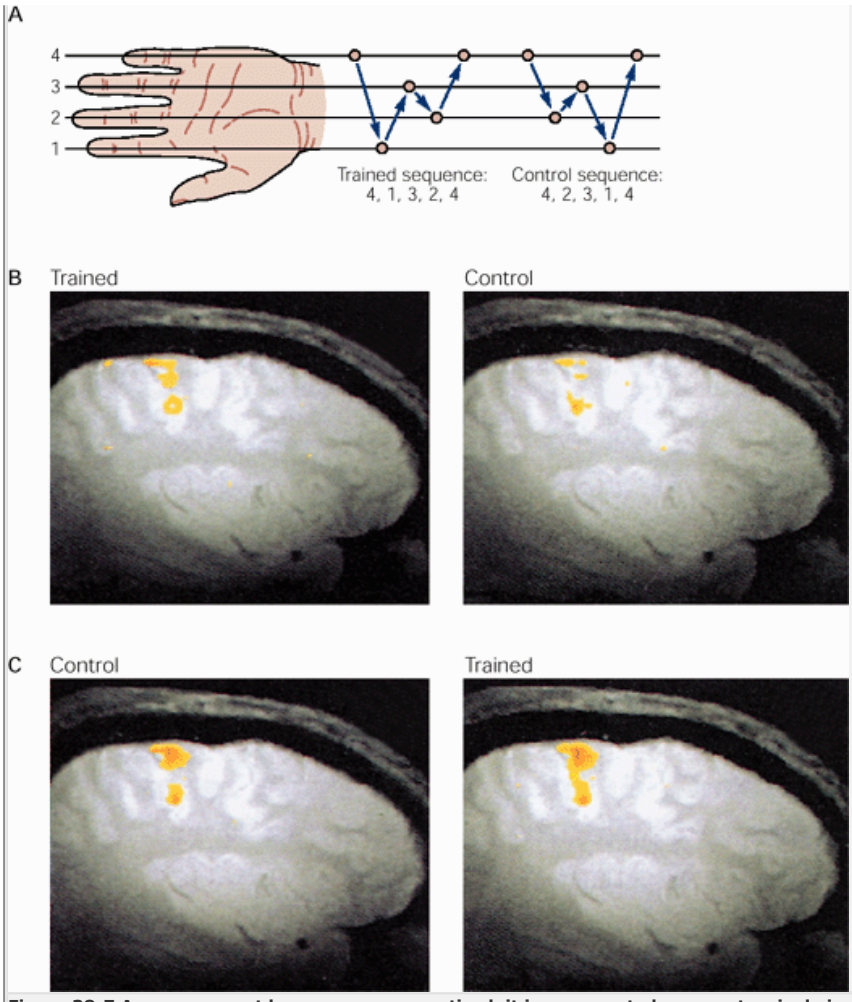

Figure 38-7 As a movement becomes more practiced, it is represented more extensively in primary motor cortex.

A. Human subjects performed two finger-opposition tasks, touching the thumb to each fingertip in the sequences shown. Digits are numbered 1 through 4. Both the practiced and the novel sequence were performed at a fixed, slow rate of two component movements per second.

B. Functional MRI scans show the area in the primary motor cortex activated during the performance of a finger-opposition sequence that had been practiced daily for 3 weeks (**left**) followed by a novel sequence (**right**). The area of activation is larger when the practiced sequence is performed. The experimenters interpret the increased area of metabolic activity as indicating that long-term practice results in a specific and more extensive representation of the trained sequence of movements in the primary motor cortex.

C. In another trial the practiced sequence followed the novel sequence, yet the area of activation in the primary motor cortex during the learned sequence is still larger. Thus the extent of activation is not merely an effect of the order in which the tasks were performed. (From Karni et al 1995.)

Corticospinal Axons Influence Spinal Motor Neurons Through Direct and Indirect Connections

Corticospinal neurons make powerful and direct excitatory connections with alpha motor neurons in the spinal cord. A unique feature of the corticospinal synapse is that successive cortical stimuli produce progressively larger excitatory postsynaptic potentials in spinal motor neurons. This potentiating connection is one of the mechanisms that permit monkeys to perform individual movements of the digits, including the grasping of small objects (Figure 38-8A) and to isolate movement of proximal joints. This ability is lost permanently after sectioning the pyramidal tracts in the medulla (Figure 38-8B) or after ablating the hand-control area of the motor cortex. Corticospinal fibers also terminate on interneurons in the spinal cord, which in turn project to alpha motor neurons. These indirect connections with motor neurons regulate a larger number of muscles than do the direct connections and so may contribute to the organization of multijointed movements such as reaching and walking.

Sectioning the medullary pyramidal tracts, which interrupts the projection of corticospinal axons from the primary motor cortex and premotor areas, produces contralateral weakness in monkeys. But the animals recover after a period of months, leaving only deficits in speed of movement and in the rate of force development. These deficits can be attributed to interruption of the projections from the primary motor cortex because

similar deficits arise from lesions in primary motor cortex but not from lesions in premotor areas. Animals with pyramidal tract lesions climb, jump, and appear generally normal. Their partial recovery is possible because cortical commands have indirect access to spinal motor neurons through the descending systems of the brain stem (Chapter 33). Nevertheless, individuated movements of the digits are lost permanently, and the wrist, elbow, and shoulder become linked in extensor or flexor synergies.

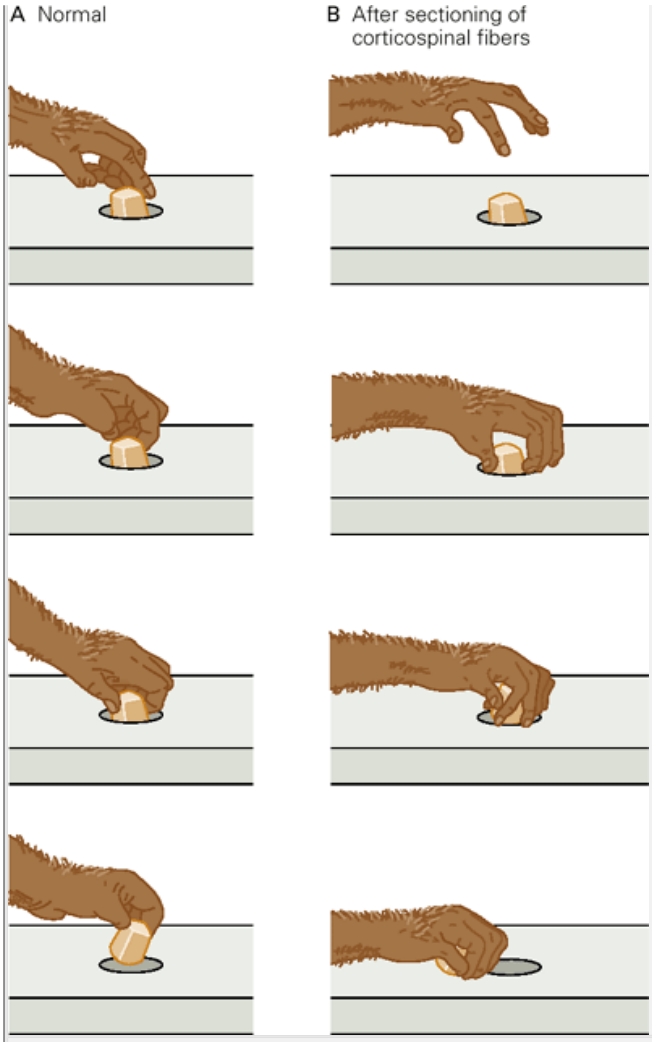

Figure 38-8 Direct corticospinal control of motor neurons is necessary for fine control of the digits.

A. A monkey is able to pick up a food morsel from a small well using the index finger and thumb.

B. After bilateral sectioning of the pyramidal tract the monkey can only remove food from the well by grabbing with the whole hand. (From Lawrence DG, Kuypers HGJM. 1968. The functional organization of the motor system in the monkey. Brain XCI.)

Corticospinal projections also have inhibitory effects on spinal motor neurons. Direct recordings in monkeys and indirect evidence from reflex testing in humans indicate that corticospinal inhibition is mediated by the Ia inhibitory interneuron, the same interneuron responsible for the reciprocal inhibition of stretch reflexes (Figure 38-9). Because these spinal interneurons receive peripheral inputs and are able to respond directly to ongoing changes in somatic sensory input, the higher centers of the brain are freed from the need to manage all the details of movements and instead can use the spinal circuits as components of more complex behaviors, much like the subroutines of a computer program.

The Primary Motor Cortex Executes Movements and Adapts Them to New Conditions

Activity in Individual Neurons of the Primary Motor Cortex Is Related to Muscle Force

To understand how cortical motor areas contribute to movement it is necessary to study how individual neurons are modulated in natural motor behaviors. This became possible in the 1960s when Edward Evarts succeeded in correlating the activity of single neurons with specific motor behaviors in active monkeys. Evarts found that activity in individual neurons in the primary motor cortex is modulated when monkeys either flex or extend the individual joints of their contralateral limbs. Individual neurons are maximally activated during movement of a particular joint and particular direction of movement. The changes in neuronal activity begin some 100 ms or more before the onset of movement.

In a classic experiment Evarts showed that, during wrist flexion, the firing of primary motor cortex neurons varied with the amount of force the animal had to exert to move its hand, not with the amplitude of the hand's displacement (Figure 38-10). The activity of these cortical neurons therefore appears to signal the direction and amplitude of muscle force required to produce a movement rather than the actual displacement of the joint.

Jun Tanji and Evarts found another, more surprising property of some primary motor cortex neurons. In these cells the baseline discharge changed while the animal waited for a signal to move in a predetermined direction. For example, a cell would change its level of baseline activity when a green light instructed the animal that an extension movement was to be made at a later signal (an instructed delay task). This pattern of activity was termed *set related* because it reflected the animal's

preparation—or *preparatory set*—to respond to a later stimulus. These discharges demonstrated that the intent to perform a movement alters the firing pattern of neurons in the primary motor cortex hundreds of milliseconds before the movement takes place.

Simple correlations of neuronal activity and behavior do not prove causality. Movement or set-related neurons might be concerned with early changes in postural muscle activity or some other process, rather than with the voluntary movement. The most common (and often the only possible) approach to relating neuronal activity to a specific behavior is to exclude confounding sources of correlation. However, in the case of primary motor cortex neurons, what is really needed is a way to know for sure whether activity that precedes a voluntary movement directly influences the muscles used in the movement. Only after a direct influence has been established can the relationship of these cells' activity to specific aspects of the movement be addressed meaningfully

A major advance in this direction was made in the mid-1970s by Eberhard Fetz and co-workers, who used the spike-triggered averaging technique (Box 38-1) to identify neurons in the primary motor cortex that project directly to motor neurons, called *corticomotoneuronal* (CM) *cells.* They found that individual CM cells project monosynaptically to more than one motor nucleus and sometimes to muscles controlling different joints. Thus, muscles are not mapped one-to-one in cortical output neurons. Most of the neurons recorded by Fetz have phasictonic patterns of activity, firing most briskly during the dynamic phase of movement and settling down to a

lower tonic rate when a steady force is reached (Figure 38-12A). For almost all neurons there is a range over which force is related linearly to firing rate. Often, however, this range is quite small, and maximal firing is achieved for relatively small forces.

Direction of Movement Is Encoded by Populations of Cortical Neurons

Most movements involve multiple joints and require sequential and temporally precise activation of multiple muscles. This raises the question of whether cells in motor cortex directly control the specific spatiotemporal patterns of muscle activation or do they encode more global features of the movement such as its direction, extent, or joint angle changes?

This was examined by Apostolos Georgopoulos, who trained monkeys to move a joystick toward visual targets located in different directions and recorded the associated changes in activity in the primary motor cortex. All neurons fired briskly before and during movements in a broad range of directions (Figure 38-13A)

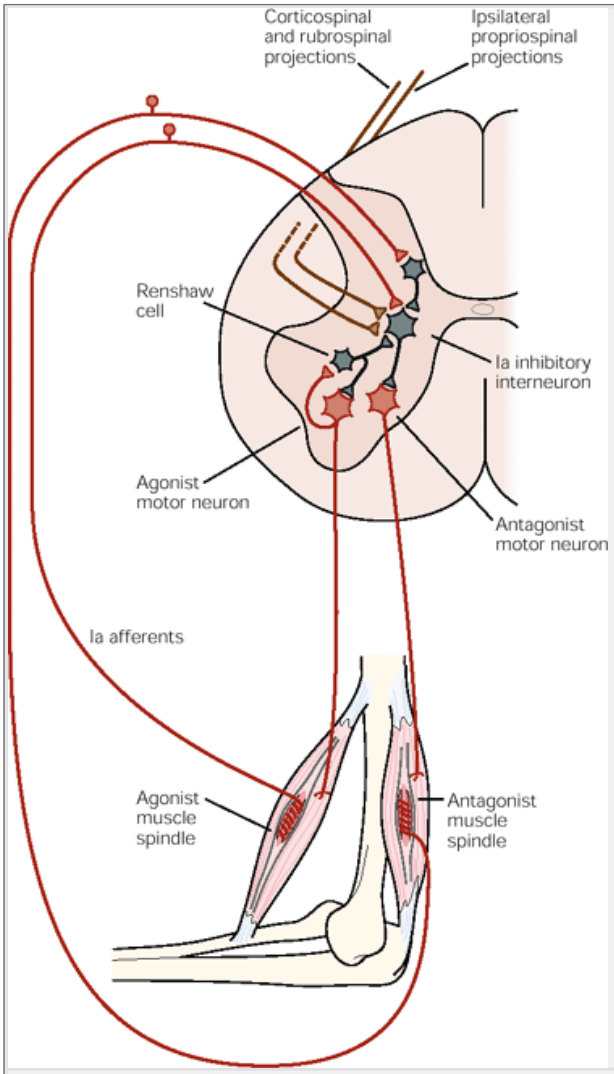

Figure 38-9 The Ia inhibitory interneuron in the spinal cord sends inhibitory signals to antagonist motor neurons when muscle spindles in the agonist muscle are activated. The interneuron receives complex excitatory and inhibitory inputs, including direct input from the motor cortex. These direct cortical connections allow the motor cortex to use reflex circuits as components of complex movements, thereby simplifying the motor cortical program. (Based on Lundberg 1979.)

How can movement direction be coded precisely by neurons that are so broadly tuned? Georgopoulos proposed that movement in a particular direction is determined not by the action of single neurons but by the net action of a large population of neurons. He suggested that the contribution of each neuron to movement in a particular direction be represented as a vector whose length indicates the level of activity during movement

in that direction. The contributions of individual cells could then be added vectorially to produce a *population vector.* In fact, the directions of such computed population vectors closely match the directions of movement (Figure 38-13B).

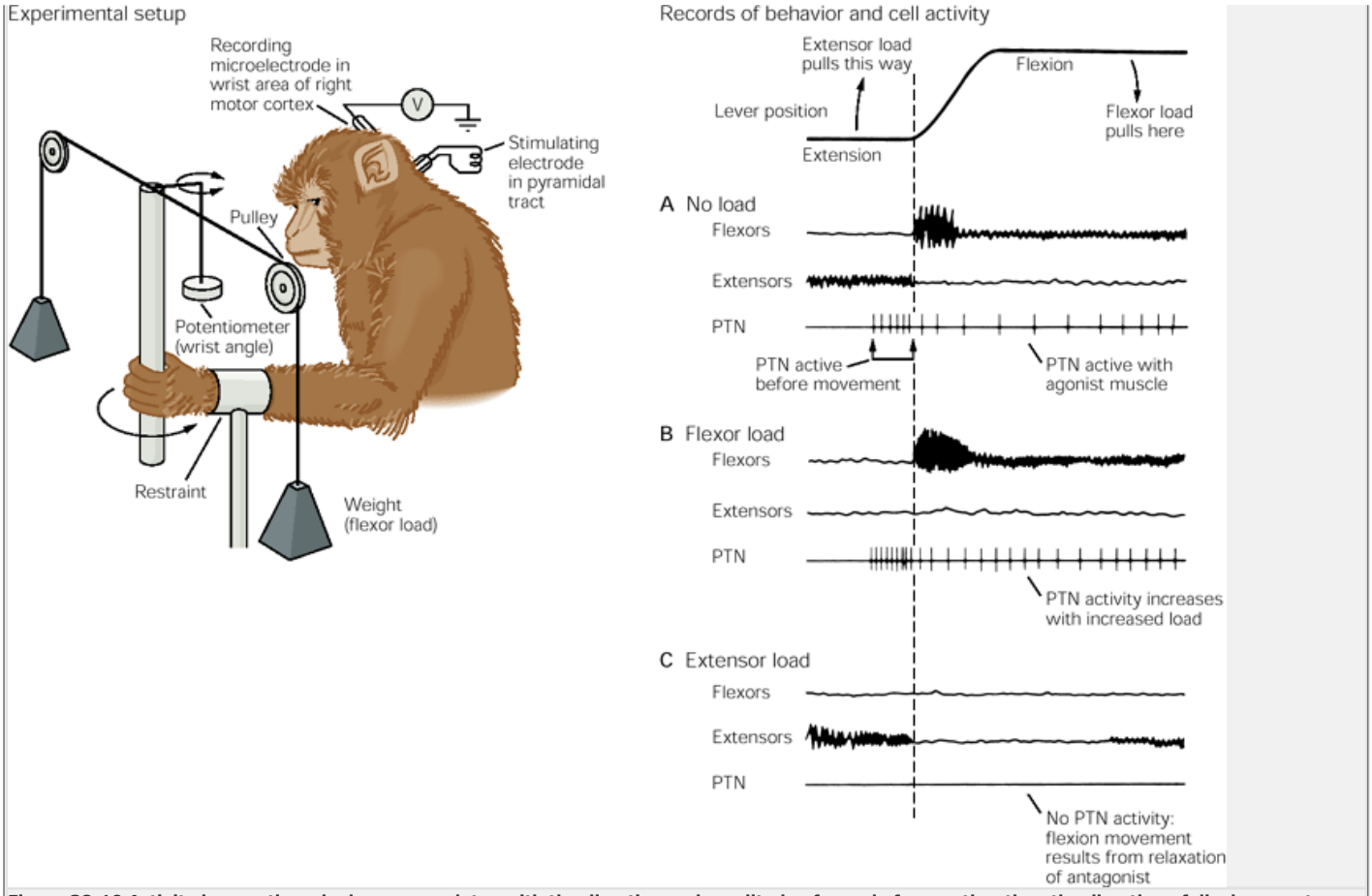

Figure 38-10 Activity in a corticospinal axon correlates with the direction and amplitude of muscle force rather than the direction of displacement. Records shown here were made while a monkey flexed its wrist under three load conditions. In each set of traces the **top trace** indicates the activity in a corticospinal neuron and the **bottom trace** wrist position, with upward deviation being flexion. When no load was applied (**A**) the neuron fired before and during flexion. When a load-opposing flexion was applied, activity in the neuron increased (**B**). When a load-assisting flexion was applied, the neuron fell silent (**C**). In all three conditions the wrist displacement was the same but the neuronal activity changed as the load changed. Thus the firing of the corticospinal neuron in this experiment is related to the force exerted during a movement and not to the displacement of the wrist. (From Evarts 1968.)

The directionally tuned neurons described by Georgopoulos are modulated strongly by the presence of external loads during reaching movements in a given direction, and this modulation depends on the force required to displace the limb. A cell's firing rate increases if a load opposes movement of the arm in the cell's preferred direction; it decreases if the load pulls the arm in the cell's preferred direction (Figure 38-14). This dependence of firing rate on load suggests that the activity of neurons in the primary motor cortex varies with the direction of forces as well as with movement direction during reaching with the whole arm. This force coding is similar to that for single-joint movements, discussed earlier.

Together these various studies show that motor cortex activity signals not only "lower level" movement parameters, such as muscle forces, but also "higher level" parameters related to the trajectory of the hand during reaching. This feature of motor cortex neurons distinguishes them from alpha motor neurons.

Box 38-1 Postspike Facilitation of Muscle Activity

Recording from cortical neurons in awake animals and relating the neuronal activity to movement parameters has led to significant insights about cortical control of movement. However, studies of this type are limited by their inability to identify functional connections between cortical neurons and the motor neurons of target muscles. This becomes possible with a technique developed by Ebehard Fetz and his colleagues called spike-triggered averaging (STA).

Cortical motor neurons with direct excitatory synaptic connections to motor neurons produce individual EPSPs with a fixed latency. Any one EPSP is unlikely to fully depolarize a motor neuron but it transiently increases the probability the motor neuron will fire by bringing it closer to threshold. The EMG profile is the sum of spike trains of a population of motor units within a muscle and is a reliable indicator of the firing of spinal motor neurons. By averaging the EMG profile over thousands of discharges of one cortical neuron, the effect of a single cortical neuron on an EMG profile can be ascertained. This averaging subtracts out random associations of cortical neuronal firing and motor unit discharge; the signal-to-noise ratio improves with the number of discharges used to compile the average.

Figure 38-11 shows the relation of the discharge of a single cortical neuron to an extension movement of the wrist. A cumulative average over 2000 discharges of the cortical neuron reveals a clear peak in the EMG profile beginning at a latency of 6 ms. This transient increase is called *postspike facilitation* and its short latency is interpreted as evidence of an underlying synaptic connection between the cortical neuron and the motor neurons.

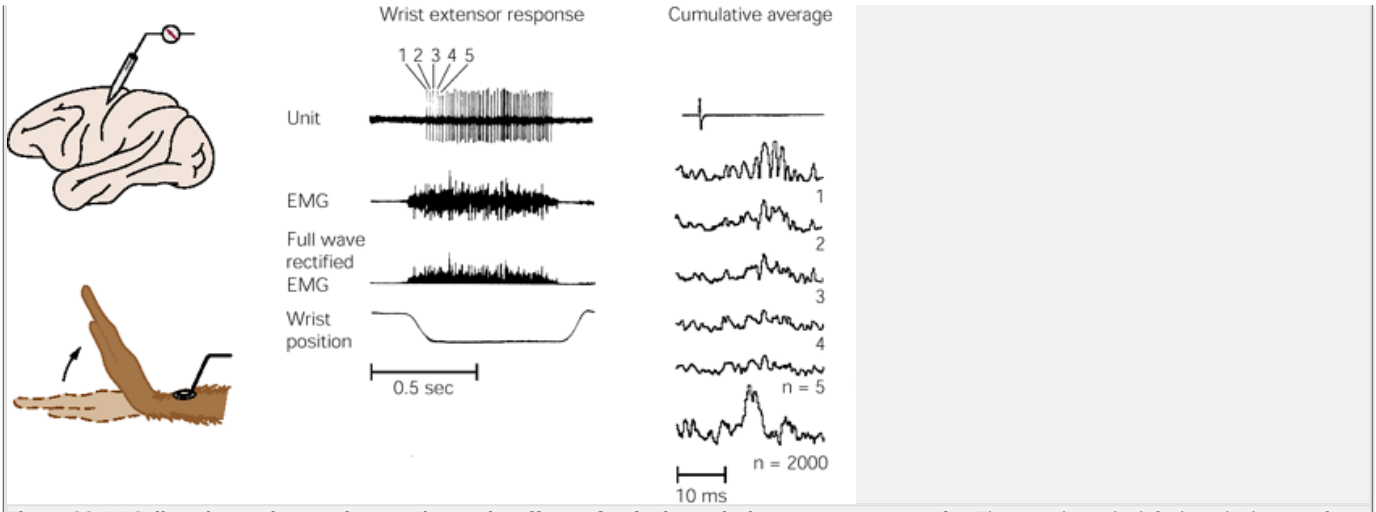

Figure 38-11 Spike-triggered averaging can detect the effects of a single cortical neuron on motor units. The records on the left show discharges of a cortical cell and normal and rectified EMG activity of one agonist muscle associated with wrist extension. From these records 30 μs segments of EMG activity associated with each cortical spike were averaged. The cumulative average of EMG segments associated with the first five spikes are shown on the right. No clear effect can be seen after averaging over only five spikes, but at 2000 spikes postspike facilitation can clearly be seen. (From Fetz and Cheney 1980.)

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Neurons in the Primary Motor Cortex Are Activated Directly by Peripheral Stimulation Under Particular Conditions

The simplest behaviors controlled by the primary motor cortex are those elicited directly by sensory stimuli. Motor cortical neurons receive strong sensory inputs from the limb whose muscles they control. When a standing human subject pulls on a handle, the sudden postural perturbation elicits a rapid counter-response in the stretched muscle at a latency shorter than a simple reaction time but longer than for a spinal reflex. However, this counter-response happens only when the person is told to resist. Such rapid motor adjustments are mediated mainly by relatively simple transcortical pathways through which somatosensory inputs reach the primary motor cortex directly via projections from the thalamus or primary sensory cortex. This transcortical pathway provides a degree of flexibility to rapid responses that is unavailable in spinal reflexes. These long-loop or transcortical responses are selectively increased in several movement disorders, such as Parkinson disease and myoclonus, while spinal reflexes remain normal.

Individual Movement of Digits Is Controlled by Patterns of Activity in a Population of Cortical Neurons

As noted earlier, anatomical studies and lesion experiments have suggested that the primary motor cortex

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plays a special role in producing individuated movement of the digits in primates.

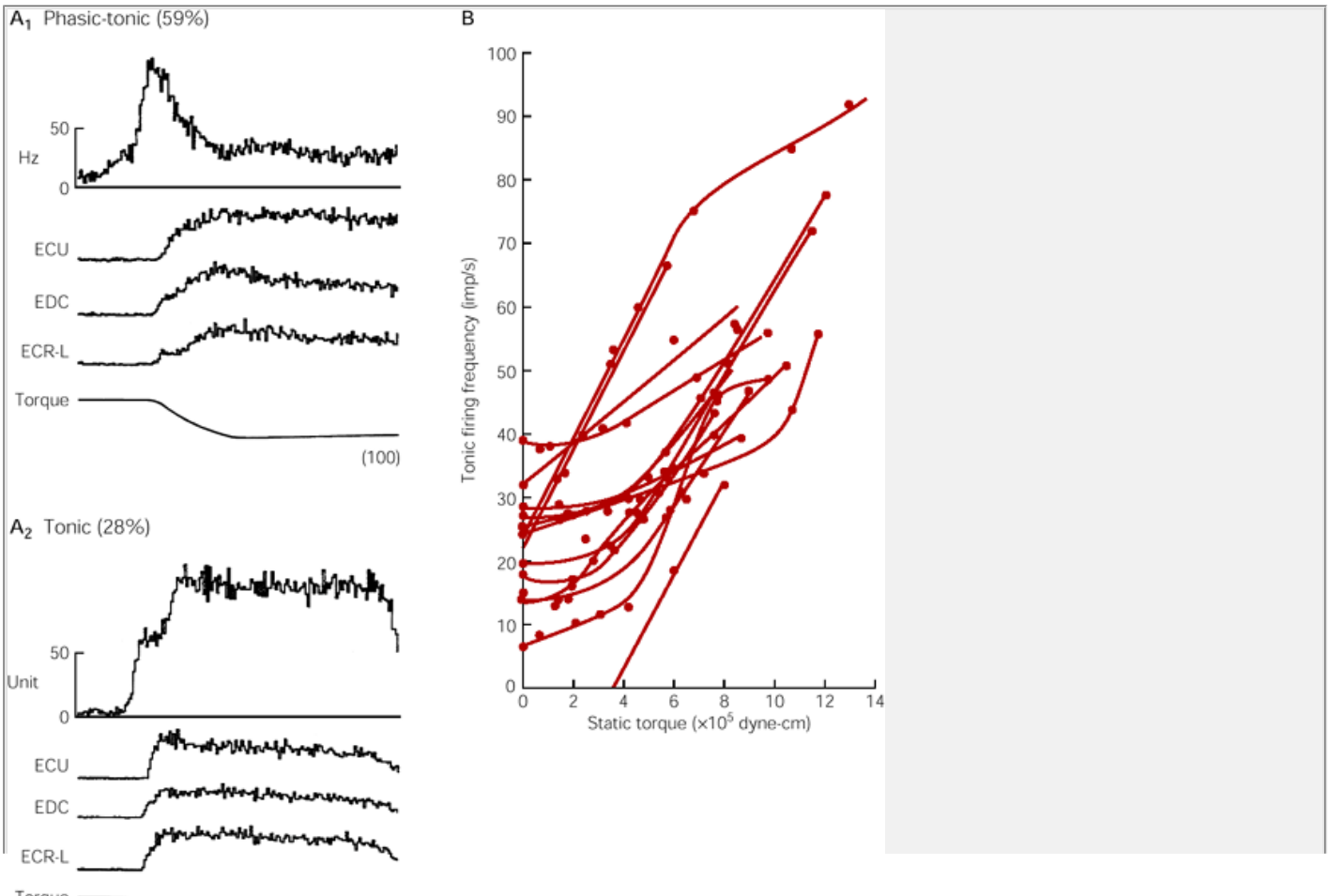

Figure 38-12 There is a direct relationship between the firing rate of motor cortical cells and force generation. (From Fetz EE and Cheney 1980.)

A. Two types of motor cortical neurons, phasic-tonic and tonic, are predominant in the primary motor cortex. Each has a characteristic response pattern during isometric wrist torques in which the torque level is reached and held. (Similar patterns are seen for torques accompanied by wrist displacement.) **1.** Phasic-tonic cell activity begins with a dynamic burst during the initial increase in torque and then decreases to a steady level when torque is maintained. **2.** Tonic cell activity follows the rise in torque and remains at a high level.

B. In both cell types activity increases with torque. The plot shows the relation between tonic firing rate, (impulses per second) and static torque during wrist extension.

Although individual neurons fire maximally when a particular finger is moved, these neurons are dispersed throughout the hand control area of primary motor cortex (Figure 35-15). The manner in which such activity is coordinated to produce a finger movement is analogous to the population coding that underlies reaching movements.

This observation is not surprising, since the digits are biomechanically coupled by common tendons and thus are not anatomically independent of each other. Moving a single digit alone requires activating and inhibiting muscles acting on all the digits. Current evidence indicates that each corticomotoneuronal (CM) cell influences activity in a small group of target muscles. Very few of these cells have been found that control only a single muscle. Even CM cells involved in individuated

finger movements have axons that diverge to more than one motor nucleus in the spinal cord. In addition, as noted earlier, the same target muscle may be influenced by CM cells that are dispersed throughout the hand representation. The cells activated will depend on the task in which the muscle is used.

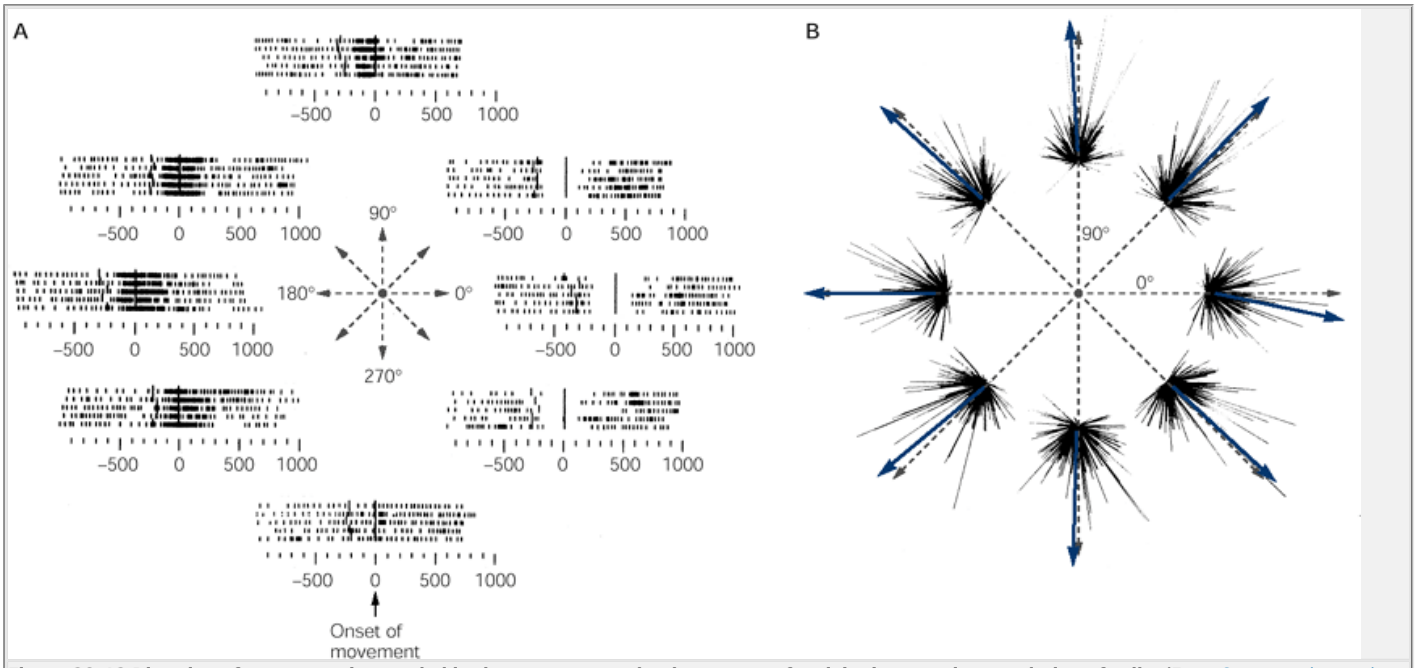

Figure 38-13 Direction of movement is encoded in the motor cortex by the pattern of activity in an entire population of cells. (From Georgopoulos et al. 1982.)

A. Motor cortical neurons are broadly tuned to the direction of movement, but individual cells fire preferentially in connection with movement in certain directions. Raster plots of the firing pattern of a single neuron during movement in eight directions show the cell firing at relatively higher rates during movements in the range from 90 degrees to 225 degrees. Different cells have different preferred movement directions. For these recordings a monkey was trained to move a handle to eight locations arranged radially in one plane around a central starting position. Each row of tics in each raster plot represents activity in a single trial; the rows are aligned at zero time (the onset of movement).

B. Cortical neurons with different preferred directions are all active during movement in a particular direction. The entirety of this activity results in a population vector that closely matches that of the direction of movement. The eight clusters shown here represent the activity of the same population of neurons during reaching movements in eight different directions. **Solid arrows** are the population vectors; **dashed arrows** are the direction of movement of the target limb.

Roger Lemon and R. B. Muir demonstrated the importance of the task in determining which neurons in the primary motor cortex will be used to control a particular muscle. They examined the activity of individual CM cells in monkeys during two different finger tasks, a power grip and a precision grip, both of which involve contraction of the intrinsic hand muscles controlled by the identified CM cells. Cells that are active during the precision grip remain silent during the power grip, even though the contraction of the target muscle is stronger for the power grip than for the precision grip (Figure 38-16).

The observation that activity in a CM cell is not invariably coupled with activation of its target muscle fundamentally distinguishes CM cells from spinal motor neurons. The finding that a distinct population of cells in the primary motor cortex is active only during the precision grip is further evidence of the special role of the primary motor cortex in controlling individuated movements of the fingers. The power grip, which does not require individual finger movements, can be controlled by descending pathways, arising either within or outside of the primary motor cortex, that diverge extensively in the spinal cord and therefore can recruit a large number of muscles in a less differentiated synergy.

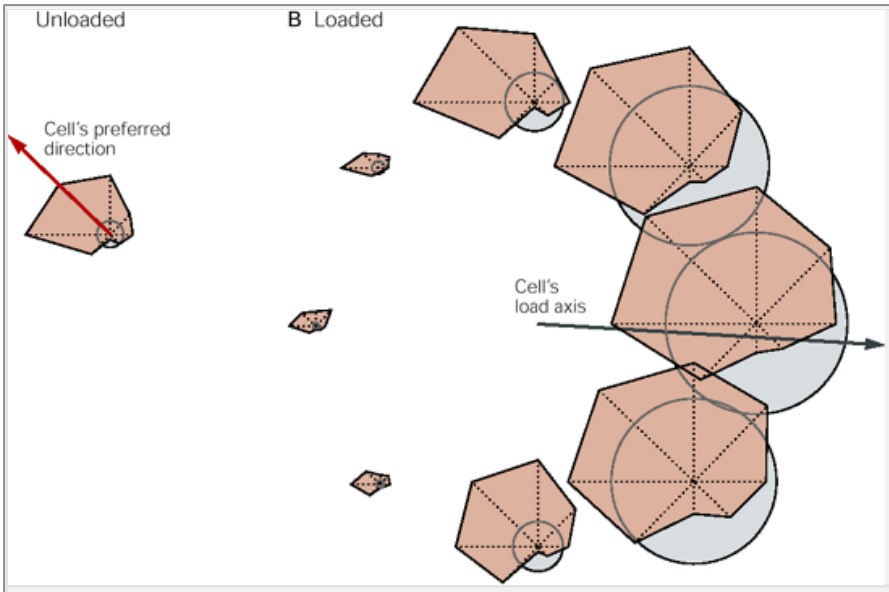

Figure 38-14 Motor cortical cells can code for the force required to maintain a trajectory. A monkey was trained to reach in eight directions while external loads pulled the arm in one of these directions. Polar plots represent the activity of a single cell in the primary motor cortex while the arm moved with external loads. The magnitude of the cell's discharge is plotted as the length of a vector extending in the direction of the executed movement (**dotted line**). The tips of all vectors are joined by a **solid line.** The radius of the circle indicates the magnitude of cell activity while holding the arm at the central starting position before movement.

A. Plot showing the preference of the cell for movement to the upper left during movements in eight directions without an external load applied to the arm.

B. Polar plots for the same cell when loads are applied in eight directions. The position of each polar plot corresponds to the direction in which the load pulled the arm. The cell's firing rate increases in all directions when the arm is pulled right. This rightward direction is the load axis of the cell, which is approximately opposite to its preferred movement direction. Thus the cell's firing rate is related to the amount of force required to maintain an arm trajectory in a given direction, not just to the direction itself. (From Kalaska et al. 1989.)

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Certain motor cortical cells fire less and less often as muscle force increases. That is, their activity is correlated negatively with force. However, like neurons with positive correlations (see Figure 38-12), these cells also facilitate their target muscles. They discharge only during tasks that require precise control of force and smooth changes in force. Thus their function may be to provide more precise derecruiting of motor units than would be afforded simply by inhibiting the so-called positive cortical neurons. This would be helpful, for example, in releasing delicate objects carefully.

In conclusion, the primary cortex has two levels of functional organization. First, a low-level control system, the CM cells, controls groups of muscles that can be brought together into task-specific combinations. Second, a higher-level control system encodes more global features of the movement. Practice and learning adjust the relation between these two levels of organization.

Each Premotor Area Contributes to Different Aspects of Motor Planning

Although the outputs of the premotor areas and the primary motor cortex overlap in the spinal cord, the inputs to the premotor areas are quite different from those to the primary motor cortex (see Figure 38-4). Moreover, damage to premotor areas causes more complex motor impairments than does damage to primary motor cortex. When a monkey with a large lesion of the premotor area is presented with food behind a transparent shield it will reach directly for the food and bump into the shield. Unlike a normal animal it is unable to incorporate visuospatial information about the shield into the kinematic plan for moving its hand.

The idea that premotor areas are involved in planning movement has received crucial support during the past 20 years from physiological and imaging studies of

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humans and monkeys performing a variety of special tasks. In monkeys distinct populations of cells are active in connection with ipsilateral movements, bilateral movements, or specific combinations of movements. Set-related and preparatory activity predominates, and cell activity is often associated primarily with specific tasks as we will see below.

Studies of the premotor areas have identified several basic features of the neural organization of motor preparation. First, movements that are initiated internally by the subject—such as the sequencing of finger movements when manipulating an object—involve primarily the supplementary motor area. Second, movements triggered by external sensory events involve primarily the lateral premotor areas. More specifically, separate populations of lateral premotor neurons map the often arbitrary relationship between stimulus and response. The lateral dorsal premotor area is also concerned with delayed action (executed later on cue), whereas the lateral ventral premotor area is concerned with conforming the hand to the shape of objects.

Third, mental rehearsal of a movement—that is, the use of visual imagery to plan a movement—invokes the same patterns of activity in the premotor and posterior parietal cortical areas as those that occur during performance of the movement. Psychophysical studies have shown that mental rehearsal of movement has a similar time course and closely simulates task performance. This observation helps explain the importance of mental rehearsal to athletes and skilled performers. Fourth, the premotor areas activated during a particular task are not the same over time but change progressively as performance becomes automatic.

The Supplementary and Presupplementary Motor Areas Play an Important Role in Learning Sequences of Discrete Movements

Motor actions are often self-initiated without an environmental cue. Nearly a full second before a self-initiated voluntary movement begins, a characteristic negative shift in cortical potentials is seen in the electroencephalogram (EEG) record of medial premotor regions, where the supplementary motor area is situated. This negative potential, referred to as the *preparatory potential* or Bereitschaft potential, signals the planning that occurs before movement is executed.

The region responsible for this negative potential was localized more precisely in a study comparing increases in regional cerebral blood flow (a measure of increases in neuronal activity) during simple, complex,

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and imagined sequences of finger movements. Complex movement sequences require more planning than do simple repetitive movements. Imagining complex movements might require the same amount of planning as real movements. As expected, during forceful repetitive finger flexions against a spring-loaded movable cylinder, increases in regional cerebral blood flow were largely confined to the contralateral primary sensorimotor hand-control region. A complex sequence of finger movements was accompanied by regional cerebral blood flow increases within the supplementary motor area. Remarkably, when the complex sequence of finger movements was simply imagined, regional cerebral blood flow increased in an area anterior to the supplementary motor area on both sides (Figure 38-17). This area,

the presupplementary motor area, provides the main input to the supplementary motor area and is discussed in detail below.

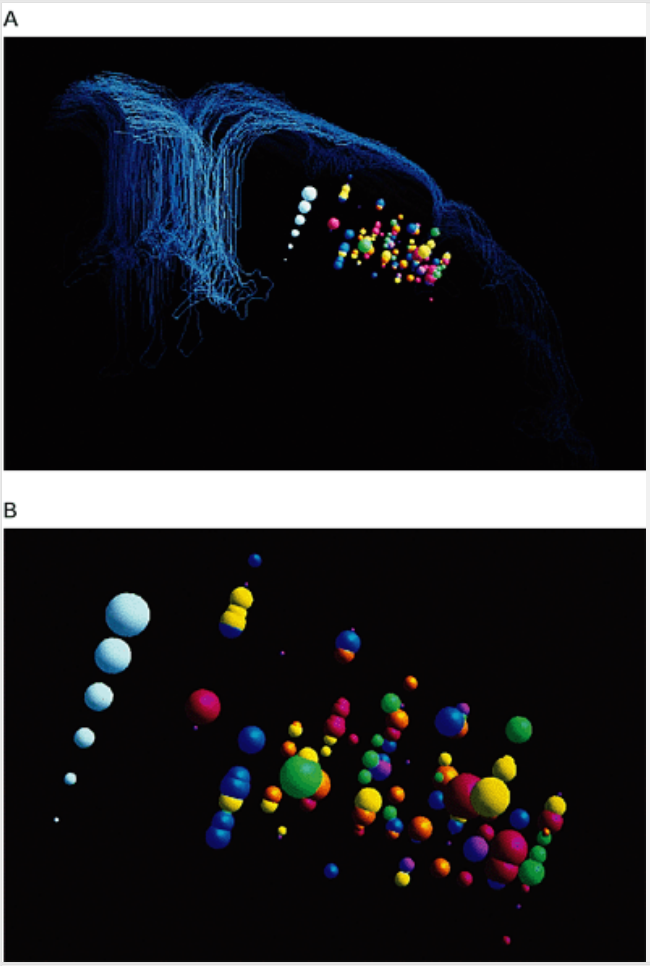

Figure 38-15 Cortical neurons that govern finger movements are distributed throughout the hand-control area of the primary motor cortex. (From Schieber and Hibbard 1993.)

A. View of the frontal pole of the monkey cortex, showing the interhemispheric fissure and the lateral convexity. The **colored dots** and **spheres** represent sites of single neurons in the hand-control region of the primary motor cortex from which recordings were made.

B. A plot of each neuron's maximal activity shows that neurons that are maximally active for a particular digit or for the wrist are not grouped together but instead are distributed throughout the hand-control area of the primary motor cortex. Each digit and the wrist are represented by a different color. The diameter of the sphere is proportional to the neuron's activity (the radii of the white spheres represent changes in firing frequency of 0, 40, 80, 120, 160, and 200 spikes per second.)

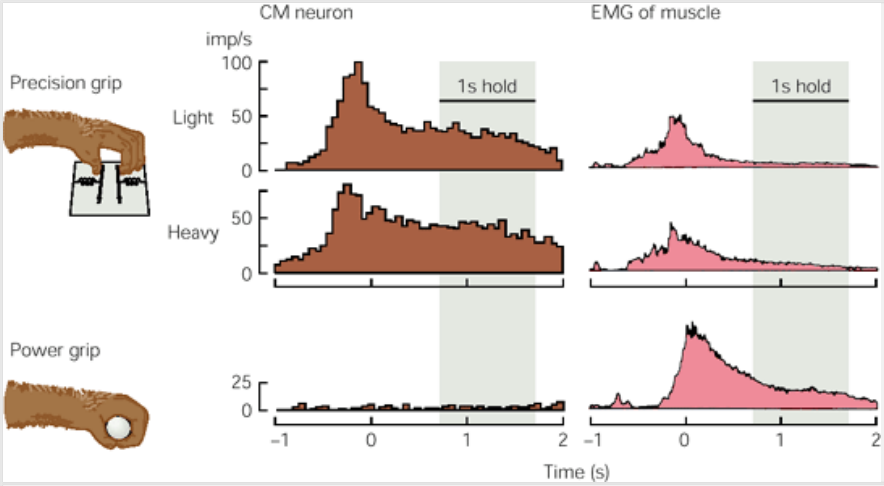

Figure 38-16 Whether an individual corticomotoneuronal (CM) cell is active depends on the motor task. The activity of a CM cell and the activity in its target muscle are not directly related. Cumulative histograms show the activity of a single neuron during a precision grip and a power grip. During the precision grip the neuron's activity is the same whether overall force is light or heavy and the level of electromyographic (EMG) activity in the target muscle is similar for both forces. During the power grip there is almost no activity in the neuron despite a greater amount of EMG activity in the muscle. Thus, even if a given motor neuron is monosynaptically connected to a given CM cell, their firing patterns do not have to parallel each other because the multiplicity of connections to motor neurons allows task flexibility. (**imp/s** = impulses per second.) (Maier et al 1993.)

The specific role of the supplementary motor area in the internal representation of sequences of movements was examined in another experiment, in which recordings were made from neurons in the primary motor cortex, supplementary motor area, and lateral premotor areas of monkeys while the animals performed two variations of an *instructed-delay task.* In this type of task subjects are taught which movements to make and later given a cue telling them when to make the movements. The monkeys in this experiment were instructed to touch three panels in a specific sequence. In one variation the instruction was visual: Three panels were lit up in a sequence that the monkeys had to follow. In the other variation the monkeys were instructed to perform a previously memorized sequence. As expected, neurons in the primary motor cortex generally discharged before and during movements to the same degree for visually guided and memorized sequences. In contrast, many

supplementary motor area neurons fired only before and during performance of a memorized sequence. The reverse was true for the lateral premotor neurons (Figure 38-18). In addition, the movement-related discharge of some supplementary motor area neurons is specific to a particular sequence of movements such as pushing followed by turning a handle. The cells do not fire in connection with other combinations of the same movements. Thus the supplementary motor area seems to be involved in preparing movement sequences from memory in the absence of visual cues.

The main cortical input to the supplementary motor area arises from the presupplementary motor area (see Figure 38-4). This region projects only to the supplementary

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motor area and has no clear somatotopy. Whereas the supplementary motor area is involved in setting the motor programs for learned sequences, the presupplementary motor area is thought to be involved in learning these sequences. For example, in one study the presupplementary motor area was preferentially activated while subjects learned a new sequence of button presses; the supplementary motor area became active only during the performance of the movements once they were learned. This motor learning likely involves a continuous interchange of information with the prefrontal cortex (area 46) and other areas of cortex.

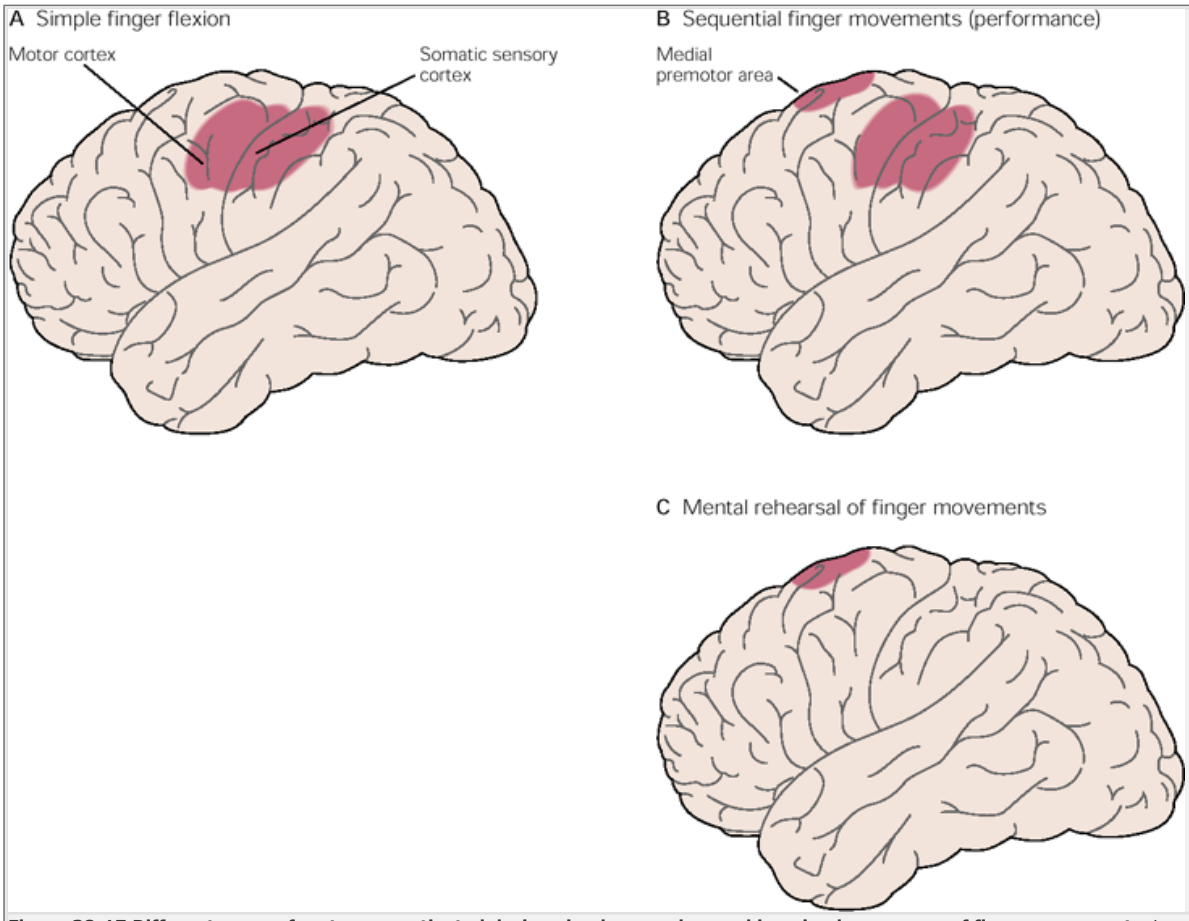

Figure 38-17 Different areas of cortex are activated during simple, complex, and imagined sequences of finger movements. Local increases in cerebral blood flow during a behavior indicate which areas of motor cortex are involved in the behavior. In the experiment illustrated here blood flow was measured by intravenously injecting radioactive xenon dissolved in a saline solution and measuring the radioactivity over different parts of cortex using arrays of detectors placed over the scalp. Because local tissue perfusion varies with neural activity, the measured radioactivity provides a good index of regional activity in the surface of the brain. (Adapted from Roland et al. 1980.)

A. When a finger is pressed repeatedly against a spring, increased blood flow is detected in the hand-control areas of the primary motor and sensory cortices. The increase in the motor area is related to the execution of the response, whereas the increase in the sensory area reflects the activation of peripheral receptors.

B. During a complex sequence of finger movements the increase in blood flow extends to the medial premotor area, which includes the supplementary motor area (SMA) and presupplementary motor area (preSMA).

C. During mental rehearsal of the same sequence illustrated in part B, blood flow increases only in the medial motor area.

When proficiency and skill are gained, the neural control of task performance can also shift from the supplementary motor area to the primary motor cortex. In one recent study with monkeys, premovement activity in the supplementary motor area during the performance of a key-pressing task disappeared after 12 months of overtraining. Subsequently, an experimental lesion in the right primary motor cortex of these overtrained monkeys caused weakness in the left digits, thereby greatly compromising the monkeys' ability to perform the task. After 21 days the monkeys had recovered sufficiently to press the keys with the same skill as before they received the lesion. Twenty-two days after the monkeys received the lesion recordings from the supplementary motor area showed that neurons were again very active before movement.

Much as extended practice influences the extent of

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motor representation in the primary motor cortex, a shift in representation occurs in the supplementary motor cortex as a task goes from being novel to automatic. Conversely, recovery of function following damage to the primary motor cortex represents a new learning challenge in which the supplementary and perhaps presupplementary motor areas participate anew.

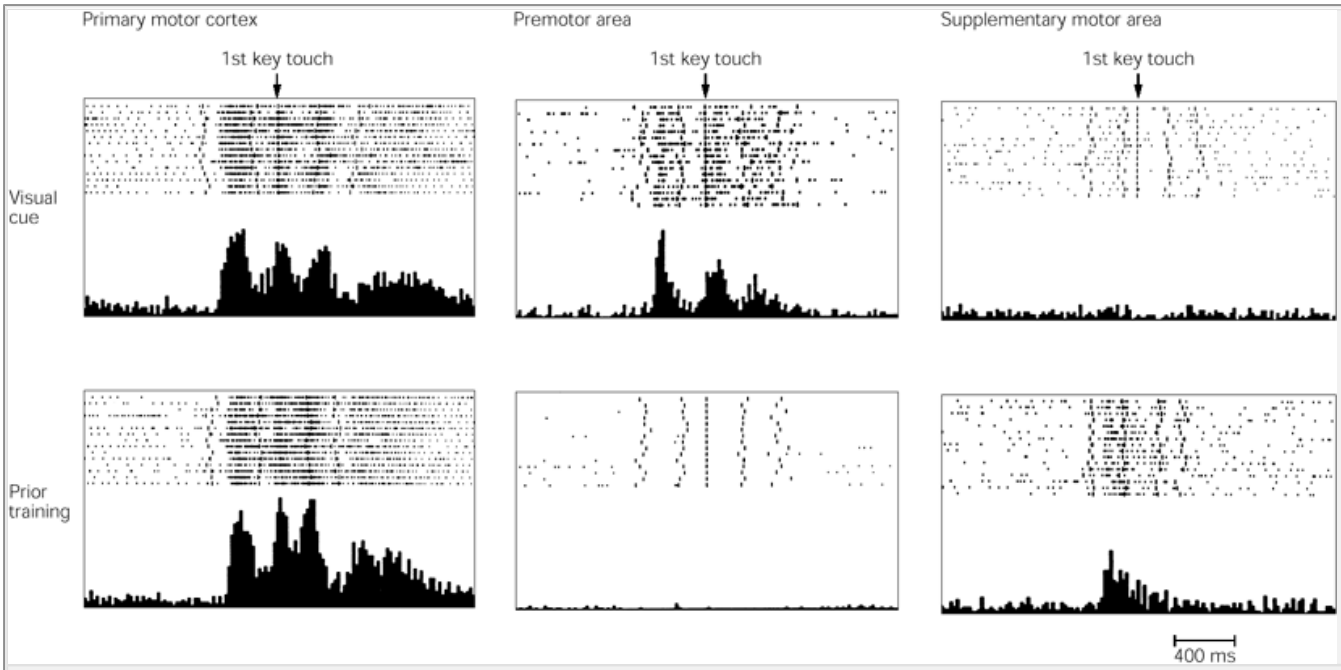

Figure 38-18 Cell activity in the motor cortex depends on whether a sequence of movements is guided by visual cues or by prior training. Monkeys were required to press three buttons either in a sequence presented by lighting three panels in turn or in a sequence they had learned previously. After being instructed to perform the observed sequence or the trained sequence, there was a delay before the animal was given a signal to initiate the movement. Raster plots represent cell discharge before and during movement on 16 trials, and the histogram shows the summed activity over all trials. Data are aligned to the onset of the first key touch. The cell in the primary cortex fired whether the sequence performed was the one learned in prior training or the one cued by lighted panels. The cell in the lateral premotor area fired only when the visually cued sequence was used, whereas the cell in the supplementary motor area fired only when the trained sequence was used. (From Mushiake 1991.)

The Lateral Premotor Areas Contribute to the Selection of Action and to Sensorimotor Transformations

Selection of appropriate action can be the result of internal reflection, which may involve evocation of mental imagery. More often, however, actions are responses to visual or auditory cues. Such cues may signify that a particular action is required immediately (eg, a red light telling us to stop) or that some type of situation is imminent in which action will be required (eg, a yellow light signaling an imminent change to red). The ability to learn new, adaptive responses to particular environmental stimuli is crucial to effective and accurate movement.

We have seen that set-related activity occurs in the primary motor cortex and supplementary motor area before movement is executed. In the primary motor cortex this activity represents specific parameters of a particular movement; in the supplementary motor area it represents a specific order of responses. In the lateral premotor areas it represents how visual or other sensory stimuli are to be used to direct the movement. Characteristically, set-related activity in the premotor area persists during the entire interval between an anticipatory cue and the signal to move (Figure 38-19).

Set-related activity in the lateral dorsal premotor area is related predominantly to sensory stimuli that do not convey spatial cues to direct movement. For example, the stimulus could be a light in a location that is not

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related to the direction in which the movement is to be executed. Thus the lateral dorsal premotor area is involved in learning to associate a particular sensory event with a specific movement (associative learning). Consistent with this, monkeys with lesions in the lateral dorsal premotor area have difficulty with associative learning. In one study monkeys were taught to associate pulling or pushing a joystick with a particular background light (red or blue). The lateral premotor cortex was then removed from both hemispheres and the animals were retrained two weeks after surgery. Although the monkeys were able to execute the required movements without impairment, none was able to relearn the association between the background color and whether to push or pull.

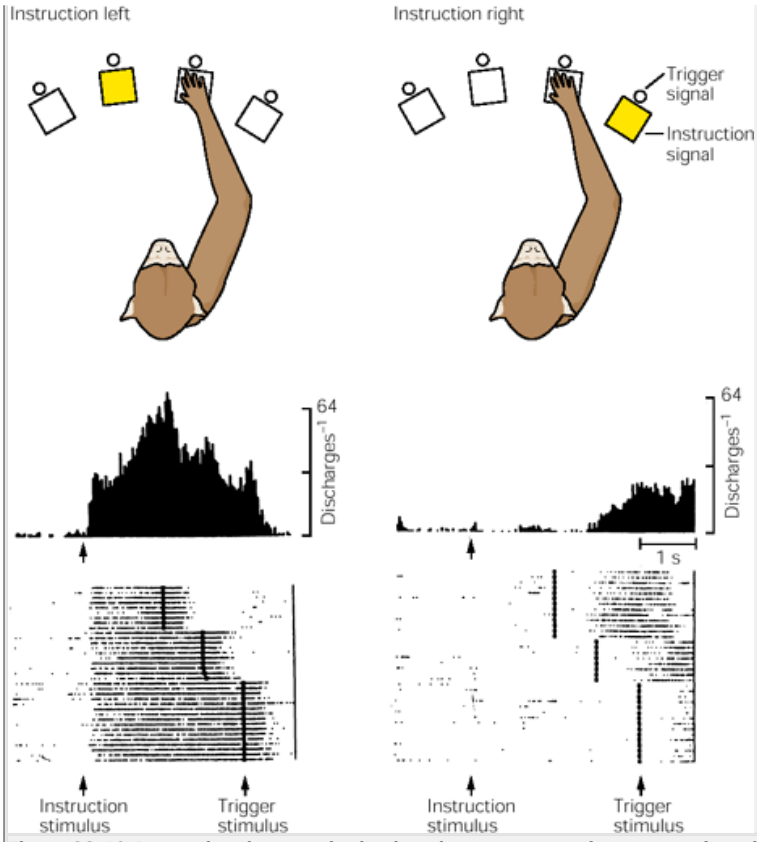

Figure 38-19 A set-related neuron in the dorsal premotor area becomes active while the monkey prepares to make a movement to the left. An instruction signal (illumination of one of four panels) tells the monkey which panel it will have to depress when a trigger signal (illumination of a nearby light-emitting diode) is presented. In the raster plots each dot on each line represents a spike in the recorded neuron. Each line is one trial, and successive trials are aligned on the onset of the instruction signal. The delay between the instruction and trigger signals varied randomly among three values. In the raster plots and histograms the responses made with each delay time are grouped to show that the discharge of the neuron coincides with the instruction signal and lasts until the response is made after the trigger signal. (From Weinrich and Wise 1982.)

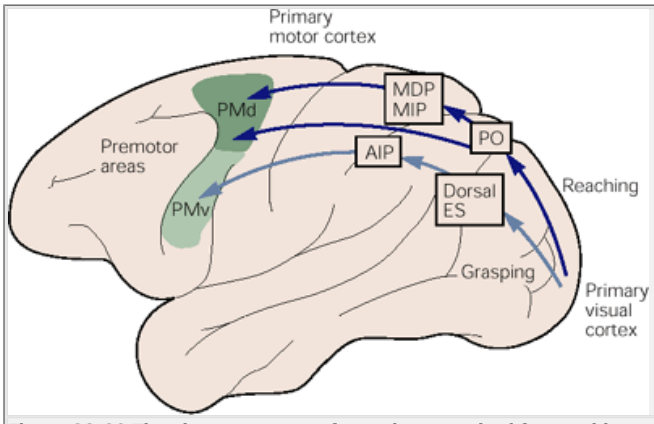

Figure 38-20 The visuomotor transformations required for reaching and grasping involve two different pathways from the primary visual cortex to the premotor areas.

Reaching. A path connects the parieto-occipital extrastriate area (**PO**) and the dorsal premotor area (**PMd**). Some of these connections reach PMd directly, and some relay via areas in the intraparietal sulcus: the medial dorsal parietal (**MDP**) and medial intraparietal (**MIP**) areas. This system is responsible for transforming visual information about the location of objects in extrapersonal space into the direction of a reaching movement.

Grasping. A path connects the dorsal extrastriate (**ES**) cortex and the ventral premotor area (**PMv**) via the anterior intraparietal area (**AIP**). This system is responsible for transforming visual information about the properties of objects, such as shape and size, into commands for effective grasping.

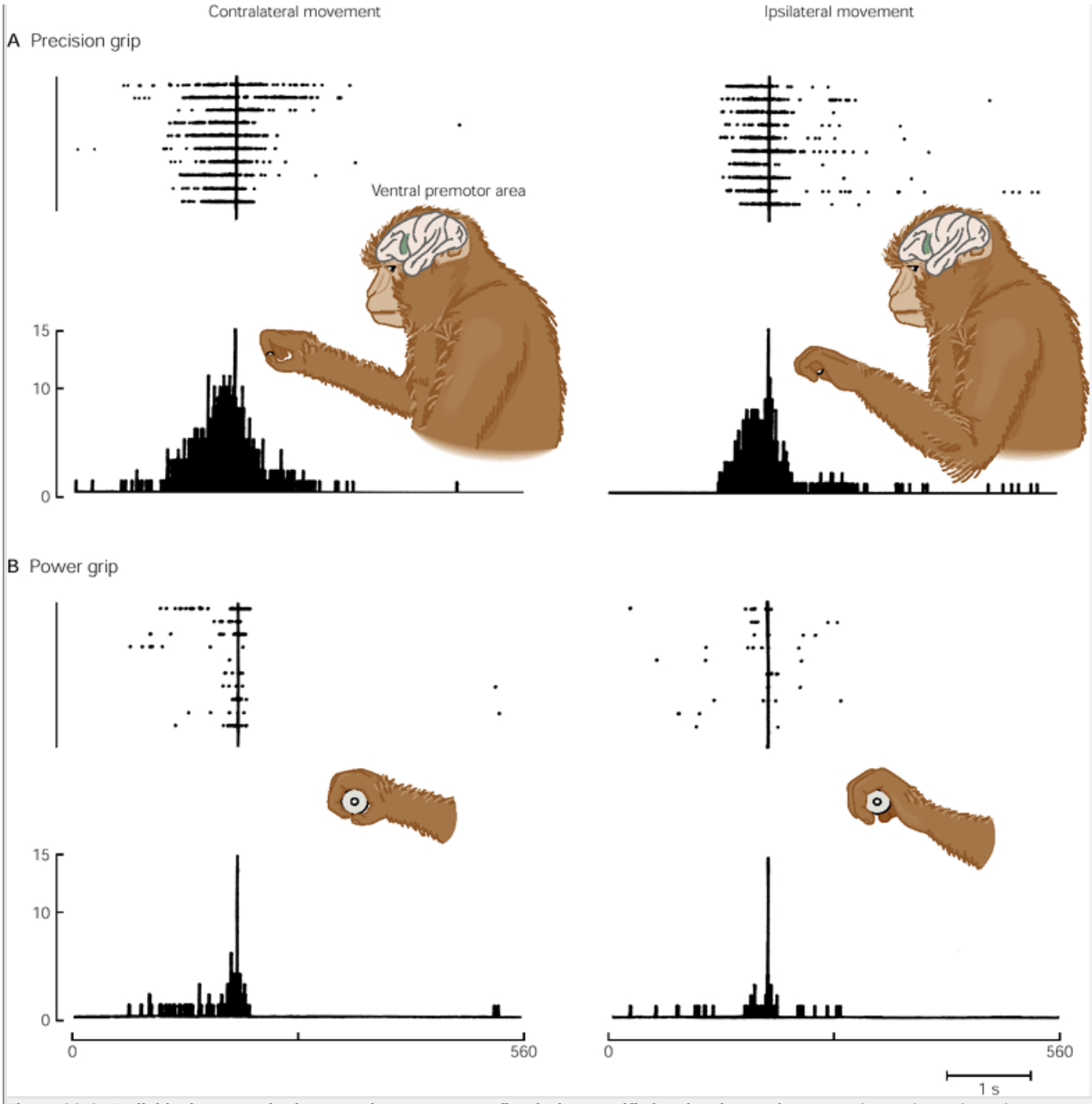

Figure 38-21 Individual neurons in the ventral premotor area fire during specific hand actions only. Raster plots and cumulative histograms show the discharge of a single neuron in the lateral ventral premotor area (F5) of a monkey during a precision grip and a power grip involving all the fingers. The cell is active during the precision grip by either arm but not during the power grip by either arm. Thus its activity is specific to the grip type employed by either hand. The fact that the neuron is active during movement of both arms excludes the possibility that this difference is due solely to the different patterns of corticospinal activation required by the two grips; if this were the case, only contralateral activation would occur. (From Rizzolatti et al. 1996.)

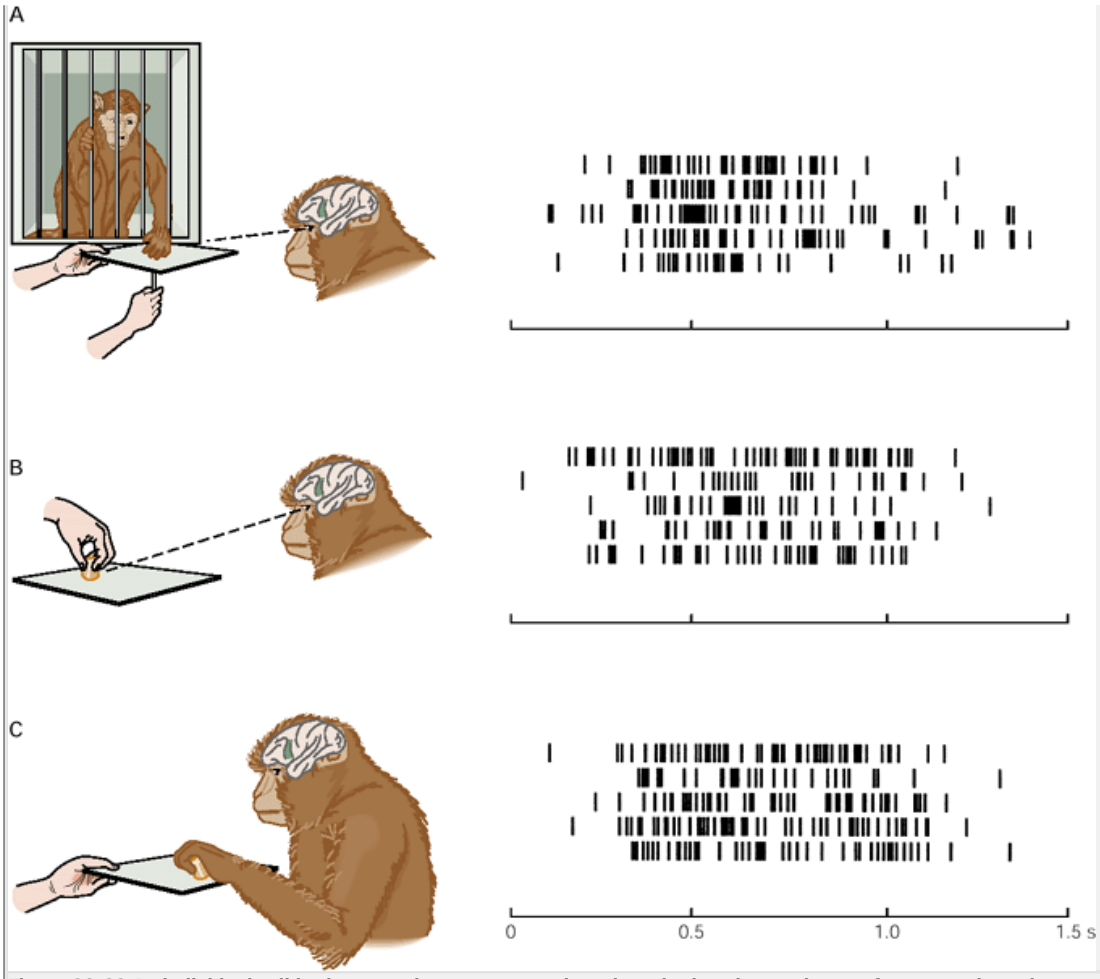

Figure 38-22 An individual cell in the ventral premotor area is active whether the monkey performs a task or observes someone else perform the task. The fact that the same cell is active during action or observation suggests that it is involved in the abstract representation of the motor task.

A. Activity in the neuron as the monkey observes another monkey make a precision group.

B. Activity in the same neuron as the monkey observes the human experimenter make the precision grip.

C. Activity in the same neuron as the monkey itself performs a precision grip. (From Rizzolotti et al 1996.)

Reaching and Grasping Are Mediated by Separate Parieto-Premotor Channels

Goal-directed movements require transformation of sensory representations of the environment into muscle-control

signals, a process termed *sensorimotor transformation.* Reaching, a goal-directed movement, requires that visual information about target location and the position of the upper limb be used to specify critical features of the upcoming arm movement. In addition, reaching is commonly coupled with grasping an object.

The parameters for reaching movement, notably direction and extent, depend on the location of the target relative to the body, shoulder, or hand. Grasping, in contrast, is governed mainly by the shape and dimensions of the object. Grasping involves first a separation of the fingers sufficient to enclose the object and then closure as the object is gripped between the pads. Separation of the fingers occurs during transport of the hand toward the object. The kinematics of grasping thus depend on the object itself and not on its location. Thus reaching and grasping are interesting behaviors to study in order to better understand the process of visuomotor transformation.

Anatomical evidence and single-cell recordings have shown that separate but parallel parieto-premotor channels mediate visuomotor transformations required for reaching and grasping (Figure 38-20). During reaching, neurons in parietal area 5 code for direction of the movement but discharge later than dorsal premotor neurons to which they are connected. These neurons could monitor ongoing movements and improve the planning and execution of subsequent reaches by premotor areas.

During grasping, different neurons in the lateral ventral premotor area of monkeys fire in connection with different hand actions and object shapes. These neurons are active throughout reach, well before the fingers begin to grasp. Moreover, different cells fire during different patterns of hand shaping. Some neurons are active only when the action is a precision grip; others are active only when the action is a swiping movement to retrieve food; still others are active only if the action is a power grip (Figure 38-21A). The cells in the lateral ventral premotor area thus seem to direct motor acts that can be guided by visual information about object shape received from the posterior parietal cortex. Another set of neurons discharges whether an object is grasped or bitten.

A unique type of neuron has been discovered in the lateral ventral premotor area. Like others, these neurons discharge when the monkey performs a specific grasping movement, but they also discharge when the monkey observes the same movement being made by another monkey or even by the experimenter. These neurons have been called *mirror neurons* (Figure 38-22).

These differnt neurons all share the characteristic of encoding a vocabulary of goal-directed behaviors rather than how these behaviors will be carried out.

The vental premotor area receives its main input from neurons with similar task related properties in the anterior intraparietal region, a region buried in the intraparietal sulcus. Recordings of these neurons were made while a monkey performed a series of tasks involving several different switches and knobs. Cells fired selectively when particular switches were grasped and also fired when the monkey visually fixated the same switch without grasping it. These cells may have a role in transforming the dimensions of an object in visual space into motor signals.

An Overall View

Our understanding of the functional organization of the motor areas of the cerebral cortex has undergone substantial change in recent years, as a new picture of the cortical control of movement has emerged. The primary motor cortex can no longer be seen as a simple motor map of the body, in which adjacent muscles or joints are represented in adjacent cortical sites. Instead, individual muscles and joints are represented repeatedly in a complex mosaic that makes it possible for the cortex to

organize combinations of movements suitable to specific tasks. Each muscle and joint is represented by columnar arrays of neurons whose axons branch and make connections with several functionally related motor nuclei. This branching is more modest for cells that control distal muscles, providing these muscles with more independent control.

In addition to terminating on spinal motor neurons, corticospinal neurons also terminate on interneurons in the spinal cord. These connections can gate reflex circuits, allowing voluntary movements to take advantage of spinal circuits, as these circuits can link local sensory input to output.

Distinct populations of motor cortical neurons appear to have specialized roles in determining specific features of motor performance. The characteristics of these different populations and their distribution within the motor areas of cortex point to a hierarchical organization of motor tasks. Thus most neurons in the primary motor cortex become active only shortly before and during movement. Neurons of the primary motor cortex differ from spinal motor neurons in that the former fire only in connection with certain tasks and spatial patterns of muscle activation (eg, precision grip versus

power grip), they encode a more restricted range of contractile force than do spinal motor neurons, and some even encode decrements in force. The kinematic details of movement are determined by population codes, the summed activity of entire populations of neurons.

In contrast to neurons in the primary motor cortex, movement-related neurons in the premotor areas may fire during movements that are related to specific tasks and not others to encode a more global feature. Set-related neurons, which are relatively rare in the primary motor cortex, are more common in premotor areas. These cells are active in the absence of any overt behavior, such as during a delay between task instructions and execution of the task. Some encode a response to be made after a delay; others encode a global sensorimotor transformation (eg, "always move at 180 degrees from the visual stimulus"). Thus, just as there is a hierarchy of spinal and supraspinal motor control, there is a hierarchy of neuronal repre-sentations of task features within the different cortical areas.

The planning and execution of voluntary movement relies on sensorimotor transformations in which representations of the external environment are integrated into motor programs. This integration is the product of premotor and primary motor areas operating in conjunction with sensory and association areas. We have seen an example of this in the communication between parietal and motor areas during visually guided reaching.

In contrast to reflex movements, voluntary movements are highly adaptable—they improve in speed and accuracy with repeated trials of practice. This adaptability may reflect an optimization process in which the minimal circuits needed to accomplish a behavior are, with training, selected from redundant sensorimotor connections. Such an optimization process could be responsible for the observed shift in the encoding of particular parameters of movement from one group of cells to another, or from one area of cortex to another, as proficiency develops.

A novel behavior initially requires processing in multiple motor and parietal areas as it is continuously monitored for errors and subsequently modified. As the behavior becomes more accurate, the need for sampling of the sensory inflow and updating of the motor program decreases and the need for the computational power of large networks lessens. For example, the presupplementary motor area is active during the learning of a behavior but becomes less active as learning progresses. After long periods of practice, when the behavior becomes automatic, activity in the supplementary motor area ceases.

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43

The Basal Ganglia

Mahlon R. DeLong

THE BASAL GANGLIA CONSIST of four nuclei, portions of which play a major role in normal voluntary movement. Unlike most other components of the motor system, however, they do not have direct input or output connections with the spinal cord. These nuclei receive their primary input from the cerebral cortex and send their output to the brain stem and, via the thalamus, back to the prefrontal, premotor, and motor cortices. The motor functions of the basal ganglia are therefore mediated, in large part, by motor areas of the frontal cortex.

Clinical observations first suggested that the basal ganglia are involved in the control of movement and the production of movement disorders. Postmortem examination of patients with Parkinson disease, Huntington disease, and hemiballismus revealed pathological changes in these subcortical nuclei. These diseases have three characteristic types of motor disturbances: (1) tremor and other involuntary movements; (2) changes in posture and muscle tone; and (3) poverty and slowness of movement without paralysis. Thus, disorders of the basal ganglia may result in either diminished movement (as in Parkinson disease) or excessive movement (as in Huntington disease). In addition to these disorders of movement, damage to the basal ganglia is associated with complex neuropsychiatric cognitive and behavioral disturbances, reflecting the wider role of these nuclei in the diverse functions of the frontal lobes.

Primarily because of the prominence of movement abnormalities associated with damage to the basal ganglia, they were believed to be major components of a motor system, independent of the pyramidal (or corticospinal) motor system, the "extrapyramidal" motor system. Thus, two different motor syndromes were

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distinguished: the *pyramidal tract syndrome*, characterized by spasticity and paralysis, and *the extrapyramidal syndrome*, characterized by involuntary movements, muscular rigidity, and immobility without paralysis.

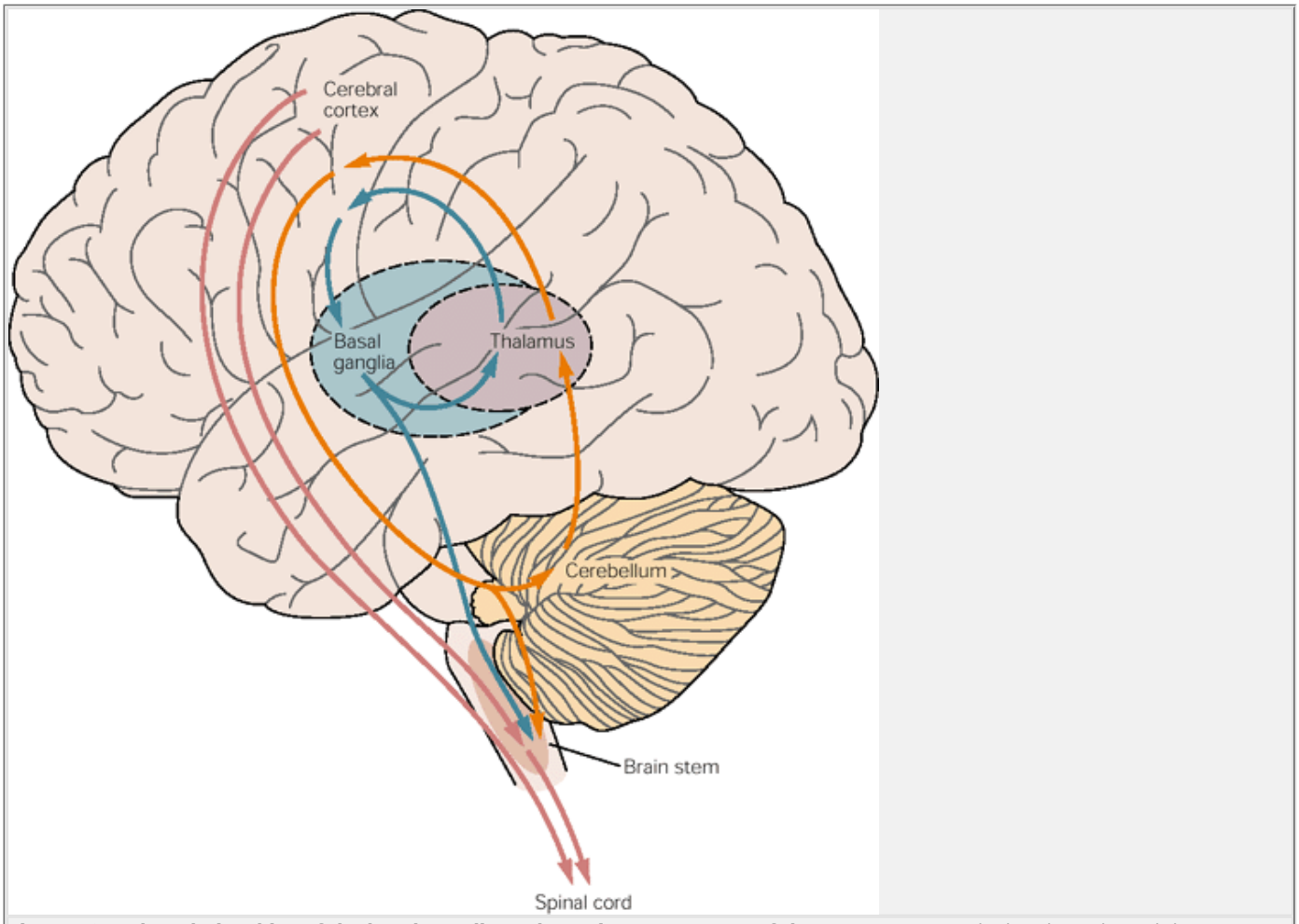

Figure 43-1 The relationships of the basal ganglia to the major components of the motor system. The basal ganglia and the cerebellum may be viewed as key elements in two parallel reentrant systems that receive input from and return their influences to the cerebral cortex through discrete and separate portions of the ventrolateral thalamus. They also influence the brain stem and, ultimately, spinal mechanisms.

There are several reasons why this simple classification is no longer satisfactory. First, we now know that, in addition to the basal ganglia and corticospinal systems, other parts of the brain participate in voluntary movement. Thus, disorders of the motor nuclei of the brain stem, red nucleus, and cerebellum also result in disturbances of movement. Second, the extrapyramidal and pyramidal systems are not truly independent but are extensively interconnected and cooperate in the control of movement. Indeed, the motor actions of the basal ganglia are mediated in

large part through the supplementary, premotor, and motor cortices via the pyramidal system.

Because they are so common, disorders of the basal ganglia have always been important in clinical neurology. Parkinson disease was the first disease of the nervous system to be identified as a molecular disease caused by a specific defect in transmitter metabolism. Therefore, in addition to providing important information about motor control, the study of diseased basal ganglia has provided a paradigm for studying the relationship of transmitters to disorders of mood, cognition, and nonmotor behavior, topics that will be considered in detail in Chapters 60 and 61. The use of a variety of anatomical, molecular, and neural imaging techniques as well as animal models of basal ganglia disorders has led to major advances in understanding the organization and function of the basal ganglia. These insights have, in turn, led to new pharmacologic and neurosurgical approaches to treatment of diseases of the basal ganglia.

The Basal Ganglia Consist of Four Nuclei

The basal ganglia consist of several interconnected subcortical nuclei with major projections to the cerebral cortex, thalamus, and certain brain stem nuclei. They receive major input from the cerebral cortex and thalamus and send their output back to the cortex (via the thalamus) and to the brain stem (Figure 43-1). Thus, the basal ganglia are major components of large cortical-

subcortical reentrant circuits linking cortex and thalamus.

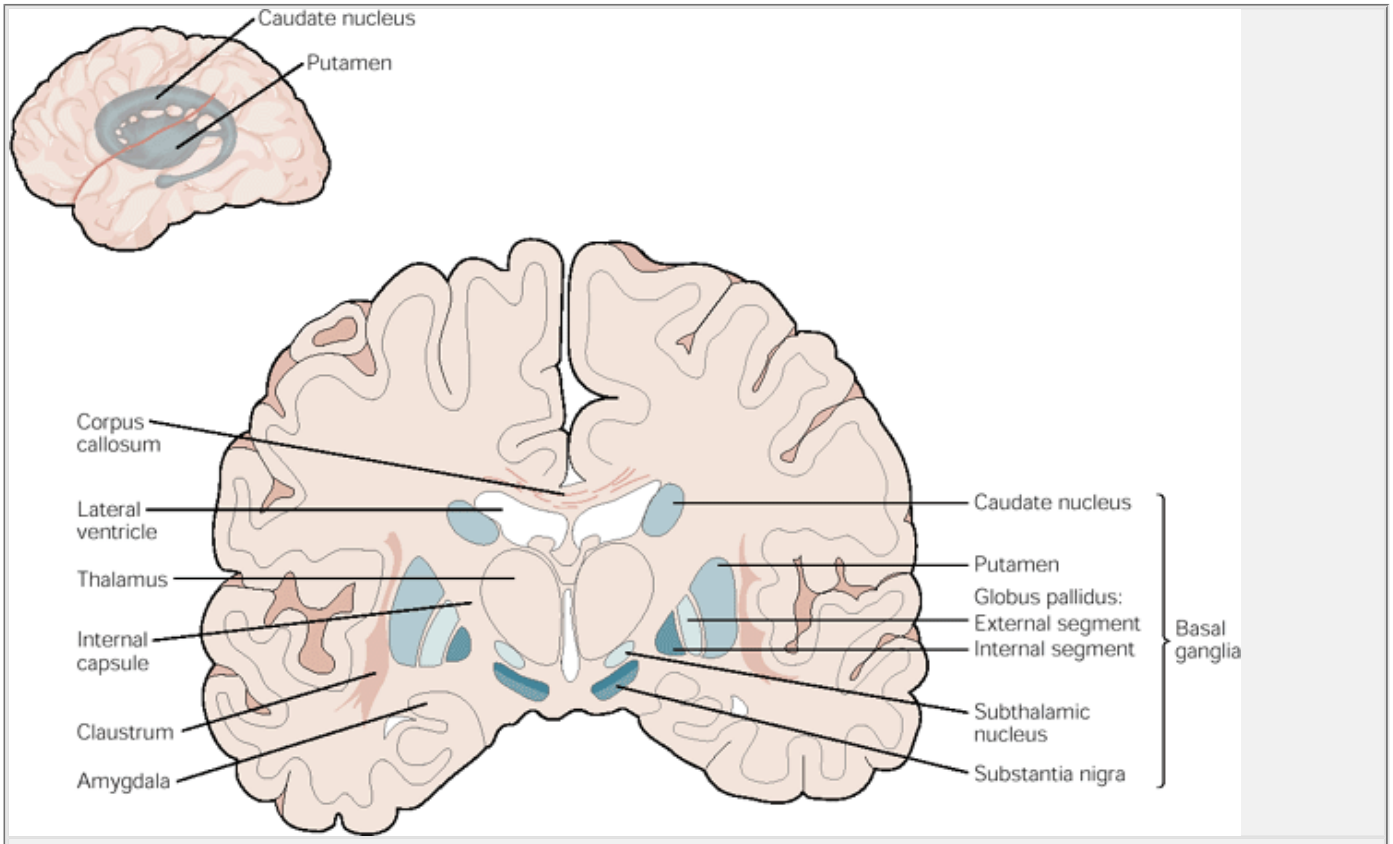

Figure 43-2 This coronal section shows the basal ganglia in relation to surrounding structures. (Adapted from Nieuwenhuys et al. 1981.)

The four principal nuclei of the basal ganglia are (1) the striatum, (2) the globus pallidus (or pallidum), (3) the substantia nigra (consisting of the pars reticulata and pars compacta), and (4) the subthalamic nucleus (Figure 43-2). The striatum consists of three important subdivisions: the caudate nucleus, the putamen, and the ventral striatum (which includes the nucleus accumbens). Except at its most anterior pole, the striatum is divided into the caudate nucleus and putamen by the *internal capsule*, a major collection of fibers that run between the neocortex and thalamus in both directions. All three subdivisions of the striatum have a common embryological origin.

The striatum is the major recipient of inputs to the basal ganglia from the cerebral cortex, thalamus, and brain stem. Its neurons project to the globus pallidus and substantia nigra. Together these two nuclei, whose cell bodies are morphologically similar, give rise to the major output projections from the basal ganglia. The globus pallidus lies medial to the putamen, just lateral to the internal capsule, and is divided into external and internal segments. The internal pallidal segment is related functionally to the pars reticulata of the substantia nigra, which lies in the midbrain on the medial side of the internal capsule. The cells of the internal pallidal segment and pars reticulata use γ-aminobutyric acid (GABA) as a neurotransmitter. Just as the caudate nucleus is separated from the putamen by the internal capsule, the internal pallidal segment is separated from the substantia nigra.

In addition to its reticular portion, the substantia nigra also has a compact zone (pars compacta). This zone is a distinct nucleus that lies dorsal to the pars reticulata although some of its neurons lie within the pars reticulata. The cells of the pars compacta are dopaminergic and also contain neuromelanin, a dark pigment derived from oxidized and polymerized dopamine. Neuromelanin, which accumulates with age in large lysosomal granules in cell bodies of dopaminergic neurons, accounts for the dark discoloration of this structure. Dopaminergic cells are also found in the ventral-tegmental area, a medial extension of the pars compacta.

The subthalamic nucleus is closely connected anatomically with both segments of the globus pallidus and the substantia nigra. It lies just below the thalamus and above the anterior portion of the substantia nigra. The glutaminergic cells of this nucleus are the only excitatory projections of the basal ganglia.

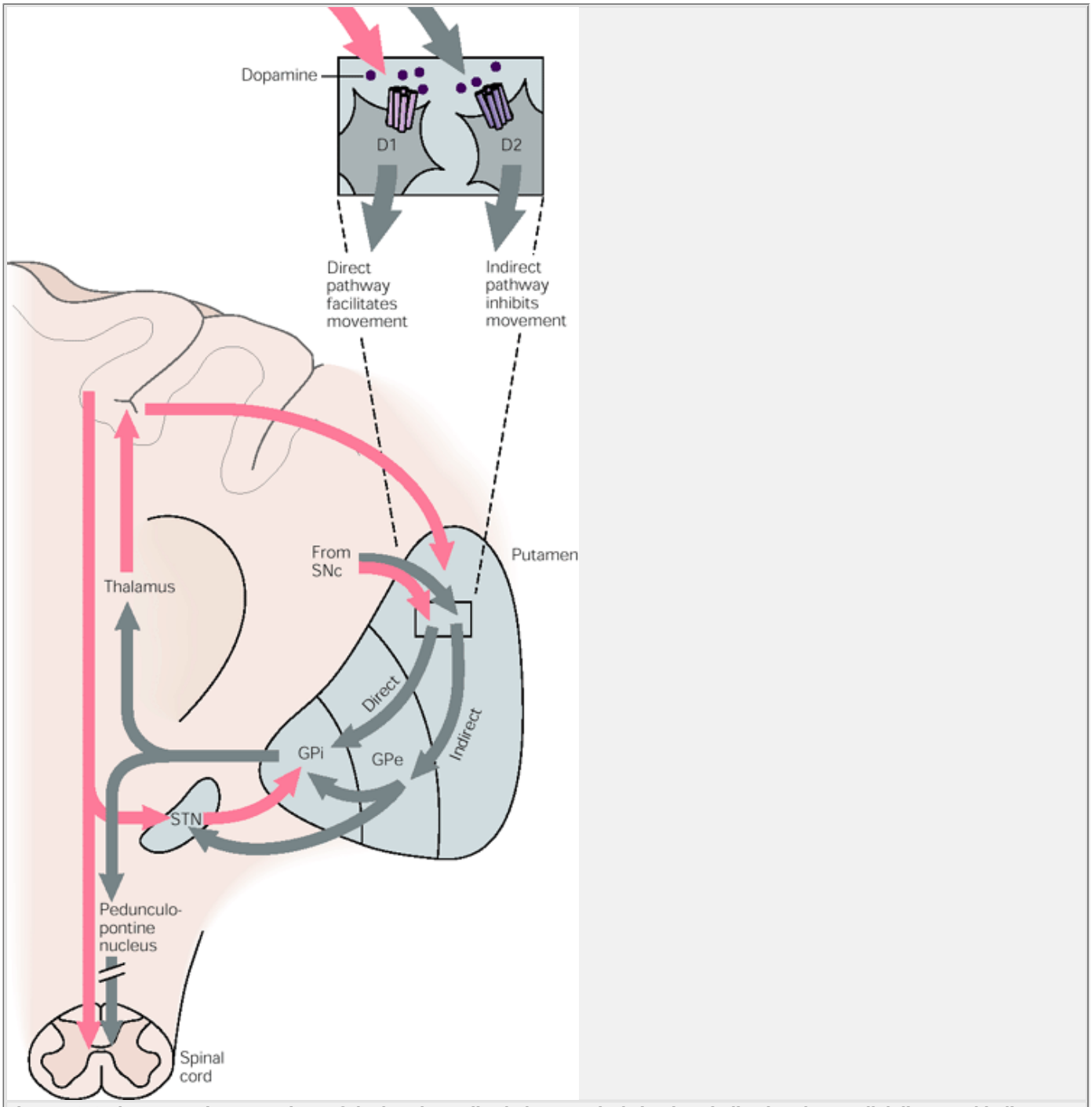

Figure 43-3 The anatomic connections of the basal ganglia-thalamocortical circuitry, indicating the parallel direct and indirect pathways from the striatum to the basal ganglia output nuclei. Two types of dopamine receptors (**D1** and **D2**) are located on different sets of output neurons in the striatum that give rise to the direct and indirect pathways. Inhibitory pathways are shown as **gray arrows;** excitatory pathways, as **pink arrows**. **GPe** = external segment of the globus pallidus; **GPi** = internal segment of the globus pallidus; **SNc** = substantia nigra pars compacta; **STN** = subthalamic nucleus.

The Striatum, the Input Nucleus to the Basal Ganglia, Is Heterogeneous in Both Its Anatomy and Function

All areas of cortex send excitatory, glutaminergic pro-jections to specific portions of the striatum. The striatum also receives excitatory inputs from the intralaminar nuclei of the thalamus, dopaminergic projections from the midbrain, and serotonergic input from the raphe nuclei.

Although the striatum appears homogeneous on routine staining, it is anatomically and functionally highly heterogeneous. It consists of two separate parts, the matrix and striosome compartments (the latter also referred to as patches). These compartments differ histochemically from one another and have different receptors. The striosome compartment receives its major input from limbic cortex and projects primarily to the substantia nigra pars compacta.

Although the striatum contains several distinct cell types, 90-95% of them are GABA-ergic medium-spiny projection neurons. These cells are both major targets of cortical input and the sole source of output. They are largely quiescent except during movement or in response to peripheral stimuli. In primates the medium-spiny neurons of the striatum can be subdivided into two groups. Those that project to the external pallidal segment express the neuropeptides enkephalin and neurotensin; those that project to the internal pallidal segment or substantia nigra pars reticulata express substance P and dynorphin.

The striatum also contains two types of local inhibitory interneurons: large cholinergic neurons and smaller cells that contain somatostatin, neuropeptide Y, or nitric oxide synthetase. Both classes of inhibitory interneurons have extensive axon collaterals that reduce the activity of the striatal output neurons. Although few in number, they are responsible for most of the tonic activity in the striatum.

The Striatum Projects to the Output Nuclei via Direct and Indirect Pathways

The two output nuclei of the basal ganglia, the internal pallidal segment and the substantia nigra pars reticulata, tonically inhibit their target nuclei in the thalamus and brain stem. This inhibitory output is thought to be modulated by two parallel pathways that run from the striatum to the two output nuclei: one direct and the other indirect. The indirect pathway passes first to the external pallidal segment and from there to the subthalamic nucleus in a purely GABA-ergic pathway, and finally from the subthalamic nucleus to the output nuclei

in an excitatory glutaminergic projection (Figure 43-3). The projection from the subthalamic nucleus is the only excitatory intrinsic connection of the basal ganglia; all others are GABA-ergic and inhibitory.

The neurons in the two output nuclei discharge tonically at high frequency. When phasic excitatory inputs transiently activate the *direct* pathway from the striatum to the pallidum, the tonically active neurons in the pallidum are briefly suppressed, thus permitting the thalamus and ultimately the cortex to be activated. In contrast, phasic activation of the *indirect* pathway transiently increases inhibition of the thalamus, as can be determined by considering the polarity of the connections between the striatum and the external pallidal segment, between the external segment and the subthalamic nucleus, and between the subthalamic nucleus and the internal pallidal segment (Figure 43-3).

Thus, the direct pathway can provide *positive* feedback and the indirect pathway *negative* feedback in the circuit between the basal ganglia and the thalamus. These efferent pathways have opposing effects on the basal ganglia output nuclei and thus on the thalamic targets of these nuclei. Activation of the direct pathway disinhibits the thalamus, thereby increasing thalamocortical activity, whereas activation of the indirect pathway further inhibits thalamocortical neurons. As a result, activation of the direct pathway facilitates movement, whereas activation of the indirect pathway inhibits movement.

The two striatal output pathways are affected differently by the dopaminergic projection from the substantia nigra pars compacta to the striatum. Striatal neurons that project directly to the two output nuclei have D1 dopamine receptors that facilitate transmission, while those that project in the indirect pathway have D2 receptors that reduce transmission.

Although their synaptic actions are different, the dopaminergic inputs to the two pathways lead to the same effect—reducing inhibition of the thalamocortical neurons and thus facilitating movements initiated in the cortex. We can now see how depletion of dopamine in the striatum, as occurs in Parkinson disease, may lead to impaired movement. Without the dopaminergic action in the striatum, activity in the output nuclei increases. This increased output in turn increases inhibition of the thalamocortical neurons that otherwise facilitate initiation of movement. Dopaminergic synapses are also found in the pallidum, the subthalamic nucleus, and the substantia nigra. Dopaminergic action at these sites, and in the cortex, could further modulate the actions of the direct and indirect pathways from the striatum.

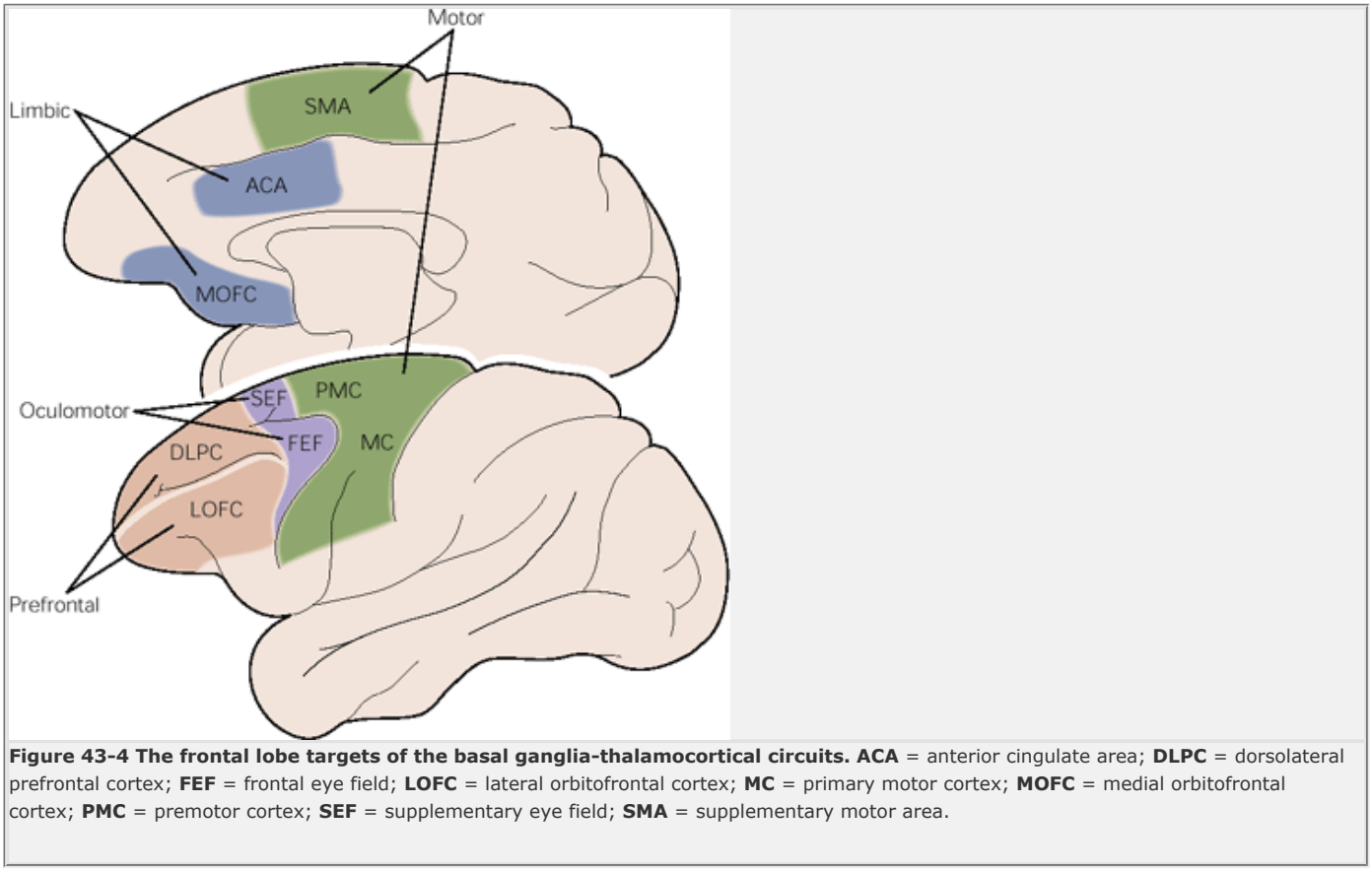

Figure 43-4 The frontal lobe targets of the basal ganglia-thalamocortical circuits. ACA = anterior cingulate area; **DLPC** = dorsolateral prefrontal cortex; **FEF** = frontal eye field; **LOFC** = lateral orbitofrontal cortex; **MC** = primary motor cortex; **MOFC** = medial orbitofrontal cortex; **PMC** = premotor cortex; **SEF** = supplementary eye field; **SMA** = supplementary motor area.

The Basal Ganglia Are the Principal Subcortical Components of a Family of Parallel Circuits Linking the Thalamus and Cerebral Cortex

The basal ganglia were traditionally thought to function only in voluntary movement. Indeed, for some time it was believed that the basal ganglia sent their entire output to the motor cortex via the thalamus and thus act as a funnel through which movement is initiated by different cortical

areas. It is now widely accepted, however, that through their interaction with the cerebral cortex the basal ganglia also contribute to a variety of behaviors other than voluntary movement, including skeletomotor, oculomotor, cognitive, and even emotional functions.

Several observations point to diversity of function. First, certain experimental and disease-related lesions of the basal ganglia produce adverse emotional and cognitive effects. This was first recognized in patients with Huntington disease. Patients with Parkinson disease also have disturbances of affect, behavior, and cognition. Second, the basal ganglia have extensive and

highly organized connections with virtually the entire cerebral cortex, as well as the hippocampus and amygdala. Finally, a wide range of motor and nonmotor behaviors have been correlated with activity in individual basal ganglia neurons in experimental animals and with metabolic activity in the basal ganglia as seen by imaging studies in humans.

The basal ganglia may be viewed as the principal subcortical components of a family of circuits linking the thalamus and cerebral cortex. These circuits are largely segregated, both structurally and functionally. Each circuit originates in a specific area of the cerebral cortex and engages different portions of the basal ganglia and thalamus. The thalamic output of each circuit is directed back to the portions of the frontal lobe from which the circuit originates. Thus, the *skeletomotor circuit* begins and ends in the precentral motor fields (the premotor cortex, the supplementary motor area, and the motor cortex); the *oculomotor circuit*, in the frontal and supplementary eye fields; the *prefrontal circuits*, in the dorsolateral prefrontal and lateral orbitofrontal cortices; and the *limbic circuit*, in the anterior cingulate area and medial orbitofrontal cortex (Figure 43-4). Each area of the neocortex projects to a discrete region of the striatum and does so in a highly topographic manner. Association areas project to the caudate and rostral putamen; sensorimotor areas project to most of the central and caudal putamen; and limbic areas project to the ventral striatum and olfactory tubercle.

The concept of segregated basal ganglia-thalamocortical circuits is a valuable anatomic and physiologic framework for understanding not only the diverse movement disorders associated with basal ganglia dysfunction but also the many-faceted neurologic and psychiatric disturbances resulting from basal ganglia disorders. Structural convergence and functional integration occur *within*, rather than between, the five identified basal ganglia-thalamocortical circuits. For example, the skeletomotor circuit has subcircuits centered on different precentral motor fields, with separate somatotopic pathways for control of leg, arm, and orofacial movements.

Within each of these subunits there may even be discrete pathways responsible for different aspects of motor processing. Injection of transsynaptically transported herpes simplex virus that is transmitted in the retrograde direction into the primary motor cortex, supplementary motor area, and lateral premotor area results in labeling of distinct populations of output neurons in the internal pallidal segment (see Figure 5-9 for technique). Virus transported in the anterograde direction was labeled in distinctly separate regions of the putamen. Given the highly topographic connections between the striatum and the pallidum and between the pallidum and the subthalamic nucleus, it is unlikely that there is significant convergence between neighboring circuits. There is, however, some anatomical evidence that the circuits converge to some degree in the substantia nigra pars reticulata.

The Skeletomotor Circuit Engages Specific Portions of the Cerebral Cortex, Basal Ganglia, and Thalamus

Since movement disorders are prominent in diseases of the basal ganglia, it is appropriate here to focus on the skeletomotor circuit. In primates the skeletomotor circuit originates in the cerebral cortex in precentral motor fields and postcentral somatosensory areas and projects largely to the putamen. The putamen is thus an important site for integration of movement related and sensory feedback information related to movement. The putamen receives topographic projections from the primary motor cortex and premotor areas, including the arcuate premotor area and the supplementary motor area. Somatosensory areas 3a, 1, 2, and 5 project in an overlapping manner to the motor portions of the putamen. Topographically organized projections from each cortical area result in a somatotopic organization of movement-related neurons in the putamen. The leg is represented in a dorsolateral zone, the orofacial region in a ventromedial zone, and the arm in a zone between the two (Figure 43-5). Each of these representations extends along virtually the entire rostrocaudal axis of the putamen. Recent anatomical and physiological data indicate that the skeletomotor circuit is further subdivided into several independent subcircuits, each centered on a specific precentral motor field.

Output neurons in the putamen project topographically to the caudoventral portions of both segments of the pallidum and to the caudolateral portions of the substantia nigra pars reticulata. In turn, the motor portions of the internal pallidal segment and substantia nigra pars reticulata send topographic projections to specific thalamic nuclei, including three ventral nuclei—the ventral lateral nucleus (pars oralis) and the lateral ventral anterior nuclei (pars parvocellularis and pars magnocellularis)—and the centromedian nucleus (see Figure 18-4 for the organization of the thalamic nuclei). The skeletomotor circuit is then closed by projections from the ventral lateral and ventral anterior (pars magnocellularis) nuclei to the supplementary motor area, from the lateral ventral anterior (pars parvocellularis) and the ventral lateral nuclei to the premotor cortex, and from

the ventral lateral and centromedian nuclei to the precentral motor fields.

Single Cell Recording Studies Provide Direct Insight into the Role of the Motor Circuits

The contribution of the basal ganglia to movement can be assessed most directly by studying the activity of neurons within the skeletomotor circuit of behaving primates, especially activity in the internal segment of the pallidum, the principal output nucleus. The onset of rapid, stimulus-triggered limb movements is proceeded first by changes in neuronal firing in the motor circuits of the cortex and only later in the basal ganglia. This sequential firing suggests that a *serial* processing occurs within the basal ganglia-thalamocortical circuits and that much of the activity within these circuits is initiated at the cortical level.

During the execution of a specific motor act, such as wrist flexion or extension, the normally high rate of spontaneous discharge in movement-related neurons in the internal pallidal segment becomes even higher in the majority of cells, but in some it decreases. Neurons that exhibit phasic decreases in discharge may play a crucial role in movement by disinhibiting the ventrolateral thalamus and thereby gating or facilitating cortically initiated movements (via excitatory thalamocortical connections). Populations of neurons that show phasic increases in discharge would have the opposite effect, further inhibiting thalamocortical neurons and thus suppressing antagonistic or competing movements.

Little is known about how movement-related signals from the direct and indirect pathways are integrated in the internal pallidal segment to control basal ganglia output. One possibility, of course, is that signals associated with a particular voluntary movement are directed over both pathways to the same population of pallidal neurons. With this arrangement, the inputs from the indirect pathway might assist in braking or

possibly smoothing the movement, while those in the direct pathway simultaneously facilitate the movement. This reciprocal regulation would be consistent with the basal ganglia's apparent role in *scaling* the amplitude or velocity of movement. Alternatively, the direct and indirect inputs associated with a particular movement could be directed to separate sets of neurons in the output nuclei of the basal ganglia. In this configuration, the skeletomotor circuit might play a dual role in modulating voluntary movements by both reinforcing the selected pattern (via the direct pathway) and suppressing potentially conflicting patterns (via the indirect pathway). This dual role could result in *focusing* the neural activity that mediates each voluntary movement in a way similar to the inhibitory surround described for various sensory systems.

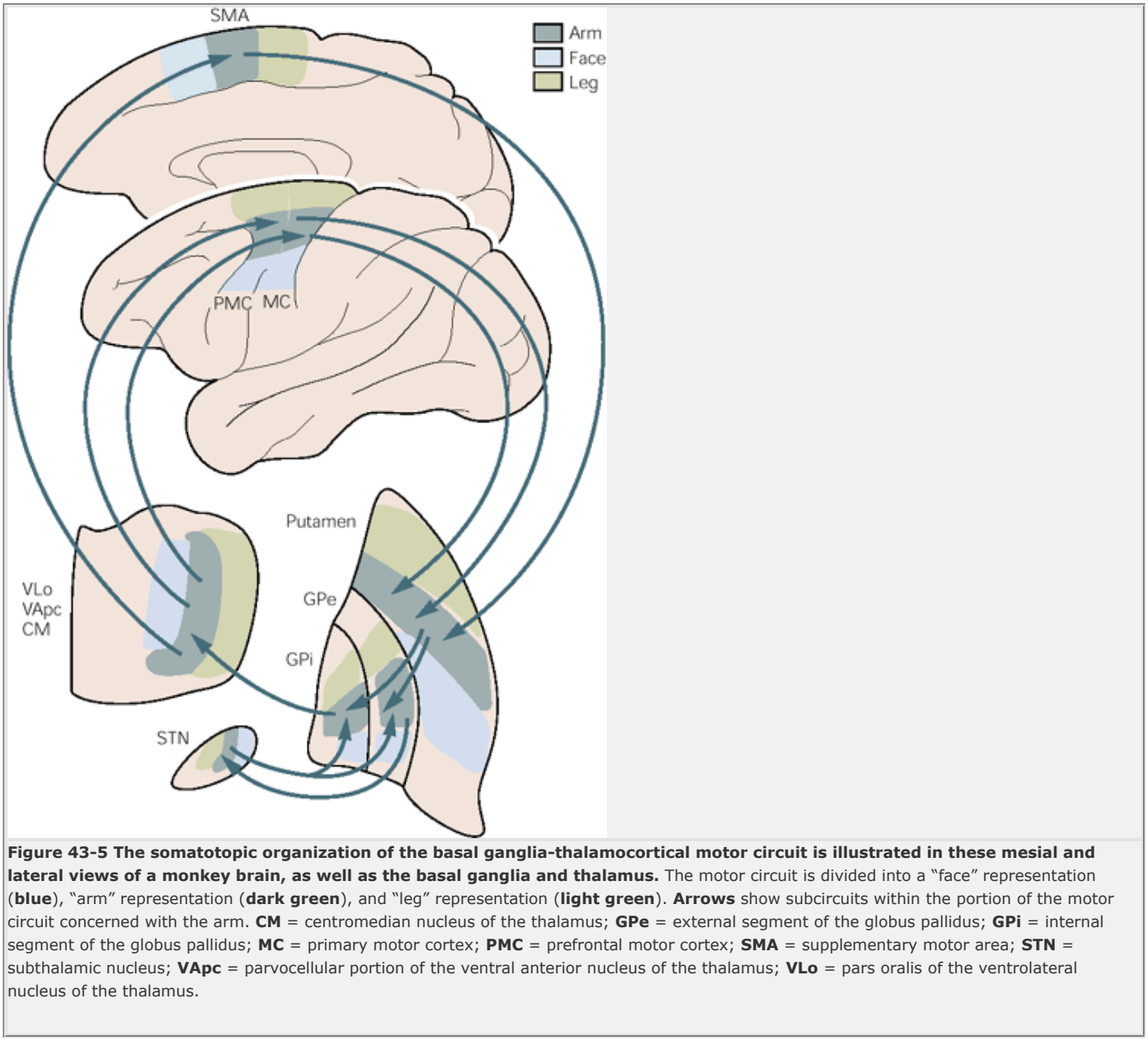

Figure 43-5 The somatotopic organization of the basal ganglia-thalamocortical motor circuit is illustrated in these mesial and lateral views of a monkey brain, as well as the basal ganglia and thalamus. The motor circuit is divided into a "face" representation (**blue**), "arm" representation (**dark green**), and "leg" representation (**light green**). **Arrows** show subcircuits within the portion of the motor circuit concerned with the arm. **CM** = centromedian nucleus of the thalamus; **GPe** = external segment of the globus pallidus; **GPi** = internal segment of the globus pallidus; **MC** = primary motor cortex; **PMC** = prefrontal motor cortex; **SMA** = supplementary motor area; **STN** = subthalamic nucleus; **VApc** = parvocellular portion of the ventral anterior nucleus of the thalamus; **VLo** = pars oralis of the ventrolateral nucleus of the thalamus.

Neuronal activity within the skeletemotor circuit has been examined in monkeys performing a variety of motor tasks. At all stages of the circuit (cortical, striatal, and pallidal) the activity of substantial proportions of movement-related neurons depends upon the direction of limb movement, independent of the pattern of muscle

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activity. These directional cells comprise 30-50% of the movement-related neurons in the supplementary motor area, motor cortex, putamen, and pallidum. All of these neurons are arranged somatotopically. In the motor cortical, but not in the basal ganglia many movement-related cells have been found whose firing does depend on the pattern of muscle activity. In trained primates, the activity in arm-related neurons of the internal pallidal segment also is clearly correlated with amplitude and velocity.

Studies combining behavioral training and single-cell recording indicate that the skeletomotor circuit is involved not only in the execution but also in the prepartion for movement. In the precentral motor fields, including the premotor cortex, supplementary motor area, and motor cortex, striking changes in discharge rate occur in some neurons after the presentation of a cue that specifies the direction of limb movement to be executed later. These changes in activity persist until the movement-triggering stimulus is presented. They thus represent a neural correlate of one of the preparatory aspects of motor control referred to as "motor set" (Chapter 38).

Directionally selective activity before movement also occurs within the putamen and the internal segment of the pallidum. Individual neurons within these structures tend to exhibit *either* preparatory (set-related) or movement-related responses, suggesting that the preparation and execution of motor action are mediated by separate subchannels in the skeletomotor circuit. In the internal segment of the pallidum subpopulations of neurons that receive input from the supplementary motor area tend to exhibit set-like preparatory responses. However, neurons receiving inputs from the motor cortex tend to exhibit phasic, movement-related responses. These different response patterns further support the idea that the skeletomotor circuit is composed of distinct subcircuits that connect to different precentral motor fields (motor cortex, supplementary motor area, and arcuate premotor area). These subcircuits may have distinctive roles in motor control and in the pathogenesis of

specific motor signs and symptoms that occur in Parkinson disease and other diseases of the basal ganglia.

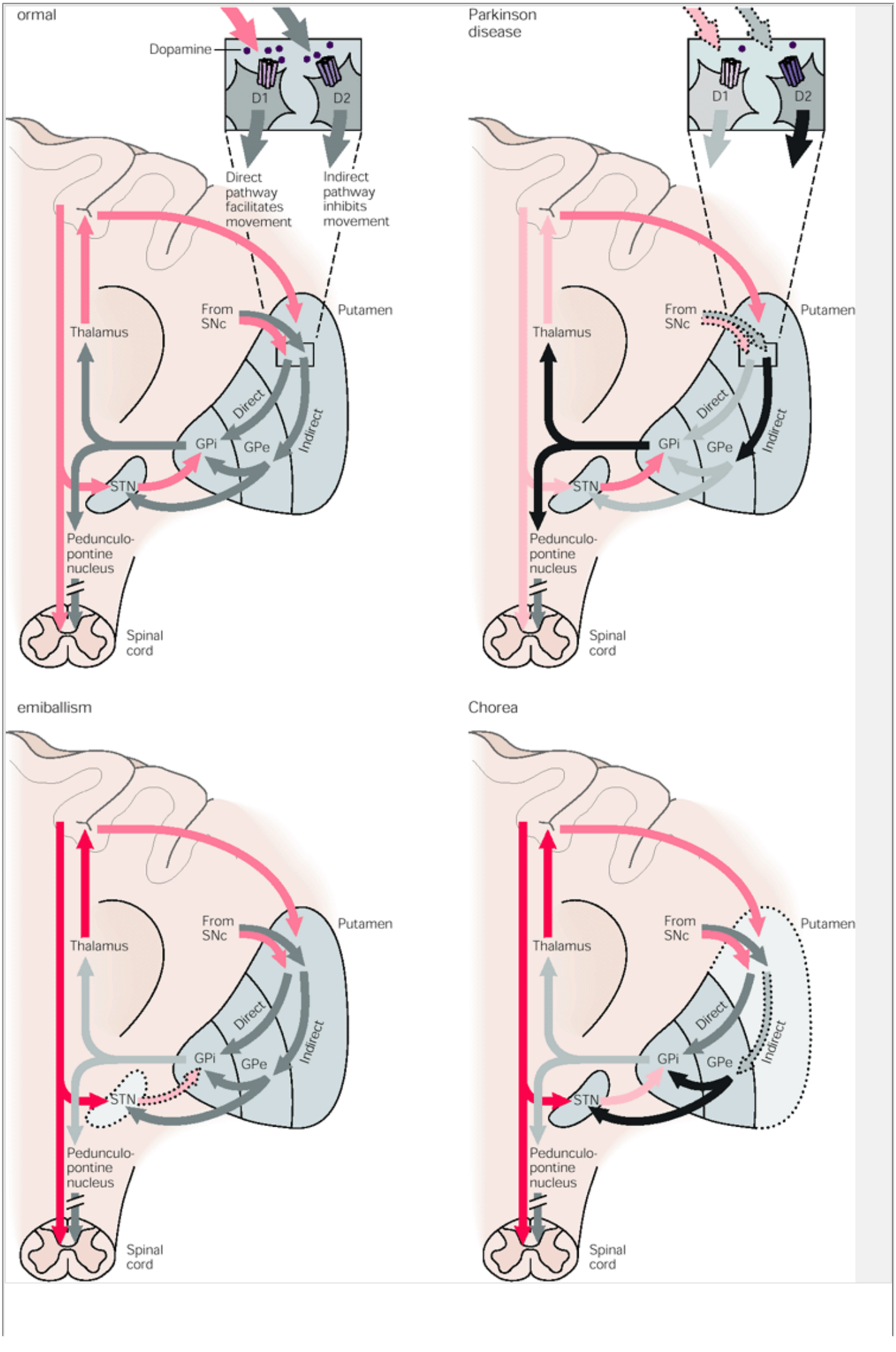

Figure 43-6 (Opposite) The basal ganglia-thalamocortical circuitry under normal conditions and in Parkinson disease, hemiballism, and chorea. Inhibitory connections are shown as gray and black arrows; excitatory connections, as pink and red. Degeneration of the nigrostriatal dopamine pathway in Parkinson disease leads to differential changes in activity in the two striatopallidal projections, indicated by changes in the darkness of the connecting arrows (**darker arrows** indicate increased neuronal activity and **lighter arrows**, decreased activity). Basal ganglia output to the thalamus is increased in Parkinson disease and decreases in ballism and chorea. **GPe** = external segment of the globus pallidus; **Gpi** = internal segment of the globus pallidus; **SNc** = substantia nigra pars compacta; **STN** = subthalamic nucleus.

Studies of the Oculomotor Circuit Provided Important Insight Into How the Skeletomotor Circuit Operates

The oculomotor circuit is involved in the control of saccadic eye movements. It originates in the frontal and supplementary motor eye fields and projects to the body of the caudate nucleus. The caudate nucleus in turn projects via the direct and indirect pathways to the lateral portions of the substantia nigra pars reticulata, which projects back to the frontal eye fields as well as to the superior colliculus. Inhibition of tonic activity in the substantia nigra pars reticulata disinhibits output neurons in the deep layers of the superior colliculus whose activity is associated with saccades. Inactivation of neurons in the pars reticulata results in involuntary saccades to the contralateral side. These observations provided the critical clue that the skeletomotor circuit might similarly disinhibit thalamocortical neurons phasically during movement, thus facilitating the intended movement.

Some Movement Disorders Result From Imbalances in the Direct and Indirect Pathways in the Basal Ganglia

Considerable progress has been made in understanding the mechanisms underlying the major movement disorders of the basal ganglia. *Hypokinetic disorders* (of which Parkinson disease is the best-known example) are characterized by impaired initiation of movement *(akinesia)* and by a reduced amplitude and velocity of voluntary movement (*bradykinesia*). They are usually accompanied by muscular rigidity (increased resistance to passive displacement) and tremor.

Hyperkinetic disorders (exemplified by Huntington disease and hemiballismus) are characterized by excessive motor activity, the symptoms of which are involuntary movements (*dyskinesias*) and decreased muscle tone (*hypotonia*). The involuntary movements may take several forms—slow, writhing movements of the extremities (athetosis); jerky, random movements of the limbs and orofacial structures (chorea); violent, large-amplitude, proximal limb movements (ballism), and more sustained abnormal postures and slower movements with underlying cocontraction of agonist and

antagonist muscles (dystonia). Various types of involuntary movements often occur in combination and some appear to have a common underlying cause. The best example is the similarity between chorea and ballism, which may simply be distal (chorea) or proximal (ballism) forms of the same underlying disorder.

In recent years the development of primate models of both hypo- and hyperkinetic disorders, induced by systemic or local administration of selective neurotoxins, has made it possible to study some of the pathophysiologic mechanisms underlying this diverse symptomatology. Both extremes of the movement disorder spectrum can now be explained as specific disturbances within the basal ganglia-thalamocortical motor circuit. Normal motor behaviors depend on a critical balance between the direct and indirect pathways from the striatum to the pallidum. In the simplest of terms, overactivity in the indirect pathway relative to the direct pathway results in hypokinetic disorders, such as Parkinson disease; underactivity in the indirect pathway results in chorea and ballism (Figure 43-6).

Overactivity in the Indirect Pathway Is a Major Factor in Parkinsonian Signs

Parkinson disease, first described by James Parkinson in 1817, is one of the most common movement disorders, affecting up to one million people in the United States alone. It is also one of the most studied and best understood. Parkinson's description still captures the characteristic posture and movements of the patients with this disease:

…involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported, with a propensity to bend the trunk forwards, and to pass from a walking to a running pace, the senses and intellects being uninjured.

The cardinal symptoms of the disease include a paucity of spontaneous movement, akinesia, bradykinesia, increased muscle tone (rigidity), and a characteristic tremor (4-5 per second) at rest. A shuffling gait as well as flexed posture and impaired balance are also prominent. The appearance of the typical patient with Parkinson disease is instantly recognizable and unforgettable: tremor, mask-like facial expression, flexed posture, and paucity and slowness of movement.

Parkinson disease is the first example of a brain disorder resulting from a deficiency of a single neurotransmitter. In the mid 1950s Arvid Carlson showed that 80% of the brain's dopamine is in the basal ganglia. Next, Oleh Horynekiewicz found that the brains of patients with Parkinson disease are deficient in dopamine, in the striatum, most severely in the putamen. In the early 1960s Parkinson disease was shown to result largely from the degeneration of dopaminergic neurons in the substantia nigra pars compacta. Walter Brikmayer and Horynekiewicz found that intravenous adminis-tration of L-dihydroxyphenylalanine (L-DOPA), the precursor of dopamine, provided a dramatic, although brief, reversal of symptoms. The subsequent demonstration by George Cotzias that gradual increases in oral administration of L-DOPA could provide significant and continuous benefit began the modern era of pharmacologic therapy. Even with the development of newer and more effective antiparkinsonian drugs, the benefits of drug therapy usually begin to wane after about five years; and troublesome side effects develop in the form of motor response fluctuations and drug related dyskinesias.

Research in Parkinson disease was recently revitalized by William Langston's discovery that drug addicts exposed to the meperidine derivative 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) develop a profound Parkinsonian state. This observation led to intense investigation of the role of exogenous toxins in the pathogenesis of Parkinson disease and to the development of a nonhuman primate animal model for experimental study. Primarily on the basis of studies in MPTP-treated primates, a working model of the pathophysiology of Parkinson disease has been developed. According to this model, loss of dopaminergic input from the substantia nigra pars compacta to the striatum leads to increased

activity in the indirect pathway and decreased activity in the direct pathway (see Figure 43-6) because of the different actions of dopamine on the two pathways (via D1 and D2 receptors, respectively). Both of these changes lead to increased activity in the internal pallidal segment, which results in increased inhibition of thalamocortical and midbrain tegmental neurons and thus the hypokinetic features of the disease.

Experiments with MPTP-treated monkeys have shown significant changes in neuronal activity along the indirect pathway. For example, microelectrode recording studies have shown that tonic activity is decreased in the external pallidal segment but increased in the subthalamic nucleus and internal pallidal segment. The changes in tonic discharge in the pallidum (and the abnormal motor signs) are reversed by systemic administration of the dopamine receptor agonist apomorphine. The excessive activity in the indirect pathway at the subthalamic nucleus appears to be an important factor in the production of parkinsonian signs, since lesioning of the subthalamic nucleus, which reduces the excessive

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excitatory drive on the internal pallidal segment, markedly ameliorates parkinsonian signs in MPTP-treated monkeys. Selective inactivation of the *sensorimotor* portion of either the subthalamic nucleus or the internal pallidal segment is sufficient to ameliorate the cardinal parkinsonian motor signs (akinesia, tremor, and rigidity) in MPTP-treated animals (Figure 43-7). Surgical lesions of the posterior (sensorimotor) portion of the internal pallidal segment (pallidotomy) in patients with advanced, medically intractable cases of Parkinson disease is also highly effective in reversing parkinsonian signs. Pallidotomy has undergone a revival in recent years as an effective treatment of patients with advanced disease whose symptoms are poorly controlled by medication alone and who experience drug-induced motor complications (as will be further discussed later).

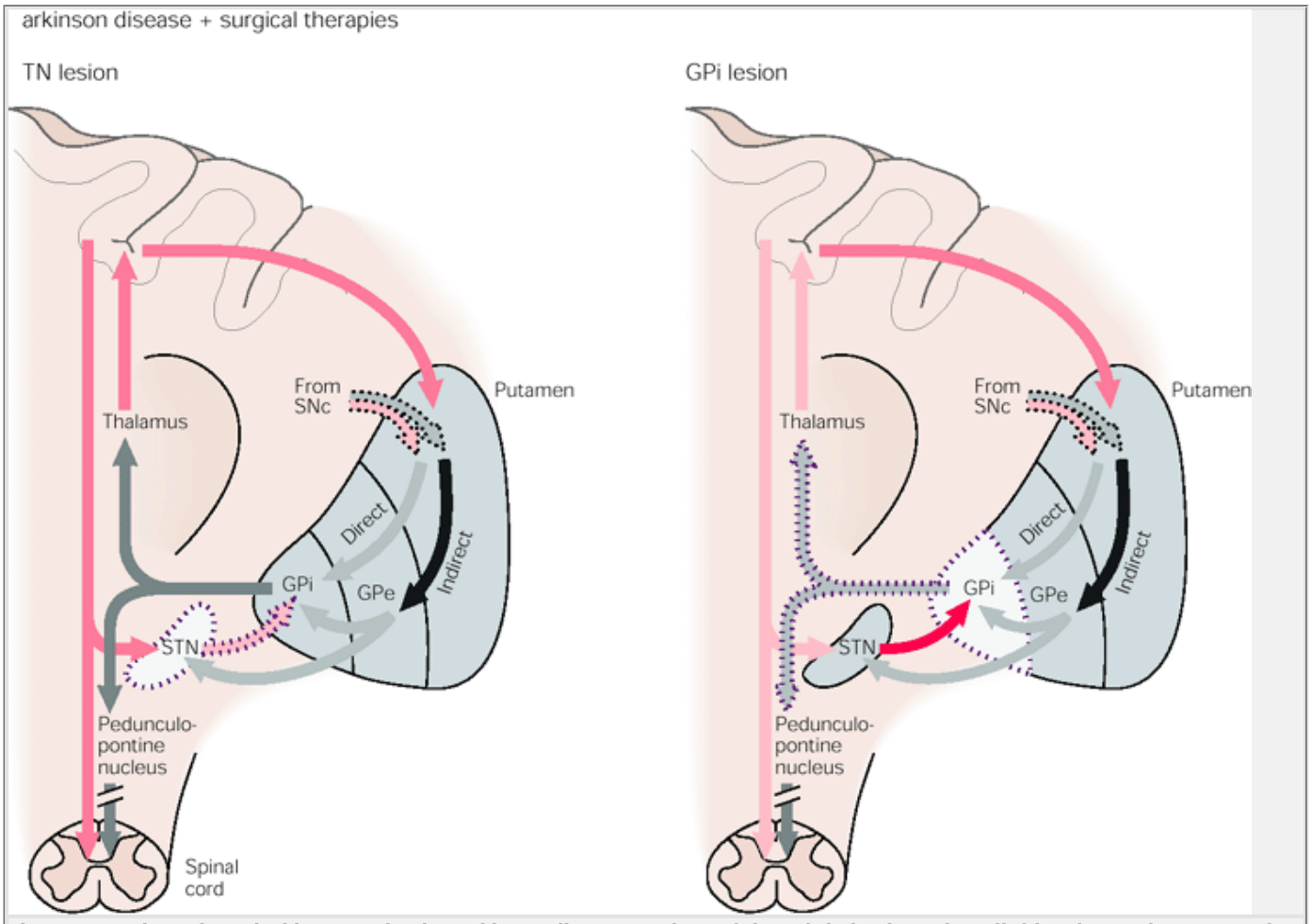

Figure 43-7 Sites of surgical intervention in Parkinson disease. Lesions of the subthalamic nucleus (left) or internal segment of the globus pallidus (right) effectively reduce parkinsonian signs and dyskinesias by respectively normalizating or eliminating abnormal and excessive output from the internal pallidal segment. GPe = external segment of the globus pallidus; GPi= internal segment of the globus pallidus; STN = subthalmic nucleus; SNc = substantia nigra pars compacta.

Thus the hypokinetic features of Parkinson disease appear to result from increased (inhibitory) output from the internal pallidal segment as a result of increased (excitatory) drive from the subthalamic nucleus. Accordingly akinesia and bradykinesia are no longer viewed as negative signs that reflect loss of basal ganglia function, but rather as positive signs that, like rigidity and tremor, result from excessive and abnormal activity in intact structures. This abnormal motor activity can be reversed by reducing or abolishing the pathological output.

In addition to the increase in tonic output of the internal pallidal segment in MPTP-treated monkeys, phasic activity also changes. These changes in the *pattern* of discharge in basal ganglia output are likely to be equally as important as the changes in the rate of discharge. Indeed, recent data suggest that tremor may be due to

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increased synchronization of oscillatory discharge within the basal ganglia nuclei. Differences in spatial temporal patterns and discharge may account for differences in clinical features among the various hyper- kinetic disorders.

The Level of Dopamine in the Basal Ganglia Is Decreased in Parkinson Disease

Measurements of dopamine in the striatum and the metabolic activity of individual basal ganglia nuclei in patients with Parkinson disease are consistent with the pathophysiologic model proposed. Uptake of dopamine in the putamen of these patients is greatly reduced, as assessed

earlier by direct biochemical assays and more recently by uptake of the precursor ^{18}F-DOPA measured by positron emission tomography (PET) (see Chapter 19). Imaging of patients with Parkinson disease has shown less synaptic activity (as measured by activated blood flow in the contralateral putamen, the anterior cingulate, the supplementary motor area, and the dorsolateral prefrontal cortex) both when the patients were moving a joystick and when they were resting. Administration of dopamine agonists increased the blood flow to the supplementary motor and anterior cingulate areas during movement tests. Surgical destruction of the pallidum in patients with Parkinson disease has been shown to restore activity in the supplementary motor and premotor areas during this same movement task. These neuroimaging studies lend strong additional support to the importance of the pallidothalamocortical portion of the motor circuit in normal movement and the production of akinesia and bradykinesia.

Underactivity in the Indirect Pathway Is a Major Factor in Hyperkinetic Disorders

Involuntary movements in patients with basal ganglia disorders may result either from clear-cut lesions of these nuclei or from imbalances in neurotransmitter systems. Apart from parkinsonism, the basal ganglia disorder for which the neuropathology is least in doubt is hemiballism. In humans, lesions (usually due to small strokes) restricted to the subthalamic nucleus may result in involuntary, often violent, movements of the contralateral limbs (called "ballism" because of the superficial resemblance of the movements to throwing). In addition to the involuntary movements of the proximal limbs, involuntary movements of more distal limbs may occur in an irregular (choreic) or more continuous writhing form.

Experimental lesions of the subthalamic nucleus in monkeys show that dyskinesias result only when lesions are made selectively in the nucleus, leaving intact the adjacent projections from the internal pallidal segment to the thalamus. More recent studies combining selective lesioning, microelectrode recording, and functional imaging provide new insights into the pathophysiology of ballism and the hyperkinetic disorders in general. The output of the internal pallidal segment is *reduced* in hemiballism, as expected if the projection from the subthalamic nucleus is excitatory. Experimental lesions of the subthalamic nucleus in monkeys significantly reduce the tonic discharge of neurons in the internal pallidal segment and decrease the phasic responses of these neurons to limb displacement. Thus hemiballism may result from disinhibition of the thalamus due to reduction in the tonic (and perhaps phasic) output from the internal pallidal segment. Reduced inhibitory input from the internal pallidal segment might permit thalamocortical neurons to respond in an exaggerated manner to cortical or other inputs, or it might increase the tendency of these neurons to discharge spontaneously, leading to involuntary movements. Alternatively, a changed discharge pattern (rather than lowered rate per se) may play a significant role. Consistent with this idea, pallidotomy relieves hemiballism and other forms of dyskinesia, as well as parkinsonian signs.

Huntington Disease Is a Heritable Hyperkinetic Disorder

The other hyperkinetic disorder most often associated with dysfunction of the basal ganglia is Huntington disease. This disease affects men and women with equal frequency, about 5-10 per 100,000. It is characterized by five features: heritability, chorea, behavioral or psychiatric disturbances, cognitive impairment (dementia), and death 15 or 20 years after onset. In most patients the onset of the disease occurs in the third to fifth decade of life. Many people have already had children by the time the disease is diagnosed.

The Gene for Huntington Disease Has Been Identified

Huntington disease is one of the first complex human disorders to be traced to a single gene, which was identified by mapping genetic polymorphisms (see Box 3-3). The disease is a highly penetrant, autosomal dominant disorder with a gene defect on chromosome 4. This gene encodes a large protein, huntingtin, the function of which has yet to be determined (Chapter 3). The protein normally is located in the cytoplasm. As we have seen

in Chapter 3, the first exon of the gene contained repeats of the trinucleotide sequence CAG, which encodes the amino acid glutamine. Whereas normal subjects have less than 40 CAG repeats in the first exon, patients with Huntington disease have more than 40 repeats. Those that have between 70 and 100 repeats develop Huntington disease as juveniles. Once expanded beyond 40 copies, the repeats become unstable and tends to increase from generation to generation, a phenomenon which accounts for genetic "anticipation," the earlier onset of the disease in the offspring than in the parent.

To determine why the CAG repeats in the first exon caused disease, the first exon from the mutant human huntingtin protein has been expressed in mice where it was found to be sufficient to cause a progressive neurological phenotype. In these mice, exon formed multiple intranuclear inclusions made up of the huntingtin protein. A similar accumulation of huntingtin protein has now been found in the nuclei of brain cells from patients with Huntington disease.

A *Drosophila* model of Huntington disease has been developed by expressing an amino terminal fragment of the human huntingtin protein containing 2, 75, and 120 repeating glutamine residues. By expressing this fragment in photoreceptor neurons of the compound eye of the fly the polyglutamine-expanded huntingtin induced neuronal degeneration much as it does in human neurons. The age on the onset and severity of the neuronal degeneration again correlated with the length of the repeat, and the nuclear localization of huntingtin again presaged neuronal degeneration.

Finally, a cellular model of Huntington disease has been created by transfecting the mutant Huntington's gene into cultured striatal neurons. Here the gene induced neurodegeneration by an apoptotic mechanism, consistent with the idea that the Huntington protein acts in the nucleus to induce apoptosis. Blocking nuclear localization of the mutant huntingtin suppresses its ability to form intranuclear inclusions and to induce apoptosis. However, this apoptotic death did not correlate with the formation of intranuclear inclusions. Full length huntingtin forms inclusions very rarely, raising the possibility that intranuclear inclusions may not play a causal role in mutant huntingtin's induced death. In fact, exposure of transfected striatal neurons to conditions that suppressed the formation of inclusions resulted in an increase in huntingin-induced death. These findings suggests that mutant huntingtin may act within the nucleus to induce neurodegeneration, but that the intranuclear inclusions themselves may reflect a defense mechanism designed to protect against the death induced by huntingtin rather than reflecting a mechanism of cell death.

Although Huntington disease is characterized by widespread loss of neurons in the brain, the pathology is seen earliest in the striatum. A common mechanism appears to underlie both the choreiform movements of Huntington disease and the dyskinetic movements in hemiballism. Striatal neurons that give rise to the indirect pathway are preferentially lost. As a result, the inhibition of neurons in the external pallidum is reduced, causing excessive discharge of these neurons and inhibition of subthalamic nucleus neurons. The resulting *functional* inactivation of the subthalamic nucleus could explain the choreiform symptoms that, in the early stages of the disease, resemble those seen in hemiballism. The

rigidity and akinesia in advanced Huntington disease are associated with the loss of the striatal neurons that project to the internal pallidal segment. This loss would reduce inhibition in the internal pallidal segment and thus increase firing in these neurons.

Drug-induced dyskinesias, which closely resemble chorea, are a side effect of dopamine replacement therapy for Parkinson disease. The pathophysiology of these pharmacologically induced dyskinesias may be in part similar to that of chorea in Huntington disease: excessive dopaminergic inhibition of the striatal neurons that project to the external pallidal segment, leading to reduced inhibition of external pallidal neurons and excessive inhibition of the subthalamic nucleus by overactive neurons in the external pallidal segment. The decrease in activity in the subthalamic nucleus would lower the output from the internal pallidal segment in a manner similar to that seen after direct inactivation of the subthalamic nucleus by surgical lesions. This decreased excitatory drive on the internal pallidal segment would be compounded by excessive dopaminergic stimulation of striatal neurons of the direct pathway and the resulting increased inhibitory input to the internal pallidum. Since administration of L-DOPA does not produce dyskinesias in normal individuals or in patients with Parkinson disease early in the course of therapy, the symptoms probably result from receptor upregulation, supersensitivity, and altered gene expression caused by prolonged administration of the drug. Intermittent dosing of L-DOPA appears to be a significant factor in the emergence of drug-induced dyskinesias.

Glutamate-Induced Neuronal Cell Death Contributes to Huntington Disease

Glutamate is the principal excitatory transmitter in the central nervous system. It excites virtually all central neurons and is present in nerve terminals at high concentration (10^{-3} M). In normal synaptic transmission the extracellular glutamate rises transiently, and this

rise is restricted to the synaptic cleft. In contrast, sustained and diffuse increases in extracellular glutamate kill neurons. This mechanism of cell death occurs primarily by the persistent action of glutamate on the *N*-methyl-D-aspartate (NMDA) type of glutamate receptors and the resulting excessive influx of Ca^{2+} (Chapter 12). Excess Ca^{2+} has several damaging consequences that lead to cytotoxicity and death. First, it can activate calcium-dependent proteases (calpains). Second, Ca^{2+} activates phospholipase A_2, which liberates arachidonic acid, leading to the production of eicosanoids, substances that produce inflammation and free radicals that cause tissue damage.

Toxic changes produced by glutamate, called *glutamate excitotoxicity*, are thought to cause cell damage and death after acute brain injury such as stroke or excessive convulsions. In addition, excitotoxicity may contribute to chronic degenerative diseases of the brain, such as Huntington disease. It has been shown that injection of NMDA agonists into the rat striatum reproduces the pattern of neuronal cell loss characteristic of Huntington disease. Thus, it is possible that the altered gene on chromosome 4 produces an abnormality that leads to excessive activation of NMDA receptors or release of glutamate.

The Basal Ganglia Also Have a Role in Cognition, Mood, and Nonmotor Behavior Function

Some circuits in the basal ganglia are involved in nonmotor aspects of behavior. These circuits originate in the prefrontal and limbic regions of the cortex and engage specific areas of the striatum, pallidum, and substantia nigra.

The *dorsolateral prefrontal circuit* originates in Brodmann's areas 9 and 10 and projects to the head of the caudate nucleus, which then projects directly and indirectly to the dorsomedial portion of the internal pallidal segment and the rostral substantia nigra pars reticulata. Projections from these regions terminate in the ventral anterior and medial dorsal thalamic nuclei, which in turn project back upon the dorsolateral prefrontal area. The dorsolateral prefrontal circuit has been implicated broadly in so-called "executive functions" (Chapter 19). These include cognitive tasks such as organizing behavioral responses and using verbal skills in problem solving. Damage to the dorsolateral prefrontal cortex or subcortical portions of the circuit is associated with a variety of behavioral abnormalities related to these cognitive functions.

The *lateral orbitofrontal circuit* arises in the lateral prefrontal cortex and projects to the ventromedial caudate nucleus. The pathway from the caudate nucleus follows that of the dorsolateral circuit (through the internal pallidal segment and substantia nigra pars reticulata and thence to the thalamus) and returns to the orbitofrontal cortex. The lateral orbitofrontal cortex appears to play a major role in mediating empathetic and socially appropriate responses. Damage to this area is associated with irritability, emotional lability, failure to respond to social cues, and lack of empathy. A neuro-psychiatric disorder thought to be associated with disturbances in the lateral orbitofrontal cortex and circuit is obsessive-compulsive disorder (Chapter 61).

The *anterior cingulate* circuit arises in the anterior cingulate gyrus and projects to the ventral striatum. The ventral striatum also receives "limbic" input from the hippocampus, amygdala, and entorhinal cortices. The projections of the ventral striatum are directed to the ventral and rostromedial pallidum and the rostrodorsal substantia nigra pars reticulata. From there the pathway continues to neurons in the paramedian portion of the medial dorsal nucleus of the thalamus, which in turn project back upon the anterior cingulate cortex. The anterior cingulate circuit appears to play an important role in motivated behavior, and it may convey reinforcing stimuli to diffuse areas of the basal ganglia and cortex via inputs through the ventral tegmental areas and the substantia nigra pars compacta. These inputs may play a major role in procedural learning (see Chapter 62). Damage to the anterior cingulate region bilaterally can cause akinetic mutism, a condition characterized by profound impairment of movement initiation.

In general, the disorders associated with dysfunction of the prefrontal cortex and corticobasal ganglia-thalamocortical circuits involve action rather than of perception or sensation. These disturbances are associated both with either intensified action (impulsivity) and flattened action (apathy). Obsessive-compulsive behavior can be viewed as a form of hyperactivity. The disturbances of mood associated with circuit dysfunction are believed to span the extremes of mania and depression. Both dopamine and serotonin, two biogenic amines that modulate neuronal activity within the circuits, are important to depression (Chapter 61).

These observations suggest that the neural mechanisms underlying complex behavioral disorders might be analogous to the dysfunctions of the motor circuits described in this chapter. Thus, schizophrenia might be viewed as a "Parkinson disease of thought." By this analogy, schizophrenic symptoms would arise from disordered modulation of prefrontal circuits. Other cognitive and emotional symptoms may similarly be equivalents of motor disturbances such as tremor, dyskinesia, and rigidity.

An Overall View

In 1949 Linus Pauling revolutionized medical thinking by coining the term "molecular disease." He and his collaborators observed the altered electrophoretic mobility of hemoglobin S and reasoned that sickle cell anemia, a disease known to be genetic, could be explained by a mutation of a gene for a specific protein. A decade later Vernon Ingram showed that this alteration in charge occurs in the amino acid sequence of hemoglobin S, where a glutamic acid residue is replaced by a valine. This change from a single negatively charged residue in normal hemoglobin to a neutral one explains the altered molecular properties of hemoglobin S, and these in turn account for the intermolecular differences and disordered cell stacking observed in sickled red cells. Thus, a single molecular change is fundamental to understanding the patient's pathology, symptoms, and prognosis.

While the explanation for other diseases may not be as simple, it is a fundamental principle of modern medicine that every disorder has a molecular basis. Research in Parkinson disease and myasthenia gravis first made the medical community realize that particular components of chemical synapses can be specific targets for disease. In myasthenia gravis the molecular target is the acetylcholine receptor. In the disorders of the basal ganglia some components of the synthesis, packaging, or turnover of dopamine and serotonin are altered. The causes of the pathological alterations of these loci, whether genetic, infectious, toxic, or degenerative, are not yet known. Although we have identified the mutant gene for Huntington disease, as yet we have no idea about the function of the protein that the wild-type gene encodes. It is clear that rational treatment for diseases of transmitter metabolism requires a good understanding of synaptic transmission in the affected pathways.

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