CHAPTER 8
SKELETOMOTOR CONTROL

KEY THEMES

- Motor control is governed by three principal circuits: the corticospinal system that carries efferent motor commands from motor cortex to the spinal circuits that carry out motor commands; and the cortico-cerebellar and cortico-basal ganglia systems, each of which processes copies of the efferent signal and feeds back to motor cortex so as to refine and/or facilitate future actions.
- The motor cortex plans and generates commands in abstract x,y,z coordinates, and the spinal cord translates these commands (often nonlinearly) into a set of muscle tensions needed to carry out the action.
- Despite its generally homuncular functional topography, primary motor cortex differs from sensory analogues in that its representation of the body surface is not highly precise, and it also represents actions that are not tied to any one part of the body.
- M1 neurons have relatively broad tuning, and precise control of movement is achieved via population coding – the summation of input from thousands of units firing at varying intensities.
- Electrophysiological and microstimulation evidence that PPC neurons contribute to planning and execution of eye movements and reaches, combined with neuropsychological evidence, have been taken as evidence that a core function of PPC may be to determine *how* visual information can be used to guide behavior.
- The unique wiring of the cerebellum makes it a key neural substrate for motor learning, fine-tuning ongoing movements, and, perhaps, encoding and refining cognitive models of the world.
- The cortico-basal ganglia-thalamic circuits integrate information from many cortical territories and use the output to gate frontal cortex activity.
- Common principles of network and neurochemical dynamics (including a key role for dopamine [DA]) across "affective," "cognitive," and "motoric" basal ganglia systems suggest that many principles of motor control generalize to these other domains of behavior.
- The acquisition and modification of stereotyped sequences of movements, including what we think of as habits, rely on principles of reinforcement learning.
- The discovery of mirror neurons in premotor cortex (PMC) has generated intriguing theories ranging from the understanding of actions and intentions of others, to atypical neurological development (e.g., autism spectrum disorder [ASD]), to the evolution of human culture.

CONTENTS

Our introduction to the frontal lobes came in *Chapter 1*, where we considered a nineteenth-century breakthrough in thinking about how the brain controls movement of the body, and one relating to the production of speech. The former is most relevant here. The observations of the neurologist Jackson gave rise to the idea of a somatotopic organization of the brain system controlling movement in the human. The electrical stimulation experiments of Fritsch and Hitzig indicated that motor cortex, in the dog, was localized to frontal cortex, and that distinct **motor effectors** contralateral to stimulation sites were represented by discrete regions within this lobe. In addition to fleshing out more detail about the structure and function of the motor system, this chapter will introduce many concepts related to the control of action that will be highly germane to many of the remaining topics to be covered in this book, including *cognitive control*, *decision making*, *language*, *social behavior*, and *consciousness*. Indeed, some have argued that much of our thought and behavior, no matter how abstract and "high level," can be construed as more-or-less abstract implementations of the same principles of motor control that we will consider in detail in this chapter.

THE ORGANIZATION OF THE MOTOR SYSTEM

The anatomy of the motor system

Primary motor cortex (M1) occupies the anterior bank of the central sulcus and the caudal portion of the precentral gyrus, a region classified as BA 4 that stretches from the medial wall of the hemisphere to the dorsal lip of the Sylvian fissure. In loose analogy to cortical sensory systems, there are two adjacent motor-related fields with "second-level functions," both sharing BA 6: the premotor cortex (PMC) of the rostral half of the precentral gyrus and the supplementary motor area (SMA) located superior to PMC and rostral to the superior-most and medial portions of M1. Unlike with sensory systems, however, the functions of M1, PMC, and SMA aren't as hierarchically organized as are, say, V1, V2, and MT. For example, each of these three motor areas sends projections from cortex to the areas of the spinal cord that directly trigger movement. (Thus, for simplicity, when describing general properties that apply to each, the term "motor cortex" will be used to refer nonspecifically to M1, PMC, and SMA.)

The motor cortices are a central hub in three circuits that carry action-related signals. The fibers carrying the signals that descend along the ventral spinal cord to trigger movements of the body are called **motor efferents**. The other two carry copies of these motor signals, but are considered **recurrent circuits** (often called "loops") in that they eventually feed back onto the frontal cortex. They implement the principle of **efference copy**, whereby a copy of the efferent signal can be used to, for example, compare the intended outcome of the outgoing motor command against information about the actual outcome (conveyed by ascending sensory signals) and, if the two don't match up, send a corrective signal back to the motor cortex so that the next movement will be more successful. Let's consider each circuit in turn.

The corticospinal tract

The giant pyramidal cells of layer V of motor cortex send axons that descend through the brain, funneling together as the internal capsule that passes between the (laterally located) lentiform nucleus of the basal ganglia and the (medially located) caudate nucleus and thalamus, decussating in the caudal brain stem, and descending in the ventral spinal cord as the corticospinal tract (*Figure 8.1*). Each corticospinal fiber activates motor neurons in the cord either via direct synaptic connections or, most typically, indirectly via local circuitry in the cord. Motor neurons send axons that innervate muscles, but because their cell bodies are located within the spinal cord, they are considered part of the CNS. Their functional organization can be considered from two perspectives: from that of the muscle, each muscle is innervated by a grouping of neurons called a motor neuron pool; from that of the individual motor neuron, it and each of the motor fibers that it innervates make up a motor unit. Motor neurons release the neurotransmitter acetyl choline (ACh) at their synapses, which are often referred to as the neuromuscular junction. More on muscles in the upcoming section on *The biomechanics of motor control*.

The cortico-cerebellar circuit

The cerebellum is an intriguing structure, in that it contains 50 billion of the roughly 80 billion neurons of the brain, yet, as the neurobiologist and theorist Giulio Tononi has noted, its complete removal has effectively no impact on the subjective sense of consciousness. It is made up of hundreds of thousands of parallel, modular (i.e., not interconnected) circuits that are constantly comparing motor output to sensory feedback so as to fine-tune the targeting and smooth execution of our movements, and to help us

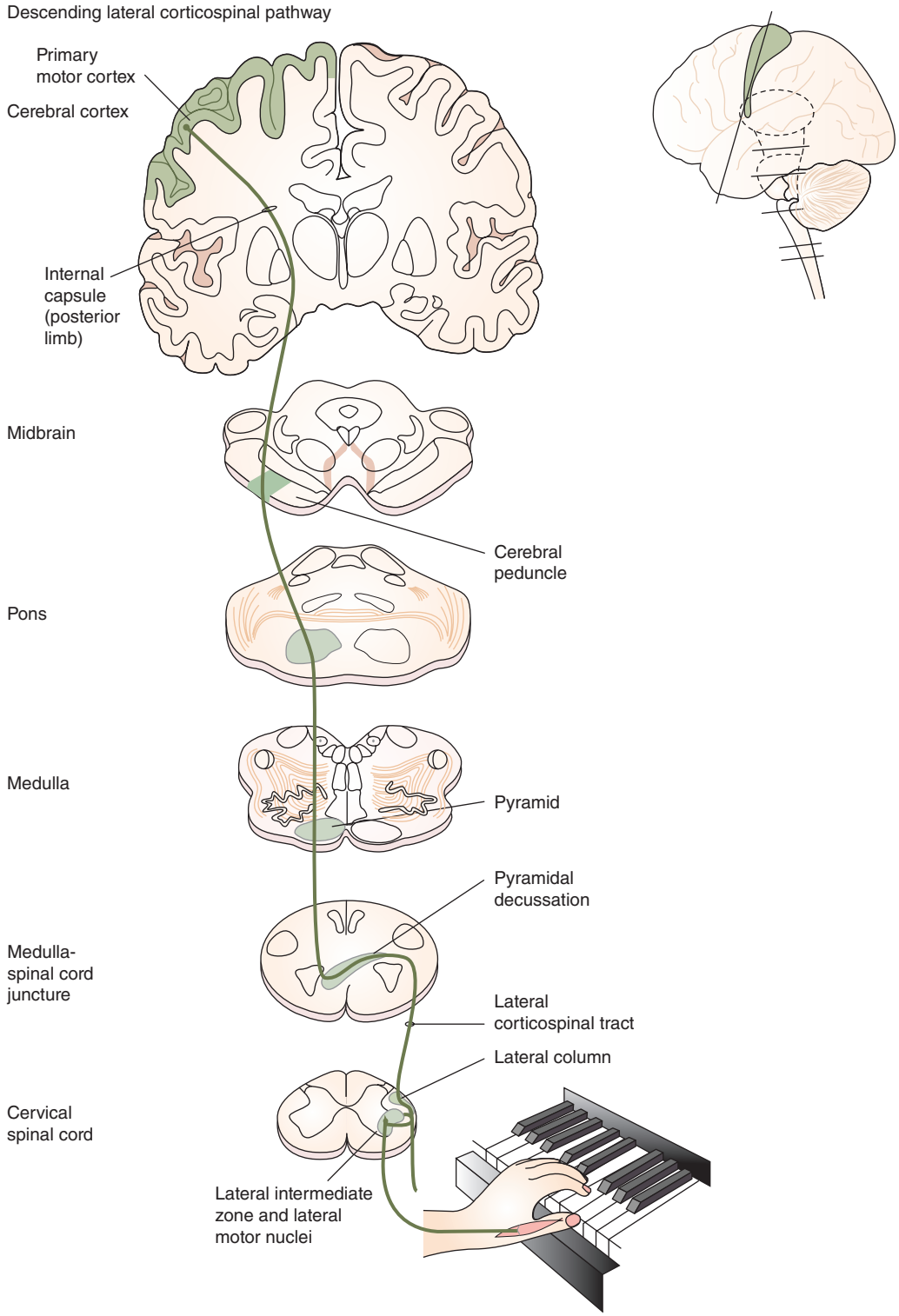

FIGURE 8.1 The descending corticospinal pathway. Source: From Kandel, Eric R., James H. Schwartz, and Thomas M. Jessell, eds. 2000. Principles of Neural Science. New York: McGraw-Hill. Reproduced with permission of McGraw-Hill.

maintain postural stability. The circuit is one-way, linking frontal cortex to pons to cerebellar cortex to cerebellar deep nuclei to thalamus and back to frontal cortex. The densely foliated cerebellar cortex is shaped like one half of a sawed-in-two tennis ball, but with thicker walls due to deep folds between the lobes of the cerebellar cortex, and the fibers projecting from this cortex to the deep nuclei lying near the "deepest" point of this concavity. Also projecting into the cerebellum are ascending projections carrying information about the periphery (touch on the skin, body configuration from muscle stretch receptors and joint-position receptors) and overall body position and balance from the vestibular system. The workings and functions of the cerebellum will be considered in the upcoming section on *Cerebellum: motor learning, balance, … and mental representation?*

The cortico-basal ganglia-thalamic circuits

This circuit and its nuclei play important roles in motor control, learning, and motivated behavior, and a variety of dysfunctions within it can result in disorders ranging from Parkinson's disease (PD) (impairing movement and high-level cognition) to unilateral neglect to pathological gambling. As illustrated in *Figure 8.2*, its unidirectional circuits

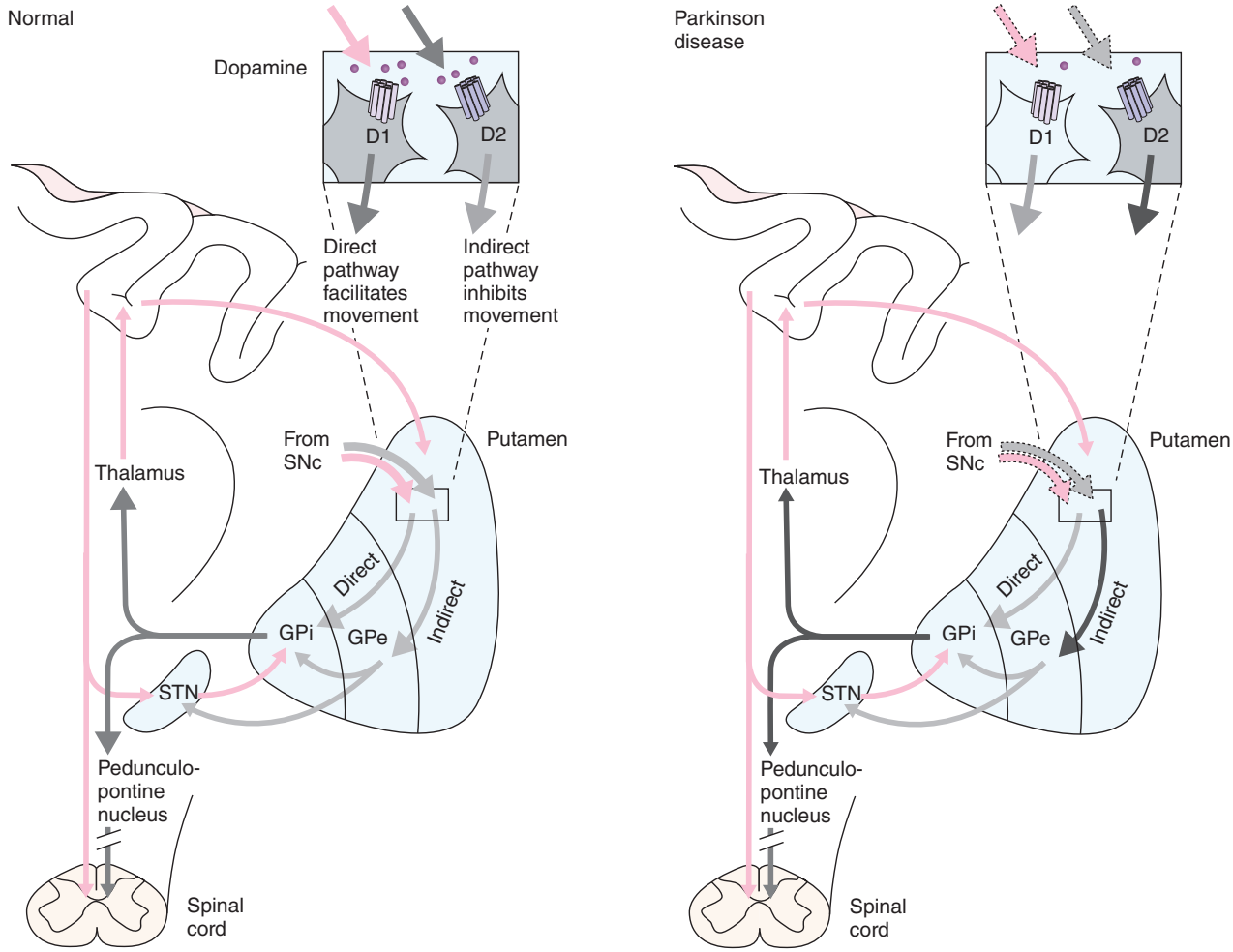

FIGURE 8.2 Schematic illustrations of the direct and indirect pathways of the basal ganglia, in the healthy ("Normal") state on the left, and in PD on the right. Red arrows connote excitatory pathways, gray inhibitory, and the change of saturation in the PD figure whether that pathway strengthens or weakens as a result of disease processes. SNc = substantia nigra pars compacta; GPe = external segment of the globus pallidus; GPi = internal segment of the globus pallidus; STN = subthalamic nucleus. Source: From Kandel, Eric R., James H. Schwartz, and Thomas M. Jessell, eds. 2000. Principles of Neural Science. New York: McGraw-Hill. Reproduced with permission of McGraw-Hill.

comprise a "direct pathway" (cortex to neostriatum to internal segment of the globus pallidus [GPi]/substantia nigra pars reticulata [SNpr] to thalamus back to cortex), an "indirect pathway" (cortex to neostriatum to external segment of the globus pallidus (GPe) to subthalamic nucleus (STN) to GPi/SNpr to thalamus back to cortex), and a "hyperdirect pathway" (cortex to STN; not shown in Figure 8.2). At the gross anatomical level, there are five relatively segregated *cortico-basal ganglia-thalamic circuits*, each associated with dissociable classes of behavior: *motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal,* and *limbic* (*Figure 8.3.A*). *Figure 8.3.B* illustrates the connectivity of the cortico-basal ganglia-thalamic motor circuit. Although the focus during this chapter will be the motor circuit, a noteworthy property of each of these circuits is the way each integrates inputs from multiple cortical regions and funnels the integrated result back onto the originating region of frontal cortex. Another common feature of these circuits is that the neostriatal node of each is densely innervated by dopaminergic fibers from a midbrain nucleus called the substantia nigra pars compacta (SNpc). (The distinctive black pigmentation of the substantia nigra ["black substance" in Latin], visible to the naked eye, derives from the high concentration in its neurons of the enzyme tyrosine hydroxylase, which is critical for the synthesis of DA.)

FUNCTIONAL PRINCIPLES OF MOTOR CONTROL

The biomechanics of motor control

Although moving the body in a coordinated fashion is something that we do effortlessly, often "thoughtlessly," this subjective facility masks a very complicated engineering problem. To summarize just one example, the movements of our arms from almost any points A to B are remarkably straight, despite the fact that executing such movements entails the precisely coordinated, simultaneous changing of joint angles – at the shoulder and the elbow (*Figure 8.4*). How does the nervous system accomplish this?

Muscles behave like springs

The tissue that puts the "motor" in "motor control," of course, is muscle. To move one's hand from point A to point B, it is necessary to contract the appropriate sets of muscles such that the joints that connect the bones of the arm move

FIGURE 8.3 The five cortico-basal ganglia-thalamic circuits. Source: From Kandel, Eric R., James H. Schwartz, and Thomas M. Jessell, eds. 2000. Principles of Neural Science. New York: McGraw-Hill. Reproduced with permission of McGraw-Hill.

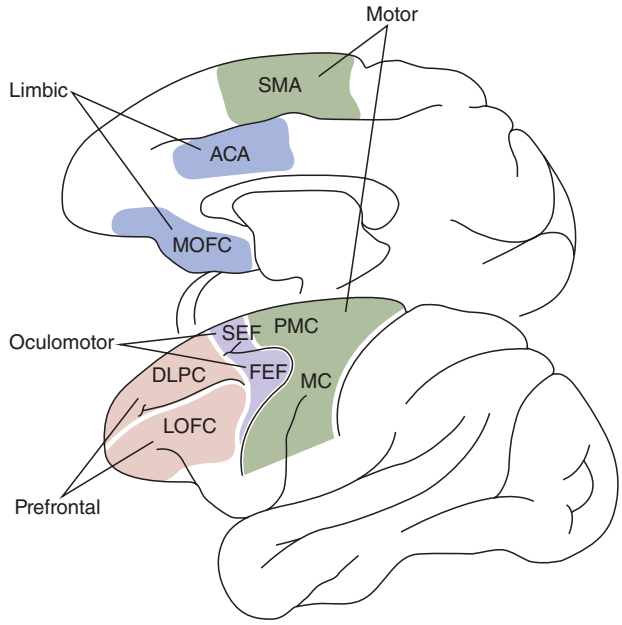

FIGURE 8.3.A Frontal targets the five loops. ACA = anterior cingulate area; MOFC = medial orbital frontal cortex; LOFC = lateral orbitofrontal cortex.

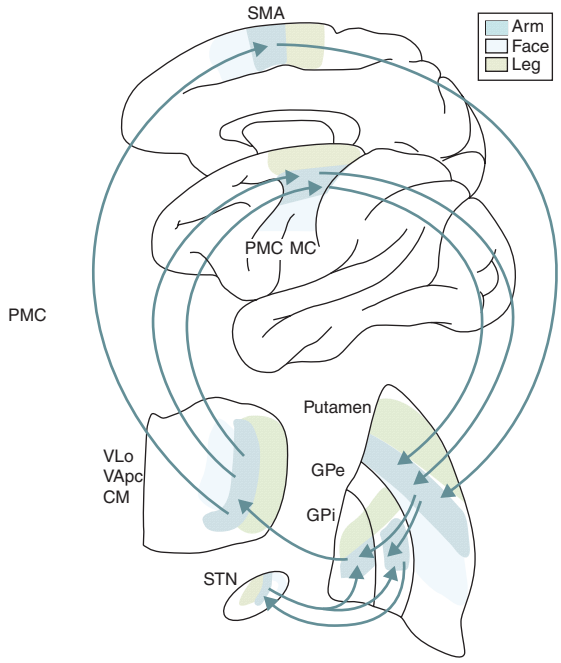

FIGURE 8.3.B Diagram of segregation of somatotopic information at each stage of the motor circuit. GPe = external segment of the globus pallidus; GPi = internal segment of the globus pallidus; STN = subthalamic nucleus; VLo = pars oralis segment of the ventrolateral (VL) nucleus of the thalamus; VApc = parvocellular segment of the ventral anterior (VA) nucleus of the thalamus; CM = centromedian nucleus of the thalamus.

in the ways illustrated in the lower columns of *Figure 8.4*. Note that at this most proximal level of motor control, any one muscle can only influence a single joint angle. For example, the antagonistically paired biceps and triceps muscles can change the angle of the elbow – nothing more. Thus, to execute even a simple "hand movement" as in *Figure 8.4*, the appropriate neural commands have to be delivered to at least four sets of muscles (biceps and triceps for the elbow, and the analogous muscles for the shoulder) in a precise, exquisitely choreographed sequence that will produce a smooth, straight motion. Note from this figure that movements to the same location, but starting from different locations, require nonlinearly different transformation of joint angles and joint angular velocities.

Fortunately, the mind-bogglingly complicated sets of nonlinear computations required each time we move our bodies are simplified by a felicitous mechanical property of muscles: they behave like springs. That is, one has only to set the tensions on a set of muscles and they will "automatically" adjust to a new equilibrium point, pulling the bones to which they are attached into a new position. Therefore, in principle, each unique location in x,y,z, coordinates within the peripersonal space of an individual has a unique set of muscle tensions associated with it. For example, from where you are currently sitting (or standing; or reclining; or whatever), there is a unique set of tensions required of the muscles controlling your shoulder, elbow, wrist, and index finger in order for you to touch your finger to this period →.← (Go ahead, do it. No one is watching.) And so, in principle, your cortex only needs to issue the command *Touch that period* and the requisite muscle-tension settings will automatically deliver your index finger to that point. The nonlinear transformations of joint angles that enable your finger to travel from wherever it was to the period that you are now pointing to "just happen" as a consequence of moving from A to B; they don't have to be explicitly calculated and commanded.

Motor computations in the spinal cord

If the motor cortex needs only to specify a new endpoint for, say, the index finger, what translates between the presumed command to *Go to X,Y,Z* and the resetting of muscle tensions? (That is, to execute a movement, each individual muscle only experiences a change in the amount of ACh being released onto it, it can't "know" anything about point *X,Y,Z*.) The answer is that this translation happens in the networks of interneurons in the spinal cord to which most corticospinal fibers project. Evidence for this was first produced in the frog,

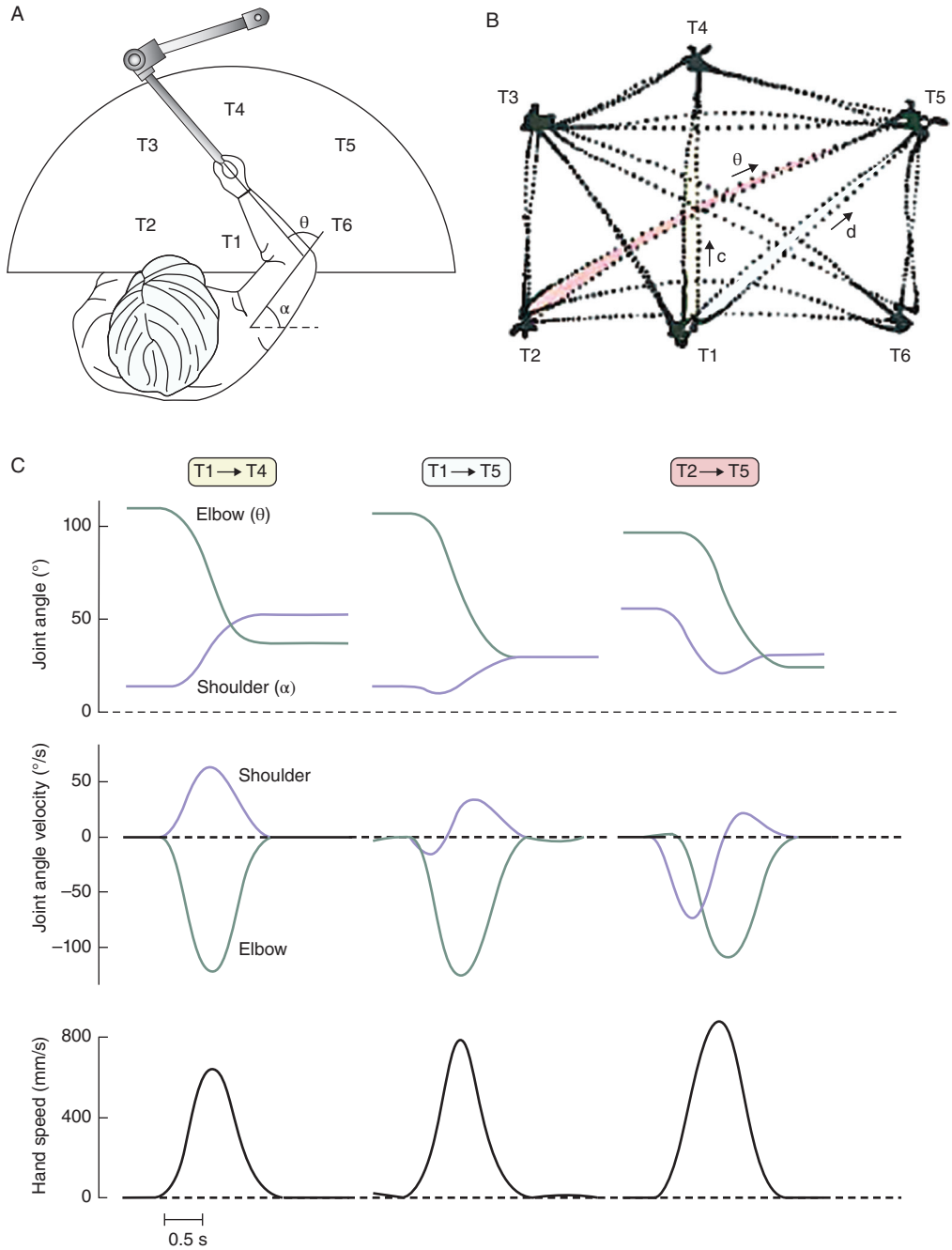

FIGURE 8.4 **A.** Top-down view of a subject grasping the handle of a manipulandum, which can be moved in a 2-D plane to each of the six targets indicated on the table. **B.** Movement paths (two between each target) for a subject. **C.** Joint angle, joint angular velocity (i.e., speed at which joint angle is changing), and hand speed plotted against time to execute each of three movements from **B.** Source: From Kandel, Eric R., James H. Schwartz, and Thomas M. Jessell, eds. 2000. Principles of Neural Science. New York: McGraw-Hill. Reproduced with permission of McGraw-Hill.

subsequently in the rat, in an experimental preparation in which all descending skeletomotor and ascending somatosensory connections between spinal cord and brain are severed. Microstimulation is then applied to the portion of the spinal cord whose motor neurons innervate, say, the left forelimb. The intriguing finding is that stimulation in this single location always brings the forepaw to the same location in space, regardless of what its starting location was. The area being stimulated, therefore, is converting that burst of electrical stimulation into the new tension settings of the muscles controlling the shoulder and elbow joints that bring the limb into that position in space. Stimulate a second spot in the cord, the limb moves to a different location. Further, a property whose importance will become evident further along in this chapter is that the simultaneous stimulation of both spots moves the limb to a third location. Therefore, in effect, the motor cortex issues the general command, and the spinal cord "takes care of the details."

In addition to being able to translate cortical commands into precise settings of muscle tensions, the spinal cord also contains what are referred to as "pattern generators." Thus, for example, early-to-mid twentieth-century experiments established that if the connections between an animal's brain and spinal cord are severed, and the animal is suspended in a harness over a treadmill, it will walk with an appropriate gait when the treadmill starts moving. Not only that, its gait adjusts appropriately to treadmill speed, from a trot to a gallop to a walk. The only explanation for such demonstrations is that remarkably sophisticated sensorimotor control circuitry exists within the spinal cord itself.

Motor cortex

Okay, so we've established that an animal can effectively walk, gallop, and trot, as appropriate, without any input from the brain. So what does the motor cortex do? (Why do we need it?) In a sentence, it controls *volitional* movement of the body. Let's take a closer look.

The motor homunculus

Unless you have just picked up this book for the first time, and opened to this chapter, you won't be surprised to learn that M1 has a rough somatotopic organization (as do at least four other regions in motor cortex). *Figure 8.5* is also taken from surgical mapping studies of Penfield and Rasmussen (1950). One important difference between the primary somatosensory and motor cortices, however, is that the latter's map lacks the same high-fidelity correspondence to different parts of the body. This is in part because the smallest unit that the motor cortex can represent corresponds to bones, rather than the surface of the skin. For example, it wouldn't make sense for M1 to represent different parts of the forearm in the way that S1 does, with a set of receptive fields that cover its entire surface. Rather, M1 represents the forearm as a unit that can be moved. Another, more fundamental, reason is that M1 represents *actions*, not just parts of the body. For example, it is often pointed out that a person's handwriting looks similar (albeit progressively sloppier) when the pen is held in the right hand vs. the left hand vs. in the mouth vs. between the toes. Thus the representation of the shape of one's handwriting must exist in a format that is accessible by any set of effectors that needs to implement it. Nonetheless, the fact that there is a mapping between different parts of M1 and different parts of the body means that motor cortex doesn't only employ purely abstract representations like "point X,Y,Z," or the shape of one's handwriting. Rather, it clearly chooses which effector(s) will be used to carry out any particular action. Further, it also controls the **kinematics** and **dynamics** of movement, such as the speed with which the arm will move, or the tightness with which the fingers will grip.

In addition to these considerations, neuroscientist Jon Kaas (2012) has proposed that if one "zooms in" from the overall somatotopic organization of M1 to look at smaller regions in greater detail, the coherent body map is "fractured" into clusters of cortical columns that are organized according to movement sequences, such as reaching, grasping, or defending the head against a blow. Thus, for example, within the large expanse of cortex that we label the "hand area," there will be columns of neurons corresponding to the arm, to the wrist, and to individual fingers, that, when activated in the appropriate sequence, produce the "reaching out and picking up food on my plate" movement sequence that that we each execute several times each day.

How do PMC and SMA differ from M1? For now, we'll content ourselves with the short-hand summary that they contribute to high-level aspects of motor control, such as planning to make a movement, imagining making a movement, and coordinating motor sequences made up of many individual actions. So that's an overview of what motor cortex does. Now, how does it work?

The neurophysiology of movement

EEG and LFP correlates

In the decade following Berger's discovery of the alpha rhythm (section *The relation between visual processing and the brain's physiological state, Chapter 4*), one of several rhythms to be discovered in the scalp EEG was the mu. Although the mu rhythm occupied the same frequency band as alpha, it differed in morphology – as a series of thin, spiky peaks

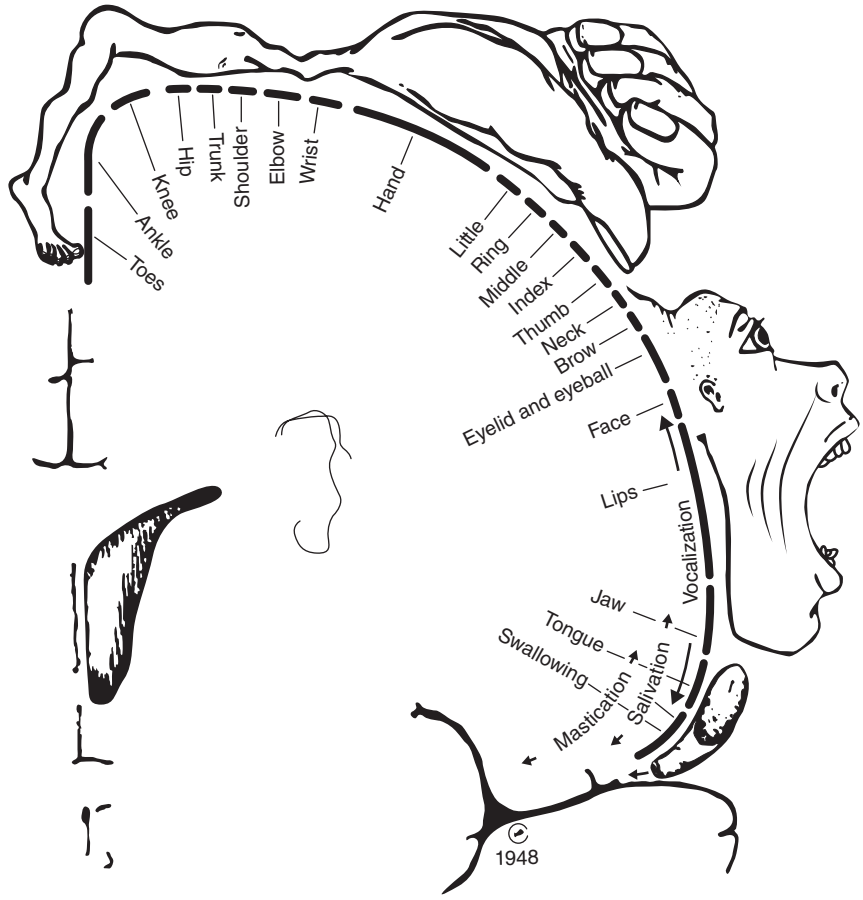

FIGURE 8.5 Penfield and Rassmussen (1950) motor homunculus. Same graphical conventions as *Figure 5.9*. Source: From Penfield, Wilder, and Theodore Rasmussen. 1950. The Cerebral Cortex of Man. A Clinical Study of Localization of Function. New York: Macmillan.

surrounded by rounded troughs (suggesting the shape of the greek letter "μ") – in topography – being maximal over central electrodes – and in function – being insensitive to perceptual factors, but being related to movement. Specifically, the amplitude of the mu rhythm is maximal when the body is at rest and begins to decline roughly 2 seconds prior to a movement. Such "mu desynchronizations" can be local to the cortical representation of the effector being moved, if one moves, for example, just the finger, toe, or tongue. Also prominent in the functioning of the motor system are EEG oscillations in the beta band. Although also inversely related to motor activity, the timing of changes in the beta band tend to be much more tightly coupled to the initiation in movement. Thus, there's a sense in which both the central mu and the central beta rhythms are analogous, for skeletomotor control, to posterior alpha for visual perception, in that they reflect a state of suppression and/or "idling" in the thalamocortical system producing them. (*Figure 8.6* illustrates mu and beta, recorded intracranially from motor cortex of a monkey performing visually guided movements of a handle from a central location to one of six radial locations [not unlike the task illustrated in *Figure 8.4*]. It also nicely illustrates how an oscillating signal can be trial-averaged to generate an ERP [as discussed in section *Analysis of time-varying signals, Chapter 3*].)

(In the 1950s, the French neurologist/neurophysiologist Henri Gastaut [1915–1995] and his colleagues made the discovery that mu desynchronization also occurs when the subject is immobile, but watching the movements of others. As we shall see further along in this chapter, this phenomenon has acquired considerable attention of late in relation to hypotheses linking autism with "mirror neurons.")

And so, we've established from scalp and LFP recordings that motor cortex is maintained in a functionally

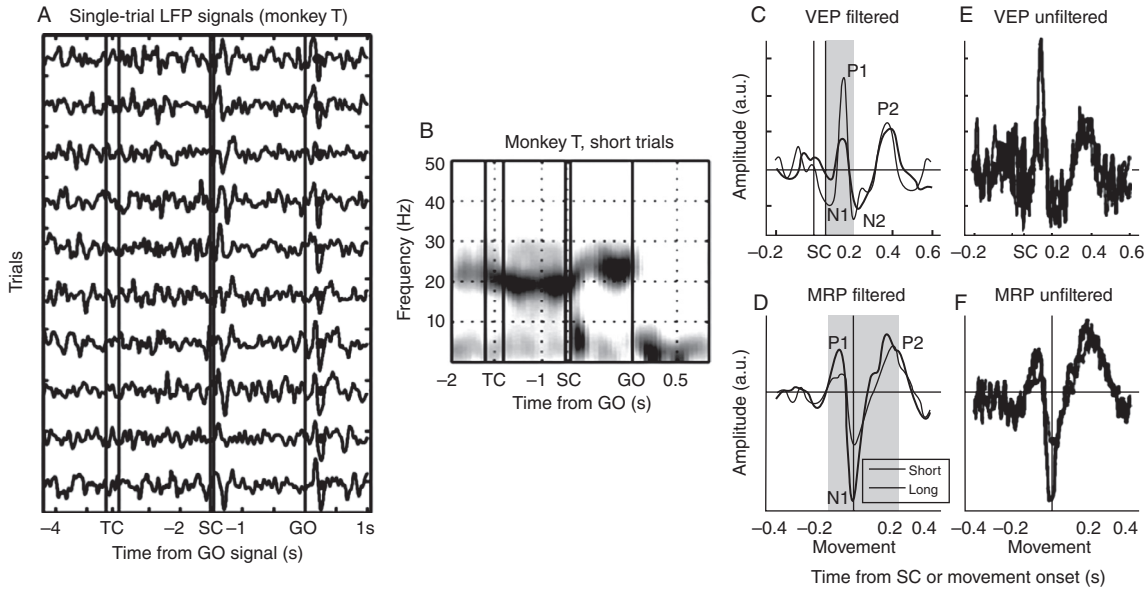

FIGURE 8.6 Movement-related dynamics in the LFP. **A** illustrates traces from several individual trials, bandpass filtered from 1 to 15 Hz (to emphasize the sensory- and motor-related evoked potentials), time-locked to the GO signal, and ordered by increasing RT (RT for each trial is indicated by a filled circle appearing in each trace; they are difficult to see, but occur at ~250 ms following the GO signal). The axis along the bottom of the figure shows the timeline of the task: TC is the "temporal cue" that informed the animal whether delay would be short (700 or 1000 ms, depending on the monkey) or long (1500 or 2000 ms); SC = the spatial cue, a visual cue that indicated the target to which the handle must be moved; GO = the signal to initiate movement; RT = "response time," defined as the lag between the GO signal and the instant when the handle began to move (i.e., movement-initiation time); MT = movement time, the time between the RT and the acquisition of the target. **B.** Time–frequency representation of trials from **A**, but without lowpass filter. Darker color corresponds to higher power. Pre-movement power is dominated by activity in the beta band, the frequency shifting from ~19 Hz to ~23 Hz after the SC, then stopping abruptly with the onset of the GO signal. Brief increases in low-frequency power correspond to evoked responses. **C** and **D.** Visual-evoked potential (VEP) and movement-related potential (MRP), respectively, time-locked to SC and RT, respectively, filtered from 1 to 15 Hz. **E** and **F.** Same data as **C** and **D**, but unfiltered. Source: From Kilavik, Bjorg Elisabeth, Joachim Confais, Adrián Ponce-Alvarez, Markus Diesmann, and Alexa Riehle. 2010. "Evoked Potentials in Motor Cortical Local Field Potentials Reflect Task Timing and Behavioral Performance." Journal of Neurophysiology 104 (5): 2338–2351. doi: 10.1152/jn.00250.2010. Reproduced with permission of The American Physiological Society (APS).

inactive state that is lifted just prior to the execution of a movement, that sensory signals triggering a movement are registered in this region, and that a large ERP immediately precedes the movement. Next, let's "drill down" to the level of the individual neuron.

Single-unit activity reveals population coding

Among the pyramidal cells of layer V of M1, one finds massive Betz cells, discovered by the Ukrainian anatomist Vladimir Alekseyevich Betz (1834–1894) only a few years after the pioneering microstimulation studies of Fritsch and Hitzig (1870; section *The localization of motor functions, Chapter 1*). These are the largest neurons in the nervous system, with large-diameter axons seemingly specialized to send neural impulses very rapidly and over long distances. (Subsequent research has established that many other neurons contribute to the corticospinal tract, with axons from Betz cells contributing only between 3% and 10% of the total.) The breakthrough insight about how these neurons actually generate coordinated movement had to wait another 100 years, for the research of Greek-born, US-based neurophysiologist Apostolos Georgopoulos and his colleagues.

Georgopoulos, Kalaska, Caminiti, and Massey (1982) recorded from the arm area of M1 from five hemispheres of four different monkeys while they performed a "center-out" task virtually identical to the one used in the experiment from *Figure 8.6*. The results, illustrated in *Figure 8.7*, revealed another important difference between M1 and

FIGURE 8.7 The electrophysiology of primary motor cortex.

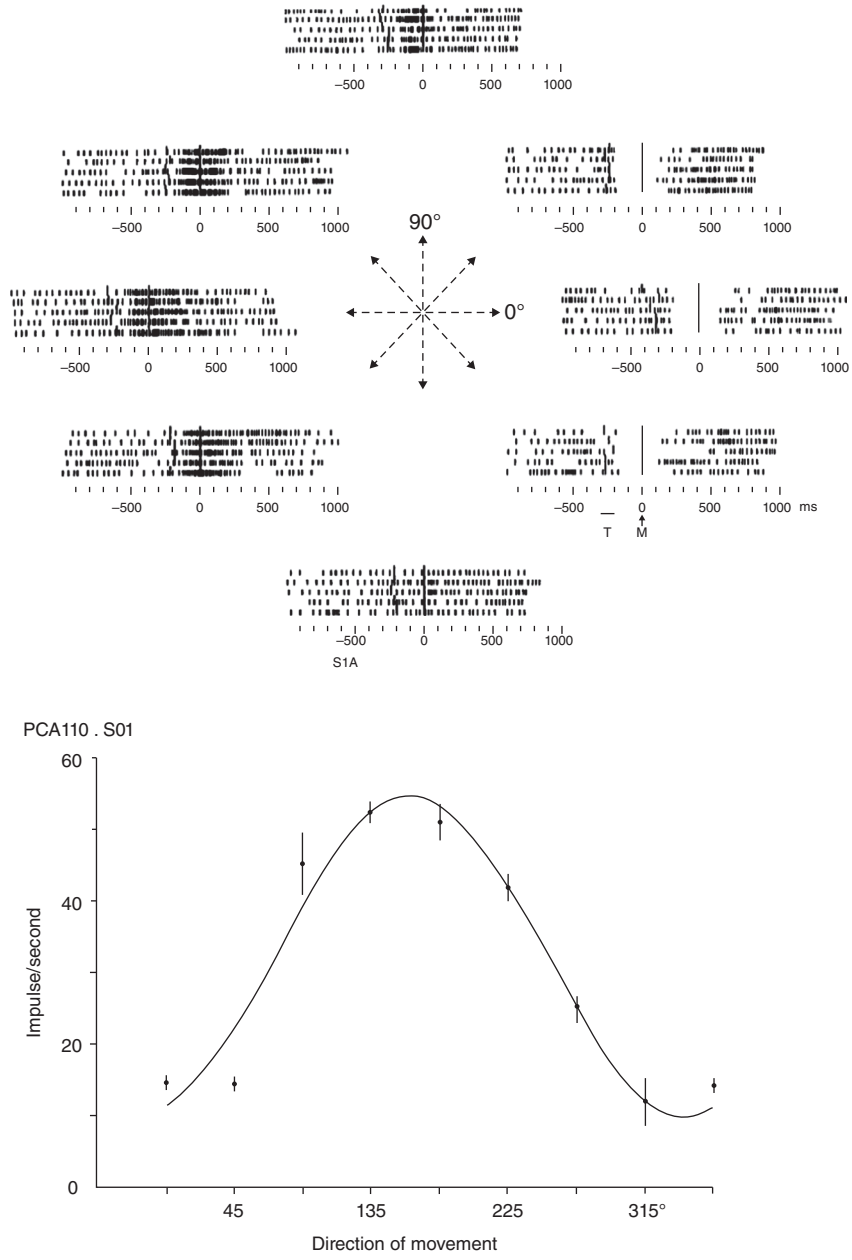

FIGURE 8.7.A Top panel displays responses of a single neuron from the arm region of M1 for each of five reaches made in each of eight directions, aligned to the time of initiation of movement (arbitrarily labeled "0"). Labels under the raster plot corresponding to movement in the 315° direction indicate the time of the GO signal (labeled "T") and initiation-of-movement time (M). Bottom panel is the tuning curve derived from these data. Source: From Georgopoulos, Apostolos P., John F. Kalaska, Roberto Caminiti, and Joe T. Massey. 1982. "On the Relations between the Direction of Two-Dimensional Arm Movements and Cell Discharge in Primate Motor Cortex." Journal of Neuroscience 2 (11): 1527–1537. Reproduced with permission of the Society of Neuroscience.

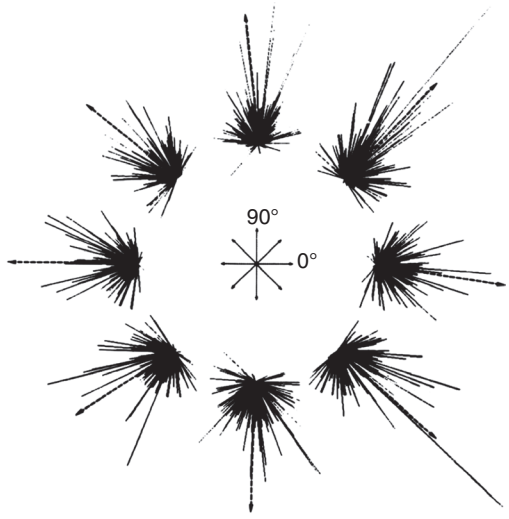

FIGURE 8.7.B Vector representation of the activity of 241 neurons recorded from the arm region of M1, for each of eight directions of movement (center of figure). Dashed lines with arrowheads are vector sums derived from each of the eight directions of movement. Source: From Georgopoulos, Apostolos P., Roberto Caminiti, John F. Kalaska, and Joe T. Massey. 1983. "Interruption of motor cortical discharge subserving aimed arm movements"." Experimental Brain Research Supplementum 7: 327–336. DOI:10.1007/BF00238775 Reproduced with permission of the Springer Nature.

the primary sensory areas that we have studied to date: instead of narrowly tuned response properties mirroring the precision of receptive fields of, for example,V1 and S1, M1 neurons had remarkably broad tuning. *Figure 8.7.A,* for example, illustrates a neuron whose responses are nearly indistinguishable for movements of 135°, 180°, and 225° (as, indeed, they are for movements of 45°, 0°, and 315°). Different neurons had different overall preferred directions: for example, if *Figure 8.7.A* illustrates a "to-the-left" neuron, others were "away-and-to-the-right" (270° being toward the animal's body), and so forth.

Upon first consideration, it's difficult to see how the activity in neurons with such broad tuning could be responsible for arm movements that we know can be much, much more fine-grained than the separated-by-45° movements required of the monkeys in this experiment. The principle must be different from what we've seen with sensory systems, for which it's customary to think of individual neurons as acting as feature detectors. Although no one really believes that a single neuron (or column) in V1 can be responsible for a single visual percept, one can nonetheless imagine, in "shorthand," that viewing a vertical line preferentially activates neurons tuned for vertical orientations, and that rotating that line ever so slightly to the right will preferentially activate different sets of neurons tuned for a slight tilt to the right. With M1 tuning properties, however, it'd be as though the V1 cell were equally responsive to orientations from 135° to 225°. How could one construct a system with elements whose tuning is so sloppy? The answer came to the research team after they considered the entire sample of 241 neurons from which they recorded in the arm area in M1: *population coding*.

Instead of thinking of the motor system as being made up of discrete "channels," each one specialized for its own narrowly defined features, *Figure 8.7.B* illustrates a fundamentally different principle of neural coding. It presents a graphical representation of the response of each of the 241 neurons to each of the eight directions of motion. Each line in each of the eight, radially arrayed "explosion" plots is a vector whose length corresponds to the firing rate of a neuron during motion in that direction. (Responses of the neuron illustrated in *Figure 8.7.A*, therefore, correspond to one of the longish vectors at the 135°, 180°, and 225° positions, to a somewhat shorter vector at 90°, to one shorter still at 270°, and to vectors of length 0 at 45°, 0°, and 315°.) The "vectorial hypothesis" proposed by Georgopoulos, Caminiti, Kalaska, and Massey (1983) makes the assumption that each neuron's activity on any given trial corresponds to the magnitude of its influence on the direction of movement on that trial. Now recall from mathematics that a vector is a way of representing a force that has a magnitude and a direction, and that if two or more forces are simultaneously present, their vectors can be combined and the resultant "vector sum" (or "vector average," depending on which operation one performs) will indicate what their combined effects will yield. This is what the dashed lines with arrowheads amid each vectorial plot represent: the empirically derived summation of all 241 vectors. Given that each vector was estimated from only five or so movement trials, and that only 241 neurons were sampled out of the millions that make up motor cortex, it's astoundingly impressive that an analysis of these neural data could produce an estimated direction of motion (the eight vector sums) that so closely corresponds to the actual direction in which the monkey moved its hand on each trial (the eight arrows in the center of the plot). What Georgopoulos and colleagues accomplished was to decipher a component of the neural code for skeletomotor control! And the key insight, one to which we

will return often for the remainder of this book, is that the principle underlying this function of the nervous system can only be understood by simultaneously considering the activity of a large population of neurons. Serially inspecting one after the next after the next would never reveal it.

I can imagine that to some readers this may seem too abstract. *Vector summation? What, is there some little homuncular mathematician perched up on the precentral gyrus, legs dangling into the central sulcus, calculating vector sums prior to each movement?* Nope. No need in this scheme to resort to the homunculus. Assuming that these are all layer V pyramidal cells, all located in the arm area, each neuron's action potentials travel to the same general area in the spinal cord, many of them destined for the same motor neuron pool. These action potentials all activate the very same networks of interneurons that were described in the earlier section on *Motor computations in the spinal cord*. In effect, it's as though 241 teensy weensy microelectrodes have been simultaneously lowered into the spinal cord. Recall that we saw previously that while stimulation of point A in the cord moved the forepaw to location X, Y, and stimulation of point B in the cord moved the forepaw to location X', Y', simultaneous stimulation of A and B moved the forepaw to X'', Y''. Thus, the vector summation that a scientist can compute through the arduous analyses and computations summarized here turns out to be a more formal description of what we had glibly summarized earlier: *the motor cortex issues the general command* (in the form of a population code), *and the spinal cord "takes care of the details."*

One of the most exciting consequences of "cracking the code," as Georgopoulos and colleagues have done with motor cortex, is that one can then *decode* new signals as they are generated. *Figure 8.8* illustrates how neural decoding is used for brain–computer interface (BCI).

FIGURE 8.8 A closed-loop BCI system for direct neural control of a robotic arm. Source: From Carmena JM, Lebedev MA, Crist RE, O'Doherty JE, Santucci DM, Dimitrov DF, et al. (2003) Learning to Control a Brain–Machine Interface for Reaching and Grasping by Primates. PLoS Biol 1(2): e42. https://doi.org/10.1371/journal.pbio.0000042.

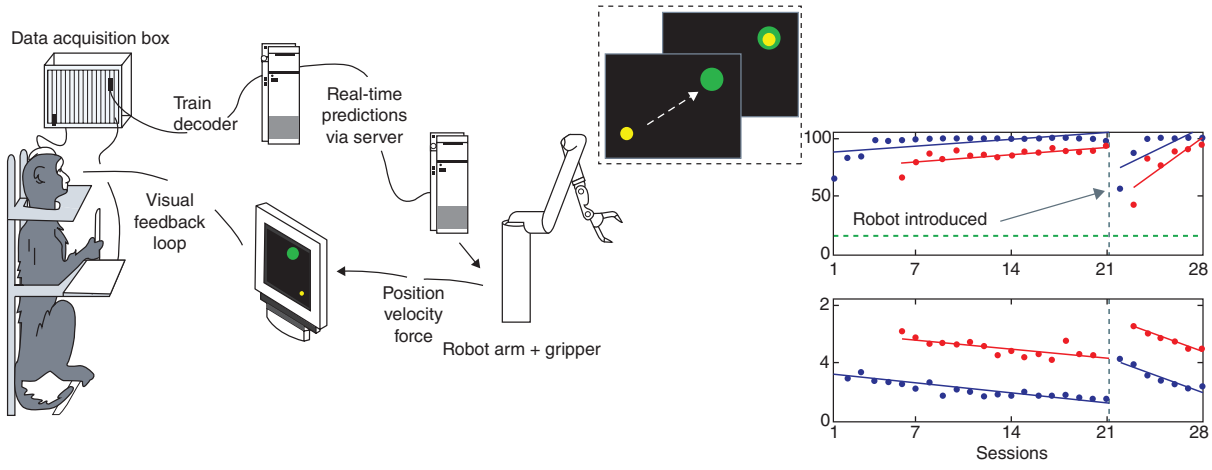

FIGURE 8.8.A The experiment started with the monkey moving a joystick that controlled the movement of a cursor on a screen (inside dotted box), and while the monkey learned to perform this task, a computer analyzed task-related neural activity from its frontal and parietal cortices, in order to learn to decode it. The experimental setup is illustrated on the left side of the image, with "Real-time predictions via server" referring to the statistical assessment of the quality of decoding on a trial-by-trial basis (i.e., *How well would we have done on this trial had we guided the cursor with neural signals rather with the joystick?*). Once decoding performance was high enough, the researchers disconnected the joystick from the system, such that the movement of the cursor was now being controlled by the monkey's neural output – "brain control mode." Performance is plotted across sessions 0–21, in joystick control mode (blue dots and regression line) vs. with brain control mode (red dots and regression line). "Robot introduced," at session 22, indicates the switch to robot control mode, when the joystick was reconnected to the display, but now it was controlled by a robotic arm, and the monkey's neural signals controlled the robotic arm. Performance on the task dropped precipitously on the first session of "robot control mode," but already by the subsequent session performance improved markedly.

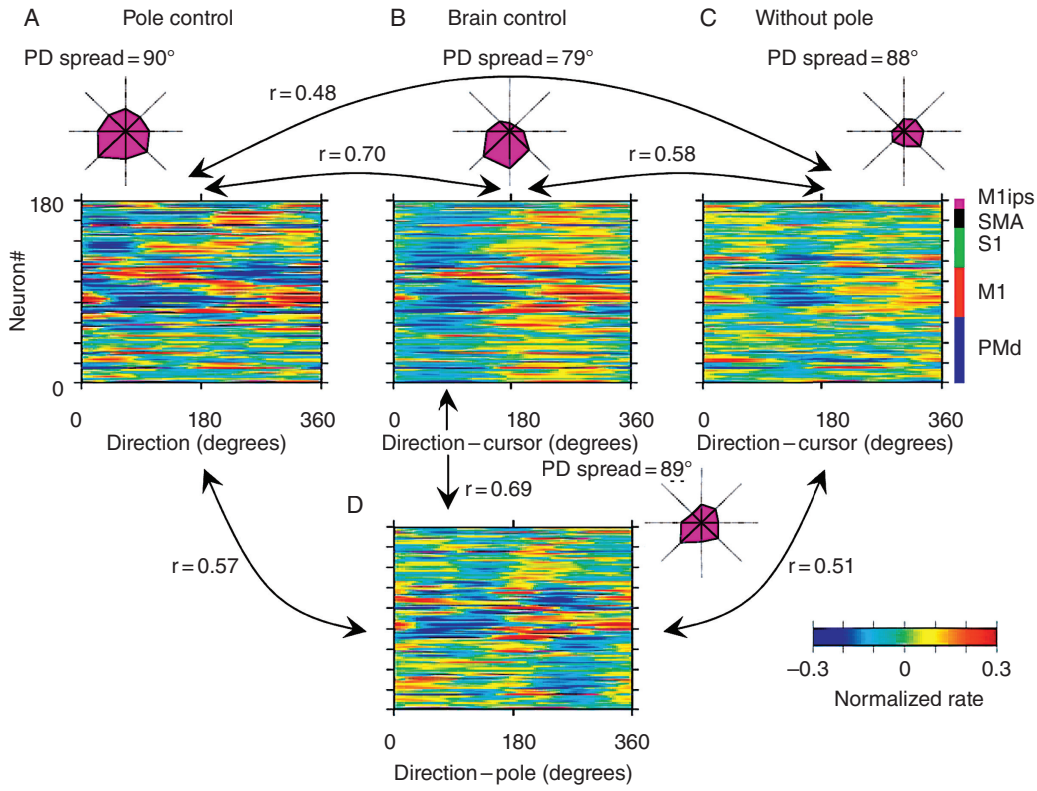

FIGURE 8.8.B Tuning curves for 180 neurons recorded from dorsal premotor cortex (PMd), M1, S1, and SMA (all contralateral to the joystick-controlling hand), and ipsilateral M1 (M1ips). (To understand the graphical convention in these plots, consider the tuning curve in *Figure 8.7.A*. If you were to look down on it from above, you'd want to color code its height at each point along the direction axis, so as to not lose this information. Otherwise it would just look like a straight black line. [The same logic applies for 2-D geographical maps that indicate the elevation of mountains vs. valleys with different colors.] Here, red indicates the highest firing rate ["altitude" in the geographical map analogy], violet the lowest. The reason for adopting this "viewed from above" display convention is that it allows the simultaneous display of an entire "stack" of tuning curves in one panel.) The plot on the left shows the tuning curves for this set of 180 neurons when the animal is performing the task in joystick (a.k.a. "pole") control mode, tuning calculated from cursor movements; the plot in the middle is from brain control mode but with the joystick still in the hand, tuning calculated from cursor movements; the bottom plot is also from brain control mode with the joystick still in the hand, but with tuning calculated from joystick movements; and the plot on the right from brain control mode with no joystick (tuning necessarily computed from cursor movements). Visual inspection suggests that the tuning of many of the neurons in this sample changes as a function of task condition. The *r* values are coefficients produced by correlating the overall similarity of direction tuning of these 180 neurons in each of four conditions. Finally, the purple polar plots illustrate the tuning of the entire sample in each condition, a "PD spread" of 90° indicating a uniform distribution, and the magnitude of the values at each axis (relative to the origin) the strength of tuning preference in that direction.

MOTOR CONTROL OUTSIDE OF MOTOR CORTEX

Parietal cortex: guiding how we move

One of the facts made clear by studies such as that summarized in *Figure 8.8* is that the neural code involved in carrying out complex actions, such as a reach followed by a grasp followed by a pull, entails much more than the vector summation of 300 or so M1 neurons. (For example, with just that information, I could be made to swing my arm so as to knock the cup of coffee off the arm of my couch, but not to grasp it and bring it to my lips.) Many regions other than M1 can contribute valuable signals for decoding movement-related neural activity. Although the study of Carmena et al. (2003; *Figure 8.8*) didn't venture

posterior of S1, others have done so, emphasizing that a greater range of cognitive factors – including intention, expectation, and reward value – might be best sampled outside of traditional motor areas. "For example, PRR [parietal reach region; see *Figure 7.7*] neural activity codes the intention to reach to an object at a particular location in space, whereas motor cortex codes the direction to move the hand" (Andersen, Musallam, and Pesaran, 2004, p. 271). The critical role for PPC for the planning and execution of visually guided action, through its contributions to sensorimotor integration and coordinate transformation, also figures prominently in the alternate framing of the ventral vs. dorsal pathways as being one of *what* vs. *how*.

A neurological dissociation between perceiving objects and acting on them

A reassessment of the "what vs. where" framework for understanding the functional specialization of the visual system (section *A functional dissociation of visual perception of what an object is vs. where it is located, Chapter 6*) was proposed by Canada-based researchers Melvin Goodale and David Milner after their detailed studies of a patient who developed a profound impairment in the ability to recognize objects (a form of visual agnosia, a syndrome that we will define and consider in detail in *Chapter 10*) after carbon monoxide inhalation produced extensive damage in lateral occipital BAs 18 and 19, but largely sparing V1. Despite this severe impairment, this patient (known by her initials "D.F.") seemed remarkably unimpaired when "directing accurate reaching movements toward objects in different orientations" (Goodale, Milner, Jakobson, and Carey, 1991, p. 155). To formalize and quantify this dissociation, which was reminiscent of that demonstrated by monkeys with IT lesions in the Pohl (1973) study (section *A functional dissociation of visual perception of what an object is vs. where it is located, Chapter 6*), Goodale and colleagues (1991) carried out the experiment illustrated in *Figure 8.9*.

In addition to the experiment illustrated in Figure 8.9, Goodale et al. (1991) also carried out an experiment that

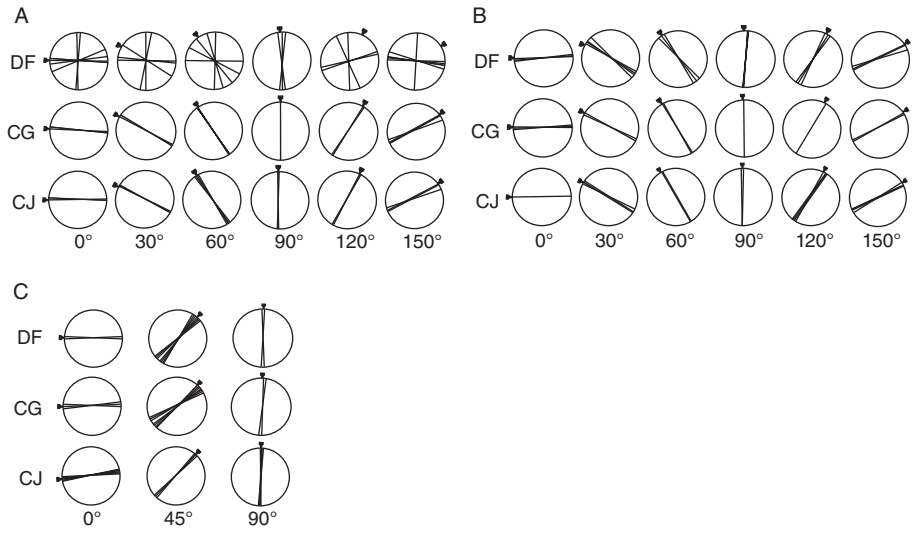

FIGURE 8.9 Is the dorsal stream important for processing "where" an object is, or "how" to interact with it? **A.** Responses on five trials at each of six different orientations in a "perception" task, in which D.F. and two control subjects were asked to match the orientation of a slot in a disk that was 45 cm distant. The true orientation of each of the six is illustrated by the small arrowheads. At all angles except 90° (i.e., vertical) D.F. was profoundly impaired. (And because each trial was started with the card held at 90°, her relatively intact performance at this orientation may be artifactual.) **B.** When asked to "post" the card by reaching to insert it into the slot (as though putting a postcard into a mail slot), D.F.'s performance was nearly as precise as that of control subjects. **C.** Performance on a mental imagery version of the matching task, in which subjects were asked to close their eyes and imagine the slot at each of three orientations. This indicates that poor performance illustrated in **A** was not due to a misunderstanding of instructions, or some other uninteresting factor. Source: From Goodale, Melvyn A., A. David Milner, Lorna S. Jakobson, and David P. Carey. 1991. "A Neurological Dissociation between Perceiving Objects and Grasping Them." Nature 349 (6305): 154–156. doi: 10.1038/349154a0. Reproduced with permission of Nature Publishing Group.

looked at a second kind of visually guided action, grasping. First subjects were asked to indicate with finger and thumb the front-to-back size of each of five plaques, ranging in shape from a 5 × 5 cm square to a 2.5 × 10 cm rectangle. These two digits were fitted with infrared light–emitting diodes so that precise measurements could be made of finger-to-thumb aperture. The results showed that, unlike control subjects, D.F.'s responses did not differ with shape. When asked to pick each of the shapes up, in contrast, she was just as accurate as control subjects.

In interpreting their findings, the authors conjectured that they did "not correspond to the two streams of output from primary visual cortex generally identified in the primate brain – a ventral one for object identification and a dorsal one for spatial localization [. . . instead, they] indicate separate processing systems not for different subsets of visual information, but for the different uses to which vision can be put." Therefore, to return to a theme from the previous chapter, this view has more in common with *intention* rather than *attention* interpretations of the neglect syndrome and of the functions of the parietal lobe.

The *Further Reading* list at the end of this chapter provides references to more recent installments of the lively debate about this idea that has continued more than two decades after its initial articulation. Furthermore, one possible resolution to the "where" vs. "how" debate is that both may be true. Kravitz, Saleem, Baker, and Mishkin (2011) have proposed that three major pathways originating in parietal cortex provide body-centered spatial information that supports three broadly defined functions: a parieto-prefrontal pathway that supports "conscious visuospatial processing," including spatial working memory (and corresponding to the classically defined "where" pathway); a parieto-premotor pathway that supports "non-conscious visuospatial processing," including visually guided action (and corresponding to Goodale and Milner's "how" pathway); and a parieto-medial temporal lobe pathway, including intermediate connections in posterior cingulate and retrosplenial regions, that supports navigation. (The last was highlighted in section *From parietal space to medial-temporal place*, *Chapter* 7.)

Cerebellum: motor learning, balance, . . . and mental representation?

From the standpoint of aesthetics, the cerebellum may be the most beautiful part of the brain: the tight foliation of its cortex (housing 10% of the volume but > 50% of the neurons of the brain); the remarkably profuse, yet "flat," dendritic arbors of its Purkinje cells; the elegant simplicity of its circuitry. As summarized previously, the cerebellum is a hub in one of the two major recurrent circuits of the motor system, serving an online error-monitoring function and feeding real-time performance information back onto frontal cortex.

Cerebellar circuitry

The cerebellum is highly modular, consisting essentially of a bank of hundreds of thousands of parallel circuits that all perform the same computational operations, but each on a different, segregated channel of information. The central processing element around which cerebellar circuits are built is the Purkinje cell. These are among the largest cells in the nervous system, with massive dendritic arbors that afford an incredibly large number of synaptic connections (estimated to be as high as 200,000 per neuron!). Despite their size and extensive and intricate branching, however, these arbors only extend through a 2-D plane. A row of Purkinje cells aligned in a "strip" that is parallel to the plane of their dendritic arbors makes up a circuit (called a "microzone"), the output of which, via Purkinje cell axons, is focused on neurons of the cerebellar deep nuclei that were discussed in the introductory section of this chapter. At a simplified level, the copy of the efferent motor command is carried into the cerebellum by climbing fibers, and information about the sensory inputs – the "context" in which an action is taken and the sensory consequences of that action – by mossy fibers. Climbing fibers are axons originating in the inferior olive in the brainstem, their name deriving from the fact that a single climbing fiber wraps around and around the basal dendrites of a single Purkinje cell, like a vine climbing a tree trunk. Climbing fibers make between 300 and 500 synaptic connections with a single Purkinje cell. Mossy fibers arise from the pons (in the brainstem), their name deriving from the distinctive "rosettes" in which they form synaptic connections with granule cells. Granule cells then send "parallel fibers" that run perpendicular to, and therefore through, the dendritic arbors of many Purkinje cells (i.e., they cut across many microzones). Individual parallel-fiber synapses on Purkinje cells are relatively weak, whereas a single action potential in a climbing fiber will reliably trigger an action potential in a Purkinje cell.

Cerebellar functions

An influential model of the computations carried out by the cerebellum, articulated by the British neuroscience polymath David Marr (1945–1980), and subsequently

refined by the American electrical engineer and roboticist James Albus (1935–2011), is summarized as follows. The premise, rooted in control theory from engineering, is that the Purkinje cells in the cerebellum contain a representation of a prediction of what the effects of a movement should be (i.e., an "internal model"). The sensory report of what the consequences of the action actually were is delivered, via parallel fibers, to the cerebellum. To the extent that the internal model and the actual consequences differ, a modification is made to the cerebellar circuitry, and the results of this assessment get forwarded to the motor cortex so that it can adjust how it commands this action the next time. In effect, the idea is that the cerebellum houses one instantiation of the predictive coding models introduced back in *Chapter 4* (section *Where does* sensation *end? Where does* perception *begin?*). In his influential 1971 paper, Albus summarized the role for the modification of cerebellar circuits in motor learning as follows:

> It is an obvious fact that continued training in motor skills improves performance. Extended practice improves dexterity and the ability to make fine discriminations and subtle movements. This fact strongly indicates that learning has no appreciable tendency to saturate with overlearning. Rather, learning appears to asymptotically approach some ideal value. This asymptotic property of learning implies that the amount of change that takes place in the nervous system is proportional to the difference between actual performance and desired performance. A difference function in turn implies error correction, which requires a decrease in excitation upon conditions of incorrect firings. (1971, p. 52)

By the Marr–Ablus model, "desired performance" is represented by the climbing fibers, which carry the copy of the efferent motor signal. When discharge of a climbing fiber triggers an action potential in a Purkinje cell, there is a refractory period that follows, during which the Purkinje cell cannot fire another action potential. If action potentials from parallel fibers arrive during this refractory period, the consequence of this is a weakening of synapses between them and the Purkinje cell. (The reason is introduced in the next section, on *Synaptic plasticity*.) This modification of synaptic strength in the cerebellum is a neural instantiation of motor learning, which we will address in the upcoming subsection on *Synaptic plasticity*. One way to think of this process is that subtle changes in cerebellar circuitry might produce subtle changes to the length of a few of the M1 neuronal activity vectors illustrated in *Figure 8.7.B*, which, in turn, would produce an ever-so-subtle change in the end point of that movement the next time it is executed.

The circuitry of the cerebellum continues to fine-tune our movements throughout our lives. Evidence for this comes from the fact that damage to the cerebellum produces abnormalities in posture, gait, reaching, and other skeletomotor functions regardless of when in life the damage is incurred.

Interestingly, some channels of the cortico-cerebellar circuit link PFC with the cerebellum, and so this computational principle presumably also carries out fine-grained, online corrective processing of high-level cognitive functions, such as those mentioned in the introductory paragraph to this chapter. The Japanese neurophysiologist Masao Ito has proposed an intriguing model that we can't detail here, but whereby, in addition to its internal models of motor behaviors, the cerebellum may also encode internal models "that reproduce the essential properties of mental representations in the cerebral cortex . . . [thereby providing a] mechanism by which intuition and implicit thought might function" (Ito, 2008, p. 304).

Synaptic plasticity

All learning and memory (with the possible exception of working memory [*Chapter 14*]) results from changes in the strength of synaptic connections between neurons.

The example of Pavlovian conditioning

What is a memory? Fundamentally, it is the association of two previously unlinked pieces of information. Let's make this more concrete by walking through a cartoon example that will be familiar to most. In the early twentieth century, the Russian physiologist Ivan Pavlov (1849–1936), whose research on the physiology of digestion garnered the Nobel Prize in 1904, noticed that dogs in his laboratory would often begin salivating in advance of the arrival of their food. Formal experimentation established that the animals could be taught to associate an arbitrarily selected stimulus (the ticking of a metronome – the *conditioned stimulus* [CS]) with the act of getting fed – the *unconditioned stimulus*. The essence of the protocol was to play the metronome sound at the time of food delivery. After several such trials, it would be sufficient to play the metronome sound, alone, and the dog would begin to salivate. In doing so, the dog was expressing a memory, because prior to the experiment the playing of a metronome sound did not produce this behavior. Therefore, it was the influence

of its recent experience that was being expressed in its behavior. If one wants to project human-like cognition onto the dog, one can speculate that hearing the metronome makes the dog think of being fed (i.e., makes it *remember* being fed the last time it heard this metronome).

Staying at this schematic, cartoon level, what must have happened within the brain of our subject? Prior to the experiment, the sound of a metronome would activate its auditory system, and would perhaps trigger an exogenous shift of attention, but certainly no activity in the digestive system. During training, this auditory circuit was active at the same time as were the olfactory circuits that processed the smell of the food and then activated what we'll call the "salivary neurons" that trigger the salivary reflex. Something about the coactivation of these two circuits led to a strengthening of the link between the auditory representation of the metronome and the salivary neurons. In effect, the dog's brain perceived an association in the world that hadn't existed previously, and modified the connectivity in its brain to represent this association. Thus, at this neural level, the memory *is* this new connection. Now, let's drill down to consider how this might come to pass.

Hebbian plasticity

One of the most influential and enduring principles in neuroscience was articulated by the Canadian Psychologist Donald Hebb (1904–1985), in his book *The Organization of Behavior* (1949): "When an Axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (p. 62). This has come to be known as "Hebb's postulate," and it has been fundamental for understanding synaptic plasticity in biological systems, as well as being the basis for learning in virtually all computational neural network models, including those introduced in section *Computational models and analytic approaches, Chapter 3*.

We won't do a deep dive into the physiological correlates of Hebb's postulate until *Chapter 11*, but for now it will be useful to apply it to our Pavlovian conditioning example. What it is saying is that there was something special about the fact that metronome-related activity in the auditory system coincided with the activity in the salivary neurons. Thus, even though the auditory activity initially had no causal role in driving the salivary neurons, something about the coincidence of activity in auditory neurons and in salivary neurons led to a strengthening of the ability of the auditory processing of the sound of the metronome to drive salivary activity, and this has to have been through the strengthening of connections. (As you might have inferred from *Chapter 5*'s treatment of *Somatosensory plasticity* and of *Phantom limbs and phantom pain*, it could not happen that, in our cartoon example, auditory neurons would send new long-range connections to salivary centers in the brain to create this memory; rather, the association must come about through the modification of the strengths of connections that already existed before the learning episode occurred.)

A final, important fact that we need to consider here is that Hebbian plasticity works in two directions. That is, what we have described is a situation in which activity in neuron A that coincides with activity in neuron B leads to a strengthening of the A-to-B synapse. As we'll see in *Chapter 11*, this strengthening is referred to as long-term potentiation (LTP). It is also the case, however, that when activity in neuron A is anticorrelated with activity in neuron B, A-to-B synapses will be weakened. Thus, when action potentials in A occur shortly *after* B has been depolarized, long-term depression (LTD) of this synapse occurs. It is LTD that implements the "error correction" in cerebellar circuits invoked by Albus (1971) in the previous section on *Cerebellar functions*.

Basal ganglia

The basal ganglia define the second major recurrent circuit of the motor system. This circuit, too, is not limited to motor control. Rather, as *Figure 8.3.A* highlights, the skeletomotor circuit is just one of five (frontal) cortical-basal ganglia-thalamic circuits. One major difference between the skeletomotor circuit and the other four is that its cortical efferents synapse in the putamen of the neostriatum, whereas three of the others target different regions of the caudate nucleus of the neostriatum, and the ACC and MOFC of the limbic circuit target the nucleus accumbens of the neostriatum (also referred to as the ventral striatum). Subsequently, each of the five circuits, although remaining segregated, bifurcates into a direct and an indirect pathway, the direct pathway linking striatum to the GPi, the GPi to thalamus, and thalamus back to cortex.

A subcortical gate on cortical activity

Although learning the wiring diagram of this circuit has been known to induce dizziness and headache in some students, the basic operating principles are actually quite

straightforward. The key to understanding its function is remembering a distinctive property of the GPi. The GPi is a tonically *active* structure. That is, its baseline state, when the circuit is not being engaged, is to steadily fire at a high frequency (~85 Hz in one study in the monkey; this will vary with species and with an animal's physiological state). Because GPi neurons are GABAergic, the default state of affairs is that the GPi maintains a steady inhibitory "clamp" on the thalamus. Now, moving one step upstream, the cells of the neostriatum that project to the GPi are also GABAergic. Thus, engaging the direct pathway in a basal ganglia circuit has the effect of phasically inhibiting the GPi's activity, thereby phasically lifting the GPi's inhibitory clamp on a small region of thalamus, and thereby allowing it to send an excitatory signal to its frontal cortical target. In this way, the basal ganglia can be construed as "gating" cortical activity.

The role of DA

Figure 8.2 illustrates another important component to the operation of the basal ganglia: the delivery of the neurotransmitter DA. DA, along with norepinephrine, serotonin, and others, is classified as a neuromodulatory neurotransmitter. That is, it's typically not thought to convey information in the way that glutamatergic neurons do, but it sets the "tone" within networks, thereby biasing the way in which glutamatergic and GABAergic signals are processed. In particular, the level of DA at a synapse influences the rate of strengthening/weakening that glutamatergic and GABAergic synapses will undergo as a result of activity. DA is synthesized in three adjacent nuclei in the midbrain. Depending on who is describing them, they are either identified as *A8*, *A9,* and *A10* or as the SNpc and the ventral tegmental area (VTA). The SNpc (or A9) delivers DA to other nuclei of the basal ganglia, most densely to the neostriatum via the **nigrostriatal tract**, and the other nuclei project primarily to neocortex.

The influence of DA on the basal ganglia can be considered at many levels, and here we'll consider three: setting the balance between the direct and indirect pathways; controlling the synchrony between subnuclei; and reinforcement learning.

Balancing between the direct and indirect pathways. We'll begin with what's illustrated in *Figure 8.2*. Although all fibers of the nigrostrial tract deliver "the same" molecule throughout the neostriatum (DA), its effects can be either excitatory or inhibitory, depending on the zone receiving this input. How can this be? The answer is that, unlike glutamate and GABA, DA receptors are not linked to membrane-spanning channels that directly gate the passage of ions. Rather, they are so-called "second-messenger-linked" receptors. It means that the binding of a molecule of DA to a DA receptor initiates a cascade of chemical events within the postsynaptic neuron, the ultimate consequences of which might be excitation or inhibition, depending on which second-messenger pathway is triggered. There are two classes of DA receptors: D1-type and D2-type. (D1-type DA receptors include D1 and D5, and D2-type include D2, D3, and D4.) In general, D1-type receptors produce a depolarizing effect and D2-type receptors a hyperpolarizing effect.

The neostriatum is made up of a checkerboard of compartmentalized zones that are dominated by D1-type or by D2-type receptors. The two types of zones are the basis for the direct vs. indirect pathways, because their outputs project to either the GPi or the GPe. One of the ways that we understand the influence of DA on this system is from decades of research on Parkinson's disease (PD), which is characterized by progressive degeneration of the SNpc, and, therefore, a progressive lowering of DA levels in the neostriatum. Motorically, PD is associated with three cardinal clinical symptoms: resting tremor in one or more limbs, muscular rigidity, and slowness to initiate movement ("bradykinesia"). One way to understand these symptoms (and, by extension, to understand the role of DA in the healthy system) is illustrated in *Figure 8.2*: the reduction of DA in the neostriatum throws off the balance of its output, such that the descending signal of the direct pathway is weakened, and that of the indirect pathway is strengthened. The direct pathway is consequently less able to impose phasic inhibition on the GPi, which, in turn, reduces excitatory drive from thalamus to cortex. This can account for the rigidity and bradykinesia seen in PD. By applying the same analysis to the Gpe one can see that a similar end point is reached.

Although it seems as though we've only considered the indirect pathway in relation to its dysfunctional activity in disease states, it is, of course, the case that it has an important role in normal brain function. One is to help control movement by sending "no-go" signals to the cortex when a possible action would be a bad choice. Another important function may be that of learning about the negative value of some behaviors. To understand why, we need to wait until we get to the section on *Habits and reinforcement learning*.

Synchrony between nuclei. For decades, neuropathologists have known that PD is associated with degeneration of the SNpc, because postmortem brains of PD patients have visibly less black pigmentation in the midbrain than do brains from non-neurological autopsies. Although DA replacement is an obvious idea for treatment, development of an effective drug was held up for years by the fact that DA cannot cross the blood–brain barrier, the layer of endothelial cells that prevents diffusion from capillaries of many substances carried in the bloodstream. A breakthrough occurred when the Swedish physician and neuropharmacologist, Arvid Carlsson, discovered that a precursor to DA, L-3,4-dihydroxyphenylalanine (commonly referred to as levodopa, or L-dopa), does cross the blood–brain barrier. Once in the brain, enzymes present in dopaminergic neurons convert L-dopa to DA. Shortly after the initial discovery, it was shown that L-dopa can be effective at alleviating motor symptoms of PD. To this day, L-dopa remains the primary pharmacological treatment for PD. (For this discovery, Carlsson was awarded the Nobel Prize in 2000.)

However, L-dopa has limitations. One is a result of the fact that the loss of DA neurons does not occur evenly across dopaminergic neurons of the midbrain. Rather, neurons of the SNpc precede those of the VTA, meaning that optimal treatment of motor symptoms with L-dopa (*Figure 8.10*) can result in an excess of DA in other brain regions, such as the PFC, which is innervated by the VTA. Dopamine's effect on the brain, like that of many neurochemicals, follows an "inverted U-shaped" function, meaning that neural function is suboptimal when the concentration is too low, optimal in a mid-range, but impaired again as the concentration gets too high. A complication with titrating the dose of L-dopa for PD patients, therefore, is finding the "Goldilocks dose" that provides optimal relief from motor symptoms, yet that won't produce cognitive impairment. This becomes increasingly difficult to do as the disease progresses, and there are fewer and fewer viable neurons remaining in the SNpc that can convert L-dopa into DA and deliver it to its striatal targets. At advanced stages of the disease, surgery is often considered the most viable option for treatment.

The first surgical treatments developed were "-otomies"; for example, a *pallidotomy* entails lesioning the GPi so as to reduce its pathologically strong inhibitory clamp on the thalamus. A *thalamotomy* most often targets the ventral intermediate nucleus of the thalamus, which has the specific effect of reducing tremor. At present, however, the most common surgical treatment for PD is so-called deep brain stimulation (DBS), in which one or more stimulating electrodes are implanted in a basal ganglia nucleus (often the STN, but, as *Figure 8.10* illustrates, other nuclei can also be targeted). The electrode is driven by a battery that is surgically implanted in the chest and can be controlled via a handheld magnet. As *Figure 8.10* makes clear, brain function is exquisitely sensitive to the precise oscillatory dynamics within and between basal ganglia nuclei. Steady, high-frequency electrical stimulation delivered to one or more of these can be an effective counter to disease-related loss of DA. Recordings from the OFF condition, when patients did not have L-dopa in their systems (i.e., they were "off their meds"), showed that the power in the LFP recorded from the STN and GPi was shifted to lower frequencies relative to the ON condition (i.e., when they were taking the clinically optimal dose of L-dopa). Even more strikingly, oscillatory coherence of LFPs between the two structures was highest at 6 Hz and 20 Hz in the OFF condition, but shifted to 70 Hz in the ON condition. It may be, therefore, that the resting tremor in PD results from a disruption of optimal oscillatory synchrony in this system. Note, also, that these indices of the oscillatory

FIGURE 8.10 The effects of dopamine-replacement therapy on oscillatory dynamics within and between basal ganglia nuclei. Source: (B): From Brown, Peter, Antonio Oliviero, Paolo Mazzone, Angelo Insola, Pietro Tonali, and Vincenzo Di Lazzaro. 2001. "Dopamine Dependency of Oscillations between Subthalamic Nucleus and Pallidum in Parkinson's Disease." Journal of Neuroscience 21 (3): 1033–1038. Reproduced with permission of the Society of Neuroscience.

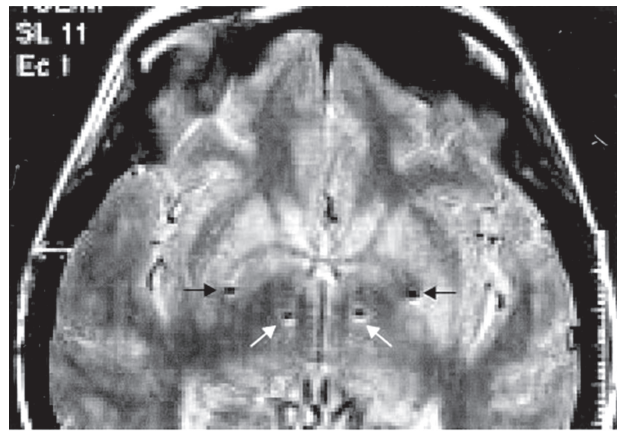

FIGURE 8.10.A Axial MR image of a patient after bilateral implantation of electrodes in the GPi (black arrows) and the STN (white arrows).

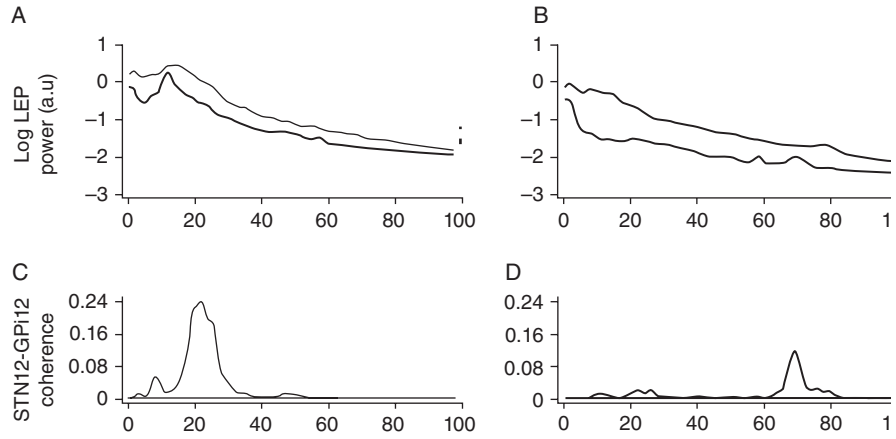

FIGURE 8.10.B Panels **A** and **C** illustrate measurements averaged over four patients when they were OFF L-dopa and **B** and **D** when they were ON. **A** and **B** show power spectra in the GPi (higher power) and the STN; **C** and **D** coherence between the two structures (i.e., the degree to which oscillations in the two structures are synchronized, at each frequency from 0 to 100 Hz, as indicated on the horizontal axis of each plot).

dynamics within and between structures give a concrete example of what is meant by references to a region's "dopaminergic tone."

Another line of research has examined oscillations in field potentials measured on the surface of M1 with ECoG electrodes, and with scalp EEG, in patients with PD. The ECoG recordings were made in patients with DBS electrodes implanted and compared cortical activity when DBS was on vs.off. The initially published finding was that ECoG recordings showed an atypically high level of phase–amplitude coupling (PAC) between the phase of the beta-band oscillation and high gamma power when DBS was off, and that the amplitude of this PAC decreased markedly when DBS was on. (For a refresher on PAC, see section Caveats and considerations for spectral analyses, Chapter 3; Figure 3.13.) This was interpreted as evidence that PD motor symptoms may be caused by cortical pyramidal cells being pathologically "locked-in" to a highly synchronous pattern of firing that prevented the quick and flexible modification of large-scale patterns of activity that underlie healthy motor control. Superficially, it suggested an electrophysiological correspondence to the bradykinetic aspects of PD. This conceptualization of the cortical pathophysiology of PD soon had to be revised, however, when it was discovered that the atypically high levels in PAC in the DBS-off recordings weren't due to periodic bursting of MUA, the standard interpretation of the high-gamma component of PAC, but were instead an artifact of the shape of the wave forms in the cortical oscillation. Specifically, the peaks of the beta oscillation were abnormally sharp in the DBS-off condition (resembling the upper right-hand quadrant in *Figure 3.13.A*), and this resulted in the spectral transform (for our purposes, the FFT) needing to add power at high frequencies to be able to represent the steep slope of the rising edge of each cycle. The effect of DBS, as it turned out, was to smooth out the peaks in the beta-band oscillation (i.e., to render the slope of the rising edge of the cycle less steep). (See Cole et al., 2017 from *Further Reading*.)

A follow-up study with scalp EEG recorded from a different group of patients showed similar results for DA-replacement medication: the beta-band oscillation recorded at central electrodes had an atypically sawtoothed shape when patients were OFF their medication, and a smoother, more sinusoidal shape when they were ON their medication. From a systems level of analysis, this suggests that one consequence of the elevated coherence at 20 Hz between GPi-STN when patients are OFF medication (*Figure 8.10.B*) may be abnormally high synchrony in the thalamic signalling to motor cortex that is gated by the cortico-basal ganglia-thalamic circuit. From a clinical perspective, this finding may have important implications for diagnosis and tracking of disease progression, because the medication-related change in the shape of the beta-band oscillation was not accompanied by a change in beta

power. That is, conventional EEG analyses that ignore waveform shape are insensitive to this effect.

Habits and reinforcement learning. For decades, the basal ganglia have been associated with "habit learning," a term that refers to the stereotyped behaviors that we engage in while carrying out everyday tasks, often multiple times each day, often with little or no awareness that we are carrying them out. One example from this author's personal experience is throwing away garbage while preparing food in the kitchen (how's that for mundane?). For years, the garbage can in our kitchen was at the end of the counter, and when working at the sink, throwing something away required a 110° (or so) pivot to the right (clockwise) and then three steps to the garbage can. Recently, however, our kitchen was renovated, and the garbage can is now (much more conveniently) located in a pull-out drawer that's immediately to the right of the sink (now you don't have to take even a step!). For the first few weeks in the newly renovated kitchen, however, when working at the sink and needing to throw something away, I would find myself having pivoted 110° to the right and having taken a step or two toward where the garbage can used to be located, before realizing that I was "following an old habit" that was no longer appropriate for that context. In terms of my subjective experience of this, I was probably thinking about the goal of whatever it was that I was doing (like what I was going to do next with this food, once I discarded the packaging that I had just removed it from) but I was obviously not volitionally "pre-planning" my route to the garbage can. Rather, knowing that I was holding something that needed to be discarded prompted the automatic, unconscious triggering of this suite of behaviors.

What processes in my brain led to the formation of this habit? It's almost certainly the case that, upon moving into the house and beginning to cook in its unfamiliar kitchen, for the first several times that I threw something away while working at the sink, I did think explicitly about what actions I needed to take. Over time, however, there developed a "fracture" in my motor homonculus (perhaps in the hand area?) that represented the behavioral sequence of throwing-something-away-when-working-at-the-sink. Before the kitchen renovation, then, anytime circumstances called for it, a signal from a higher-level motor area, likely in SMA, would engage the circuits in my putamen that would temporarily lift the gate on the cortical representation of throwing-something-away-when-working-at-the-sink, and off I would go. The formation of this habit was produced by a particular kind of learning called reinforcement learning.

Reinforcement learning is a computational approach to learning that is enormously influential in automation, robotics, and artificial intelligence (AI). More recently, it has also become highly influential as a model for understanding certain types of learning in the nervous system, and it will make appearances in many chapters after this one, particularly in the final section of the book on *High-Level Cognition*. Here we will introduce some of its key principles, and how these inform how we understand the contributions of the basal ganglia to motor control.

Interestingly, the discipline of reinforcement learning was first inspired by findings from studies of Pavlovian conditioning, particularly the phenomenon of "blocking," and the Rescorla–Wagner model (Rescorla and Wagner, 1972) that was developed to explain it. We can illustrate blocking by returning to the metronome-and-food procedure that we considered in the previous section. Now, after the animal has learned the association of *metronome predicts food*, we introduce a second arbitrary "CS," let's say a flashing light. If we pretend, in this example, that 10 trials of presenting metronome + food had been sufficient to produce active salivation when the metronome was played alone, in our new experiment, for trials 11 through 20, we'll play the metronome and flash the light when food is presented. The critical question is, if, on the 21st trial, only the light is flashed, does it produce salivation? (That is, has the dog now learned to also associate the light with the presentation of food?) The answer is no. In the parlance of the animal learning literature, the previous learning of the association of the metronome with food has "blocked" the association of the light with food. The reason that this effect is important is that it demonstrates that the mere temporal co-occurence of two events is not sufficient for associative learning to occur. What Resconla and Wagner proposed was that learning only happens when an event violates the animal's expectations, i.e., when its prediction of what should happen in a particular situation is wrong. In the parlance reinforcement learning, this prediction error is called a "reward," and the goal of reinforcement learning algorithms is to maximize the reward.

What does this all have to do with DA and the basal ganglia? To answer this, we need to jump from New Haven, CT, in the 1970s (Rescorla and Wagner, 1972) to Fribourg, Switzerland, in the 1980s, where understanding the linkage between motor control and DA was the goal of the Mexican neurophysiologist Ranulfo Romo and his then-postdoctoral mentor the Swiss neurophysiologist Wolfram Schultz. Despite the well-characterized motor deficits of patients with PD, and the equally well-known

palliative effects of L-dopa treatment, no direct linkage had been made between midbrain DA neurons and motor behaviors. To their surprise, Romo and Schultz (1990) failed to find evidence that these cells responded to movement; instead, they seemed to respond to motivational and reward factors. Romo later noted: "It took us about 5 years to publish the paper because nobody was going to buy this idea that those neurons were not associated with movement, but reward" (Downey, 2006, p. 14264). Once they did finally get it published, however, it was quickly realized that these findings had profound implications for such topics as learning, motivated behavior, decision making, and addiction. And, importantly for our current focus on reinforcement learning, midbrain DA neurons seemed to be broadcasting information about prediction errors to the neostriatum and to cortex (*Figure 8.11*).

Before leaving this section on reinforcement learning, there's one more important point to be made. Although one will often read about DA as being related to reward, it's not the case that the release of DA at a synapse is somehow akin to, say, a grade-school student being given a $10 bill for every A she brings home on her report card. Rather, the cell biological effects of DA are such that, when mediated by D1-type receptors, they enhance membrane excitability. Thus, a positive RPE (i.e., an elevated level of DA) increases the likelihood that concurrent activity at corticostriatal synapses will have potentiating effects, whereas a negative RPE (i.e., a pause in firing that lowers the level of DA) increases the likelihood that this same activity will have depressing effects. The fact that the opposite is true for neurons with a higher density of D2-type receptors allows us to finish the explanation of how the indirect pathway may have an important role in learning the negative value of some actions. The idea is that because the indirect pathway is governed by the inhibitory effects of DA on D2 receptors, it is during the pauses in the tonic release of DA that constitute negative RPEs (*Figure 8.11*, group *B*) that neostriatal neurons in the indirect pathway experience transient increases in excitability and, consequently, a boost in the plasticity of their synaptic connections with incoming cortical fibers. Thus, it is in conjunction with "disappointments," or situations in which outcomes are worse than expected, that reinforcement learning is strongest in the indirect pathway. It follows from this fact that experiments have shown that interfering with D1 functioning impairs reward learning and interfering with D2 functioning impairs avoidance learning.

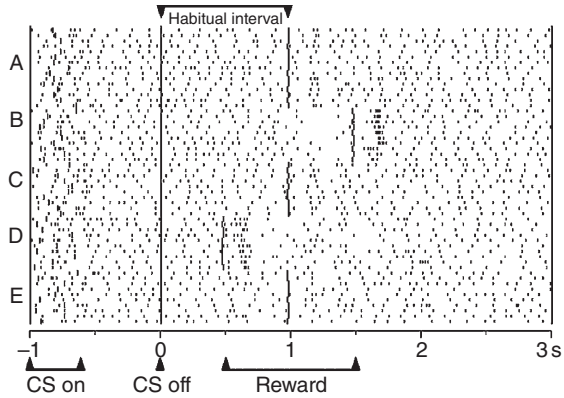

FIGURE 8.11 The reward prediction error (RPE) signal. Each row shows activity in a midbrain DA neuron during a well-learned Pavlovian conditioning task in which the offset of the CS is followed by a reward 1 second later (the habitual interval). When the expected outcome occurs (groups A, C, and E), there is no change in firing rate. When the reward is unexpectedly delayed (B), there is a brief pause in firing – a negative RPE signal – then an elevated burst upon the unexpected, later delivery – a positive RPE signal. When the reward is unexpectedly delivered early (D), there is a positive RPE – an elevated burst signaling its delivery – and an absence of the spike that is perfectly aligned with reward delivery on habitual trials. Source: From Wolfram Schultz, "Behavioral Theories and the Neurophysiology of Reward", Annual Review of Psychology. Vol. 57:87–115. Copyright 2005. Reproduced with permissions of Annual Reviews.

COGNITIVE FUNCTIONS OF THE MOTOR SYSTEM

As suggested at the beginning of this chapter, many have argued that high-level cognition may have evolved over millennia as increasingly abstracted versions of motor control. Ito's (2008) proposal of mental models represented in the cerebellum would fall into this category. Also consistent with this idea is the fact that the cortico-basal ganglia-thalamic circuits of the PFC and the ACC/LOFC operate on the same principles as does the motor circuit that we have focused on in this chapter. Two additional examples of this idea have come from the Italian neurophysiologist Giacomo Rizzolatti and his colleagues. One is the "premotor theory of attention," the idea that attention may "have evolved from"/"be a byproduct of" motor preparation. This theory will receive considerable attention in the next chapter, when we take up oculomotor control and the control of attention. In the meantime, this chapter concludes with another of Rizzolatti's discoveries: mirror neurons.

Mirror neurons

Sector F5 is a subregion of PMC, located immediately caudal to the ventral branch of the arcuate sulcus, that has been shown in recording and microstimulation experiments to be involved in the high-level representation of actions involving the hand and the mouth. Different neurons, for example, respond selectively to grasping, tearing, or holding movements. In a study carried out by Gallese, Fadiga, Fogassi, and Rizzolatti (1996), upon isolating a neuron in

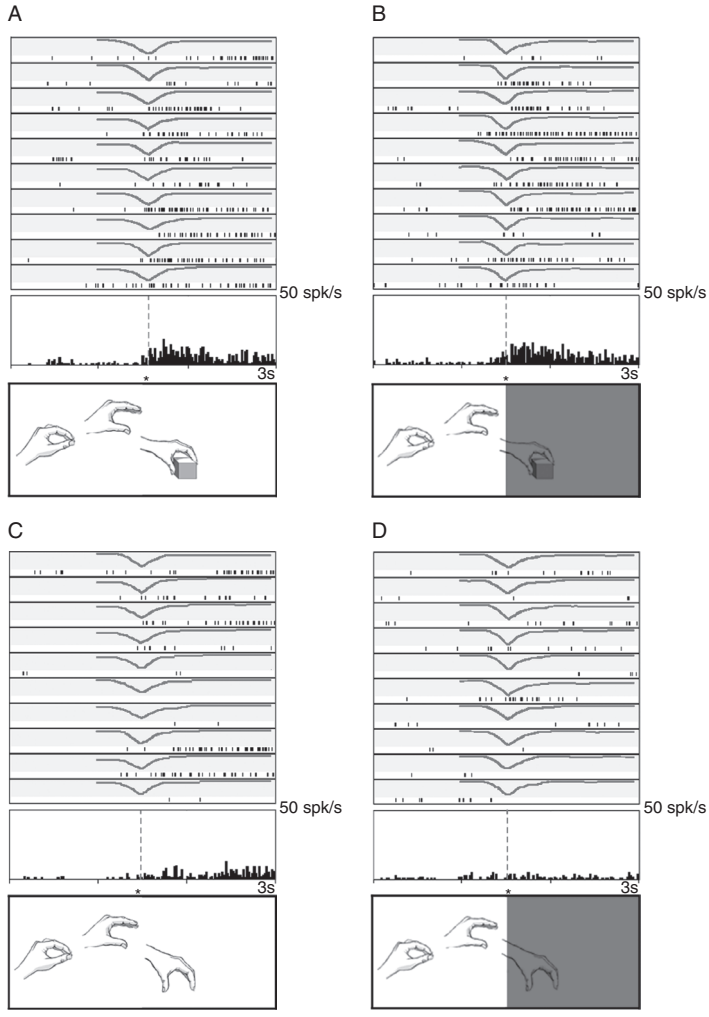

FIGURE 8.12 Mirror neurons in PMC of the monkey. Responses of an F5 neuron in a study carried out by Dr. Maria Alessandra Umiltà, in which the monkey watched while an experimenter reached to either grasp an object (panels **A** and **B**) or to mimic the same action but in the absence of the object. In between the monkey and the table on which the object was displayed was a metal frame that could either be empty (panels **A** and **C**) or hold an opaque screen, thereby blocking the monkey's view of this location (panels **B** and **D**). For all four trial types, neural activity is aligned to the moment in time when the reaching hand passed the boundary of the frame (and, therefore, became no longer visible in **B** and **D**). (The waveforms above each row of rasters illustrate the location of the hand relative to the boundary of the frame as a function of time, aligned the same as neural data.) Note how the neuron only responds to the act of grasping a physical object, not to the identical movement when the object was absent, and that it does so regardless of the presence or absence of the screen. Source: From M.A. Umiltà, E. Kohler, V. Gallese, L. Fogassi, L. Fadiga, C. Keysers, G. Rizzolatti, "I Know What You Are Doing A Neurophysiological Study", Neuron. Copyright 2001. Reproduced with permission of Elsevier.

F5, the investigators would present the monkey with an item of food on a tray, either within or outside of the animal's reach, as well as with objects of various sizes. The size manipulation enabled distinguishing between three types of grip: "precision grip" (thumb and index finger); "prehension grip" (thumb opposite fingers to extract an object from a deep, narrow container); and "whole-hand prehension." This procedure can be construed as analogous to the procedure for determining the visual response properties of a neuron in IT cortex by presenting it with a series of objects.

The novel innovation of this study was that the testing battery also included an experimenter performing several actions while the monkey watched: grasping a piece of food from a tray, bringing the food to their mouth, giving the food to a second experimenter, etc. Of 532 neurons recorded from F5, 92 discharged to specific actions by the monkey *and* to the observed actions of an experimenter. These were dubbed "mirror neurons." The actions that mirror neurons responded to were categorized as shown in *Table 8.1*.

The responses summarized in *Table 8.1* were insensitive to manipulation of factors related to the animal's reference frame, such as side of the body the actions were performed on, or distance of the observed actor. Importantly, however, these neurons did not respond when their preferred action was performed as mimicry (e.g., experimenter pretending to pick up a piece of food when there was no object on the tray; *Figure 8.12*), or when observing the same action performed with tools (forceps or pliers) instead of the hand.

In this study, 31.5% of mirror neurons were classified as being "strictly congruent," meaning that they responded preferentially to the same action, regardless of whether the animal was observing an experimenter performing the action or executing the action itself; and 61% were classified as "broadly congruent" – preferred observed and executed actions were similar, but not identical. For example, one such neuron responded vigorously during *observation* of a precision grip and observation of whole-hand prehension, but only responded to *execution* of a precision grip. The remainder were "noncongruent" with regard to preferred observed vs. executed action(s).

The authors suggested that mirror neurons are sensitive to the meaning of an action, rather than to its precise sensory or motoric properties. They further speculated that mirror neurons may underlie learning through imitation (prevalent in humans as well as in nonhuman primates), as well as, possibly, speech perception in humans.

TABLE 8.1 Actions that mirror neurons responded to in Gallese et al. (1996) study

Observed hand actions	Number of neurons
Neurons with one preferred action	
Grasping	30
Placing	7
Manipulating	7
Hands interaction	5
Holding	2
Neurons with two preferred actions	
Grasping/placing	20
Grasping/manipulating	3
Grasping/hands interaction	3
Grasping/holding	5
Grasping/grasping with the mouth	3
Placing/holding	1
Hands interaction/holding	1
Neurons with three preferred actions	
Grasping/placing/manipulating	1
Grasping/placing/holding	4

Holding a mirror up to nature?

Mirror neurons have been among the "hottest" topics of research in contemporary cognitive neuroscience. One factor driving this interest is that many believe that they offer a neural basis for many popular schools of thought in cognitive psychology, including embodied cognition, common coding theory, and the motor theory of speech perception. The last one was referenced by Gallese and colleagues (1996). It is a theory, first proposed in the 1960s, that an important component of speech perception is the "listener" watching the mouth of the talker, and simulating in her mind the larynx, tongue, and lip movements being made by the talker. Gallese and colleagues (1996) speculated that the F5 region in the monkey may bear homologies to Broca's area in the human – the region of left inferior PFC that we first encountered in *Chapter 1*, and will do so again in *Chapter 19*.

With regard to ASD, some have proposed that dysfunction of the mirror system underlies the disorder. One high-profile study (Dapretto et al., 2005) compared fMRI activity in typically developing adolescents vs. "high-functioning" children with ASD on tasks requiring passive observation vs. mimicking of visually presented facial expressions. The findings indicated that, although behavioral performance was comparable between the two groups, "the ASD group showed no activity in the mirror area in the pars opercularis" (Dapretto et al., 2005, p. 29). Note that, strictly speaking, the assertion of "no activity" cannot, literally, be true. If it were, pars opercularis in these subjects would have been necrotic. Indeed, despite this statement, the authors further reported that the level of activity in this region that purportedly showed "no activity" correlated negatively with ASD subjects' scores on two scales, indicating that "the greater the activity in this critical component of the [mirror neuron system] during imitation, the higher a child's level of functioning in the social domain" (pp. 29–30).

In response to this embrace of mirror neurons as a factor accounting for important human behaviors, and their pathological dysfunction, cautionary voices have been raised. For these, the reader is directed to two opinion pieces, one entitled "A Mirror up to Nature" (Dinstein, Thomas, Behrmann, and Heeger, 2008), and a second entitled "Eight Problems for the Mirror Neuron Theory of Action Understanding in Monkeys and Humans" (Hickok, 2009), both listed under *Further Reading*.

IT'S ALL ABOUT ACTION

The principles of motor control lie at the core of understanding human behavior. On one level, this must literally be true, because we cannot *behave* without the release of ACh at the neuromuscular junction causing the contraction of muscle, nor all the steps that precede this event. At a deeper level, we have also seen that circuits identical to those responsible for the triggering of a motor command and for the fine-tuning of its execution apply those same computations to signals from prefrontal areas associated with our most abstract thoughts and our most powerful feelings. It will serve us well, therefore, as we delve further from the sensory and motor peripheries, in the exploration of "higher levels" of cognition, to be at the ready with such principles and concepts as population coding, efference copy, neuromodulatory tone, and RPE signals.

END-OF-CHAPTER QUESTIONS

1. What is the principle of efference copy? Name two major systems that work on this principle.
2. What does it mean to say that muscles behave like springs? How does the motor system take advantage of this property?
3. In what way(s) is the motor homunculus similar to the somatosensory homunculus? In what way(s) are they different?
4. Explain how population coding across hundreds of broadly tuned units can produce exquisitely precise movements.
5. What principle do you think better captures the function of the parietal cortex, processing *where* objects are located in the visual world, or computing *how* to act on the world based on visual input? Or, alternatively, can both be valid? Support your answer with empirical evidence.
6. How is a copy of the efferent motor signal processed in the cerebellum? What is the result?
7. What are two consequences of basal ganglia functioning of reducing levels of DA in the neostriatum, as occurs in PD?
8. What are the fundamental principles of reinforcement learning? In what way do these seem to be carried out by the basal ganglia nuclei?
9. What properties distinguish mirror neurons of PMC from "conventional" neurons in this region? What functions might such neurons enable?

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