

22 The Anatomy and Physiology of the Motor System in Humans

ANA SOLODKIN, PETR HLUSTIK, & GIOVANNI BUCCINO

INTRODUCTION

Sensation and volition, so far as they are connected with corporeal motions, are functions of the brain alone... The will operating in the brain only, by a motion begun there and propagated along the nerves, produces the contraction of the muscles.

– William Cullen (1710–1790)

The behavioral *repertoire* of humans is broad, extending from simple behaviors such as sensory perception to more complex cognitive behaviors like language or creativity. Interestingly, no matter how simple or complex are these behaviors, they share without exception the common feature that their expression is a motor act. For the motor system to implement this large variety of cognitive behaviors, there must be an evolutionary bias toward a highly sophisticated and expanded organization of the system. Indeed, according to some (Freund, 1983), association cortical motor regions are among the cortical areas that have changed the most from non-human to human primates. They further manifest a parallel increase in complexity of their connectivity patterns (Zilles et al., 1995). This means that while subcortical motor regions (from spinal cord to cerebellum and basal ganglia) might not be that dissimilar among mammals, cortical motor regions have changed significantly, reflecting a link between motor output and cognitive processing.

This chapter on motor physiology intends to provide an overview on how the nervous system has implemented the ability to produce complex motor behaviors in the human. Although the following sections will place special emphasis on “skilled” movements, some comments on rhythmic movements will also be included.

Coordination of movements between the upper limbs is a function highly distributed across the animal kingdom, from tetrapod taxa to primates (Iwaniuk & Whishaw, 1999). Although this coordination can be considered to be homologous across species, and although the movements *per se* are not very different between animal species and humans, there are two aspects of this homology to highlight: First is that there are at least two types of limb

synchronization, one involving simpler, generally rhythmic, movements and another incorporating more complex movements. The simplest movements are generally associated with posture and locomotion and are, at least in part, controlled subcortically (Poppele & Bosco, 2003), generated in specialized circuits originally described as “motor pattern generators” (Grillner & Wallen, 1985; Pearson, 1995). By contrast, more complex movements, sometimes called “skilled” movements, have evolved to the highest levels in humans. In terms of evolutionary biology, motor skill refers to the “ability to solve a motor problem correctly, quickly, rationally and resourcefully” (Bernstein, 1996, cited in Wiesendanger, 1999). According to Wiesendanger (1999), the high degree of development of hand dexterity in hominids is reflected by the fact that they not only have the ability to use tools but are also able to fabricate them. In this context, the concept of hand dexterity implies goal-directed action that has been previously learned and practiced. Throughout evolution, the increase in hand skill, tool making and vertical locomotion (that freed the hands), has been accompanied by a parallel increase in the size of cortical motor association areas. Anatomically, this increase is specifically related to an increased volume of neuropil, reflecting an increase in the complexity of connectivity (Zilles et al., 1995).

Albeit somewhat artificial, an anatomical division of regions involved in the production of movement can be instructive in understanding the physiology of the human motor system (Figure 22.1). The brain stem and spinal cord can be viewed as the regions of the central nervous system that contain the interneuronal-motoneuronal networks responsible for the production of reflexive and rhythmic motor behaviors. These networks can be regulated by descending modulation from the cerebral cortex (to produce voluntary movements) or from sensory afferents from the peripheral nerves to produce reflexes. Sherrington (1906) called this the *final common pathway* to denote the fact that this is the final output from the whole system to the muscles. The Basal Ganglia and the Cerebellum are important regions of the Central Nervous System that play a crucial role in the coordination of

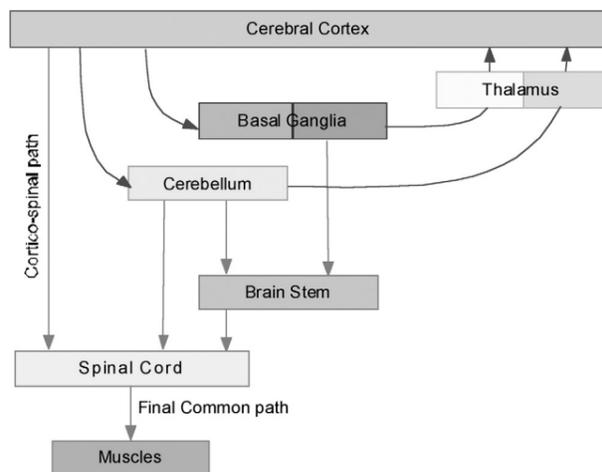


Figure 22.1. Diagram of the general organization of the Motor System in Humans. This figure depicts a simplified organization of the motor system in humans. Note the variety of descending pathways originating from the cerebral cortex that will finally convey into the final common pathway on its way to the effector muscles. The cerebellum (CRB) and the basal ganglia (BG) are important components of this system since they not only have descending inputs into the brain-stem, but also, they are part of closed loops from and to the cerebral cortex. Note that even when both loops pass through the thalamus towards the cerebral cortex, each one of them has a private line in different thalamic regions. Modified from: Heimer L (1994). *The human brain and spinal cord: functional neuroanatomy and dissection guide*. 2nd. Ed. Springer Verlag.

movement by exerting a modulatory influence on most of the cerebral cortex. These complex regions form two important re-entrant systems to the cerebral cortex (as seen in Figure 22.1), where they can produce widespread effects. Finally, the motor cortical regions are interesting to study particularly in the context of cognitive functions. Some of these cortical motor regions are among the regions that have suffered a large change through evolution, as commented previously (Freund, 1983), but others included in modern maps of motor anatomy (Rizzolatti, Luppino, & Matelli, 1998) are located mainly in the parietal lobule, and have not traditionally been considered integral areas for motor control. Because of the inherent importance of skilled movements in the evolution of species, including humans, this chapter will provide some specific examples (motor imagery, motor imitation, and motor learning) to illustrate potential interactions between movement production and higher cognitive functions.

METHODS FOR THE STUDY OF HUMAN MOTOR PHYSIOLOGY: HISTORICAL PERSPECTIVE

Neuroanatomical substrate of motor functions

To know the brain... is equivalent to ascertaining the material course of thought and will, to discovering the intimate history of life in its perpetual duel with external forces.

– Santiago Ramón y Cajal (1852–1934)

The concept and study of human motor function (along with all other brain functions) progressed greatly with advances in science and anatomy starting in the late 18th century, when sophisticated techniques of brain tissue fixation and sectioning provided a new window on the three-dimensional anatomy of the brain. Since Schwann proposed the cell theory in 1839, the field of histology and microscopic anatomy developed rapidly. In 1906, the Nobel Prize in Physiology or Medicine was awarded to Camillo Golgi and Santiago Ramón y Cajal in recognition

of their studies on the structure of the nervous system. In fact, their approach provided for the first time the notion of the neuron as the basic unit of the nervous system.

Regionally specific features of the central brain region were described by Betz (1874), making one of the first steps toward the microstructural, cytoarchitectonic parcellation of the entire human cerebral cortex, a task later pioneered by Campbell (1905), Elliot Smith (1907), and, most prominently, Brodmann (1909) (Figure 22.2). Cortical fields associated with motor function were further differentiated by the Vogts (Vogt & Vogt, 1919), who, among other advances, divided the premotor regions (BA 6) into two subregions, a division later justified by physiological differences in human and non-human primates.

Contemporary anatomical methods of the motor system are based on the visualization of specific groups of brain cells (both neurons and glia) using immunological methods. These cells are detected using specific antibodies against proteins present in cell organelles or in chemical elements contained in them (e.g., neurotransmitters). This method has uncovered specific groups of cells (e.g., pyramidal cells or glial and endothelial cells) as well as cells that contain specific neurotransmitters (e.g., GABA, glutamate, amines, NO) or specific proteins, some of which are present only in certain states (e.g., apoptosis, the process of programmed cell death). Since these techniques are performed *post-mortem*, they have facilitated construction of chemo-architectonic maps of the brain in humans as well as animals, thus permitting direct comparison among species. As an example of these neurochemical techniques, Figure 22.3 shows the giant Betz cells located in the primary motor cortex (M1) in humans detected with an antibody against a non-phosphorylated neurofilament protein called SMI-32. Note the great detail that can be achieved with this type of method. For an interesting example of these techniques, we refer the reader to the chemoarchitectonic maps based on the distribution of transmitter and neuromodulator receptors in the human brain (Zilles et al., 2002).

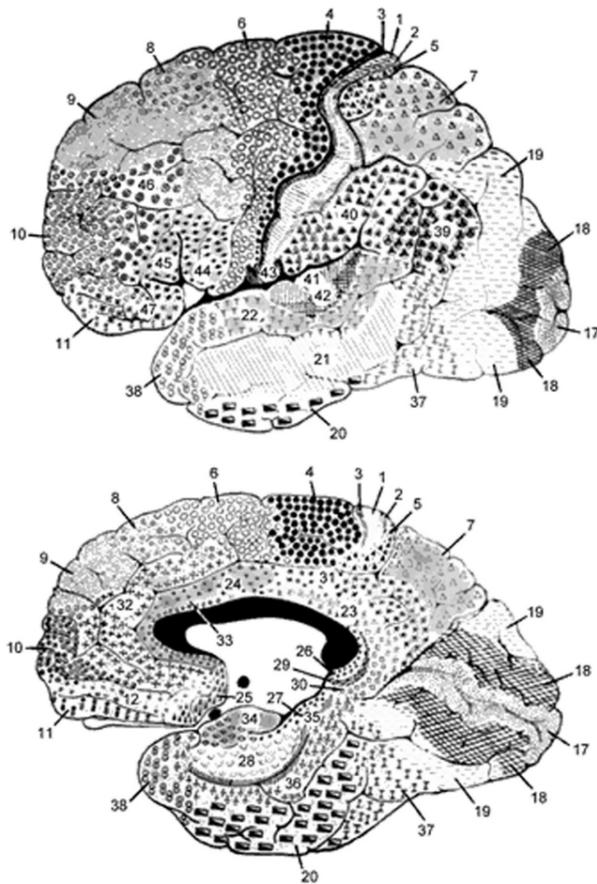


Figure 22.2. Brodmann's cytoarchitectonic map of the human cerebral cortex. These numbers are still commonly used to refer to different brain regions. The reason for its universal use is perhaps the fact that by describing anatomical differences among cortical areas, implicitly he provided a map for functional differences as well.

Relating brain lesions to motor deficits

Effects of brain lesions on human behavior have been observed for centuries. The Edwin Smith papyrus provided the first written record about a case of hemiplegia after (closed) head injury, as well as cases of motor and sensory deficits after spinal cord injury. In 1760, Arne-Charles Lorry demonstrated that damage to the cerebellum affects motor coordination (Finger, 1994).

Nineteenth-century physicians studied patients with lesions to understand the cortical localization of function, including language (Broca, 1861) and motor function. Hughlings Jackson and Charcot (Charcot, 1877; Jackson, 1863; Jackson, 1873), studied both irritative (seizure-generating) lesions and stroke, and summarized their observations of motor abnormalities. They proposed, along with other motor features, an orderly gross somatotopic arrangement of motor control. In the precentral gyrus (i.e., M1), the head subdivision was localized most ventrally and laterally near the lateral sulcus, hand and

arm dorsal to the head, and trunk and leg most superiorly and extending onto the medial surface of the hemisphere.

Subsequent lesion studies (Foerster, 1909; Freund, 1987) generally replicated earlier findings, rather than providing novel information on finer aspects of motor control. The reason for this is that cortical lesions are typically large (Bogousslavsky & Caplan, 1995) and affect several motor cortical areas and/or a substantial portion of each. On the other hand, deficits resulting from a cortical lesion and limited to certain fingers or certain arm movements were reported early in the twentieth century (Foerster, 1909; Foerster, 1936a). With the availability of non-invasive brain imaging (X-ray computed tomography, CT, or magnetic resonance imaging, MRI), small brain lesions can now be detected *in vivo*, allowing clinical-pathological correlations in patients with small and/or transient motor deficits. Taking advantage of these methodological advances, several recent clinical studies described either focal finger pareses or pareses with radial/ulnar predominance with small lacunes of the precentral gyrus revealed on MRI (e.g., Lee, Han, & Heo,



Figure 22.3. Microphotograph of human Betz cells in the human. These motor neurons were stained with an antibody against a non-phosphorylated neurofilament protein found only in pyramidal cells. The microphotograph from neurons located in layer V of the human primary motor cortex, give rise to some (not all) of the descending fibers of the corticospinal pathway that will terminate in the spinal cord.

1998). Although such cases have been known to clinicians, they were dismissed as uninformative exceptions in previous discussions of human motor cortical organization.

Nineteen-century pioneers of the lesion method, Broca and Wernicke, also made an important distinction between lesions located in the gray and the white matter, thus differentiating cortical syndromes from “conduction” syndromes. The concept of white matter or “conduction” syndromes was further developed by Dejerine and Liepmann and reached maximal expression with Norman Geschwind (1965), who described specific syndromes in both animals and men in terms of disconnections among cortical brain regions.

Geschwind’s approach to understanding neurological deficits was important not only because he highlighted the connections among brain regions as being the recipients of function, but also because he included in his analysis the actual connectivity patterns of the brain. In fact, among his speculations was the suggestion that the increase in association cortical areas in man would provide new connectivity patterns (not present in animals) to explain the presence of novel interrelationships among areas producing new functions (like language). The limitation of this early perspective, however, is that neurological syndromes were still described as specific lesions in specific white matter pathways, perpetuating in some sense, the localizationist approach to behavior.

The connectionist approach however, has been constantly evolving, and as we will see in the last part of this section, new methodological approaches for the study of the physiology of the CNS in humans, like brain imaging, are making feasible a more comprehensive study of the relationship between brain and behavior.

Electrical stimulation and ablation studies

Proceeding from these observations on the effect of natural lesions, pioneering physiologists conducted animal vivisection experiments and electrical stimulation and ablation studies on animals, including monkeys and apes.

Flourens (1824) conducted ablation and stimulation experiments examining motor functions of the cerebellum (where his conclusions regarding its role in coordination of voluntary movements remain valid) and cerebral hemispheres (where his method was inappropriate and therefore his conclusions, incorrect). German physiologists Fritsch and Hitzig (1870) carried out electrical stimulation studies in a canine model. Their findings overthrew three theories that had stood since Flourens: they established cortical excitability, a role for the primary motor cortex in the mechanism of movements, and cerebral localization.

Building on the efforts of Jackson and of Fritsch and Hitzig, Ferrier published detailed studies (1873; 1875) of cortical localization in non-human primates. He thus established stimulation mapping as a reliable experimental method. Ferrier also proposed that motor centers,

besides leading the “accomplishment of acts of volition”, form the organic centers for the memory of “accomplished acts”, that is, allow storage of learned movements. These early studies culminated in the work of Charles Scott Sherrington (1906), whose work “The Integrative Action of the Nervous System” formed the basic framework for the rest of the twentieth century. Similar information was also collected in the human, almost exclusively in patients planned for brain surgery (most often for epilepsy), rather than in healthy brains (but see: Bartholow, 1874).

Electrical stimulation of exposed cortical surface in patients scheduled for brain surgery (e.g., Cushing, 1909) confirmed the presence of somatotopic representations along the precentral and postcentral gyri (M1 and S1 respectively). Furthermore, an orderly arrangement was also found within the hand, where thumb was found most laterally and little finger most medially (Foerster, 1936b; Foerster & Penfield, 1930; Penfield & Boldrey, 1937). Most of these pioneering authors also commented on the complexity of the observed arrangement and the early researchers also reported on many complex features of primary motor cortex organization, such as overlapping functional codes of different movements and dynamic changes of function performed by a particular cortical location. For example, Jackson (1873) noted that although a single part of the body is represented “preponderating” (sic) in one area of the human precentral gyrus, it is also represented in other parts of the gyrus, though to a different degree and in different combinations with other body parts. Like Sherrington (on the instability of cortical point), Foerster observed that from a single precentral locus, repeated surface stimulation evokes a series of different movements of individual fingers, from which he concluded that each stimulation point on the motor cortex contains neurons representing different body parts (Foerster, 1936a). Finally, Penfield and Boldrey (1937) showed overlap of the motor cortical sites at which stimulation evoked movements of different fingers. They expressly warned against an oversimplified interpretation of their famous homunculus cartoon (See Figure 22.4).

Single-neuron recording in the cerebral cortex of awake, behaving primates (and, rarely, humans). Until the late 1970s, most human mental processes, including complex motor control, were not amenable to direct experimental analysis. Since that time, however, several different approaches have been developed to characterize the neural substrates of information processing.

Ed Evarts, studying the neural correlates of movement and, subsequently, Vernon Mountcastle and his colleagues, focusing on somatic sensation, helped establish the study of internal representations of specified behaviors by studying the activity of single neurons in the cerebral cortex in intact, awake, behaving primates that are trained to do particular motor or perceptual tasks. Human studies with cortical single-neuron recordings are rare. Goldring and Ratcheson (1972), for example, confirmed active and

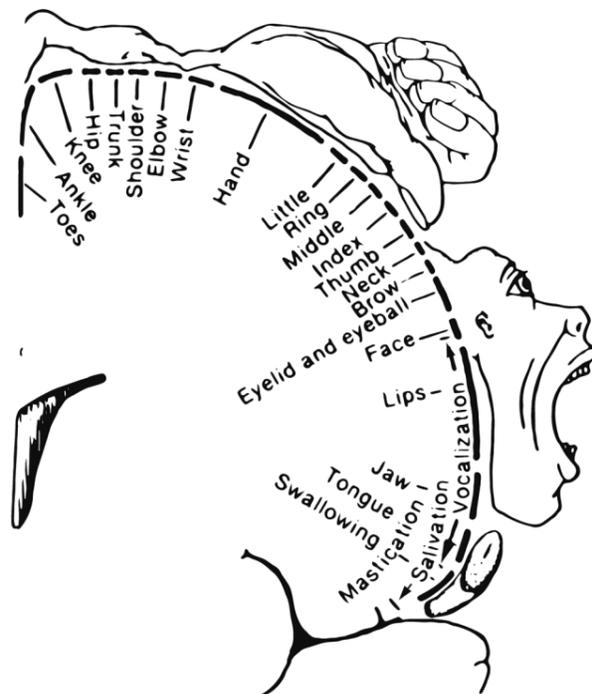


Figure 22.4. Somatotopic Organization of the primary motor cortex in Humans. Schematic representation of the location of different body parts within the primary motor cortex. Note that the areas that have the larger representations are the fingers, face and mouth. Even though when Penfield suggested a careful interpretation of the diagram since the divisions for each body part are overlapped, this diagram has been used extensively and sometimes over interpreted.

passive movement-related neuronal activity in human M1, while auditory and tactile stimuli produced no effect. For further examples see Engel et al. (2005).

These important studies (seldom done in humans) highlight the importance of the intrinsic features of the individual neuron with respect to function. However, they neglected the effects of ensembles of neurons in the generation of such behaviors. Additional methodological approaches, discussed in the following sections, provide a systems approach by determining the effects of activation at the population level on the production of motor behavior.

Electrophysiology methods

Electroencephalogram (EEG) – motor-related potentials. A noninvasive window on dynamic nervous system functioning was opened by the development of techniques to study nerve conduction and electroencephalography (EEG) by Sir Richard Caton in animals and Hans Berger in humans (1929). This methodological approach refers to the scalp recording of electrical field potentials generated on the surface of the cortical mantle. The analysis of this continuous EEG recording is based on the frequency of the signals and on the morphology of the waves.

In contrast, “evoked potentials” or “event-related potentials” (ERP) refer to changes in the patterns of activation produced by specific stimuli. The earliest experimental evoked potentials were described by Waldo in 1933, and the first EEG related to a human motor act was reported by Bates (1951), who described a negative potential after movement onset, originally interpreted as a re-afferent sensory evoked potential. Different instrumental settings were required to detect the very slow changes or DC shifts reflecting preparatory movement-related components of the EEG signal: contingent negative variation (CNV) (Walter et al., 1964) and the *Bereitschaftspotential* or readiness potential (BP/RP), (Kornhuber & Deecke, 1965), which are markers of motor preparation for externally cued or internally initiated movements, respectively. The RP initially localizes to the midline but its amplitude becomes greater over the hemisphere contralateral to the responding hand (for a review, see: Coles, 1989). Another motor-associated phenomenon is EEG (event-related) desynchronization (ERD), observed contralaterally to the moving hand. All of these electrophysiological phenomena – RP, CNV, and ERD – have been related to different aspects of motor programming and have also been investigated and found pathological in patients with motor dysfunction, such as dystonia (Kaδovskπ, 2002).

Magnetoencephalography (MEG). One of the great limitations of the classical electrophysiological techniques (EEG and ERP) is their inability to record and/or localize electrical field potentials from brain regions that do not originate on the brain surface or close to the scalp. This limitation does not apply to the relatively new technique of magnetoencephalography (MEG) that detects the magnetic field generated by the neuronal electrical activity (Hari & Kaukoranta, 1985). MEG technology has grown from a single-channel to multi-channel techniques, and currently achieves spatial localization of dipole sources down to a few millimeters. MEG has been used to map movement-related magnetic fields, (e.g., Antervo et al., 1983), and has contributed to study of motor control timing (because of its excellent temporal resolution) and complex motor control, such as the study of motor correlates of long-term skilled motor practice (Elbert et al., 1995).

Transcranial electrical and magnetic stimulation (TMS)

Although direct electrical stimulation of the human brain has been possible only with the use of invasive techniques during neurosurgical procedures (see, for instance, Penfield & Rasmussen, 1950), the knowledge gained with this method in animal experiments is impressive. Thus, it is not difficult to understand the tremendous value in developing a technique to stimulate motor regions in a non-invasive manner in neurologically intact humans. Such a technique should not have direct contact with the motor regions (i.e., performed outside of the skull), and at the

same time, it should be painless. Electrical activation from the scalp (Levy, York, McCaffrey, & Tanzer, 1984) fulfills the first requirement but not the second. Hence, the alternative has been to induce electrical currents within the brain with time-varying magnetic fields (Faraday's law).

The history of magnetic stimulation is relatively recent (for review see Kobayashi & Pascual-Leone, 2003). The first report of a time-variable magnetic field producing physiological changes in the brain was written by d'Arsonval in 1896. In his study, a volunteer reported phosphenes and vertigo when his head was stimulated by a coil at 42 Hz (not surprising he got those effects since that is a high frequency by today's standards).

Several subsequent studies were performed, many by stimulation of peripheral nerves rather than cortex, but these studies led to methodological refinements regarding the quality of the magnetic pulse needed to produce a response with minimal risk to the subjects. In the study of Barker et al. (1985), brief transcranial magnetic stimulation pulses over the motor cortex excited the corticospinal pathway (from M1 to spinal cord) and generated electromyographic signals (motor evoked potentials, MEPs), with or without brief contractions in the peripheral muscles. TMS has been widely used since that time to study the motor system in humans, both healthy and diseased. TMS helps to assess the excitability of the primary motor cortex and the corticospinal pathway, which can be enhanced during spontaneous mild voluntary contraction (Mills, Murray, & Hess, 1987), motor preparation (Barker, Jalinous, & Freeston, 1985) or motor imagery (Rossini et al., 1999), as well as after successful motor recovery from hemiparetic stroke (Liepert et al., 1998). For this, it has become a clinical tool as well. More sophisticated physiological studies have shown that the facilitation of responses in hand muscles produced by voluntary contraction is also present when contralateral muscles are used, but not when a leg muscle is contracted. These results demonstrate a close functional influence of one cortical hemisphere on the other, probably involving neural activity at both spinal and cortical levels.

Motor evoked potentials can also be obtained by stimulation of the spinal cord (Figure 22.5) or the cerebellum. Not surprisingly in these cases, the latency of the MEPs is shorter and the conduction velocity is faster when compared to the stimulation in the primary motor cortex. These latter examples highlight further the value of TMS in assessing motor physiology.

Brain imaging

Following the development of quantitative methods for measuring whole brain blood flow and metabolism in animals by Kety and his colleagues (Landau et al., 1955), David Ingvar, Neils Lassen, and their Scandinavian colleagues introduced methods applicable to humans that permitted regional blood flow measurements by using scintillation detectors arrayed like a helmet over the head

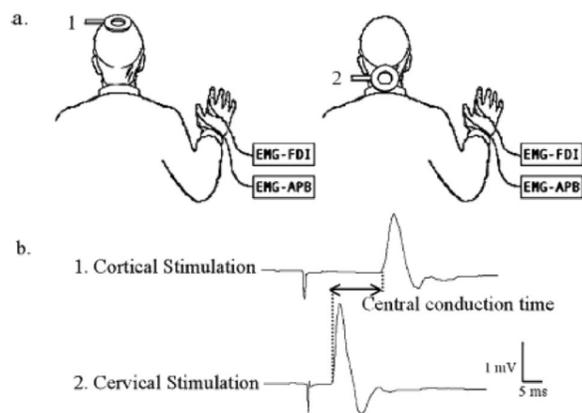


Figure 22.5. Principle of transcranial magnetic stimulation. **a.** Representation of the placement of the stimulating coil (on the scalp overlying the primary motor cortex and over the cervical spinal cord targeting the dorsal roots). These cartoons show also the recording sites on hand muscles (either the first dorsal interosseus (FDI) or the abductor pollicis brevis (APB)) where the motor evoked potentials are recorded. **b.** Panels showing the actual muscle response (MEPs) as a result of the stimulation at the level of the cortex (1) and in the spinal cord (2). Note the difference in latency for each response. The central conduction time is calculated by the difference between them. From: Maeda and Pascual-Leone (2003). *Transcranial magnetic stimulation: studying motor neurophysiology of psychiatric disorders*. *Psychopharmac.* 168:359–376. With permission of Dr. Pascual-Leone.

(Lassen et al., 1963). They subsequently demonstrated that blood flow changed regionally during changes in brain functional activity in humans (Ingvar & Risberg, 1965). This approach was not initially embraced by many neuroscientists or psychologists, an interesting indifference that was to disappear almost completely in the 1980s.

Applying image reconstruction techniques introduced in X-ray computed tomography, researchers envisioned another type of tomography, positron emission tomography (PET), which created *in vivo* autoradiograms of blood flow and glucose metabolism reflecting brain function (Ter-Pogossian et al., 1975). As expressed by Marcus Raichle (Raichle et al., 1983), "a new era of functional brain mapping began."

One of the advantages of PET is the possibility to simultaneously investigate different physiological processes. For example, studying regional cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO₂) (Fox, Mintun, & Raichle, 1986) uncovered their uncoupling during cortical activation, which has provided a physiological mechanism to explain the functioning of subsequently developed functional MRI (see below).

Functional brain imaging with PET targeted many issues in the organization of the human motor system, (see, for example Passingham, 1998).

Magnetic resonance imaging (MRI) and spectroscopy (MRS). MRI has pushed non-invasive brain imaging yet another step further towards our understanding of the

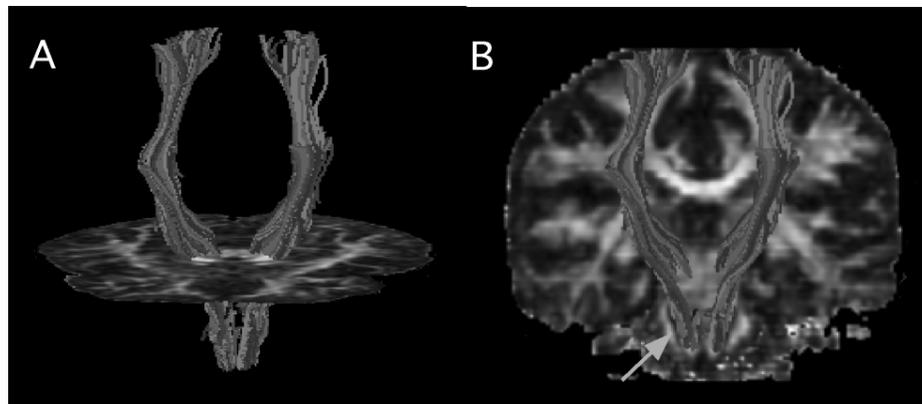


Figure 22.6. Image of the cortico-spinal path of humans using DTI. These figures show in blue, cortico-spinal fibers going from cortical motor and sensory areas, in their way to brain-stem and spinal cord. **a.** Descending fibers shown in three dimensions, crossing through an axial structural MRI. **b.** Same fibers superimposed to a coronal MRI slice. Note how the right and left parts of the pathway get close together at the level of the medulla where they will cross over to the contralateral side. Courtesy of K. Arfanakis. Department of Biomedical Engineering, Illinois Institute of Technology (IIT).

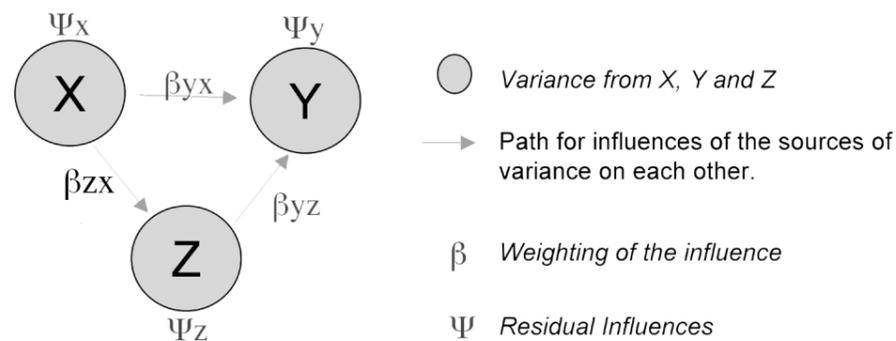
mind-brain relationship. MRI provides significantly higher sensitivity than other structural imaging techniques like CT in the detection of abnormal or malconfigured brain tissue, as well as providing higher resolution in the anatomical features of normal brains. The benefit of morphological MRI in detecting small brain lesions and thus allowing fine-grained lesion studies has been already mentioned. However, the main new feature of this methodology is that the MR scanner may be “tuned” to detect other properties of brain tissue (beyond anatomy), providing information on brain metabolism, function or connectivity. Magnetic resonance spectroscopy, functional MRI (fMRI) and diffusion tensor imaging (DTI) represent three such applications, and the acquired data from each MR modality can be easily integrated within the same studied brain.

Functional MRI takes advantage of similar tissue processes as other previous functional imaging methods, e.g., single photon emission computed tomography (SPECT) and PET, namely the rise in local metabolism and local cerebral blood flow with increased synaptic activity. The most frequently used blood oxygenation level-dependent (BOLD) fMRI technique (Ogawa et al., 1990) exploits the uncoupling of oxygen consumption and blood flow: changes in blood flow are accompanied by much smaller changes in oxygen consumption. Thus, the venous blood leaving active cerebral tissue contains relatively more oxygenated hemoglobin. Since hemoglobin oxygenation changes its magnetic properties, this change in blood oxygen content at the site of brain activation can be detected with MRI.

Free from the radiation load of emission-computed tomographic methods and faster in acquiring functional brain mapping data, fMRI has allowed an explosion of functional brain experiments to investigate brain responses to myriad tasks and stimuli, not in the least from

the motor domain. High spatial resolution has enabled the study of cortical organization on a millimeter scale for example, to study somatotopy within the hand area of the motor cortex (Hlustik et al., 2001). The reader is referred to review articles (e.g., Jezzard, Matthews, & Smith, 2001; Picard & Strick, 2001, and fMRI textbooks) and fMRI textbooks (Jezzard, Matthews, & Smith, 2001; Moonen & Bandettini, 1999) for examples of applications to the study of the motor system. It should be mentioned that fMRI (as well as other functional brain mapping techniques) is most useful when combined with (or preceded by) well-conceived behavioral experiments, as in the work of cognitive scientists (for review, see Posner & Raichle, 1994).

DTI can probe, *in vivo*, the intrinsic diffusion properties of water in deep tissues (Basser, Mattiello, & LeBihan, 1994). One of the most interesting aspects of DTI is that it describes not only the magnitude of the diffusion of water but also, the degree of “anisotropic diffusion” (diffusion in a preferential direction) and its primary direction. When DTI is applied to the central nervous system, it has revealed that the diffusion of water in the white matter is “anisotropic.” The suggested reason for this anisotropy is the ordered structure of axons and myelin sheaths, which imposes a heavy constraint on the diffusion of water in directions perpendicular to the axons but not parallel to them. In this way, information about diffusion acquired with DTI can be translated into the detection and assessment of pathways in the brain as well as to changes in the pathways related to pathology. Diffusion tensor imaging is a promising technique that potentially can allow us to trace and measure, for the first time, pathways in the human brain *in vivo*. Figure 22.6 shows the path tracing of the cortico-spinal pathway in a human without neurological disease. The traced path has been superimposed on an anatomical MRI section in the axial and the coronal



STRUCTURAL EQUATIONS:

$$X = \psi_x$$

$$Z = \beta_{zx}X + \psi_z$$

$$Y = \beta_{yx}X + \beta_{yz}Z + \psi_y$$

Figure 22.7. Theoretical Principle for the determination of the Structural equation models. This diagram shows a simple algorithm describing the effects of regions X, Y and Z onto each other (effective connectivity: element “ β ” plus an error variable Ψ representing unknown influences). An important aspect of the model, differentiating it from some other multivariate methods is that it explicitly represents directionality of effects since it assumes a causal relationship of one area over others with which it is anatomically connected. *Modified from: McIntosh and Gonzalez-Lima (1994). Structural Equation Modelling and its Application to Network Analysis in Functional Brain Imaging. Human Brain Mapping, 2: 2–22.*

planes. Note the origin of this pathway (in the cerebral cortex) descending through the brain stem to cross over at the level of the medulla. Refer to a recent review (Mesulam, 2005) for additional information.

Computer modeling

Computer science also has made a distinctive contribution to systems neuroscience. Learning and memory have been modeled by associative neural networks of Hopfield and others, and the back-propagation learning algorithm of Rumelhart and Hinton. They have shown that complex behaviors could arise from the intrinsic properties of neural nets. Computer models simulate some aspects of the activity of large populations of neurons, thus providing an environment for testing possible neural implementations of particular behaviors in the brain. Neuronal network properties go well beyond the properties of individual neurons and provide for the emergent properties that are commonly referred to as higher brain functions. Computational approaches along these lines, and especially when combined with psychophysics, as in the work of Terry Sejnowski, Steven Lisberger, Richard Andersen, Emilio Bizzi, and Tony Movshon, have been informative in suggesting explanations for functional properties and capabilities of specific neural systems. In the motor domain, for example, modeling suggested a possible mechanism of aligning cortical motor and somatosensory maps (Chen & Reggia, 1996).

An additional approach to computer modeling has been the construction of networks of activation based on PET

and fMRI imaging data. Several tactics have been proposed for using network analysis based on brain imaging data. Notable examples are principal and independent components analysis, and structural equation modeling (SEM). The description of brain imaging data using structural equation modeling as depicted in Figure 22.7 (Buchel & Friston, 1997; Gonzalez-Lima & McIntosh, 1994; Horwitz, Friston, & Taylor, 2000) has produced a conceptual change in the way we interpret such data. In particular, by characterizing networks of activation, SEM describes the functional influence of a specific anatomical brain region on other areas with which it is anatomically connected. The emphasis thereby changes from the individual brain regions active in each condition to the relationships among them. This functional influence of one region over others is called “effective connectivity.” In the past, McIntosh and his collaborators (1999, 2000) have referred to the modulation of effective connectivity over time or over different conditions as “neural context” to denote the fact that a single anatomical region can play different roles depending on its interactions with regions with whom it is related. This means that behavior will be generated depending on the dynamics of the temporo-spatial relationships among brain regions. An example of SEM applied to the study of motor physiology can be found in this chapter in the section dedicated to motor imagery.

Combined methodology

Added power can be gained by combining different complementary research techniques within the same subject

and study. For example, combination of fMRI and EEG/MEG yields data with both high structural resolution (benefit of fMRI) and high temporal resolution (EEG/EMG). In a different way, DTI allows more advanced network analysis of fMRI data by providing direct within-subject estimates of brain connections among the active regions.

Another approach combines functional mapping of active brain areas during specific behavioral conditions with subsequent studies of single neuronal activity in the corresponding areas in the brains of conscious monkeys carrying out essentially the same behavioral task. This combined approach in monkeys and humans promises to be a powerful tool for analyzing those complex higher-brain functions that have correlates in non-human primates.

THE ANATOMICAL ORGANIZATION OF THE MOTOR SYSTEM: A MODERN VIEW

In the previous section of this chapter, we highlighted the methods used for the study of motor physiology and anatomy in humans. However, even when not explicitly stated, the section also suggested the importance of neural networks for understanding motor control mechanisms. This section on anatomy of the motor system will emphasize pathways of the brain associated with motor control.

Concretely, we can consider the motor pathways as belonging to one of three distinct categories: Descending pathways that produce the actual movement; re-entrant circuits that modulate the ongoing activation of other motor circuits; and cortico-cortical pathways determining interactions among motor cortical regions. Because of the prominent role of the cortex in the generation of motor cognitive functions, our emphasis will be biased towards the latter connections.

Descending pathways

The role of the descending pathways includes not only the regulation of skeletal muscles (i.e., from reflexes to skilled voluntary movements), but also the regulation of smooth muscle for autonomic control. Descending pathways (e.g., cortico-spinal path) that originate in the cerebral cortex terminate in the brain stem for the control of head and face movements and in the spinal cord for the control of the rest of the body. These however, are not the only descending pathways. Additional paths originate in brain stem nuclei (red *nucleus*, vestibular *nuclei*, superior *colliculus*), also terminating in the spinal cord. Because of its prominent role in the control of voluntary movements in humans, we will limit our description to the descending pathways originating in the cortical regions, i.e., the corticospinal path. A depiction of this pathway in a human *in vivo* as seen with diffusion tensor imaging can be appreciated in Figure 22.6.

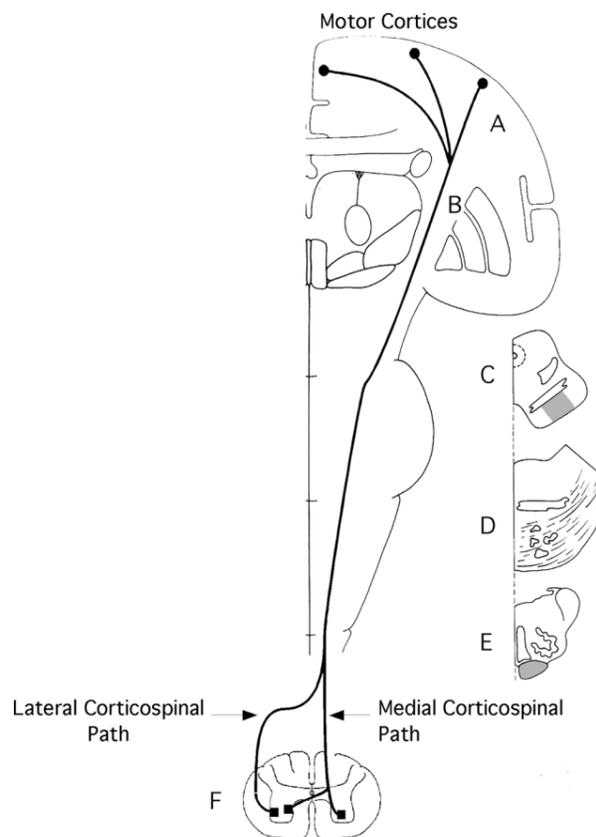


Figure 22.8. Trajectory of the medial and lateral corticospinal path. **a:** Corona radiata; **b:** Internal capsule; **c:** Midbrain; **d:** Pons; **e:** Medulla; **f:** Spinal cord. Note the somatotopic termination in the spinal cord, of the medial and lateral components of the pathway carrying information for proximal and distal movements respectively. Modified from: Haines D. E. (1987) *Neuroanatomy. An Atlas of Structures, Sections and Systems. Second Ed.* Urban & Schwarzenberg, Germany.

Corticospinal pathway. The neurons of origin of this pathway are located in several cortical regions (all displaying somatotopic organization). Among them, the primary motor (Brodmann's area 4; M1) and sensory (especially BA3; S1) cortices, the premotor regions (BA 6 medial and lateral or supplementary motor area: SMA and lateral premotor cortices: LPMC respectively), and the anterior cingulate motor area: CMA (BA 24). This descending pathway has two different components: one is a pathway that descends laterally in the spinal cord and controls the movements of the distal muscles (hands); the other is a medially descending pathway that controls the movements of the proximal muscles (trunk). Whereas the entire lateral corticospinal path crosses over to the contralateral side at the level of the medulla (resulting in a contralateral motor control of hands), the medial path does not cross. As a consequence, injury to the right primary motor cortex produces a deficit in the left hand and vice versa.

Figure 22.8 shows the trajectory of both components of the corticospinal path through the different levels of the brain (from cerebral cortex to spinal cord).

The corticospinal path originates in deep layers of several motor and sensory regions in the cerebral cortex. The axons of these neurons descend through the *corona radiata* and form a tight bundle descending in the internal capsule. The pathway continues on its way down forming the middle portion of the cerebral peduncles in the midbrain. After that, the compact bundle passes through the pons on its way to the medulla, where in its lower levels, all the fibers forming the lateral cortico-spinal path cross but the fibers forming the medial path do not. The final destination of the bundle is in the spinal cord, where these long axons synapse either in the motoneuronal pool, in the interneurons located in the middle portion of the central grey, or in the sensory neurons located in the posterior horn. As seen in Figure 22.8 the spinal cord also has a somatotopic organization: whereas the lateral corticospinal path terminates in the motoneuronal pool located in the lateral regions of the anterior horn, the medial path terminates bilaterally in the medial motoneuronal pool. In turn, the axons of the spinal motoneurons travel in the peripheral nerves to reach and synapse in the appropriate muscles.

The organization of the motor path that controls muscles in face and head have a very similar organization, except that the termination of the cortical neurons is not at the level of the spinal cord but at the level of the brain-stem (cortico-bulbar path), where they synapse with the cranial nerve nuclei in *lieu* of the spinal cord.

Re-entrant circuits

There are two important subcortical motor regions intimately related to the cortex: the basal ganglia and the cerebellum. These structures are sometimes referred to as forming an "extrapyramidal" system to distinguish them from the "pyramidal" corticospinal system. These structures modulate motor activation through two re-entrant circuits to the cortex via the thalamus.

Cerebellum. The cerebellum plays an important role in the coordination of fine movements and in the control of posture. This structure consists of a number of central nuclei surrounded by hemispheres whose intrinsic anatomy resembles the layered organization of the cerebral cortex. The cerebellum receives a variety of afferent inputs from subcortical regions in spinal cord and brain-stem (reticular formation, inferior olive, vestibular system, raphe nuclei), conveying information for the control of reflexes involved in posture and eye position during head movements (Heimer, 1983). In addition, the cerebellum receives inputs from motor and sensory cortical regions, instantiating its role in the modulation of voluntary movements. Output from cerebellum terminates mostly in the red nucleus in the midbrain and the ventral lateral nucleus (VL) of the thalamus. This thalamic nucleus projects to several cortical motor regions, closing a loop between cerebellum and cortex. For a review of the cortical regions receiv-

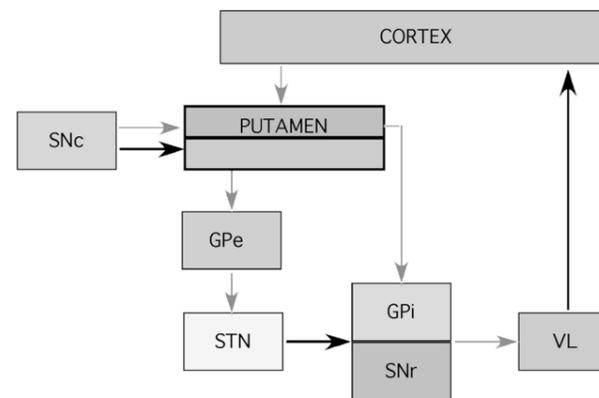


Figure 22.9. Direct and indirect motor paths between basal ganglia and cerebral cortex. Schematic representation of the two re-entrant motor circuits between the basal ganglia and the cerebral cortex. Excitatory projections are represented by the dark arrows and the inhibitory projections by the light grey. **SNc:** Substantia nigra pars compacta; **SNr:** Substantia nigra pars reticulata; **GPe:** external portion of Globus pallidus; **GPi:** internal portion of Globus pallidus; **STN:** sub-thalamic nuclei; **VL:** ventral-lateral nucleus of thalamus.

ing indirect inputs from cerebellum see the work by Peter Strick (Middleton & Strick, 1997).

Basal ganglia. A primary function of the basal ganglia is motor control. The basal ganglia consist of two large structures, the caudate and lentiform *nuclei*. The lentiform *nucleus* is composed of the putamen and the *globus pallidus*. Due to similarities between the putamen and the caudate, some authors group them together under the term *striatum*.

Figure 22.9 shows the main inputs and outputs from the basal ganglia involved in motor control. By far, the cerebral cortex provides the main input to the basal ganglia through the putamen, with all cortical areas sending afferents to it. In addition, the putamen receives well-known dopaminergic input from the *sustantia nigra pars compacta*. Two paths loop back from the putamen to the cortex, one direct and the other indirect. The direct path goes to the internal *globus pallidus*, which in turn projects to thalamus, specifically the ventro-anterior and ventral lateral *nuclei*, (independent of the cerebellar input to these nuclei). The final part of the pathway originates in thalamus and projects to cortical motor regions. The indirect path goes from putamen to external *globus pallidus*, and from there, to the subthalamic nuclei. The path then projects to the internal *globus pallidus* and the *sustantia nigra pars reticulata* regions that project to VL thalamus and then to motor cortices. An interesting aspect of these two pathways is the large number of inhibitory connections (represented in Figure 22.9 with grey arrows producing double inhibitory effects). A number of researchers have attempted, with limited success, to apply this network to understanding the motor deficits of Parkinson's disease. What it is clear is that the basal ganglia are not only involved in the modulation of

motor functions, but also play a role in cognitive functions (Middleton & Strick, 1994).

Cortico-cortical connections

Neurophysiological, cytoarchitectonic, and histochemical studies have radically altered our view on the cortical motor system over the last two decades. Until then, the prevailing notion was that the cortical motor system consisted of three main sectors: the primary motor cortex (M1), lying in the precentral gyrus, the premotor cortex (LPMC) located in the precentral gyrus in front of the primary motor cortex, and the supplementary motor area (SMA) on the mesial surface of the hemisphere. The primary motor cortex was thought to be involved in the actual execution of movements, while the premotor and the supplementary motor areas were thought to be more involved in motor planning. Numerous cytoarchitectonic and histochemical studies have challenged this view. Figure 22.10 shows a modern subdivision of the cortical motor areas originally proposed by Massimo Matelli and coworkers (1985). Figure 22.10 clearly illustrates that the organization of the motor system is more complex than previously thought. In fact, this system consists of numerous areas, each indicated by a number. F1 corresponds to the classically defined primary motor cortex (area 4 of Brodmann); the premotor cortex (BA 6) is further divided into a ventral premotor cortex (LPMCv) and a dorsal premotor cortex (LPMCd). The ventral premotor cortex consists of two distinct areas: area F5 (BA 44 in humans), rostrally located, and area F4 (LPMCv in humans), caudally located. The dorsal premotor cortex is also composed of two areas: area F2, rostrally located (rostral LPMCd in humans) and area F7 (caudal LPMCd in humans), caudally located. On the mesial surface of the hemisphere, the premotor cortex includes a caudal area (area F3, which corresponds to the classically defined SMA in humans) and a rostral area (area F6, also called pre-SMA in humans). An additional area shown in both species is the cingulate motor region (CMA or BA 24c and 23c).

Each of these cortical areas is not only anatomically distinct, but also functionally distinct, since they display specific motor representations of actions somatotopically represented (e.g., hand or mouth). At the same time, motor acts involving a specific body part may be represented in several areas. This multiple motor representation of actions is due to the fact that each area codes for a different aspect of the action. For example, among other features, grasping an apple implies knowing *where* the apple is and *how* big it is. In order to grasp an object properly, one needs to localize it in space, code its pragmatic features, and determine the position of the body in relation to the object. Different areas of the motor system play a specific role in this coding.

All areas in the motor system are connected to additional regions of the cerebral cortex. Some of them (F1-

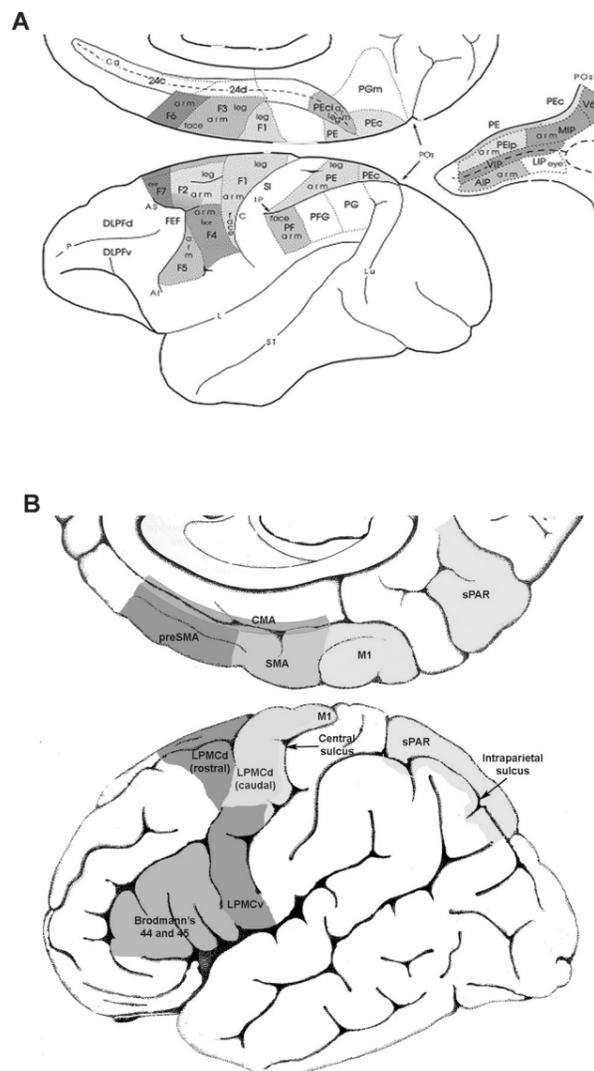


Figure 22.10. Cortical maps of the motor regions in macaque and humans. **A:** Cortical regions in the parietal and frontal lobes in the macaque. **B:** Cortical motor regions in humans. Similar colors between species suggest homology. Modified from Rizolatti, Luppino and Matelli (1998). *The organization of the cortical motor system: New concepts. Electr. Clin. Neurophysiol. 106: 283–296.*

F5, i.e., M1, posterior LPMCd, SMA, LPMCv, and Broca's area) are connected to specific areas located in the posterior parietal lobe, whereas some others (area F6 and area F7, i.e., preSMA and rostral LPMCd) are connected to the prefrontal cortex. Interestingly, while motor areas heavily connected to parietal regions project to spinal cord, motor areas heavily connected pre-frontal regions do not. Furthermore, areas functionally connected to the parietal lobule form a fronto-parietal circuit, devoted to a sensory-motor transformation necessary to act properly on an object and to perform actions accurately. In addition, whereas the prefrontal regions are more devoted to motor planning, cingulate motor regions are involved in motor control related to emotional expression.

It is beyond the scope of the present chapter to describe in detail all of the motor cortical circuits and their functional roles. We will consider three such circuits as examples of the organization of skilled movements. Although most data come from anatomical and physiological studies carried out in the monkey, there is increasing evidence that the same organization is also present in the human brain. When available, data will be reported to show a parallel functional organization in both species.

AIP-F5 circuit for grasping. Area F5 (BA 44 in humans) lies in the rostral part of F4 (LPMCv). Electrophysiological studies have shown that this area contains motor representations for both mouth and hand object-directed actions. Neurons found in this region discharge when one executes specific goal-directed actions like grasping a piece of food with the hand or the mouth, holding it, tearing and manipulating it. There are even neurons that discharge with specific types of grasping. Notable examples of this include precision grip (a prehension obtained opposing the index finger and the thumb, e.g. grasping a piece of food); finger prehension (obtained by opposing the thumb and the other fingers, e.g., grasping a pen); whole hand prehension (obtained by closing the whole hand around an object, e.g., grasping a little ball). Since their discovery, it has been proposed that these neurons build up a “vocabulary” of hand/mouth actions that, like words in a language, can be used in different contexts, whenever appropriate.

Besides motor properties, neurons in area F5 also encode visual features. Based on their visual properties, F5 neurons are divided into a) mirror neurons and b) canonical neurons. Mirror neurons (that will be described in a latter section in this chapter) are neurons that discharge not only when the monkey performs a specific object-directed action with the hand or the mouth, but also when it observes another individual (monkey or human) doing the same or a similar action. They are called “mirror” because the observed action seems to be reflected like in a mirror in the motor representation coded by the neuron. Canonical neurons are not different from mirror neurons as far as their motor properties are concerned, but their visual response is triggered by the observation of an object congruent to the type of action coded by the neuron. For example, if a canonical neuron codes precision grip, it may respond to the observation of a piece of food (which is an object normally grasped with a precision grip). It has been proposed that canonical neurons are able to “describe” the observed object in motor terms and therefore “translate” the pragmatic features integrating them into the appropriate action. Area F5 is intimately connected with the intraparietal area (AIP), an area located inside the intraparietal sulcus. Electrophysiological studies in neurons of area AIP show that they share common features with those of area F5. Most of these neurons discharge during the execution of hand and finger actions (like grasping), activation that in some of them can be modified by visual stimuli. During the act of grasping, for example, area AIP can extract relevant

physical features of the object, whereas area F5 selects the most appropriate type of prehension among those present in the motor “vocabulary” of the area.

Although data coming from monkey studies are not easily comparable to those obtained in humans, there is increasing evidence from brain imaging studies that a fronto-parietal circuit like monkey AIP-F5 is also present. During an fMRI experiment in which participants were required to grasp and manipulate different objects, the main active areas were the LPMCv (including Broca’s region) and an area inside the intraparietal sulcus in the parietal lobe, which could be considered the human homologue of area AIP (Binkofski et al., 1999). Furthermore, patients with lesions within the intraparietal sulcus, are not able to grasp and manipulate objects reinforcing the role of this area similar to that in non-human primates.

VIP-F4 circuit for space coding. Area F4 lies in the caudal part of the ventral premotor cortex in the monkey. In humans, it is the most ventral portion of the pre-central gyrus (LPMCv). Electrophysiological studies have shown that this area contains a motor representation of proximal arm and mouth actions, the data showing that neurons discharge during the execution of reaching movements directed towards or away from the body. F4 neurons also respond to visual and tactile stimuli. Hence, depending on their responses to sensory stimuli (visual and somatosensory), they can be uni- or bimodal. For instance, bimodal neurons respond not only to tactile, but also to visual stimuli presented in the space adjacent to the tactile receptive fields (personal space), thus forming a single responsive region that includes the skin and the space adjacent to it. Most interesting is the fact that the coordinate system in which visual receptive fields are coded is in somato-centered coordinates (i.e., their location is independent of eye position). Area F4 is connected with the ventral intraparietal area (VIP). Again, neurons of area VIP share common features with those of area F4 since they can be uni- or bimodal. What is the role of the VIP-F4 circuit? It has been proposed that this circuit plays a role in coding personal space by transforming the location of objects in space in order to execute appropriate movements to reach them.

Area F2-V6A-MIP circuit for online up-dating of grasping actions. Area F2 lies in the caudal part of the dorsal premotor cortex in the monkey and in the dorsal portion of the pre-central gyrus in humans (LPMCd). Electrophysiological studies have shown that this area has a rough somatotopic organization, with hindlimb movements located medial to the superior precentral dimple and forelimb movements located in the cortex lateral to it. A recent study (Fogassi et al., 2001) showed that this region displays (a) purely motor neurons, which discharge during grasping conditions; (b) visually modulated neurons, that are active during grasping accompanied with visual perception of an object; and (c) visuomotor neurons, that discharge during the perception of objects in the absence of

any overt movement. Taken together, these data indicate that area F2, like area F5, plays an important role in the control of goal-directed hand actions. Area F2 receives its major visual inputs from area MIP, in the superior parietal lobule, and from area V6A in the occipital lobule. Although visual properties of area MIP are not very well-known, recent findings suggest that this area responds to the presentation of 3-dimensional objects. As for area V6A, it has been reported that neurons in this area are sensitive to the hand-target interactions, thus supporting its role in the visual monitoring of hand position in space. One can conclude that during grasping, the circuit F2–MIP/V6A could be updating on-line the configuration and the orientation of the hand when it reaches for objects.

MOTOR PHYSIOLOGY

Subcortical motor control: Reflexes and central pattern generators

The spinal cord and brain stem play an important role in the generation of movement because a large number of specialized motor circuits are located there. As an example, consider the generation of voluntary movements. Once voluntary movements are initiated, their production requires the activation of specialized circuits located in the spinal cord that in turn activates the corresponding muscles. Furthermore, since different segments of the spinal cord control different body parts, it is easy to understand that the production of complex movements requires the sequential activation of various levels of the spinal cord. In this section we will review two examples of such circuits: reflexes and central pattern generators.

Reflexes

Reflexes are stereotyped movements triggered by somatosensory stimulation. Spinal reflexes can be initiated by stimulation of receptors in the joints, muscles and the skin, with the resulting motor response controlled entirely within circuits located in the spinal cord and brain stem.

Is there a role for reflexive activity? Reflexes are ecologically important because they produce adaptive movements when integrated with centrally generated motor commands. Thus reflexes are an essential part of complex movements. For instance, multiple sensory stimulation is produced during coordinated movements (information coming from joints, muscles and skin), providing feedback to the system to help with production of coordinated and smooth movements. When perturbations in the environment occur, sensory feedback information produces a reflexive response, making possible small adjustments in the ongoing movement. These adjustments are especially important in the control of tone in proximal musculature related to the maintenance of posture.

In early studies, reflexes were considered stereotyped unchangeable movements. Most recent observations, how-

ever, have shown that reflexes have a degree of flexibility and can adjust to changes in the external or internal environment. In other words, reflexes show plasticity. This feature makes them more interesting, since it implies a possible role in motor learning or recovery of motor function after neurological damage.

The stretch reflex. The stretch reflex is one of the better known reflexes since it is used in clinical practice, but it is also one of the simplest spinal reflexes, employing a neural circuit of few elements. This reflex is illustrated in Figure 22.11.

The stimulus that produces the quadriceps stretch reflex is typically a tap on the patellar tendon in the knee, although any action that stretches this muscle has the equivalent effect. When the muscle is stretched, sensory receptors (muscle spindles) located in the muscle fire in response. This produces electrical firing of the spindle afferents (called Ia afferents) that make direct synaptic contact with spinal motoneurons innervating the *quadriceps*. In other words, this network forms a loop, since it returns to the same muscle where the stimulated spindles are located. In addition, this type of circuit is called “monosynaptic” because it has a single synapse (between the Ia afferents and the motoneurons) in the spinal cord.

Since the synaptic contact between the Ia afferents and the motoneurons that innervate the *quadriceps* are excitatory, their activation triggers the motoneuron to fire, and in turn produces a contraction of this muscle.

While this is occurring, a concomitant pathway is involved in the reflex. The Ia afferent fiber activated by the stretch of the quadriceps muscle also makes a synaptic contact with inhibitory interneurons located in the spinal cord.

These interneurons inhibit the motoneurons innervating a knee flexor muscle (in this case the *semitendinosus*), an antagonist of the *quadriceps* (i.e., when it contracts, it produces the opposite movement), producing flexion of the knee in contrast to the extension produced by the *quadriceps*. The inhibition of the antagonist allows the *quadriceps* to contract easier since the *semitendinosus* relaxes. The end result of this balance is the well-known movement of leg (lift) when the patellar tendon is stimulated.

Because the inhibitory circuit includes more than one synapse (one between the Ia afferent and the interneurons and a second one between the interneurons and the motoneurons), the pathway is considered to be “polysynaptic.”

The balance of excitation and inhibition between agonist and antagonist muscles is called “reciprocal inhibition” and the spinal circuit associated with it is called “reciprocal innervation.” This important concept was described by one of the greatest physiologists ever to live who was already mentioned in the history section, Sherrington (1906), and refers to the fact that when a group of muscles is excited, the antagonist muscles to that first group of muscles are inhibited. The balance between excitation and inhibition

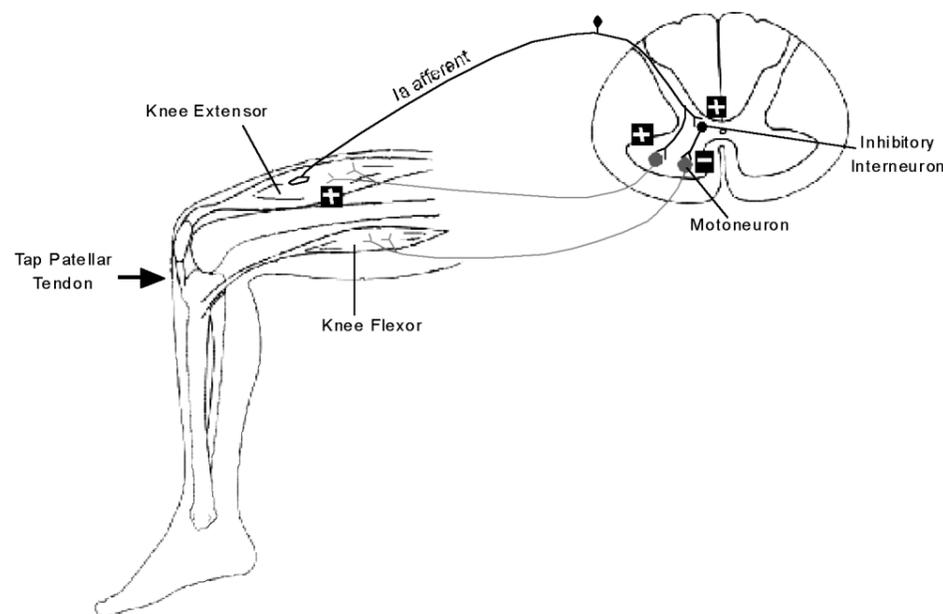


Figure 22.11. Circuit associated with the production of the flexor reflex in humans. Schematic representation of the two circuits associated with the generation of the knee jerk reflex. The monosynaptic circuit (marked with positive signs) is excited producing the contraction of the *quadriceps* muscle. At the same time, a polysynaptic circuit is involved with the difference that it involves inhibitory interneurons in the spinal cord (marked by the minus sign), that will produce a relaxation of the antagonist muscle. Modified from Boron WF and Boulpaep EL. (2003) *Medical Physiology*. Saunders. Elsevier Science (USA).

of reciprocal musculature is critical to the coordinated movement of the joints.

These examples of spinal reflexes illustrate a limited portion of what occurs constantly throughout the body to maintain posture. Sensory information is constantly delivered from the body. Control of posture (static or changing) requires incoming sensory information not only from muscles, tendons and skin but also from vestibular and visual receptors. These inputs originate in brain-stem, cerebellum and different levels of the spinal cord, and are integrated rapidly in the spinal cord through the activation of proprio-spinal paths whose function is the interconnection of different levels of the spinal cord and brain stem. The point of this example is to illustrate not only the apparent complexity of keeping posture (through activation of reflex activity) and the importance of reflexes in this control, but also, to illustrate the fact that all these adjustments are done automatically, without conscious control. This points out another feature of the motor system: Although we are aware of the initiation of some (voluntary) movements, not all movements are in the conscious realm. This fact becomes critical in situations where recovery of motor function is desired (after injury for instance) or for motor learning.

Central pattern generators (CPGs)

For years, the importance of network activation in the generation of motor behaviors by the CNS has been widely recognized. In this context, the motor system has often

been described as having a “hierarchical organization” (Wiesendanger & Wise, 1992) to define a situation where this complex system is composed of a number of relatively automatic subsystems capable of performing a specific task but also influenced by “general commands” initiated in higher levels or through sensory feedback (Arshavsky, 2003). This means that higher centers do not control individual elements within the lower circuits but rather, provide commands by which these latter networks can perform their tasks. The result of this organization is a highly efficient system.

Remarkable examples of these “autonomous centers” are what have been called: “Central Pattern Generators or CPGs.” The CPGs have been associated with the control of automatic, basic motor patterns such as locomotion, respiration, swallowing, chewing, swimming, scratching, and defensive behaviors, among others.

Formally the CPGs are defined as the neuronal networks that produce a basic motor output in the absence of sensory feedback. More precisely, Marsden has defined the CPG as: “a set of muscle commands (or motor program) which are structured before movement begins and which can be sent to the muscle with the correct timing so that the entire sequence is carried out in the absence of peripheral feedback.” What this means is that the direct electrical stimulation of specific circuits will produce rhythmic activation associated with complex motor acts as stepping or galloping, swimming, swallowing or breathing. Since stimulation in these studies is not “natural,” the resulting

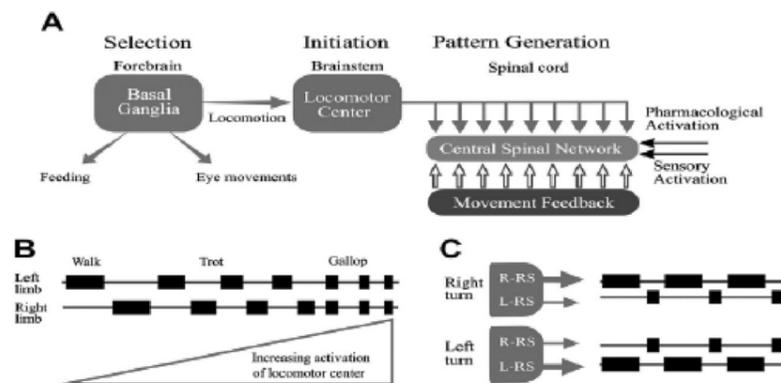


Figure 22.12. General organization of CPGs in vertebrates. Schematic representation of locomotion in vertebrates, that shows also the general organization of the CPGs. **a:** Forebrain structures initialize the spinal CPG activation. The resulting rhythmic activation is then modulated by sensory and pharmacological inputs. **b:** Representation of the interlimb coordination in quadrupeds. Note the alternation of the rhythm between both sides of the cord. **c:** Reticular activation leads to an asymmetrical pattern that will result in the animal turning to one side. From: Grillner et al. (2000). *The intrinsic function of a motor system—from ion channels to networks and behavior.* Brain Res. 886: 224–236. With permission of S. Grillner.

motor behavior is called “fictive behavior” (for instance “fictive locomotion” etc.) to denote their distance from the ecological movements. Such fictive movements tend to be more stereotyped than true ecological movements.

Although it has been suggested that the structure of CPGs are genetically determined and their physiology does not depend on experience, they in fact can be modulated by sensory feedback and descending inputs. Because this influence from descending inputs and sensory feedback changes their functioning, the preferred approach to studying CPGs has been by isolating them from these influences. The easiest way to do this has been to use invertebrates (Arshavsky, 2003; Grillner et al., 2000; Marder, 2000; Marder & Bucher, 2001). This approach has provided a large amount of information on the physiology and anatomy of CPGs. In vertebrates, the methods of choice have been the use of isolation methods such as spinalization (Jankowska et al., 1967; McCrea, 1998) where the spinal cord is isolated anatomically from higher regions of the central nervous system or by the administration of pharmacological agents such as *curare* that eliminates the proprioceptive sensory input to the cord (Kiehn & Kjaerulff, 1998).

In general, these studies have focused on CPGs that generate rhythmic activity present extensively throughout the phylogenetic scale, from invertebrates (like mollusks and crustacea) to vertebrates (including mammals). In the latter, CPGs are typically located at the level of the spinal cord (for locomotion and scratching) and at the level of the brainstem for other motor behaviors such as respiration, swallowing and chewing.

The general organization of CPGs in mammals is depicted in Figure 22.12 (Grillner et al., 2000) where the influence of descending systems and sensory information is shown to highlight the fact that these circuits are highly regulated. In order to understand better the physiology

of these circuits, it is important to mention that all CPGs share several features:

- (a)** The intrinsic properties of the neurons within the CPGs are important in the generation of the rhythmic motor behaviors. For instance, some neurons of the circuit are driven by pacemaker neurons. So the rhythmic activity is generated by the synaptic contact between the pacemakers (or core oscillators) and other neurons that do not have a rhythmic activity on themselves.
- (b)** Even though it was previously thought that the generation of motor rhythmic behavior was solely through a chain of reflexes, the current view is that a central circuit generates the rhythmic patterns of activity including some reflexive activation (Marder & Bucher, 2001) and some other elements not part of the reflexive circuits.
- (c)** CPGs are regulated by neuromodulators. Depending on the function of the CPG, they receive inputs from descending, sensory or hormonal origins. The function of these inputs is to initiate the movement (descending control), whereas in other cases (hormonal, sensory), these inputs either terminate or regulate the rhythmic activity.
- (d)** Some complex motor behaviors might be produced by the coordination of one or more CPGs. A classic example is swimming (studied extensively in lampreys and frogs). Swimming behavior implies the simultaneous coordination of several body segments (up and down or right and left) and in consequence the coordination of several spinal segments is essential. In these animals, each spinal segment produces motor patterns that organize the local swimming movements (Marder & Bucher, 2001). It has been suggested that coordinated movements of the whole body result from the coupling of the individual CPGs along the cord. This coupling implies

the simultaneous coordination of several CPGs and the regulation of independent movements by each one in the same fashion as the control of posture was described in a previous section.

(e) Rhythmic movements associated with CPGs tend to be stereotyped (especially fictive movements) and some studies suggest, might be genetically determined (Marder & Bucher, 2001).

Locomotion. Traditionally, the spinal cord has been associated with the generation of non-flexible, automatic, simple motor behaviors. However, the types of motor behaviors that can be generated through spinal circuits can be much more complex than previously thought. This section will discuss one such circuit that generates locomotion.

The generation of locomotion within the spinal cord is particularly interesting because it is present in humans and is quite complex in that it involves long motor sequences and can be modified. Unfortunately, locomotion in humans with reference to the presence of CPGs has been difficult to assess due to obvious experimental limitations. Nonetheless, lesions to the spinal cord provide some data on this topic, and this will be presented at the end of this section.

Locomotion in mammals. The study of CPGs and locomotion in mammals has employed several experimental approaches: (a) spinalization of the animals where the spinal cord is isolated from higher centers; (b) administration of pharmacological agents such as *curare* that prevents sensory proprioceptive information from reaching the spinal cord; and (c) isolation of spinal neurons forming the CPGs (as in invertebrates) in neonatal rats (but not mature animals).

The study of locomotion in mammals has a long history, beginning with the pioneering work of Sherrington (1910), who determined that the spinal cord of cats has enough reflexive-related circuitry to produce by itself the rhythmic flexor-extensor pattern during locomotion. Almost simultaneously, Brown (1911) performed more descriptive studies in spinalized plus deafferented (i.e., no sensory inputs) cats where he confirmed the ability of these animals to perform stepping behavior in the absence of afferent input. He suggested that the spinal cord contains intrinsic circuits able to produce locomotion. Today, several studies in deafferented and spinalized animals have shown that the spinal cord can produce what has been called “fictive locomotion”, i.e., rhythmic patterns of activity in circuits that would drive rhythmic muscle movement (Marder, 2001). Furthermore, the most current theories (Jankowska et al., 1967) describing the CPGs for locomotion in mammals are a combination of reflex activation plus additional elements forming a complex circuit.

The existence of CPGs for locomotion have been demonstrated in several species with the interesting fact that the general organization seems quite similar in all species studied, even though the locomotion patterns seem at some level very different (from swimming to walking to trotting or running).

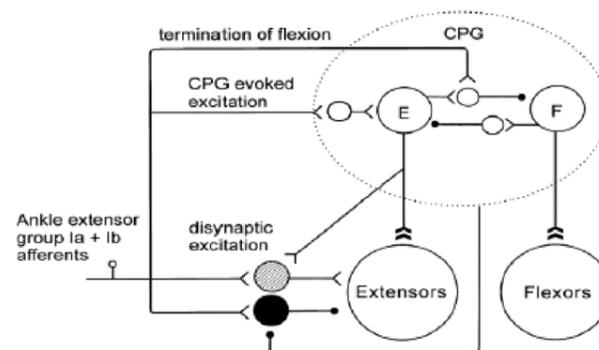


Figure 22.13. Theoretical network associated with the production of fictive locomotion in mammals. Schematic representation of the actual spinal generator. Inhibitory connections are represented by filled circles and excitatory connections by open forks. This model highlights the importance of reflexive activity between flexors and extensors. From: McCrea (1998). *Neuronal basis of afferent-evoked enhancement of locomotor activity*. *Ann. NY Acad. Sci.* 860: 216–225. With permission of D.A. McCrea.

Figure 22.13 depicts the hypothetical anatomical arrangement of a spinal CPG of the cat’s spinal cord (McCrea, 1998). According to McCrea (2001) there are several relevant features of CPGs for locomotion in four paw mammals:

1. Since the rhythmic motor behavior during locomotion is stereotyped, the role of segmental reflexes circuits is to compensate for changes in the environment.
2. Fictive locomotion in decerebrate animals can be triggered by electrical stimulation of the midbrain or by the administration of adrenergic agents.
3. Afferent inputs can modulate the rhythmicity of locomotion. Even when it is clear that the rhythmic activation of neurons within the spinal cord during fictive locomotion is quite close to the activation during real movement, it is nevertheless not identical. More and more studies have shown the great relevance of sensory input as a determinant aspect of CPGs physiology especially for its role in adapting the CPGs activation to constant changes in the environment. The roles associated with sensory input are: Reinforcement of CPG activity related to load-bearing muscles; regulation of timing depending on the actual task performed and the facilitation of phase transitions (MacKay-Lyons, 2002).
4. Rhythmic activity is generated by the reciprocal inhibition of two sets of interneurons located on each side of the spinal cord – an extensor circuit and a flexor circuit – each exciting their corresponding motoneurons.
5. Supraspinal centers can regulate the activation of spinal CPGs for locomotion. Even though it is clear that CPGs can be activated in the absence of supraspinal centers, these regions play an important role in several aspects of locomotion, since they are crucial to the initiation of CPG activity and in controlling the intensity of their activity, maintaining equilibrium during locomotion, adapting limb movement to changes in

external conditions and coordinating locomotion with other motor acts. Among the supraspinal regions that have been associated with this control are the primary motor and sensory cortical regions, the cerebellum, and the basal ganglia.

Locomotion in humans. Based on the large number of studies on locomotion in animal species, an obvious question is to what extent human walking can be understood using similar principles.

Intuitively, human walking has obvious differences with other types of mammalian locomotion. First, humans walk erect on two legs; at the moment of the contact with the ground, the leg is almost completely extended and the body part that touches the ground first is the heel. One of the consequences of this is that simultaneous activation of flexors and extensors is present at heel contact (rather than in phase like other animals) (Capaday, 2002). Furthermore, when people suffer complete transections of the spinal cord, that is, the spinal cord is completely isolated from the rest of the supra-spinal regions, one would expect recovery of locomotion with direct electrical stimulation of the spinal cord. Unfortunately, as we know, this is not the case.

In contrast to these differences with other mammals, locomotion in humans shares some features with both mammals and with other classes. Among these parallels:

1. Some spinal control of locomotion in humans is performed through the regulation of reflexes, especially the stretch reflex, which is thought to make a high contribution to walking in humans.
2. Sensory input is critical to the control and modulation of walking in humans. One suggestion has been that the stance-to-swing transition is promoted when the hip is extended, and the load in ankle extensors is decreased (these changes captured by sensory receptors) (Capaday, 2002).
3. The corticospinal pathway is involved in the initiation of walking (Capaday et al., 1999).
4. Lastly is the question of the existence (or not) of locomotion CPGs proper in the human spinal cord. The presence of CPGs for human walking would have tremendous implications for recovery of spinal cord lesions, with the option of activating them (as in other species) through sensory inputs, neuromodulators (like dopamine or adrenaline), or with direct electrical stimulation. As mentioned, the answer is not clear and at first glance, seems implausible. However, favoring the notion that human walking is performed with the participation of CPGs, it is possible to elicit rhythmic activity within the spinal cord of humans with intact sensory inputs, suggesting the existence of specialized circuits. Human spinal CPGs are undoubtedly weaker than those of other mammals, because after complete spinal cord injury, pharmacological interventions do not produce walking in humans as they do in rats and cats. More promising results, however, have been seen after partial transection

of the spinal cord, where a combination of pharmacological activation plus treadmill training has produced some improvement in locomotion of these patients.

MOTOR BEHAVIOR AND COGNITION

In the following sections, we will describe three examples of motor behavior closely related to complex cognitive functions. The idea is to provide a sense of the complexity of motor physiology in the context of cognitive processes. It is important, however, to understand that each of these examples (motor imagery, motor imitation, and motor learning) is intimately interrelated, even when presented as independent phenomena.

Motor imagery

Some cognitive psychologists (Annett, 1996) have suggested a distinction between two types of knowledge: explicit and implicit (or “knowing what” and “knowing how”). One of the features is that whereas explicit knowledge can easily be described verbally, implicit or procedural knowledge cannot. Motor acts tend to fall into the category of implicit knowledge, and as such, motor imagery can be considered the internal representation of the motor act.

Motor acts are triggered either by external sensory stimuli or by internal commands, implying that the central nervous system needs constantly to merge or transform sensory (or internal) codes into motor commands. As suggested by Passingham, Toni, & Rushworth (2000), this could be achieved through the use of what he calls “high-level representations” (or “cross-domain mappings” Wise, di Pellegrino, & Boussaoud, 1996) where stimuli and actions must be represented (see also the cortico-cortical connections section in this chapter). In other words, motor imagery could be considered the internal representation of previously learned movements.

In the most general sense, motor imagery refers to the “mental rehearsal of simple or complex motor acts that is not accompanied by overt body movements” (Jeannerod, 1995; Porro et al., 1996).

Although the definition appears simple, people asked to perform motor imagery do not make an unambiguous interpretation unless instructed more specifically. In particular, people generally perform this mental rehearsal of movements according to one of two strategies: (1) they produce a visual representation of their moving limb; or (2) they mentally simulate the movements associated with a kinesthetic feeling of the movement. In the first case, the person is a spectator of the movements (external imagery). We will refer to this behavior as visual imagery (VI). In the second case, the person is a performer (internal imagery). We will refer to this behavior as kinetic imagery (KI).

In fact, each of these strategies of motor imagery has different properties: For example, while KI is difficult to verbalize, VI is not. Whereas KI follows Fitt’s law (i.e., the imagined movement associated with KI shows the

same limitations as movements during execution), VI does not. This means that during KI, a person cannot perform movements at a higher rate than during overt execution, and this still holds after brain injury, when both execution and KI are diminished correspondingly. In contrast, during VI, a person can imagine movements that far exceed the physiological limitations of the execution (for review see Jeannerod, 1995). Moreover, certain physiological changes associated with KI mimic those occurring during execution, whereas during VI, they do not. For example, whereas electromyographic (EMG) activity during KI shows an increase in voltage in the muscles corresponding to movement execution, there are no such changes during VI (Fadiga et al., 1999). Furthermore, the excitability of the cortico-spinal pathway measured with transcranial magnetic stimulation is increased during KI but not VI (Abbruzzese et al., 1999; Fadiga et al., 1999; Rossini et al., 1999). In addition, if these imagery tasks involve strenuous movements, KI (but not VI) will show concomitant changes in autonomic function similar to those present during execution, including increases in heart and respiratory rates as well as in end-tidal PCO_2 (Decety et al., 1991; Oishi, Kasai, & Maeshima, 2000).

Since KI shares more physiological characteristics with the movement execution than does VI, it has been associated more closely with motor functions *per se* such as motor preparation, imitation and anticipation, restraining and the refining of motor abilities (Deiber et al., 1998; Jeannerod, 1995; Lotze et al., 1999; Stephan & Frackowiak, 1996). However, even when this correlation between motor execution and KI has been made, it is still not clear if KI and VI are sensory representations associated with the motor act or if they are in fact, true storage motor representations. This outstanding issue has been elucidated using a number of different techniques although the most revealing results have been obtained with functional brain imaging techniques. In the next section, we describe some conclusions that we have reached regarding motor imagery using modern techniques.

The physiology of motor imagery

With respect to imaging studies, several accounts of areas activated during KI or VI have been reported using PET or fMRI. Even though some of the studies do not differentiate between KI and VI, there are several features common to most of them (Jeannerod, 2001; Kim et al., 1995; Roland et al., 1980; Sanes, 1994; Stephan & Frackowiak, 1996). In general, studies have shown that several areas are activated during motor imagery tasks. Included in these active regions are the following: SMA, superior and inferior parietal lobule, LPMCd and LPMCv, pre-frontal areas, inferior frontal gyrus (BA44), superior temporal gyrus, M1, S1, secondary sensory area, insular cortex, anterior cingulate cortex, superior temporal gyrus, basal ganglia, and cerebellum. This extensive activation pattern suggests a complex distributed circuit. In studies that compared execution to motor imagery, it was found that even though the active

areas tend to be similar between the two conditions, in general, volumes of activation are larger during execution than during motor imagery (Gerardin et al., 2000; Jeannerod, 2001; Stephan & Frackowiak, 1996). A controversial point in some of these studies is the role of M1 during imagery, since its activation is not seen consistently in all studies and if seen, it is always less active than during execution (Beisteiner et al., 1995; Fadiga et al., 1999; Hashimoto & Rothwell, 1999). The lack of M1 involvement during motor imagery has been explained as the way the system avoids overt movements during imagery.

In summary, these studies suggest that the volume of brain activation differs between execution and motor imagery and that with few exceptions the distribution of activation tends to be similar in the two conditions.

So we have here an interesting riddle: on the one hand it seems that executing a movement and having KI of the same movement produce similar patterns of activation in the brain. However, moving is not the same as imagining that one is moving. What is the difference? In the following section, we demonstrate how brain imaging data provided a novel perspective on human motor neurophysiology.

There is no doubt that studies in systems neuroscience have benefited tremendously from the development of techniques such as functional Magnetic Resonance Imaging (fMRI). However, image analysis in fMRI has generally focused on enumerating areas of activation under different behavioral conditions, rather than characterizing the networks involved in the generation of those behaviors. Thus, with respect to localizational assumptions, these studies are analogous to lesion analysis studies, and incorporate some of the same advantages and limitations.

An alternative approach has been the efforts by some to assess networks of activation through the evaluation of effective connectivity among areas activated during different behavioral conditions (Buchel & Friston, 1997; Gonzalez-Lima & McIntosh, 1994; Horwitz et al., 2000). These models provide an interesting new perspective on experimental design and data analysis since they give an analytical approach to understanding integrated systems.

Network analysis in motor imagery

What does it mean to understand networks of activity? One of the most interesting features of the physiology of the CNS is the influence of regions on each other by means of established anatomical connections. Interestingly, not only have these connectivity patterns increased through the evolution of the cerebral cortex (Zilles et al., 1995) but in addition, the patterns of connections are not random: not all regions connect with all regions but rather, form specific patterns of connections. In terms of physiology, it means that changes in one region produce concomitant changes in regions anatomically connected to it. Although brain imaging has provided maps of regional activation, thereby giving an initial understanding to the neural basis of cognition, so far, we have not been able to establish the effect that one particular region is exerting upon the

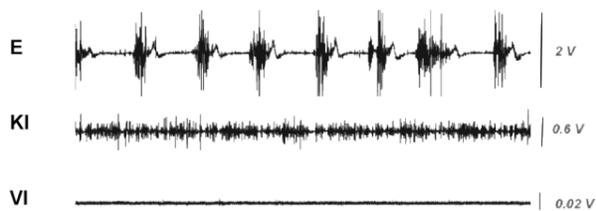


Figure 22.14. Electromyographic recordings during E, KI and VI. The upper trace shows EMG activation in the FDI during finger opposition movements. The second trace during KI and the third trace during VI. Muscle tone increased during KI but not during VI that did not differ from rest.

regions connected to it. Connectivity modeling is allowing us for the first time to quantify the effect of one region (node) over others. The directional effect of one region upon another as mentioned in the historical section, is called “effective connectivity.”

Following this idea of connectivity analysis, the present section will describe effective connectivity in networks associated with three different conditions: execution of hand movements (E), and kinetic and visual imagery of these same movements (KI and VI). These networks can help to inform about a possible role of “motor imagery” in the improvement of motor skill in normal subjects and in recovery after neurological damage. In normal subjects, for instance, motor imagery is used by athletes and professional musicians, where it is called “mental rehearsal,” to improve performance. By the same token, motor imagery is used therapeutically after stroke to stimulate recovery of motor abilities (Yaguez et al., 1999).

In a recent study, we aimed to understand the networks underlying hand motor imagery as compared to actual execution. This study was performed using fMRI (Solodkin et al., 2004). The first step in the study was to assess the subjects’ ability to perform kinetic imagery: One of the issues during motor imagery is the difficulty detecting if people are actually performing the task correctly. In general, most people will tend to perform visual imagery rather than kinetic imagery. For this, and before the subjects were

scanned for the fMRI session, outside the scanner, they were asked to perform either a finger opposition movement and both kinetic and visual imagery of the same movement. During the task practice, EMG was recorded in the first dorsal *interosseus*, one of the muscles controlling the opposition of the thumb and the index fingers. The results of this part of the study are illustrated in Figure 22.14. During execution, the EMG showed the typical muscle spindles associated with the contraction of muscles. As expected, these spindles were not present during either type of imagery, since during these tasks, there was no overt movement of the fingers. However, the EMG recordings during kinetic and visual imagery were not identical; kinetic imagery produced an increase in muscle tone (seen by the amplitude of the recorded band) whereas the muscle tone during visual imagery was identical to rest. This observation not only demonstrated that the participants were performing kinetic imagery correctly, but also illustrates the fact that kinetic imagery is associated with motor preparation that involves a change in the voltage of the involved muscles, shifting them closer to the contraction threshold (they are facilitated).

Second, an fMRI study was performed: The task during the fMRI session was as follow: The fingers of the dominant hand were numbered from 1 to 4 (1 = index, 2 = middle, 3 = ring, 4 = pinky). Numbers from 1 to 4 appeared randomly on a screen, and for each one, subjects performed the corresponding finger-thumb opposition. The task was externally paced at a rate of 2 Hz. The motor task paradigm included the execution of those movements alternated with either one of the two imagery conditions (KI or VI).

Figure 22.15 shows the fMRI activation patterns for each condition (the arrows are pointing to the central sulcus for guidance).

Note that the volumes of activation in the primary motor cortex during execution are larger than that seen during kinetic imagery (Jeannerod, 1995; Kim et al., 1995), general trend for all areas during the imagery tasks.

Third, we determined the networks of activation: By determining networks of activation, Structural equation

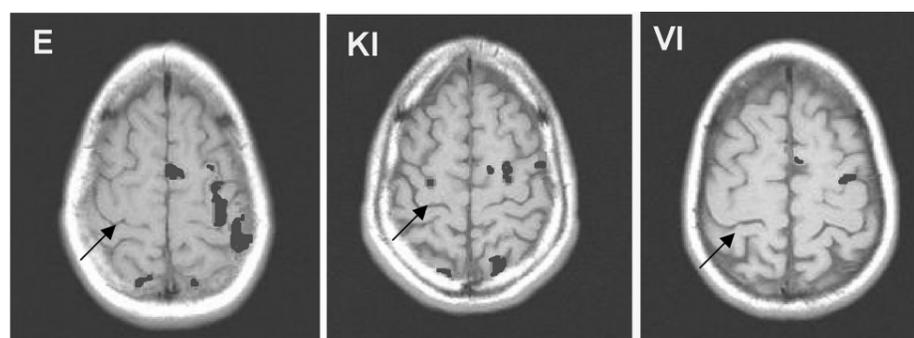


Figure 22.15. Single subject fMRI during E, KI and VI. Brain activation was seen in several sensory and motor areas during execution (E), kinetic imagery (KI) and visual imagery (VI). These axial slices depict regions at the level of the hand motor area of M1. For orientation purposes, the arrows are pointing to the central sulcus. Note that volumes of activation were much larger during E than during KI or VI. Since these are radiological images, the left side of the figure represents the right hemisphere.

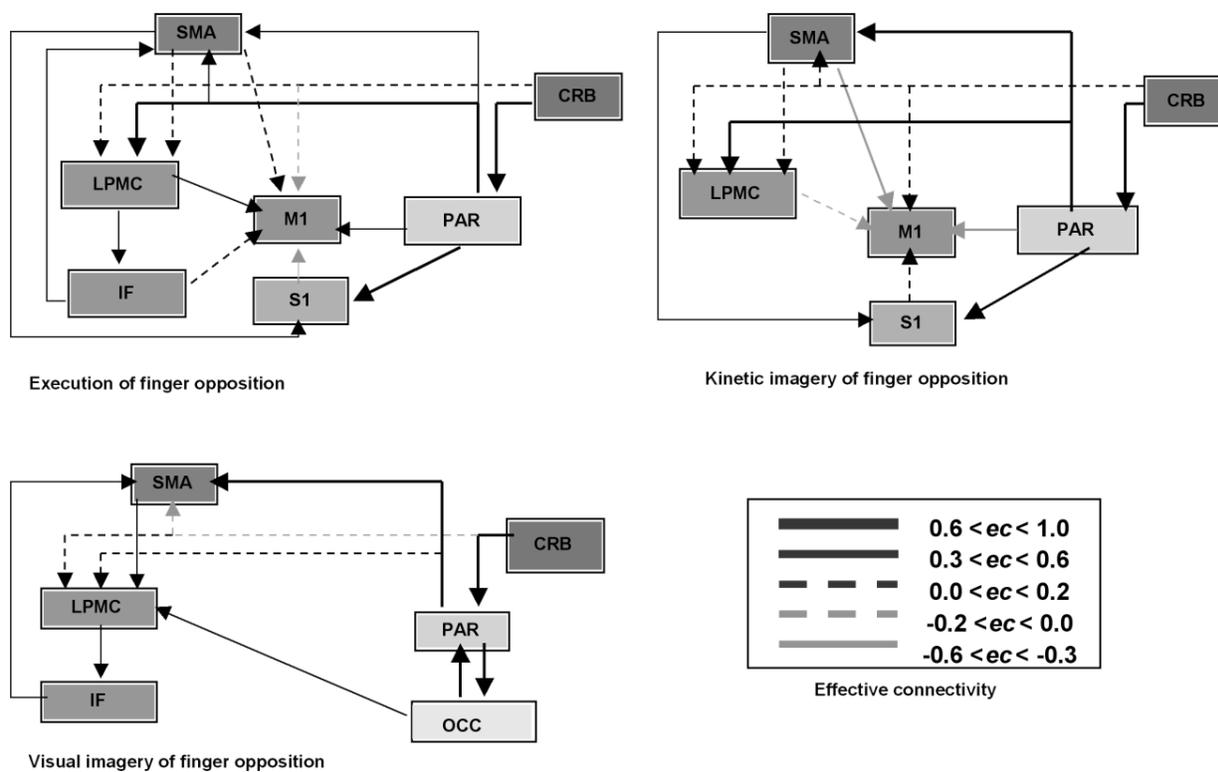


Figure 22.16. Final networks for E, KI, and VI. This figure depicts the values of effective connections during the three experimental conditions. Note the close parallels between E and KI except in the connections between association motor areas and superior parietal lobule with M1. In contrast, the patterns of connectivity in the VI conditions were biased towards visual areas.

modeling (SEM) describes the functional influences among anatomical brain regions. The emphasis thereby changes from the individual brain regions active in each condition to the relationships among them. The results of the present study demonstrated that independent of the volumes of activation *per se*, there are clear differences (and similarities) in the networks for E, KI and VI. The following figure shows the networks associated with each condition.

As shown in Figure 22.16, E and KI are closely related tasks, since they share several, identical parts of the network. The VI condition differs the most. These results show that resulting networks can differentiate among conditions that activate the same regions by means of effective connectivity values, but also they denote if they are facilitatory (positive) or not (negative). These parallels suggest that influences among areas involved in sensory-motor integration are kept constant during E and KI. Thus during KI and E, not only are similar areas active, but the relative influence of these areas on each other also remains constant. This notion reinforces further the idea of KI as a true motor behavior, a postulate also supported by behavioral data, since KI has been associated with motor preparation, imitation and anticipation, motor restraint, motor execution, and motor learning (Deiber et al., 1998; Jeannerod, 1995).

In contrast, there are some differences between E and KI. The most notable differences were found in the inputs

to M1. During KI, many of the inputs from association areas (PAR and SMA) to M1 are strong and negative compared to their effect during execution. These negative values could be interpreted as a suppression effect (McIntosh & Gonzalez-Lima, 1998) of SMA and PAR on M1, since during KI there are no overt movements. The fact that these connectivity values change from weak and positive to strong and negative during a task with no overt movements (KI) provides a new perspective on how the motor system might be encoding information. In other words, we have two closely related tasks (E and KI), involving activation in similar areas, and with several similar interrelationships. Yet even when the volumes of activation in M1 during KI are not that different, the influence exerted by SMA and PAR is opposite their influence during E. This exemplifies how network analysis can provide a new perspective on the neurophysiology of the motor system by describing how changes in the interrelationships among areas can generate different motor behaviors.

Understanding actions done by others: the mirror neuron system

The mirror neuron system in monkeys

Many of the original studies done in the mirror system used non-human primates as experimental subjects. Because of this, we will refer first to this data followed by studies in

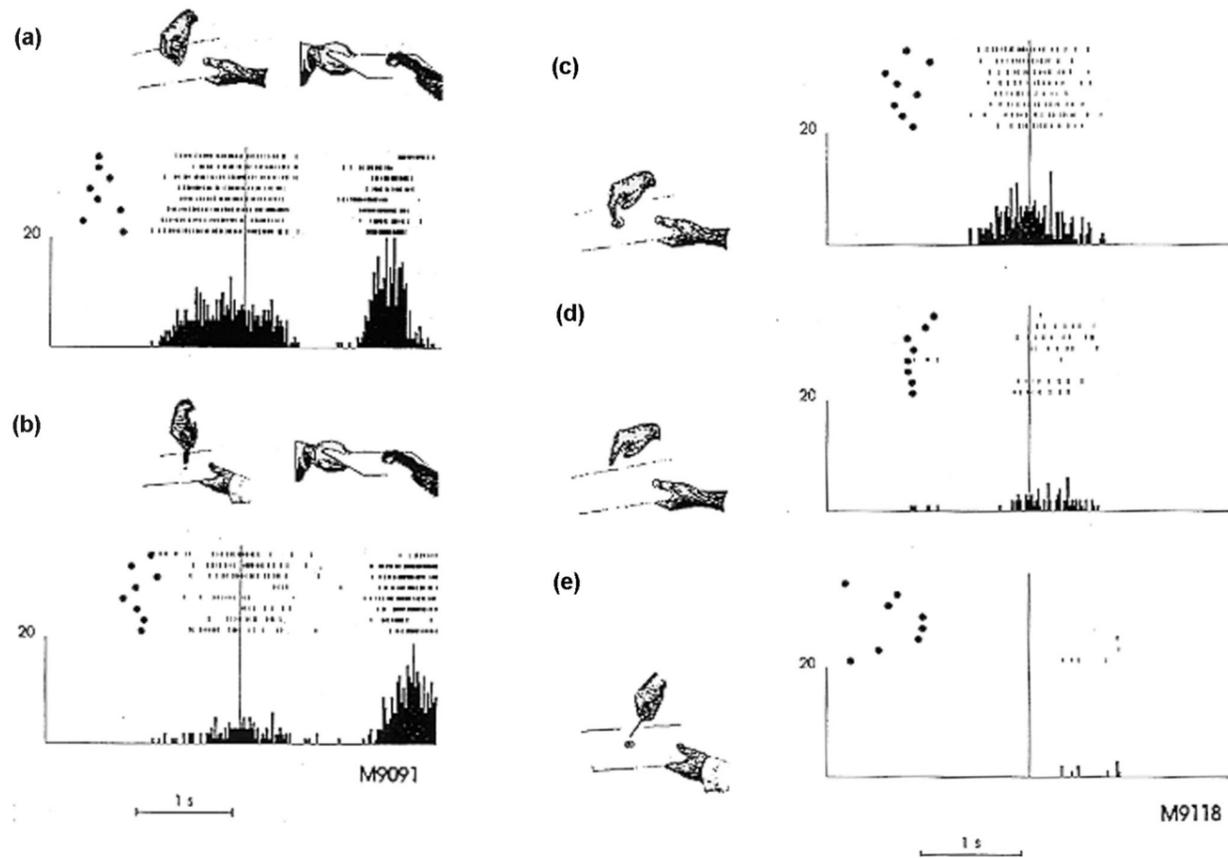


Figure 22.17. Mirror system in macaques. Firing patterns of neurons located in F5 from the observation and the execution of grasping movements. The discharge patterns of mirror neurons during action observation, are similar to execution ((a) left panel) or (c) but not during action observation when a tool is involved ((b) left panel) and (e) nor when the object is missing (d). Modified from: Rizzolatti et al. (1996). *Premotor cortex and the recognition of motor actions. Cogn. Brain Res. 3: 131–141.*

humans. As previously stated, electrophysiological studies have shown that area F5 contains a motor representation of mouth and hand goal-directed actions (Rizzolatti et al., 1988). Some of the neurons in this area (mirror neurons) discharge during the execution of both hand and mouth goal-directed actions, and also respond when the monkey observes another monkey or a human performing the same or a similar action (Gallese et al., 1996; Rizzolatti et al., 1996). The visual properties of mirror neurons resemble those of neurons found in the superior temporal sulcus (STS) region. These neurons, like mirror neurons, respond to the visual presentation of goal-directed hand actions, of walking, turning the head, moving the hand and bending the torso (for a review see Carey, 1996). However, differently from mirror neurons described in area F5, neurons described in the STS region do not discharge during the execution of any of the actions that may trigger them visually. The congruence between the action motorly coded by the neuron and that triggering the same neuron visually may be very strict: in this case only the observation of an action which is identical to that coded by the neuron can activate it. More often, this congruence is broader; in this case, the observed and the executed action coded

by the neuron match the goal of the action rather than the movements necessary to execute it. Some important features of mirror neurons should be highlighted: during action observation they discharge only when a biological effector (a hand, for example) interacts with an object; if the action is performed with a tool the neuron does not discharge. Mirror neurons are not active either when the observed action is simply mimicked, that is, executed in the absence of the object. Finally, mirror neurons do not discharge during the mere visual presentation of an object (Figure 22.17). Up to now only mirror neurons related to hand actions were described. More recently it has been demonstrated that in area F5 there are also mirror neurons which discharge during the execution and observation of mouth actions. Not surprisingly, most of the mouth mirror neurons become active during the execution and observation of mouth feeding behaviors such as grasping, sucking or breaking food. However, some of these neurons respond during the execution and observation of oral communicative actions such as lip-smacking (Ferrari et al., 2003).

Since their discovery, the preferred hypothesis has been that mirror neurons might play an important role both in action recognition and action understanding (Jeannerod

et al., 1995). If mirror neurons are responsible for action recognition, then these neurons should discharge also when the monkey cannot see the whole sequence of an action, provided that the goal of the observed action can be clearly inferred. A recent electrophysiological study (Umiltà et al., 2001) supports the claim that mirror neurons may infer the goal of an action. In this experiment, two conditions were presented: in the first one (vision condition) the animal could see the whole sequence of a hand goal-directed action, in the second one (hidden condition) the final part of the action was hidden from the sight of the monkey by means of a screen. In this last condition, however, the animal was shown that an object, for example a piece of food, was placed behind the screen preventing the observation of the final part of the performed action. The results showed that mirror neurons discharge not only during the observation of action, but also when the final part of it is hidden. As a control, a mimicked action was presented in the same conditions. As expected, in this case, the neuron did not discharge either in the full vision condition or in the hidden condition.

Actions may be recognized also from their typical sound, when presented acoustically. For example, we can recognize that an individual is manipulating some keys simply from the typical sound this action produces, even when we cannot see the individual performing it. Besides visual properties, a recent monkey experiment has demonstrated that about 15% of mirror neurons also respond to the presentation of the sound typical for a specific action. These neurons are called audio-visual mirror neurons (Kohler et al., 2002). Audio-visual mirror neurons could be used to recognize actions done by other individuals, when presented acoustically. It has been argued that these neurons code the action content, which may be triggered either visually or acoustically, thus representing a possible step for the acquisition of language. It is worth noting that for anatomical and physiological reasons area F5 is considered the monkey homologue of human Broca's region (Binkofski & Buccino, 2004; Petrides & Pandya, 1984; Rizzolatti & Arbib, 1998).

The mirror neuron system in humans

There is increasing evidence that a mirror neuron system also exists in humans. Converging data supporting this notion come from experiments carried out with neurophysiological, behavioral, and brain imaging techniques.

Neurophysiological studies. The first evidence of the existence of a mirror neuron system in humans was provided by Fadiga et al. (1995). During this experiment, a single pulse with transcranial magnetic stimulation (TMS) was delivered while subjects were observing an experimenter performing various hand actions in front of them. As control condition, single pulse TMS was delivered during object observation, dimming detection and observation of arm movements. Motor evoked potentials (MEPs) were recorded from extrinsic and intrinsic hand muscles.

Results showed that during hand action observation, but not in the other conditions, there was an increase in the amplitude of the motor evoked potentials recorded from the hand muscles, normally recruited when the observed action is actually performed by the observer. These results were recently confirmed by Strafella and Paus (2000). Furthermore, using the same technique, Gangitano et al. (2001) found that during the observation of hand actions not only there is an increase of MEPs amplitude in the muscles involved in the actual execution of the observed action, but MEPs are modulated in a fashion strictly resembling the time-course of the observed action. Taken together, the TMS data support the notion of a mirror neuron system coupling action execution and action observation in terms of both the muscles involved and the temporal sequence of the action.

Similar to these results are those obtained by Cochin et al. (1999) using quantified electroencephalography (qEEG). In this study "mu" activity was blocked during both the observation and execution of various hand actions, when compared to rest. It is worth recalling that similar results were observed by Gastaut and Bert (1954), who noted the suppression of "mu" activity in humans during the movie presentation of various actions, results also obtained by Hari and co-workers using magnetoencephalography (MEG) (Makela et al., 1993). In this study it was found a suppression of 15–25 Hz activity originated in the precentral motor cortex, during the execution and, to a less extent, during the observation of object manipulation. All of these studies provide further evidence that observation and execution of action share common neural substrates.

Behavioral studies. Evidence in favor of the existence of a mirror neuron system also derives from neuropsychological studies using behavioral paradigms. Brass (2000) investigated how movement observation could affect movement execution in a stimulus-response compatibility paradigm. Using a reaction time paradigm, they contrasted the role of symbolic cues during the observation of finger movements and during the execution of the same finger movements. Subjects were faster to respond when the finger movement was the relevant stimulus. Moreover the degree of similarity between the observed and executed movement led to a further advantage in the execution of the observed movement. These results provide a strong evidence for an influence of the observed movement on the execution of that movement. Similar results were obtained by Craighero et al. (2002) in a study where subjects were required to prepare to grasp as fast as possible a bar oriented either clockwise or counter-clockwise, after presentation of a picture showing the right hand. Two experiments were carried out: in the first experiment the picture represented the final required position of the hand to grasp the bar, as seen through a mirror. In a second experiment, in addition to stimuli used in experiment one, other two pictures were presented, obtained rotating of 90° the hand shown

in the pictures used in Experiment 1. In both experiments, responses of the subjects were faster when the hand orientation of the picture corresponded to that achieved by the hand at the end of action, when actually executed. Moreover the responses were globally faster when the stimuli were not rotated.

Brain imaging studies. All the cited studies provide little, if any, insight on the localization of the mirror neuron system in humans. This issue has been addressed by a number of brain imaging studies.

In an early positron emission tomography (PET) experiment aimed at identifying the brain areas active during action observation, Rizzolatti et al. (1996), comparing hand action observation with the observation of an object, found activation of Broca's region, the middle temporal gyrus and the superior temporal sulcus region. Broca's region is classically considered an area devoted to speech production. Recently, however, it has been demonstrated that in this area, a motor representation of hand actions is also present (Binkofski & Buccino, 2004; Binkofski et al., 1999; Ehrsson et al., 2000). Given the homology between Broca's area and area F5 in the monkey, (where mirror neurons were originally discovered), this study provided the first evidence on the anatomical localization of the mirror neuron system for hand actions in humans.

A recent fMRI study showed that in humans, the mirror neuron system is complex and related to different body actions performed not only with the hand, but also with the foot and the mouth. Buccino et al. (2001) asked subjects to observe video-sequences presenting different actions performed with the mouth, the hand and the foot, respectively. The actions shown were either transitive (the mouth/hand/foot acted on an object) or intransitive (the mouth/hand/foot action was performed without an object). The following actions were presented: biting an apple, grasping a cup, grasping a ball, kicking a ball, and pushing a brake. As a control, subjects were asked to observe a static image of each action.

The observation of both transitive and intransitive actions, compared to the observation of a static image of the same action, led to the activation of different regions in the premotor cortex and Broca's area, depending on the body part involved in the observed action. The different regions largely overlapped those where classical studies (Penfield & Rasmussen, 1950) had shown a somatotopically organized motor representation of the different effectors (Figure 22.18). Moreover, during the observation of transitive actions, distinct sectors in the inferior parietal lobule were active, including areas inside and around the intraparietal sulcus, with localization depending on the body part involved in the observed action. All activations found in this study are shown in Figure 22.18.

On the whole, this study strongly supports the claim that, as in the actual execution of actions, during action observation different, somatotopically organized fronto-parietal circuits are recruited (Jeannerod et al., 1995; Rizzolatti &

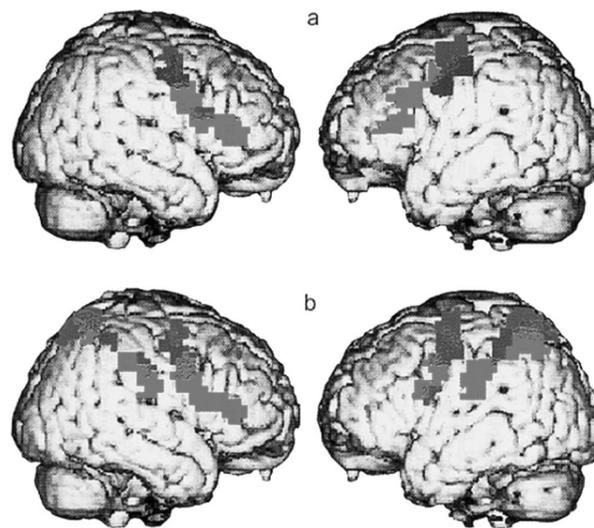


Figure 22.18. Mirror system in humans. Somatotopic fMRI activation in parietal and premotor regions during observation of intransitive (a) and transitive (b) actions in humans. **Red:** mouth related movements; **green:** hand related movements; **blue:** foot related movements.

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Fadiga, 1998). In this context, it is worth noting that mirror neurons, similar to those described in area F5, have recently been reported by Gallese et al. (2002) in the inferior parietal lobule of the monkey (area PF).

Contrast between the mirror system in humans and monkeys

As previously stated, in the monkey the mirror neuron system can be activated when the animal observes an experimenter, a member belonging to other species (non-conspecific), while performing a similar action motorily-coded by the neuron. A recent fMRI study (Buccino et al., 2004) addressed whether we recognize action performed by non-conspecifics using the same neural structures involved in the recognition of action performed by con-specifics (same species). In this study, normal subjects were asked to carefully observe different mouth actions performed by a man, a monkey, and a dog, respectively. Two kinds of mouth actions were visually presented: biting a piece of food and oral communicative actions (human silent speech, monkey lip-smacking, and silent dog barking). The results showed that during the observation of biting, there is a clear activation of the *pars opercularis* of the inferior frontal gyrus and of the inferior parietal lobule, regardless of the species performing the action. Interestingly, during the observation of oral communicative mouth actions, a different pattern of activation was observed, this time depending on the species performing them. During the observation of silent speech (human), there was a clear activation of Broca's area in both hemispheres, with a leftward asymmetry; during the observation of lip smacking (monkey) there was only a small bilateral activation in the *pars opercularis* of Broca's area, with no clear asymmetry

between the two hemispheres. Finally during the observation of silent dog barking no activation was found in Broca's area, but activation was present only in the right superior temporal sulcus region. The results of the experiment strongly suggest that action performed by other individuals, including non-conspicuous, may be recognized in two different ways: for actions like biting or silent speech reading, there is a motor resonance of the cortical circuits involved in the actual execution of the observed actions. In other words their recognition relies on the mirror neuron system. For actions like barking, this resonance is missing. In the first case there is a "personal" knowledge of the action observed, in the sense that it is mapped on the observer's motor repertoire and therefore the observer has a direct, personal experience of its execution (e.g., I recognize it because I am able to do the same action I am looking at). In the second case, although the viewed actions are still recognized as biological motion (as suggested by the activation of the STS region), personal knowledge about these actions is lacking because the observer has no direct experience of the observed action in motor terms (e.g., I can approximately imitate a dog barking, but, as a matter of fact, I am not able to do it).

Finally, it is well known that we can recognize actions even when we look at point lights attached to the joints of an actor in motion. Early brain imaging studies on this issue demonstrated that observation of point-light biological motion leads to activation of superior temporal cortical areas. These early studies failed to show any activation in the motor system. The results of a very recent fMRI study, however, showed that areas responding selectively to point-light biological motion are found not only in the lateral and inferior temporal cortex but also in the pre-motor cortex. This result suggests that, although there is no direct matching between the observed action and the motor repertoire of the observer, in the case of point light biological motion the motor system is involved in filling in the simplified motor pattern obtained with point-lights and in "humanizing" the observed action.

MOTOR LEARNING AND MOTOR CORTICAL PLASTICITY

The areas of procedural learning, motor memory, and motor skill acquisition have been traditionally studied independently by different scientific disciplines. Psychology has a long tradition of studying human procedural memory and behavioral changes during skill acquisition without the possibility of observing the underlying cerebral processes. For the past 20+ years, neuroscience has emphasized the study of adult brain plasticity, including motor cortical plasticity, resulting from biological as well as environmental and behavioral changes. Finally, neurology and rehabilitation have studied deficits of motor behavior after stroke and re-gaining of motor skill during recovery and rehabilitation. Recently, noninvasive human imaging methods have provided a unique opportunity to

combine the research methods across disciplines to allow a more complete picture of the issues involved. Understanding the mechanisms and the subsequent optimization of the motor learning process are desirable for different fields of human activity: developing and improving manual skills for a job, training in sports, and neurological rehabilitation.

Motor learning and motor memory

Motor learning has been studied within several disciplines, although the acquired knowledge has not been fully integrated across disciplines. Psychology has studied both acquisition of complex motor behavior (skill) (i.e., motor learning) and the storage and representation of this acquired knowledge (i.e., motor memory). It is generally accepted that knowledge of skills or procedural ("how") memory is distinct from knowledge of facts or declarative ("what") memory (Cohen & Squire, 1980; Squire, 1987b). Procedural memory is acquired incrementally, is modality-specific, does not allow for storage of individual events, and is usually associated with motor skill learning (Squire, 1987a). Most commonly, psychological theories view learning and memory in abstract terms, without any consideration of possible neuronal correlates of their proposed components. This is in contrast to similar endeavors from the neuroscience community (Fuster, 1995). Recently, the integrative field of cognitive neuroscience has been trying to focus simultaneous attention on both behavioral issues and neurobiological substrates and constraints imposed by the nervous system (e.g. Clegg, DiGirolamo, & Keele, 1998).

The term "motor learning" may be used in a broad sense in the psychological and neuroscience literature to encompass many processes, including the following (Strangman, 1998):

Adaptation: This is the simplest process during which existing behavior is modified or rescaled in response to environment. Examples of adaptation are habituation, sensitization, and vestibulo-ocular reflex (Raymond, Lisberger, & Mauk, 1996; Squire, 1987b).

Conditional motor association: This involves learning to associate an available motor response with a given stimulus (Halsband & Freund, 1990; Petrides, 1985, 1997). Most monkey learning studies belong into this category.

Finally, motor learning in the narrow sense is a process that leads to the acquisition of a novel response pattern that involves little or no functional trade-off for other movements. While adaptation and conditional motor association modify an existing behavior or connect it with a particular stimulus, motor learning enriches the individual's motor repertoire.

Motor learning may vary according to the type of motor control necessary for successful task performance

(Strangman, 1998). Tasks that do not rely on somatosensory feedback are called open-loop (e.g., dart throwing, penalty kick in soccer). The movements are usually so rapid (under 500 ms) that there is not enough time to process proprioceptive feedback. The second class of tasks is closed-loop, and such actions are mediated and error-corrected in real time by somatosensory feedback (e.g., gymnastics, figure skating). This dichotomy is somewhat artificial, as the amount of somatosensory feedback and subsequent self-correction can vary continuously. Still, considering the importance of proprioceptive input for cortical motor processing, it is likely that the amount of this internal feedback modulates the learning process in a significant way.

One of the issues addressed by research in motor learning is the transfer of training, that is, transfer of behavioral improvement on one task to a different task, a movement effector (e.g., from one hand to the other), or the environment (Adams, 1987). Performance benefit from practice on specific motor skills often does not correlate with, or transfer to, similar but non-identical tasks. Performance on these "transfer tasks" is usually substantially poorer for subjects that practiced the original but not the transfer task (Adams, 1987).

Practicing under highly structured conditions (different skills practiced in blocks) leads to faster learning but poorer transfer of skills than training by randomly mixing different skills. There seems to be a trade-off between practice variability and learning time on one hand, and between practice variability and behavior generalization on the other (Strangman, 1998).

There is not a clear understanding in the behavioral literature on the kind of practice that is the most beneficial. It is understood, though, that (a) subjects should distribute practice over time rather than participate in one massed practice session, (b) subjects should get feedback on how they are performing, and (c) the task should be easy enough to make at least occasional success possible (Strangman, 1998).

Neuroscience: Motor learning and memory in the brain

Neuroscience arrived at the topic of motor learning and memory from a different direction than the behavioral sciences. The speculative connection between the structure of the nervous system and acquisition of skilled behavior was made at least a hundred years ago. Ramón y Cajal mentions in his autobiography (1923) at a conference presentation in 1893 when he suggested the encoding of skill through modulation of neuronal connections. In this presentation, he offered an

explanation of the adaptation and professional skills (physical education, language operations, writing, playing the piano, mastering fencing, etc.) by the progressive strengthening of nervous pathways...excited by the pass of a wave, as well as by the creation of new cellular appendages (den-

dritic growth and elongation or branching of nervous collaterals, non-congenital), capable of improving the adjustment and extension of the contacts, and of organizing completely new relationships between neurons that were originally not connected.

– Translation Dr. Ana Solodkin

More recently, the discovery of plastic changes in the adult mammalian brain have provided new evidence to explain mechanisms of motor learning and memory. Most of the research has focused on primary motor and sensory cortices, since the anatomical and functional organization of these areas had been well described, thus simplifying the investigation of plastic changes. The following section will review the research on plasticity of the primary motor cortex, the area most relevant to motor learning.

Plasticity in animal and human M1

Several animal studies have demonstrated that the representations of muscles or movements in adult primary motor cortex can undergo plastic changes in response to peripheral or central lesions or altered experience. Motor maps have been shown to change in response to peripheral motor nerve lesions in the rat (Donoghue, Suner, & Sanes, 1990), repetitive cortical stimulation in the monkey (Nudo, Jenkins, & Merzenich, 1990), pharmacological modulation of intracortical inhibition in the rat (Jacobs & Donoghue, 1991), change of rat limb configuration (Sanes, Wang, & Donoghue, 1992), motor practice (Nudo, Wise, SiFuentes, & Milliken, 1996) or cortical lesions in the monkey (Nudo & Milliken, 1996; Nudo, Milliken, Jenkins, & Merzenich, 1996) found expansion of the motor cortical representations of muscles/movements that were used during a several week long session when monkeys learned to retrieve food pellets from small wells. In another primate study with long-term movement practice, M1 neurons that have been initially silent begin firing (Kennedy & Bakay, 1997). The extent of newly emerged cortical finger representation was correlated with recovery after stroke destroying the original finger representation (Nudo et al., 1996).

Several cellular mechanisms have been implicated to explain the observed plasticity, including unmasking or potentiation of existing but normally ineffective neural connections, axonal sprouting with new synapse formation, or a combination of these. Changes in motor maps after the application of bicuculline, an antagonist of the inhibitory neurotransmitter GABA (Jacobs & Donoghue, 1991), have been taken as evidence that a part of the wide network of available neural connections is functionally suppressed through intracortical inhibition. Long-term potentiation of cortico-cortical synapses has been observed in cat motor cortex (Keller, Arissian, & Asanuma, 1990), as has the appearance of new synapses after damage to deep cerebellar nuclei (Keller, Iriki, & Asanuma, 1990) or long-term thalamic stimulation (Keller, Arissian, & Asanuma, 1992). Increased synaptogenesis and early immediate gene *c-fos* expression have been associated

with motor acrobatic learning in rat motor cortex (Kleim et al., 1996). Furthermore, the strength of intrinsic connections in M1 is dynamically modifiable through long-term potentiation (Aroniadou & Keller, 1995; Hess & Donoghue, 1994). Finally, the extent of horizontal connections has been shown to correlate well with the extent of plastic changes in motor cortical representations after transection of efferent connections in the rat (Huntley, 1997).

Human motor plasticity

Changes of primary motor cortical organization have also been observed in adult humans. Expansion and shifts in motor maps occur after central or peripheral neurological lesion such as stroke (Weiller et al., 1993), amyotrophic lateral sclerosis (Kew et al., 1994), arm amputation (Kew et al., 1994; Pascual-Leone et al., 1996) and facial paralysis (Rijntjes et al., 1997). Remapping within M1 was suggested as one possible mechanism of motor function recovery after stroke (Weiller et al., 1993). One type of map change observed within M1 as a result of brain injury or disease was a shift of hand area laterally and ventrally, into the presumed face area, over a distance of up to 10 mm (Kew et al., 1994; Rijntjes et al., 1997; Weiller et al., 1993).

Similar changes have been described in the absence of motor system injury. Practice of Braille reading and motor learning caused expansion of scalp area from which movement could be evoked by transcranial stimulation (Pascual-Leone et al., 1993; Pascual-Leone, Grafman, & Hallett, 1994). Prolonged leg immobilization, on the other hand, caused shrinking of the scalp area for excitation of a leg muscle (Liepert, Tegenthoff, & Malin, 1995). Several studies of human motor learning have observed changes within M1 (Karni et al., 1995; Kawashima, Roland, & O'Sullivan, 1994; Pascual-Leone et al., 1995), even though M1 is only one of the multiple cerebral areas supposedly involved in motor learning (Halsband & Freund, 1993b). A newly acquired motor skill may take advantage of movement segments that are formed by combining neural units of M1 (segmental learning) and retrieved during the execution of the acquired skill (Asanuma & Keller, 1991). The possible anatomical substrate for the co-activation of an ensemble of neurons during skilled movement is the network of horizontal corticocortical connections observed within monkey M1 (Huntley & Jones, 1991).

Cortical activation size and learning

If one accepts the assumption that increasing skill and automaticity for a specific movement originates from changes of cortical motor function, the next question regards the character and direction of such changes. There is an intuitive concept that skill reflects efficiency at the cortical level and that such skill would translate into less cortical activation during functional imaging, implying either that neural units are firing less, fewer neural units are firing action potentials, or both. On the other hand, there is

both nonhuman primate (see above) and human evidence that practice increases, rather than decreases the area of cortex associated with the practiced movement (at least in the time frame of several weeks).

Human motor learning studies have commonly reported that movement practice leads to recruitment of additional motor cortex, with the appearance of new active cortical fields (Kawashima et al., 1994), and expansion of the cortical territory corresponding to the practiced muscles/movements of several millimeters up to several centimeters (Karni et al., 1995; Pascual-Leone et al., 1995). Subjects who practiced a five-finger piano exercise for 2 hours a day for 5 days showed an enlarging motor cortical area targeting the long finger flexors and extensors, followed by a decreased threshold for activation as they learned the skill (Pascual-Leone et al., 1993).

Karni et al. (1995), compared fMRI activation caused by two sequential finger movements involving the same fingers. The sequences had five components and each involved fingers 2–5 touching the thumb in a particular order. One of the sequences was repeatedly practiced over several weeks. While the extent of cortex activated with either sequence was similar at the beginning of the study, after training the primary cortical activation by the practiced finger sequence was significantly larger than activation caused by the non-practiced sequence. The area of evoked response in M1 for the trained sequence did not extend beyond the hand representation, which was mapped in a subset of the subjects by independent finger movements. However, the amount of change in the rest of the motor map was not addressed to establish whether the learning was competing for cortical output neurons or instead whether it enhanced sharing of neurons. The relationship between the observed expansion and the localization of other hand movements was also not described. Finally, the study was limited to M1, although there is evidence that other motor and somatosensory regions participate in learning of new motor skills (see below).

In addition to investigating the effect of short- and medium-term experimental motor training on the motor cortex, correlation has also been sought between very long-term practice of skilled movements and the motor system. Although right-hand dominance for skilled movements is typical for humans, hand preference has also been observed in monkeys (Nudo et al., 1992). The monkey motor cortex controlling the preferred hand has been found to contain a larger and more complex hand area when studied with intracortical microstimulation (Nudo et al., 1992). Studies of human M1 structural asymmetry related to handedness have found asymmetry in the depth of the central sulcus, with the left hemisphere bigger than the right in right-handers, and a less prominent opposite asymmetry in left-handers (Amunts et al., 1996; White & Hardy, 1995). Microstructural asymmetry has been found in post-mortem brains, with a larger neuropil compartment (containing dendrites, axons, and synapses) in the left (dominant) motor cortex (Amunts et al., 1996). The

authors suggest that this finding reflects a greater density of intracortical horizontal connections in the cortex serving the dominant hand (Amunts et al., 1996). Callosal connections from the opposite motor cortex comprise another possible source of increased connectivity, but callosal connection density is very low in the monkey motor hand areas and seems to be inversely related to the development of independent fine movements (Zant & Strick, 1978). Callosal connections have also been suggested to be a potential hindrance for independent movements of one hand (Gould et al., 1986). Another anatomical study did not find any asymmetry in the size of the precentral motor cortex in post-mortem human brains (White et al., 1997).

The effect of long-term bimanual practice (i.e., playing a musical keyboard instrument) on brain structure was studied by Amunts et al. (1997). The asymmetry of central sulcus depth observed in control subjects was diminished in musicians and this effect was proportional to the age of inception of music training. Similarly, finger-tapping performance of musicians was more symmetrical, due to significantly better performance of the nondominant left hand. A right-larger-than-left difference was found in the strength of cortical magnetic fields evoked by moving left versus right fingers in the primary motor cortex of string players (Elbert et al., 1995). All this evidence seems to further support the notion that long-term practice changes the motor cortex on both microscopic and macroscopic levels.

Contribution of other motor and somatosensory areas to motor learning

Regions other than M1 have also been implicated in motor learning and motor plasticity. Changes in the supplementary motor area (SMA), premotor cortex (LPMC), cingulate motor area (CMA), and areas of the parietal lobe have all been associated with motor skill acquisition (Halsband & Freund, 1993a).

Primate SMA neurons participate in preparatory rather than movement-related activity (Aizawa & Tanji, 1994; Wiesendanger, 1986) and their activity is modulated by learning. After a motor task (keypress movement in response to a visual trigger) had been extensively over-trained (12 months) in monkeys, very few, if any, SMA neurons remained active before movement onset (Aizawa et al., 1991). The authors suggest that SMA neuronal activity during a simple task is redundant and therefore eliminated over time to increase efficiency through division of labor. It might be inferred that even during a complex motor task, non-primary motor activation can be gradually eliminated at the same time-scale as the movement is increasingly encoded in M1. However, after M1 damage, SMA activity reappears (Aizawa et al., 1991). Similarly, in a human study of motor learning, SMA was active early during motor skill acquisition (Grafton, Hazeltine, & Ivry, 1998) but not later during transfer of skill from hand to arm. In contrast to these results and the theoret-

ical model they suggest, Jenkins et al. (1994) found SMA activation in a human study of motor sequence learning to be stronger during performance of a pre-learned sequence than during new learning. It is thus possible that some type of movement sequences becomes represented in the SMA rather than M1 over the course of learning. Human imaging studies using PET has also shown prominent activation of LPMC and parietal association cortex in early stages of motor learning (Jenkins et al., 1994).

Participation of primary somatosensory cortex in motor cortical plasticity

Primary somatosensory cortex is also thought to play a role in the plasticity of M1. While ablation of somatosensory cortex does not markedly worsen motor performance in the monkey (Asanuma & Arissian, 1984), it prevents learning of new motor skills (Pavrides, Miyashita, & Asanuma, 1993). The importance of S1 for motor learning is most likely due to processing of proprioceptive feedback, the absence of which degrades skilled movements (Bossom, 1974) and slows or blocks the acquisition of new motor skills (Rothwell et al., 1982). Changes in forelimb configuration have caused expansion of the M1 forelimb motor area into the representation of face in the rat (Sanes, Wang, & Donoghue, 1992).

As mentioned above, proprioceptive afferent information mainly reaches area 3a (Jones, 1983) and, to a lesser degree, area 3b (Heath, Hore, & Phillips, 1976), with further processing in area 2. It has been suggested that each of these areas has a separate somatotopic map in the monkey (Kaas et al., 1979) and these maps have been found to show plastic changes in response to manipulation of the periphery or cortex (Courtemanche, Sun, & Lamarre, 1997; Kaas, Florence, & Neeraj, 1997; Merzenich et al., 1984). Changes in the 3a map have been studied with training of fine touch on the skin (Recanzone, Merzenich, & Dinse, 1992) and after experimental cortical stroke in area 3b (Xerri et al., 1998). Acquisition of a motor skill dependent on fine touch caused reorganization in area 3b (Xerri et al., 1999), but it is not known whether area 3a also reorganizes during motor skill acquisition and whether it thus possibly contributes to the reorganization in M1.

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