I. INTRODUCTION

The distinct property that characterizes animals’ behavior is their capacity to generate movements. Some movements are determined by internal or external stimuli. They are called reflexes. Others are manifestations of a centrally generated intention to act. They are called voluntary actions. Intention to act might originate in several ways. It might originate from bodily needs or from higher order deliberations. In voluntary actions what counts is that the individual has the intention to achieve an overarching goal, and this overarching goal determines a series of movements leading to its achievement.

Because of their capacity to generate movements voluntarily, animals move in their environment looking for stimuli that may satisfy their immediate or future needs. When they find something appropriate for their need, they might interact with it. In voluntary behavior stimuli, however, do not determine the response, they only set the occasion for it. Therefore, according to their needs, animals may respond to the same stimulus in different ways. They may approach it, avoid it, or even ignore it.

In this review we address two action-related issues. The first is how animals are able to organize object-directed actions. We will first briefly discuss this issue examining the behavior of species with relatively poor corticalization (frogs and then rodents). Next, we examine how primates, a species endowed with a complex brain, solve the same problems. Our aim is not to give a complete picture of the neurophysiological process underlying the visuomotor transformation that leads from object to action, but rather to outline the general principles underlying this behavior.

In the second part of this review we examine the role that the cortical motor system plays in understanding the behavior of others. Although the notion that there is a strict link between action execution and action perception is not new (356), the notion that there is a mechanism, the mirror...
II. VISUOMOTOR BEHAVIOR: GENERAL PRINCIPLES

In one of the most authoritative textbooks of physiology of the end of the last century, *The Medical Physiology*, edited by Vernon Mountcastle, Elwood Henneman (166) started the chapter on Motor System with the following sentence: “The motor systems of the brain exist to translate thought, sensation and emotion into movement. At present the initial steps of this process lie beyond analysis. We do not know how voluntary movements are engendered nor where the ‘orders’ come from.” This sentence expresses with clarity and elegance the difficulty to understand how the motor system could organize motor behavior. In fact, accepting the standard view on cortical organization of that time, the visual and motor systems were two incommunicado worlds devoid of any clear functional link. What was the standard view about vision? The view was that vision provides the observer with a global perceptual representation of the external world. This representation is unitary, precedes motor activity, and is used for organizing all types of actions from gazing to walking, from escaping to interacting with objects. This view of the visual system was radically wrong. By accepting it, it is indeed impossible to understand how actions are organized. In the next paragraphs we will show where the error stood.

In 1973 Ingle (177) published a series of fundamental studies on frogs’ vision. Ingle studied two frogs’ basic visuomotor behaviors: 1) turning and snapping at small prey-like objects, and 2) jumping away from large looming discs. The experiments were carried out before and after removal of the optic tectum, the most important visuomotor integration center in amphibians. Following unilateral removal of the optic tectum, frogs totally ignored stimuli presented in the field contralateral to the ablated tectum. However, over the next month, vision recovered and the frog started to turn and snap in response to prey-like objects presented in the contralateral formerly blind visual field and to react in response to threatening stimuli shown in that field. However, the observed responses were quite bizarre. When presented with prey-stimuli in the formerly blind contralateral field, the frogs, instead of turning and snapping towards them, directed their responses toward locations in the ipsilateral field. Similarly, when a large threatening disc was suddenly introduced into the field opposite to the lesion, the frogs jumped towards it, instead of avoiding it (FIGURE 1).

What had happened? Unlike in mammals, in frogs the projections from the retina to the brain regrow after transection. In agreement with this well-known fact, histological analysis revealed that the transected optic tract regenerated. However, its sprouting axons, finding no tectum on their brain side, crossed the midline and innervated the opposite tectum. The behavior of the “rewired” frogs is now easy to explain. When stimuli were shown to the left eye, they elicited the behavior proper of the left tectum, rather than of right tectum as normally occurs, hence the paradoxical responses.

The interpretation that following surgery the entire perceptual world of the rewired frog was inverted with the percep-

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Table 1. Terms used to describe motor actions and comprehension

<table>
<thead>
<tr>
<th>Terms and Meanings</th>
<th>Execution</th>
<th>Observation</th>
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</thead>
<tbody>
<tr>
<td><strong>Movement</strong></td>
<td>Displacement of a body-part regardless of the intended goal (e.g., movement evoked by electrical stimulation of the motor cortex).</td>
<td>Understanding the goal of a motor act done by another individual implies the understanding of “what” the other is doing (e.g., grasping an object).</td>
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<tr>
<td><strong>Motor act</strong></td>
<td>A series of body-part movements that allow an individual to reach a goal (e.g., grasping an object).</td>
<td>Understanding a goal of a motor action done by another individual implies the understanding of “why” the other is doing it, that is the action overarching intention (e.g., grasping for eating).</td>
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<tr>
<td><strong>Motor action</strong></td>
<td>A series of motor acts (e.g., reaching, grasping, bringing to the mouth) that allow an individual to fulfill their intention (e.g., eating).</td>
<td>A further level, possibly not related to the mirror mechanism, is the understanding of the reasons underlying the observed motor action (e.g., eating because hungry or for other reasons).</td>
</tr>
<tr>
<td><strong>Observation</strong></td>
<td>An attempt to replicate internally a motor act or a motor action either spontaneously or under instruction.</td>
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Table includes the “technical” meaning of the terms used in this review to describe the different elements forming motor actions and their comprehension (goal and intention).
tion remaining unitary was ruled out by a subsequent experiment. A barrier was placed in front of a rewired frog. The frog was touched on the rear and escaped by jumping away. In contrast to their paradoxical behavior shown with prey-stimuli and looming discs, the frogs jumped correctly, as normal frog, and avoided to hit the barrier placed in front of them. Such behavior was observed immediately after the unilateral tectum ablation, when the animals still neglected the contralateral stimuli.

The dissociation between the behaviors just described is due to the different neural substrates that mediate them. In the case of prey-catching and looming disk avoidance, the behavior is mediated by the tectum, while in the case of locomotion around barrier, it is the pretectal system that mediates it. These findings show that what counts in the organization of the visuomotor responses is the neural pathway linking the visual input to the motor centers and not the “perception” of spatial location of the stimulus. There is no such thing as a unified representation of the external word. The frogs possess a parallel set of independent visuomotor circuits that are activated by specific stimuli present in the environment and determine the appropriate responses. What counts for behavior is not space “perception” but the activity of these motor centers.

The organization of the visual system in parallel visuomotor circuits is not a feature unique to amphibians. Other vertebrate classes show a similar organization. For many years, however, the evidence was rather limited in mammals because studies on vision were typically formulated in these species in terms of perception and cognition, ignoring the visual control of motor output. A notable exception was the work of Goodale and co-workers on rats (151) and gerbils (267). These authors showed a striking homology in neural architecture between amphibians and rodents. They suggested that a series of independent parallel visuomotor circuits is an evolutionary ancient characteristic of all vertebrate brains.

The encephalon of primates, and humans in particular, is characterized by the enormous development of the cerebral cortex. This development correlates with an extraordinary increase of sensory, motor, and cognitive capacities. A large part of the evolutionary new primate cerebral cortex is formed by areas traditionally called “association areas.” The classical view of the functional role of the association areas (posterior parietal lobe and the inferotemporal cortex) was that they “put together” (associate) information coming from different sensory modalities. The results of these associations are percepts. As will be shown in the next paragraphs, these conclusions are simplistic. In the case of parietal lobe, they misrepresent the neurophysiological organization of the posterior parietal cortex, while in the case of inferotemporal lobe, they jump to conclusions far beyond the established facts.

III. THE ANATOMICAL ORGANIZATION OF THE MOTOR CORTEX OF PRIMATES

The first detailed cytoarchitectonic map of human cerebral cortex was published by Campbell in 1905 (59). In his map he distinguished the cortex located immediately in front of the central sulcus (“precentral” cortex) from the cortex located in front of it and caudal to the prefrontal lobe (the “intermediate precentral cortex”). According to Campbell, the precentral cortex is directly involved in motor control,
while the intermediate sector is involved in higher order motor functions. Subsequently, Brodmann in 1909 (44) identified two motor areas (area 4 and area 6), both characterized by an agranular structure. The idea that this architectonic organization reflects functional differences was advanced by Fulton (126) who showed that the ablation of area 6 (defined as “premotor cortex”) in primates produces specific deficits of skilled movements.

The existence of a higher order motor area located rostral to area 4 was challenged by electrophysiological studies employing surface electrical stimulation. Woolsey et al. (406) identified a somatotopic map on the lateral surface of the agranular frontal cortex and stated that area 4 and the caudal part of area 6 form a functional entity: the primary motor cortex (M1). The same authors identified a second complete somatotopic motor representation located on the mesial sector of area 6: the “supplementary motor area” (SMA). Finally, the rostral part of area 6, whose electrical stimulation did not produce body movements, was considered not to be part of the motor cortex. Woolsey et al. (406) wrote “no single cytoarchitectural area of any worker coincides with the extent of our precentral field.”

More recently, neuroanatomical research has significantly boosted the study of the organization of motor cortex. This led to the notion that in both monkeys and humans the motor cortex is formed by several distinct areas, each of them connected in a specific manner with other cortical areas. In the next sections, we will present these data.

A. The Agranular Frontal Cortex in the Monkey

The monkey agranular frontal cortex (motor cortex) is located between the fundus of the central sulcus and that of the arcuate sulcus. According to Brodmann (44), it consists of two areas: area 4 and area 6. This oversimplified subdivision of motor cortex was criticized by several authors, e.g., Vogt and Vogt in 1919 (396) and von Bonin and Bailey in 1947 (397), who all found a much more complex map of the motor cortex (FIGURE 2). Modern studies, which combined the classic architectonic methods with new histological techniques (e.g., neurochemistry, immunohistochemistry, receptor autoradiography, etc.), confirmed that in the agranular frontal cortex there is multiplicity of anatomical distinct areas.

A modern map of the monkey motor cortex based on the works of Matelli and co-workers (31, 259, 260) is shown in FIGURE 3. These authors, in analogy with von Economo and Koskinas (398), named the different motor and premotor areas using the letter F (“frontal”) and consecutive Arabic numbers (F1-F7). In this map, F1 indicates the primary motor cortex (or M1, roughly corresponding to area 4), while the three gross anatomical sectors of Brodmann’s area 6 (mesial, dorsal, and ventral) each results to be formed by a caudal and a rostral subdivision.

B. Classification of Frontal Motor Areas and Their Cortico-cortical and Descending Connections

The brain regions, with which the frontal motor cortex is mostly connected, are as follows: the parietal cortex, the prefrontal lobe, and cingulate cortex (334). The output from the parietal cortex is the major source of input to the primary motor area and the caudal premotor areas (F3, F4, F5c, and F5p). The posterior parietal cortex, similarly to the motor cortex, is formed by a mosaic of areas (FIGURE 3), each of which deals with specific aspects of sensory information and with the control of specific effectors (mouth, hand, arm, and eyes). The areas of the inferior parietal lobule (IPL) and the posterior areas of the superior parietal lobule (SPL) process visual and somatosensory information, whereas the rostral sectors of both lobules, SPL in particular, deal mostly with somatosensory information (58, 173, 332, 344, 403).

The parietal and motor areas are strictly linked one with another (see Ref. 329). It is, therefore, possible to identify the existence of a large number of cortical circuits formed by parietal and motor areas. Typically, these circuits link SPL with dorsal and mesial premotor areas, and IPL with ventral premotor areas. Functional evidence, when available, indicates that parietal and frontal areas forming each of these circuits have common properties. Thus each of these circuits is specifically involved in particular aspects of sensory-motor transformation and represents the functional units of the cortical motor system.

As far as the visual input is concerned, the parieto-frontal circuits can be grouped into two major pathways: a dorsal one, linking SPL with the dorsal premotor cortex, and a ventral one, linking IPL with the ventral premotor cortex (335). The input to SPL and IPL originates mostly from two distinct extrastriate visual areas: area V6 and MT, respectively (12, 81, 131, 229, 343). On this basis, it has been proposed that the classical dorsal stream should be subdivided into two separate streams: the dorso-dorsal involved in visuomotor transformation for online control of movements, and the ventro-dorsal involved in the organization of goal-directed motor act and in various cognitive functions (335). In this respect, note that, IPL, but not SPL, is connected with polymodal areas of the superior temporal sulcus (STS) and with the inferotemporal cortex where semantic information on objects is encoded (37, 229, 282, 343, 358).

Prefrontal projections to the agranular frontal cortex are primarily directed to the rostral premotor areas: F6, F7 and F5a (23, 145, 146, 236, 237, 315, 334, 349). Prefrontal
input to F7, except for the supplementary eye field (SEF), originates only from the dorsal part of the prefrontal cortex (DLPF), while afferences to F6 and the SEF originate from both DLPF and the ventral (VLPF) part of the prefrontal cortex; finally, input to F5a originates only from VLPF. In addition, F6 and the SEF are the targets of strong afferents originating from the rostral cingulate cortex (area 24c).

The organization of the corticospinal and corticobulbar projections is in agreement with the subdivision of the premotor areas into rostral and caudal areas. Strick and coworkers (103, 162, 163) showed that the corticospinal projections originate almost exclusively from the primary motor area and caudal premotor areas. It is also of interest to note that each caudal premotor area displays somatotopically organized connections with each other and with F1. Although F1 is the only sector directly connected to the bulbar and spinal motor neuron pools (312), all caudal premotor areas have access to the spinal cord and can be thus involved in the generation and control of movements, both through F1, or in parallel with it.

The descending output of the rostral premotor areas terminates in various parts of the brain stem, but not in the spinal cord (196). These areas are not directly connected with F1, but are richly connected with other motor areas. The only exception is the dorso-rostral part of F7 (SEF) (352). This oculomotor area is strongly linked with the frontal eye field (FEF) (351). These data indicate that rostral premotor areas could play a role in the generation of motor behavior only indirectly, through their subcortical projections or their connections with the caudal premotor areas.

Taken together, these data indicate a different functional role for caudal and rostral premotor areas. The former transform sensory information into potential motor acts.
the latter are involved in the control of movements at the higher level. More specifically, the rostral areas receive information concerning agent’s goal, motivation and spatial, and non-spatial information from the prefrontal, cingulate, and opercular frontal cortex. This information is then conveyed to the caudal premotor areas determining when and which potential motor acts, coded in these areas, might become actual actions.

### C. Architectonics of Macaque and Human Motor Cortex

The cytoarchitectonics of the areas forming the monkey motor cortex have been extensively studied. Here are their main features. Area F1 has a low cell density, poor lamination, absence of layer IV, and a very prominent layer V with giant pyramidal cells arranged in multiple rows (259). Area F2 is poorly laminated but different from F1, contains only few scattered giant pyramidal cells. Lower layer III is characterized by medium-sized pyramids distributed in a thin row. Layer V is denser than in F1. Area F3 is also poorly laminated, but shows an increase in cellular density in the lower part of layer III and in layer Va. Giant pyramidal cells are almost absent. The ventral premotor cortex consists of two areas: area F4 and area F5. In area F4, the overall cell density is low, and pyramidal size tends to increase from superficial to deep layer III. In layer V, large pyramidal cells are scattered especially in its dorsal part, near the spur of the arcuate sulcus. Area F5 is clearly laminated and shows a cell density higher than F4. Area F5 has been recently subdivided into three sectors: F5p, F5a, and F5c (31). F5p is characterized by a relatively homogeneous layer III, a cell dense layer Va, and the presence of relatively large pyramids in layer Vb. F5c is characterized by a poorly laminated appearance, resulting from an overall homogeneity in cell population. Finally, F5a is characterized by the presence of relatively large pyramids in lowest layer III and a prominent and homogeneous layer V (FIGURE 4). Area F6, unlike areas F1 and F3, is clearly laminated and has a dark and very prominent layer V, well distinct from the less dense layers III and VI. Area F7 is clearly laminated and differs from F2 in two aspects: the presence of a prominent layer V and the subdivision of layer VI into two parts. Subsequent cytoarchitectonic studies confirmed and extended the knowledge on the anatomical structure of this cortical region.

Cytoarchitectonic features of the human motor cortex are similar to that of the macaque monkey. Low cell density, poor lamination, absence of layer IV, and giant pyramidal cells (Betz cells) in layer V characterize the precentral motor cortex (Brodmann area 4) also in human brain, while scattered or absent giant pyramidal cells and densely packed pyramids in lower layer III characterize Brodmann area 6. Close to the midline, the rostral border of area 4 lies on the cortical convexity. Moving ventrally and laterally, this border moves in caudal direction and eventually ends in the depth of the central sulcus.

The mesial cortical surface is cytoarchitectonically similar in humans and macaques. In particular, Zilles and co-workers (412, 413) found that areas F3 and F6 and human areas 6αa and 6αβ of Vogt and Vogt are strikingly similar (396). Other similarities have been found on neurochemical bases (147, 412, 413). Altogether, these data strongly suggest that human mesial areas 6αa and 6αβ are homologous to ma-
caque areas F3 (SMA proper) and F6 (pre-SMA), respectively. The border between the primary motor cortex and area SMA proper (F3) coincides in humans approximately with the vertical plane through the posterior commissure (VCP line), while the border between area pre-SMA and SMA proper coincides with the vertical plane through the anterior commissure (VCA line) (412). The border between SMA proper and pre-SMA as well as its position at the antero-posterior level of the VCA line has been confirmed by means of diffusion magnetic resonance imaging studies (85, 189, 219).

The dorsolateral part of the human premotor cortex is formed by two major sectors: the dorsal (PMd) and ventral (PMv) premotor cortex, each showing a specific pattern of connections (353, 382). PMd is connected with superior parietal cortex, dorsal prefrontal cortex, and cingulate cortex; PMv with inferior parietal cortex and ventral prefrontal cortex.

Taken together, architectonic studies of the human agranular frontal cortex show that this cortical region is formed by a mosaic of architectonic areas. Spatial congruence between architectonic borders and macroscopic landmarks in the human cortex is less clear and less consistent than in the macaque. This variability is a factor that has to be taken into consideration in the interpretation of activation foci in functional imaging studies. Classical cytoarchitectonic maps, based on observations of one or few brains, do not provide information on interindividual variability. Recent
IV. FUNCTIONAL ORGANIZATION OF ACTION EXECUTION IN PRIMATES

A. Movement Execution: Areas F1 and F3

1. Area F1

The primary motor cortex of monkey (area F1) is a nodal point of convergence of inputs from the caudal premotor and parietal areas, and plays a major role in movement execution. In particular, F1 is fundamental for the control of independent finger movements (see Ref. 312), a function that relies on direct cortico-motoneuronal projections, originating from F1 (223, 224, 325). The electrical stimulation of F1 shows a somatotopic organization: a leg field is located on the medial cortical surface and extends on the dorsolateral convexity, an arm field lies in an intermediate position, and a face field occupies a ventrolateral position. Within the arm field, proximal movements tend to be represented rostrally and distal movements caudally, in the anterior bank of the central sulcus.

Evarts (108) found that single neurons in this area typically became active before the onset of muscle electric activity. Asanuma and Rosén (16) proposed that the primary motor cortex is organized in terms of cortical columns, each of which related to a single muscle. A different organization was described by Kwan and co-workers (216, 277). They found a “core and surround” (horseshoe-shaped) movement representation in M1. Digit movements were represented in the “core,” located mostly within the bank of the central sulcus; wrist, elbow, and shoulder movements were located in the “surround” where they formed parallel bands on the cortical convexity. Other studies described a “fractured” somatotopy. According to them, different but overlapping neuronal populations encode arm, hand, and digit movements. There is now general agreement that the primary motor cortical organization is in term of movements (and motor acts) and not in term of muscles and joints (347).

A population of neurons recorded in the motor cortex discharges during reaching arm movements (143). The activity of each neuron is strongest for a specific direction (preferred direction) and weakest for the opposite one. Furthermore, its activity pattern describes a broad directional tuning curve, decreasing gradually from the preferred to the opposite direction. Different cells have different preferred directions. Numerous neurons with different preferred directions discharge at different intensities during each movement, and the vectorial addition of all neurons contribution produces a population vector that corresponds closely to the actual movement direction (143, 192).

One of the oldest ways to investigate the functional role of an anatomical area is to evaluate the deficits occurring in specific aspects of behavior following brain damage. In monkeys, lesions involving the internal capsule determine spastic paralysis. In contrast lesions confined to the pyramidal tract or to the primary motor area produce flaccid paralysis (218, 383; for a review, see Refs. 223, 224). Most deficits tend to compensate over time, even if skilled hand functions never completely recover.

2. Area F3

Similarly to area F1, area F3 (or SMA proper) is electrically excitable with low-intensity currents and contains a complete motor map of the contralateral body. Some important differences distinguish, however, the two areas. In F1, proximal and distal movements are anatomically segregated, while the activity of most F3 neurons is less strictly coupled to specific body parts and instead appears to be associated with coordinated movements of the hand, arm, head, or trunk (238). Furthermore, electrical stimulation typically evokes single joint movements in F1, while two or more joints are most often observed after stimulation of F3 (238, 265). Finally, in F3, the proximal movements are much more represented than the distal ones (238, 303, 406). Interestingly, a subpopulation of F3 neurons code specific sequences of movements (375), suggesting a role of this area in the sequential organization of learned multiple movements (377).

The functional role of area F3 appears to be that of controlling motor activity in a global way. Furthermore, this area plays a role in predictive postural adjustments. With the use of information about the body-parts position in a given moment, it prepares the posture necessary for the impending movements (256). F3 is also involved in learning motor sequences (168).

B. Planning and Execution of Arm Movements: Area F2

Planning an action implies the necessity to decide which movements to execute to achieve a specific goal. Numerous studies, in particular of the dorsal premotor cortex, have attempted to identify the neural substrate underlying movements planning and execution. This was generally done by inserting a delay between the instruction about what movement (usually arm movements) to perform and the cue to actually execute it (84, 403). The results showed that none of the studied cortical areas (including area F1 and area F2) hosts a homogeneous population of neurons dedicated only to planning or execution. Neurons, devoted to this function, are present in both areas and in particular in F2.
Area F2 is an electrically excitable area showing a rough somatotopic organization. The leg is represented dorsal to the superior precentral dimple and the arm ventral to it (103, 162, 214, 322). Numerous F2 neurons show somatosensory responses, mainly to proprioceptive input. Neurons in its ventro-rostral sector (F2vr) also respond to visual stimuli (322, 323). One of the most interesting finding about F2 neurons concerns the feature of their discharge. Wise and co-workers (403) distinguished three types of neurons: 1) signal-related neurons, discharging at the appearance of the instruction stimulus; 2) set-related neurons, discharging during the delay period before the go signal; and 3) movement-related neurons, discharging in association with movement onset. The activity of single neurons and populations during the delay period of reach-to-grasp tasks conveys information necessary for correctly reach an object, controlling the direction of the arm movement (FIGURE 5) (77, 84). Furthermore, F2 neurons also integrate information about target location and arm to be used to plan actions (171). F2vr sector is also involved in the control of the configuration of the hand for reaching to grasp movements (323).

It is important to stress that the dorsal (F2d) and ventro-rostral (F2vr) sectors of area F2 differ in the pattern of cortical connections: F2d is mainly connected with parietal areas PEc and P2; F2vr has strong connections with parietal areas MIP and V6A (22, 132, 258). Furthermore, F2vr, but not F2d, is target of a minor, but consistent projection from the dorsal part of prefrontal area 46 (46d, as defined in Ref. 240). Several parietal areas, especially those connected with area F2vr, share with this latter some functional properties. In particular, they contain neurons active during the execution of reaching movements and responds not only to somatosensory, but also to visual stimuli (43, 81, 130, 180, 193, 250).

C. The Pragmatic Coding of Peripersonal Space: Area F4

Our intuitive idea of space is that of a single continuous entity that extends in all directions and within which objects have locations relative to one another and the observer. According to classical neurology, the neural counterpart of the subjective space perception is a single map located in the parietal lobe constructed by the association of inputs from different sensory modalities (see Ref. 86). This unified, multimodal representation of the world is assumed to provide all the information necessary for acting on an object and is shared by the different motor circuits that control eyes, arms, hands, and other effectors. An alternative more recent view is that there are many maps each encoding space in terms of different effector movements. These spatial representations emerge as a result of interactions of individuals with their environment and define a series of motor relations determined by the properties of a particular effector. The sense of space arises from our motor interactions with the world (see Refs. 242, 311).

Lesion studies and single neuron recordings are consistent with this last view. They indicate the existence of two main types of space: the space within our arm reach (“peripersonal space”) and a space outside it (“extrapersonal space”). Ablation of PMv in the monkey determines a syndrome characterized by the lack of awareness of the contralateral side of the body and of the space around it (“peripersonal neglect”) (336). Far stimuli were perceived normally as in nonlesioned monkeys. The premotor area crucially involved in encoding peripersonal space is area F4 (123).

Electrical stimulation and single neuron studies showed that area F4 contains a representation of arm, neck, face, and mouth movements (123, 142, 150). Prolonged electrical stimulation elicits a complex protective movement pattern similar to that performed by monkeys when presented with actual threat (153). Most F4 neurons discharge during the execution of goal-directed motor acts, such as reaching for food and bringing it to the mouth (142). F4 neurons also respond to sensory stimuli. According to their responses, they can be subdivided into two main classes: unimodal (tactile) and bimodal (visual and tactile) neurons (123, 142). The tactile receptive fields (RFs) are large and predominantly located on the face, arm, and the upper part of the body. The visual RFs are three-dimensional fields located around different body parts in register with the tactile fields. The visual RFs are independent of the eye position and are anchored to the tactile one (FIGURE 6). Some F4 neurons have also an auditory RF in register with the visual and tactile ones (123, 142, 154).

It has been suggested that the visual responses in many F4 bimodal neurons represent a potential motor act within the peripersonal space. Indeed, the RFs of many F4 bimodal neurons expand in depth when tested with approaching stimuli moving at increasing velocities (123). This indicates that these neurons do not encode space in geometric terms, but encode it dynamically to allow the preparation of appropriate motor acts.

Area F4 is strongly connected with parietal areas PF, PFG, and VIP (12, 24, 73, 74, 229, 257, 280, 343). In particular, area PF is the source of somatosensory input related to the face and the mouth, while PFG and VIP send somatosensory input related to the forelimb and visual information that they receive from areas involved in the visual motion analysis (MT, MST, FST) (41, 81, 262, 389). The main parietal node for representation of peripersonal space is area VIP. The electrical stimulation of this evokes head and arm movements (82, 379). Most neurons in VIP respond to the presentation of visual moving stimuli (79, 80, 102). Among them there are bimodal neurons, whose properties are for many aspects similar to those of F4. Their
visual RFs are located in space sectors corresponding to the tactile fields (FIGURE 6) (102). Recently, bimodal spatial neurons have also been found in area PFG, where also arm-hand motor acts are represented (344). This area appears therefore to represent a second parietal node for peripersonal space coding.

D. Goal Coding and the “Vocabulary of Motor Acts”: Area F5

To execute an action (e.g., grasping and eating a peace of food), one must have a prior intention (to eat the food), select a sequence of motor acts (reaching, grasping, bringing to the
mouth, biting), and finally execute this sequence. This view on action organization implies the organization of different elements at different hierarchical levels: movements, motor acts, actions (see Table 1). For achieving the action intention, single elements must be linked one to the other according to a precise temporal structure, so to generate the “kinetic melody” (241) that characterizes normal behavior.

While F1 is crucial for movement execution (see above), area F5 plays a fundamental role in encoding hand and mouth motor acts (116, 142, 167, 215, 328). This statement is based on single neuron studies that showed that most F5 neurons encode specific motor acts such as grasping, breaking, holding, rather than the individual movements that form them (328). Neurons discharging for a specific motor act typically do not discharge during the execution of similar movements aimed at a different goal, for example, a neuron that discharges during finger movements for grasping an object does not discharge during similar movements aimed at scratching. Furthermore, some of F5 neurons discharge when the same goal is achieved by using different effectors (e.g., the right hand, the left hand, or the mouth), and thus requires a completely different set of movements (Figure 7A). Many neurons code specific types of grip, such as precision grip, whole hand prehension, or finger prehension. Finally, concerning the timing of grasping, some neurons discharge during the whole motor act (e.g., opening and closure of the hand), while others

FIGURE 6. Response properties of bimodal neurons in area F4 and VIP. A, top: examples of different types of tactile and visual RFs of F4 bimodal neurons. Solids around different body parts indicate the 3D visual RFs. Bottom: example of an F4 bimodal neuron the visual RF of which is independent of eye position. The monkey had to fixate an LED (fixation position indicated by the asterisks) and released a bar upon its dimming. During fixation a 3D stimulus was moved toward and away from the monkey face at constant velocity inside (left) and outside (right) of the visual receptive field. Each panel shows horizontal and vertical eye position, rasters, and histograms representing the neuronal response and the variation in time between the stimulus and the monkey. Large dots in the rasters indicate dimming of the fixation point. The neuron tactile RF was located on the lower face. The stimulus direction reversed when the stimulus was a few centimeters from the tactile RF. Note that the discharge is present when the visual stimulus is moved toward the tactile RF independent of eye position, and consequently is not related to a retinocentric frame of reference. Abscissae, time; ordinates, spikes per bin; bin width, 20 ms. [Modified from Fogassi et al. (123).] B, lateral view of the monkey brain showing the location of area F4 and VIP. C, top: schematic representation of somatosensory and visual RFs of VIP neurons. The shaded areas on the monkey and screen represent tactile and visual RF surfaces, the arrows the preferred direction of motion. Bottom: neuron with direction selective responses to tactile and visual stimulation. Single trial rasters and histograms below the cartoons are synchronized on stimulus movement onset (vertical line). The neuron responds best to a tactile stimulus moving front to back on the side of the head and to a large stimulus moving in the same direction in the far contralateral visual periphery. Vertical calibration bar (left) corresponds to 100 impulses/s; tick marks on horizontal axis are 200 ms apart. [Modified from Duhamel et al. (102).]
only during a certain part of it (e.g., shaping of the hand or tacking possession of the object).

On these bases, it has been proposed that F5 contains a “vocabulary” of motor acts (328). This motor vocabulary is constituted of “words,” each of which is represented by a population of F5 neurons. Some of them encode the general goal of a motor act, others encode how a specific goal-directed motor act must be executed, and others specify the temporal aspects of the motor act to be executed (186). A further demonstration that F5 neurons encode motor acts has been recently provided by a study in which the same motor goal (i.e., taking possession of food) was achieved by means of opposite movements (387). Monkeys grasped objects using normal pliers, which require hand closure to take possession of the object, and reverse pliers, that instead require hand opening to achieve the same goal. Most of F5 neurons encode goal achievement (e.g., taking possession of
the target) independent of the specific fingers movement (flexion or extension) required to achieve it [FIGURE 7B].

Most of the data discussed in this section derive from the study of the neuronal properties of F5p and F5c. Both these sectors are densely anatomically connected with the parietal cortex and in particular with areas AIP, PF, PFG, and SII (37, 74, 145, 239, 257, 308, 343). Interestingly, F5 and PFG share numerous functional properties (34, 173, 222, 344). In particular, both areas contain motor neurons encoding motor acts.

Recently, the issue of how the intention of an action, i.e., the overarching goal of a series of motor acts, is encoded in the nervous system has been studied in PFG and in F5, using an identical paradigms. Grasping neurons were recorded in two conditions: in one the monkey grasped a piece of food and brought it to the mouth for eating; in the other, it grasped an object or a piece of food to place it into a container (35, 121). Some neurons showed a stronger discharge when the monkey grasped food to bring it to its mouth, and weaker or absent when it grasped food to put it into a container. Others had an opposite behavior [FIGURE 7C]. Note that the difference in response in the two conditions was observed during grasping that was executed in the same way. Furthermore, factors such as grasping force, kinematics of reaching movements, type of stimulus, and motivation could not account for the context-specific activation of the neurons (34, 121). The activation of these neurons, together with that of the other neurons within the same sequence of motor acts, represents the neural correlate of its overarching goal, which is the intention of the acting individual. This concept will be developed later in the section on action and intention understanding.

E. Visuomotor Transformations for Grasping

In addition to purely motor neurons, area F5 contains neurons also responding to sensory stimuli. Many of them respond to somatosensory stimuli, but a consistent percentage (~25%) is responsive to the presentation of visual stimuli (328). Among these latter, a set discharges in response to the presentation of 3D objects (275, 324). These neurons are called canonical neurons [FIGURE 8A]. They are mostly located in area F5p.

Canonical neurons are activated by objects of a specific size, shape, and orientation. Visual and motor object specificities are reciprocally congruent. There is evidence that the response of canonical neurons to the presentation of visual stimuli cannot be accounted for in terms of motor preparation. In fact, these neurons also respond when the monkey is not required to grasp the presented object, but simply to observe it (275). The interpretation of the discharge of canonical neurons is that these neurons encode the stimulus motorically: when an object is seen, the discharge of canonical neurons encode a potential motor act congruent with the properties of the presented object, independently of whether the act will be executed or not.

F5p is strongly connected with the anterior intraparietal area (AIP) (37, 144, 239). The functional properties of this area have been extensively studied by Sakata and co-workers (276, 347, 373). AIP neurons can be subdivided into three main classes: “motor-dominant,” “visual and motor,” and “visual-dominant” neurons. Motor-dominant neurons discharge during grasping and holding both when the grasping action is performed in light and when it is executed in complete darkness; they do not discharge during object fixation. Visual-dominant neurons become active when grasping is performed in light, but not in dark. They respond to simple object fixation. Visual and motor neurons discharge during object fixation and during grasping in light and in dark [FIGURE 8B].

Objects can be grasped with various grips depending, not only on their affordances, but also according to different behavioral context. In recent studies, Scherberger and co-workers (30, 120) trained monkeys to grasp a handle with

**FIGURE 7.** Goal and intention encoding in areas F5 and PFG. A, top left: lateral view of the monkey brain showing the location of area F5. Bottom right: discharge of an F5 neuron active during grasping with the mouth, the right hand, and the left hand. Conventions are as in [FIGURE 6A]. [Modified from Rizzolatti et al. (328), with kind permission from Springer Science and Business Media.] B: example of an F5 neuron discharging during grasping with normal and reverse pliers. Top: pliers and hand movements necessary for grasping with the two types of pliers. Bottom: rasters and histograms of the neurons’ discharge during grasping with pliers. The alignments are with the end of the grasping closure phase (asterisks). The traces below each histogram indicate the hand position, recorded with a potentiometer, expressed as function of the distance between the pliers handles. When the trace goes down, the hand closes; when it goes up, it opens. The values on the vertical axes indicate the voltage change measured with the potentiometer. Other conventions are as in [FIGURE 6A]. [Modified from Umilta et al. (387). Copyright 2008 National Academy of Sciences, U.S.A.] C: example of motor neuron in PFG modulated by action intention. Top left: lateral view of the monkey brain showing area PFG. Top right: paradigm used for the motor task. The monkey, starting from a fixed position, reaches and grasps a piece of food or an object, then it brings the food to the mouth and eats it (II, grasp-to-eat), or places it into a container (II/III, grasp-to-place). Bottom left: activity of three IPL neurons during grasping in the two actions. Rasters and histograms are aligned with the moment when the monkey touched the object to be grasped. Red bars, monkey releases the hand from the starting position; green bars, monkey touches the container. Conventions are as in [FIGURE 6A]. Bottom right: responses of the population of neurons selective for grasping to eat and grasping to place. The vertical lines in the two panels indicate the moment when the monkey touched the object and the moment in which the grasping was completed, respectively. The y-axes are in normalized units. [Modified from Fogassi et al. (121). Reprinted with permission from AAAS.]
two different grip types on the bases of distinct contextual cues (lights of different colors). They found that in both AIP and F5, a set of neurons were active after cue presentation, showing context-dependent grasp planning activity.

The evidence that AIP and F5 are two nodes of a circuit for visuomotor transformations for grasping received a strong support from inactivation studies. Transient inactivation obtained by injection of muscimol, in either monkey AIP (129) or area F5 (122), produced a dramatic deficit in the capacity to shape the hand according to the object physical features. Once touched, the object was correctly grasped, thus showing the lack of motor deficits.

How do the visuomotor transformations for grasping occur? There are various models that try to explain the role that AIP and F5 play in this process (112, 120, 186, 334, 373). A common idea underlying these models is that when an object is observed, AIP neurons extract specific aspects of its physical properties (affordances as defined by Gibson, Ref. 149) and provide F5 with the description of the possible ways in which the object could be to grasped. On the basis of the intention of the individual and the context, the prefrontal lobe selects AIP visuomotor neurons and neurons in F5 that coding the most appropriate grip. The information relative to the chosen grip is then sent from F5 to F1, where the different movements necessary to grasp the object are selected and the final command for its execution is generated. Recent physiological data from Lemon and co-workers (75, 313, 361) confirmed this point showing that the electrical stimulation of F5 facilitates F1 motor output to hand muscles. In addition to the output from F5 to F1, descending pathways directly linking F5p with the propriospinal system (38) could also play a role in grip generation. The connections with the cervical propriospinal neurons appear to play also a role in the control of dexterous fingers movements, as shown by functional recovery after brain lesions (178, 204).

F. Possible Functions of the Rostral Premotor Areas: Decision of When to Act, the Organization of Motor Sequences and Motor Learning: Area F6

The presence of potential motor acts, coded in the posterior motor areas, implies that there should be a system control-
...ling these motor acts, either permitting their transformations into actions, or preventing their implementation. This control system, which comprises many prefrontal and cingulate areas, also includes the rostral premotor areas.

Evidence that a sector of the premotor region plays a control on motor execution has been provided by electroencephalographic (EEG) studies in humans (95). These studies showed that, about 1 s before movement onset, a slowly increasing negative potential, the “Bereitschaftspotential” (or “readiness potential”) occurs in the motor region with its maximum close to the cortical mesial surface. On this basis, Kornhuber (207) suggested that the mesial motor cortex specifies when a movement has to be done. Interestingly, the amplitude of this potential is wider when it precedes self-paced movements than when it precedes those externally driven (181). These data suggest that the mesial motor cortex plays a role in selecting and allowing voluntary actions and, in particular, self-initiated movements. However, the low spatial resolution of EEG technique does not allow one to identify precisely the source of this potential, whose precise location remains controversial.

Single neuron recordings in the monkey suggest that the mesial region controlling action selection and initiation mainly corresponds to area F6 (pre-SMA). This area is weakly excitatory to electrical stimulation. The movements observed using currents of high intensities are slow, complex, and concern mainly the forelimbs (238). Single neuron recording studies showed that visual responses are common in this area, while somatosensory responses are rare. Furthermore, differently form F1 and F3 neurons, whose discharge slightly precedes movement onset, the vast majority of F6 neurons discharge well in advance of movement initiation (7, 261).

Tanji and co-workers (375–377) studied the role of the medial premotor areas during the performance of movement sequences. They trained monkeys to execute three different acts (push, pull, and turn of a manipulandum) in different orders, separated by a waiting time. F6 neurons typically discharge during the interval between one particular act and another (e.g., during the preparation of a push following a pull), or having a particular rank order inside the sequence (e.g., third act in the sequence, irrespective of the type of movement executed, FIGURE 9A). These results prompted the authors to conclude that F6 neurons contribute to the organization of complex motor sequences. In addition to this role, F6 neurons seem also to code time interval per se, when crucial for behavior (264, 278).

While Tanji and co-workers studied the activity of F5 neurons during motor sequences consisting of three discrete motor acts, Nakamura et al. (279a) investigated the role of F6 in the sequential execution of multiple reaching, directed to different spatial positions. Monkeys were presented with a panel hosting 16 LEDs, 2 of which could be turned on, and had to press them in a specific order. When the first sequence (“set”) was learned, another sequence was shown. Finally, a “hyperset” formed by five different sets was presented. The results showed that F6 neurons discharged when the monkeys were learning a new sequence and at the beginning of a correct sequence performance. In contrast, they showed almost no activity during task execution when the monkeys had mastered the hyperset (FIGURE 9B).

Hikosaka and co-workers (346) also examined the activity of F6 (pre-SMA) in humans. In an fMRI experiment, three learning paradigms similar to that employed in monkey experiment were used. In one of them, the subjects were required to respond on the basis of learned color associations, and not on the basis of learned sequence. It was found that area F6 was activated also in this condition. It appears therefore that area F6 plays a fundamental role in controlling action execution in general and not only during sequential actions.

A similar role for F6 was also proposed by Rizzolatti et al. (333). These authors studied the activity of single neurons in monkey F6 by employing a naturalistic setting. Their results showed that F6 neurons do not specifically control distal or proximal movements, but are active when monkeys were presented with objects possible targets of motor acts. Typically, F6 neurons increased their discharge when an object entered into the monkey reaching space. These neurons, however, did not code the peripersonal space, because the discharge was present only if the approaching stimulus was target of an actual monkey’s movement and no RF could be mapped. What they appear to code is, in contrast, the possibility to act on an object. Indeed, their activity strongly depended on the contingencies of stimulus presentation (near or far, presence or absence of obstacles to action) and on motivational factors (FIGURE 9C).

F6 is strongly connected with dorsal and ventral sectors of the prefrontal area 46, with the rostral cingulate area 24c and with the caudal premotor areas (236, 237). It is therefore a site of convergence of information about objects and locations in space memory, temporal planning of actions, and motivation, which are then used for action selection and initiation.

G. Functions of the Other Rostral Premotor Areas

Unlike the other premotor areas, very little is known on the functional proprieties of the two other rostral premotor areas: areas F7 and F5a. Here we summarize their connections and some preliminary functional data.
1. Area F7

Area F7 is formed by two sectors. The dorsal sector, the supplementary eye field (SEF) is an oculomotor area. Its functional properties will not be dealt with in the present review. The ventral sector of F7 (F7-non SEF) is mostly involved in the control of body movements. The discharge of some neurons in this area is related to both arm and eye movements (125). Part of these neurons show visual responses when the location of the stimulus is the same of the target of an arm movement (392).

A

Push Pull Turn Pull Push

Push Turn Pull Pull Push

Turn Push Pull Pull Push

B

New Hypersets

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Contralateral Hand

Ipsilateral Hand

Learned Hypersets

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Contra lateral Hand

Ipsilateral Hand
F7 is strongly connected with the dorsal part of the dorso-lateral prefrontal cortex, mainly with area 46d and area 8b (240). There are also weak connections with the parietal areas FGm and V6A (132, 238). Lesions involving the sector of F7-non SEF impair the performance of monkeys in previously learned motor association tasks and prevent new learning (see Ref. 297). It is very likely that this area, together with area F6, plays a role in motor learning.

2. Area F5a

Area F5 is a caudal premotor area. Recent anatomical data showed, however, that its rostral sector F5a is part of the “family” of the rostral premotor areas (31). F5a displays transitional architectonic features between those of the agranular-premotor cortex and those of the granular-prefrontal one (32). More specifically, it is characterized by the presence of some rare granular cells, a homogeneous and prominent layer V, a low SMI-32 immunoreactivity with medium-sized pyramids, and a high density of calbindin-immunopositive nonpyramidal neurons over the whole layer III (FIGURE 4). The classification of F5a as a rostral premotor area is in line with the proposed homology of this area with human area 6R1 of Amunts and Zilles (11), which is part of Broca’s region.

As far as its cortical connections are concerned, F5a is characterized by strong connections with the ventral prefrontal areas 12 and 46v, and the rostral frontal operculum (144, 145). Inside the premotor region, in addition to strong connections with the other F5 sectors, F5a is also densely connected with area F6. Altogether this connection pattern indicates that F5a could be the gate through which higher-order information coming from the ventral prefrontal cortex access the motor cortex.

A role of area F5a in cognitive-motor functions is also demonstrated by some physiological studies, not specifically targeting this area, but probably involving it. These studies show that F5a plays a role in the evaluation and comparison of current and remembered sensory information for perceptual decisions (225, 340) and in the evaluation of the outcomes of these decisions for future behavior (295, 296).

V. THE MIRROR NEURON MECHANISM

As discussed at the beginning of this review, the ideas on the functional role of the motor system radically changed in these last 20 years. One of the major reasons for this change was the discovery of the “mirror mechanism.” The essence of this mechanism is the following. There are neurons, located in various part of the nervous system, that encode a specific motor behavior and which, in addition, are activated by the observation of motor behavior similar to that they encode motorically. Thus an observed action produces, in the observer’s brain, a motor activation, as if the observer was actually programming its execution (see Ref. 337).

The mirror mechanism has been found in monkeys, humans (see below), and, more recently, in birds (197, 314). In monkeys and humans, neurons endowed with the mirror mechanism have been discovered in cortical center controlling actions devoid of emotional content (“cold actions”), but also in centers involved in emotions, like the insula and the cingulate cortex (128, 367). In birds, mirror neurons have been described in motor centers involved in song productions (197, 314). These findings indicate that the mirror mechanisms have radically different functions that depend on its anatomical location.

In this review we discuss only the mirror functions related to “cold” action. Our review of mirror functions is subdivided into two parts. In the first we review the functional role of the mirror mechanism in monkeys, and in the second

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**Figure 9.** Functional properties of area F6. A: discharges of a F6 (pre-SMA) neuron whose activity increased when the monkey was preparing to initiate the third movement, irrespective of the movement type (push, pull, or turn). In the raster displays, each row represents a trial; dots, individual discharges of the neuron; filled squares, the occurrence of signals that triggered each movement; plus, the onset of movement. The histograms show sum discharges over 9 trials. The bin width is 40 ms. [Modified from Shima and Tanji (359).] B: activity of an F6 (pre-SMA) neuron for new hypersets and learned hypersets (see text). Spike activity, shown by rasters and histograms, are aligned at the time when the monkey pressed the first button for each set. Only activity for correctly executed trials is shown: the first trial at top, the last at bottom. Inverted triangles in the raster indicates other task-related events (stimulus onset and second button press). For the new hypersets, the cell showed phasic activity for every set before the first button press; for the learned hypersets, it was nearly silent except for the 1st trial. Note that the activity for the new hyperset decreased as learning proceeded. Top 3 rows: data when the monkey used the hand contralateral to the recording site. Bottom row: data when the ipsilateral hand was used. Correct orders of button presses for the hypersets used are shown below. [Modified from Nakamura et al. (279a).] C: top: cartoons of the sequence of reaching-grasping task during testing of neurons in F6. Top sequence: reaching-grasping in vision. An object was presented and moved by means of a mechanical carrier toward the monkey who gazed on it, and, when reachable, reached and grasped it. White lines, monkey gaze; yellow curve, approximate extension of reaching distance. Bottom sequence: reaching-grasping without visual control. The vision of the target is prevented, and the movement is executed without visual guidance. Bottom: F6 neuron active during premovement and movement periods. a and b: reaching and grasping in response to a visual object; c: same action toward a hidden object. In the left panel, the activity is aligned (vertical line) with the onset of the saccades elicited by the object approaching the monkey. In the middle and right panels, the activity is aligned with the time when the monkey touched the object; the dashed line in the histograms represents the average time of movement onset. Triangles on the individual trial lines indicate the saccade on the target in the visual condition. [Modified from Rizzolatti et al. (333).]
we examine its role in humans. We refer to the ensemble of cortical motor centers endowed with the mirror mechanism as the mirror neuron system (or mirror system).

VI. MIRROR NEURON SYSTEM IN MONKEYS

A. Mirror Neurons of Area F5

1. Basic properties

Mirror neurons are a distinct class of motor neurons that discharge both when a monkey performs a specific motor act and when it observes the same or a similar motor act done by another individual (monkey or human) (FIGURE 10). The motor properties of F5 mirror neurons are similar to those of other neurons of this area. Unlike canonical neurons, they do not respond to presentation of objects, including “interesting” objects like food. Observation of intransitive actions is ineffective in triggering mirror neurons (98, 127, 330).

A fundamental property of mirror neurons is that they respond to the observation of motor acts having the same goal as that they encode motorically. According to the first descriptions of F5 mirror neurons, the observation of actions done with tools was ineffective in triggering these neurons (127, 330). Further investigations reported, however, that a set of mirror neurons discharged in response to tool actions (327). More recently, these findings were confirmed by Rochat et al. (338) (see also Ref. 301).

The first experiments on mirror neurons investigated mostly the upper sector of F5, i.e., the sector in which hand actions are represented. Subsequently, the ventral part of F5, related to mouth movements, was also explored (116). The results showed that ~25% of neurons in this part of F5 have mirror properties. Mouth mirror neurons were subdivided into two classes: ingestive and communicative neurons. Ingestive mirror neurons (~80% of the total amount of the recorded mouth mirror neurons) discharge when the monkey observes actions related to ingestive functions (biting, grasping food with the mouth, or sucking). Communicative mirror neurons responded to the observation of communicative gesture such as, for example, lip smacking. However, as the ingestive mirror neurons, they strongly discharged during the performance of ingestive acts. The reason for the discrepancy between the effective visual input (communicative) and the effective active motor act (ingestive) is not clear. Hypotheses on language evolution suggest that communicative gestures derived from ingestive actions (243, 394). On this basis, one may argue that the communicative mouth mirror neurons reflect a stage of corticalization of communication not yet freed from the original ingestive functions of this area.

2. Mirror neurons of area F5 code the goal of the motor acts

A crucial issue concerning the mirror neurons is their role in cognition. Before addressing this issue one must address, however, a preliminary problem: what do the parieto-frontal mirror neurons encode when they discharge in response to the observation of others’ actions? The response is straightforward. In the case of extracellular recording (like in all studies described up to now), what is studied is the neurons’ output. This is true both for action execution and for action observation. Thus, if one knows what a neuron encodes during the execution of a motor act, one also knows what it encodes during the observation of motor act done by another individual. The output of a neuron does not change in relation to how the neuron is triggered. Thus, since there is compelling evidence that, during active behavior, the neurons of area F5 encode the goal of motor acts, also the observation of motor acts done by others must generate the representation of the motor act goal.

An interesting issue is whether to activate F5 neurons is necessary the vision of the motor act done by another individual or is enough to have information sufficient for understanding the goal of others’ motor act even in the absence of its vision. This point is crucial for establishing the generalization capacity of the mirror neurons. If mirror neurons mediate goal understanding, regardless the stimulus contingencies, it is reasonable to conclude that their activity reflects the meaning of the observed motor act. Two series of experiments addressed this problem. The first tested whether F5 mirror neurons were able to recognize the motor acts from their sound (206), and the second tested...
whether the understanding of a motor act, based on some memory clues, can trigger their activity (388).

Kohler et al. (206) studied mirror neurons while the monkey was observing a motor act characterized by a typical sound for an action (e.g., ripping a piece of paper), and while this sound was presented without the vision of the corresponding motor act. The results showed that ∼15% of mirror neurons responding to the presentation of motor act accompanied by sounds also responded to the presentation of the sound alone. Control experiment showed that the response to the sound of motor acts did not depend on unspecific factors such as arousal or the emotional content of the stimuli (Figure 11).

The logic of the second experiment (388) was the following: if mirror neurons respond to the goal of a motor act, they should also discharge when monkey has sufficient information to produce a mental representation of what another individual is doing, even in the absence of visual information. Neurons were tested in two conditions. In one, the monkey saw an object-directed action (“full vision” condition); in the other, the same action was presented but with its final part hidden (“hidden” condition). A piece of food was placed behind the screen with the monkey being aware of its presence. The results showed that neurons responding to the observation of grasping in the full vision condition also discharge in the hidden condition. It appears therefore that is the meaning of the observed actions, and not the vision of it, that trigger mirror neurons.

Although some authors interpreted the results of this experiment in terms of action prediction, this interpretation goes beyond the data. When a mirror neuron fires, its discharge describes the goal of a given motor act. It “says” what happened here and now, i.e., grasping. The same is valid for the “hidden” condition of the study by Umilta et al. (388). Because there is sufficient information in the context for understanding the motor act, the neuron signals the goal of the observed motor act, exactly as when the grasping is visible. Prediction is an arbitrary interpretation.

Taken together, the two experiments described above show that mirror neurons respond to the goal of the observed motor act also in the absence of visual cues. These cues trigger mirror neurons only insomuch as they allow the understanding the goal of motor act. When goal comprehension is possible on other bases, mirror neurons are able to signal it, even in the absence of visual stimuli.

3. Factors influencing the discharge of F5 mirror neurons: space, valence, view and type of the stimuli

Already in the early studies of mirror neurons, it was noted that other factors than mere action observation could influence the discharge of mirror neurons. Among them, the hand the experimenter used for interacting with objects and the spatial (left or right) location of the experimenter’s motor act (see Ref. 127).

A recent study addressed a specific aspect of this issue (54) and, namely, whether the location of the stimuli near the monkey (peripersonal space) or far from it (extrapersonal space) was instrumental in triggering F5 mirror neurons. The results showed that about half of the recorded neurons were modulated by the spatial location of the observed motor act. Of these, ∼50% preferred stimuli presented in the peripersonal space and 50% stimuli presented in the extrapersonal space. In a subsequent experiment, the nature of this representation was investigated. Specifically, it was tested whether space was represented in F5 in terms of the distance from the monkey’s body (metric representation) or in terms of working space (operational representation). An experiment was, therefore, carried out in which a transparent panel was introduced between the monkey and the site of the action. This prevented the monkey, which obviously saw the action, from the possibility to interact with objects in its peripersonal space. In a purely metric representation, this manipulation would leave the peripersonal and extrapersonal regions unchanged, while in an operational representation it would lead to a remapping of the peripersonal into extrapersonal space. By using this paradigm it was
found that ~50% of tested mirror neurons, all selective for peripersonal space, changed their tuning properties. That is, after positioning of the frontal panel, these mirror neurons lost their tuning. These results indicate that area F5 neurons encode space in two different ways. The first is purely metric and depends only on the distance between the monkey’s body and observed actions, while the second one is action-centered and depends on the possibility of the monkey to execute a motor act in a given space region close to its body.

Most experiments on mirror neurons have been performed using what is called “naturalistic testing.” This testing consists of recreating, during the experiment, a quasi-real life condition with the experimenter placed in front of the monkey and manipulating food, feeding the monkey, and performing a variety of other actions (98, 127, 330). Mirror neurons were discovered thanks to the naturalistic testing. It is obvious, however, that the precision of this method is limited by the variability of the experimenter’s movements. To test mirror neurons in a quantitative way, one must use a more controlled setup and, especially, standardized stimuli like filmed actions. But, are these stimuli effective? Because there were some negative, although rather anecdotic results, on this point, the problem of the efficacy of filmed actions was formally addressed by Caggiano et al. (53). They trained monkeys to fixate a central spot during film presentation and compared the neuron responses to those obtained during naturalistic testing. The results revealed that 43% of the tested neurons showed no significant preference for either type of action stimulus. The remaining neurons exhibited (in almost all cases) a stronger response for naturalistic motor acts. These findings opened the possibility to examine in a more quantitative way the property of mirror neurons.

One of these studies investigated the view dependence of the visual responses of mirror neurons (53). To this purpose movies were presented showing the same motor act (grasping) seen from three different viewpoints: from the monkey’s perspective (subjective point of view) (0°), from a side view (90°), and from the frontal view (180°). The results showed that the large majority of tested neurons (74%) were view-dependent, i.e., they showed a significant discharge preference for at least one view. In the remaining neurons (26%) the responses did not vary in the three view conditions. There are two possible interpretations of these data. The first is similar to that concerning the spatial properties of mirror neurons. When a grasping neuron fires, it can “say” only an undifferentiated “grasping.” However, if different sets of view-dependent mirror neurons have different anatomical connections, their firing determine or prompt the activation of other neurons allowing in this way an adequate preparation to the observed stimulus. Another possible interpretation of the role of view dependent neurons is that their discharge is conveyed through descending (top-down) selective connections to higher-level visual areas, thus binding the goal of the observed motor act (visually unspecified grasping) with its pictorial description.

From the data presented above it is clear that spatial aspects of the observed actions may modulate the responses of mirror neurons. The recent anatomical discovery that information on object semantics reaches F5 (see anatomical section) raised the question of whether the value of the object acted upon by others may influence the activity of mirror neurons. This problem was recently addressed in three experiments (52). The results showed that a large subset of mirror neurons in F5 is influenced by the subjective value of the object on which the observed action is performed. These data imply that a subset of F5 mirror neurons have access to key information that may be useful to shape the behavior of the observer, according to the value of the object grasped by another individual.

Recently an experiment investigated the output of area F5 by recording from identified pyramidal tract neurons (PTNs) and by testing them for possible mirror properties (211). It was found that ~50% of the tested PTNs were modulated by action observation. This finding indicates that mirror neuron activity can be transmitted directly to the spinal cord via PTNs. It was also found that several PTNs (17/64) showed suppression of discharge during action observation, while they fired during active grasping. The authors suggested that inhibitory effect might play a role in preventing movement generation during action observation.

In a following study, the same authors recorded from PTNs originating from primary motor cortex (F1) (395). Many of them were modulated during action observation. Most PTNs increased their discharge during observation (“facilitation-type” mirror neurons), while others showed reduced discharge (“suppression-type” mirror neurons). By comparing the properties of PTNs F1 mirror neurons with those of PTNs F5 mirror neurons they found that the visual response in F1 was much weaker than in F5. Thus, although many F1 PTNs discharge during action observation, their input to spinal cord circuitry might be insufficient to produce overt muscle activity. Taken together with previous data on F5 PTNs, these findings indicate that motor goal understanding is not function of F5 mirror neurons, but rather of the activation of complex motor schema that involves corticospinal tract neurons.

B. Mirror Neurons and Motor Intention

Understanding: Areas PFG and Area F5

The observation of a motor act done by another individual allows the observer to understand the goal of the observed motor act, but often also the intention behind it. Intention
understanding can be based on how the agent interacts with the object. For example, a glass of beer grasped by its body indicates the desire to drink the beer, while the same glass grasped by the top suggests the intention to move the glass. Even when two grips are identical, one may guess the intention of the agent from the object the agent is grasping or from the context. In this section we present experiments showing that mirror neurons are involved, besides in encoding the goal of the motor acts also in motor intention understanding.

The first experiments trying to assess a possible relation between motor intention and mirror activity were carried out in the inferior parietal lobule, mostly in area PFG. As described in previous sections, the motor organization of area AIP and PFG is based on goal-directed motor acts (121, 276). In both these areas, there are neurons encoding specific motor acts and specific types of grip. Furthermore, both these areas contain mirror neurons whose general properties are similar to those of area F5. The experiments consisted of two parts (121). In the first part, monkeys were trained to grasp objects with two different intentions: eating or placing using the same grip (motor paradigm). In the second part, monkeys observed the experimenter grasping object with two different intentions using the same grip (visual paradigm). Neurons were recorded from IPL (mostly PFG), and their discharge during grasping was studied in the motor and visual paradigm. The results obtained during active grasping showed that two-third of IPL grasping neurons discharge with a different intensity according to the overarching goal (intention) of the action in which grasping motor act was embedded (action-constrained neurons). Examples of action-constrained grasping neurons are shown in FIGURE 7C.

This organization of motor acts represent, most likely, the mechanism on the basis of a fluid action execution. Neurons that encode a specific motor act within a given action are linked with neurons that encode the following motor act. Thus motor chains that represent the entire action are formed. These motor chains represent the neural substrate for implementing the agent’s motor intention.

The aim of the second part of the experiment (visual paradigm) was to find out whether the visual responses of action-constrained neurons were modulated by the overarching goal of the actions in which the motor acts were embedded. The results showed that the intensity of the discharge of the majority of IPL mirror neurons was modulated by the agent’s intention. Examples are shown in FIGURE 12.

The discharge of action-constrained grasping neurons is longer in their specific action than in other actions. It is likely that this prolonged discharge facilitates the next motor act in the executed action. Data on the receptive field properties of parietal neurons are in accord with this interpretation. They show that neurons that encode the next motor act in an action sequence (408) are activated by...
movements performed actively or passively. Thus, when an action-constrained grasping neuron became active, it triggers the whole motor chain in the observer that in this way may grasp the agent intention.

Bonini et al. (34) recorded neurons from F5 applying the same two-intention paradigms. The results showed that also area F5 contains “action-constrained” grasping neurons active both during action execution and action observation. The authors concluded that the similarities between mirror neuron properties of the two areas indicate that they constitute a functional circuit underlying others’ intention understanding.

C. The Mirror Neuron Circuit for Hand Action and Some Considerations on Its Functional Role

1. The mirror neuron circuit for hand actions

Single neuron recording is undoubtedly the best technique for understanding brain mechanisms. However, to have a global picture of areas involved in a given function, brain-imaging techniques are of invaluable help. The first study that employed fMRI for defining the areas active during the observation of motor acts in monkeys was carried out by Nelissen et al. (283). The focus of this study was the frontal lobe areas. By using a ROI analysis, they found that video clips showing a hand grasping an object activate the premotor areas F5a and F5c and the prefrontal areas 45B. When instead of a hand the video clip showed an individual grasping an object, activation was also present in F5c. Finally, area 45B, but not the various sectors of premotor F5, responded to shape presentation. Area 45B appears therefore to be a higher order area where converges both object and action information.

In a subsequent fMRI study, the same authors examined the activations in the monkey STS region and posterior parietal lobe during the observation of grasping actions (282). As in the previous study, videos were presented where either only a grasping hand or an entire person was shown grasping an object with his hand. Both types of videos activated areas in the depths of lower and upper banks of STS, and areas PFG and AIP (FIGURE 13). A further ROI analysis showed that, relative to static control and scrambled stimuli, two areas were active in IPL: PFG on the convexity and AIP within the intraparietal sulcus. Areas consistently more active during action observation than during control conditions in STS were MT/V5, FST, LST, LB2, and STPm.

The large number of STS areas active during action observation raise the question of which of them sends information to the two parietal areas involved in grasping coding. To solve this problem, retrograde tracers were injected into areas AIP and PFG. Injections into area AIP yielded a wide-
spread ipsilateral STS labeling. In particular, three sectors of the STS were strongly labeled: MSTd, a sector in the middle portion of the upper bank near the fundus, and one in LB2 (FIGURE 13). The consistency analysis (the presence of labeling in all studied monkeys) indicated, however, that consistent labeling was only observed in LB2 and laterally in the inferior temporal cortex. Injections into area PFG produced labeling concentrated in three sectors of the ipsilateral upper bank of the STS (FIGURE 13 area MSTd, STPm, and UB1). These data were confirmed by the consistency analysis. It is important to note that of among these labeled sectors, only STPm showed a consistent activation during grasping action observation.

In conclusion, these data indicate that action information from STS is sent to the ventral premotor cortex (F5) along two distinct functional pathways. One pathway links the upper bank of the STS with area PFG that, in turn, projects to area F5c. The other connects the lower bank of the STS with area AIP that in turns projects to areas F5a and F5p. Both pathways provide information necessary for understanding the observed motor act. However, they possibly provide different information for understanding the intention underlying the motor act. The first pathway is concerned with the agent of the motor act, while the second route is more concerned with the details of hand grip and object semantics and may aid in understanding motor acts with respect to these factors.

2. The functional role of visual and motor areas in action understanding

The circuit activated by action observation includes parietal and premotor areas with motor properties and a series of higher-order purely visual areas. Why should the areas with motor properties be involved in the understanding of motor acts? While should the activation of visual areas be not sufficient? Indeed, as shown by Perrett and colleagues (188, 306), STS neurons visually describe the actions of others, a finding confirmed by several fMRI studies showing a similar role for STS in humans (8, 319, 407). However, if there is no doubt that the action analysis carried out by STS neurons represents a fundamental step for understanding others’ behavior, it also seems highly implausible that STS may accomplish the process of action understanding by itself (337). In fact, crucial for action understanding are those areas that contain neurons that encode the goal with a high degree of generality. With the problem posed in these terms, the evidence shows that generalization is an aspect that characterizes the parieto-frontal mirror network rather than STS neurons. In fact, although STS neurons may encode motor acts, they are unable to generalize the action goal (188, 306). In contrast, parieto-frontal mirror neurons are able to encode the goal of the observed motor acts regardless of whether motor acts are performed with the mouth, the hands, or even with a tool.

This hypothesis that the activation of mirror neurons plays a fundamental role in action understanding is referred to as “direct matching hypothesis” (329). This hypothesis maintains that, given that neurons in the ventral premotor cortex encode the goal of a motor act, when they became active during the observation of a motor act done by others, the goal of that motor act is represented in the observer’s motor system and hence understood. Note that, as discussed above, it is not the activity of mirror neurons per se that allows others’ action understanding, but the fact that the activation of mirror neurons “ignites” a large number of neurons located in other motor centers, among which the basal ganglia (6, 248) and cortico-spinal tract (395). The congruence between the exogenously generate motor schema and that endogenously generated during voluntary actions allows the understanding of the goal of the observed motor act (see Ref. 337).

An alternative interpretation has been proposed by Kilner et al. (199, 200). According to these authors the role of mirror neurons in understanding the goals of the observed motor acts is better accounted for within a predictive coding framework. In the predictive coding framework, each level of cortical hierarchy employs a generative model to predict representation in the level below. Backward connections convey the prediction to the lower level where it is compared with the representation in the subordinate level to produce a prediction error. This prediction error is then sent back to the higher level, via forward connections, to adjust the neuronal representation of sensory cause.

The strong point of “direct matching hypothesis” is the view that excitation of the mirror neurons (and the consequent activation of specific motor schemata) allows the understanding of the goal of an observed motor act regardless of how it is executed (generalization). The weakness is that it is a strictly forward model that does not take into account backward projections, present in large number in the parieto-frontal circuits.

In contrast, the notion that top-down mechanism plays an important role in action understanding is one of the big assets of the “prediction hypothesis” of mirror neurons activity. However, as recently stated by Kilner et al. (199, 200), this hypothesis requires a prior expectation about the goal and the intention of the observed action. To solve this problem, Kilner (199) suggested that this prior expectation is mediated by a circuit that includes middle temporal gyrus and area 47. While there is no doubt that the context and the object semantics might be important cues for understanding the intention underlying a given motor act, this is not necessary for understanding the goal of a motor act. Direct activation of parietal and premotor neurons is sufficient for this purpose.
D. Mirror Neurons in Area VIP

The studies on the mirror mechanism we discussed up to now were focused on how this mechanism contributes to the understanding of the actions performed by others. Is mirror mechanism also involved in understanding observed action that an individual does towards his/her own body? This issue was addressed by Ishida et al. (179) by studying the proprieties of area VIP coding peripersonal space. As mentioned above, in area VIP there are bimodal, visual, and tactile neurons. Their tactile receptive fields are located predominantly on the face, and the visual receptive fields are in spatial register with the tactile ones (80, 102).

Single neurons were recorded from monkey VIP. The studied neurons showed tactile receptive fields and visual receptive fields in spatial register with the tactile ones. The extent of the peripersonal space of each neuron was delimited. Then the stimulus was presented outside it, at a distance of 120 cm. No visual response could be elicited at this distance. However, if an experimenter moved inside the monkey visual field standing at a distance of 120 cm from it, and waved his hand close to his own body parts that corresponded to that where was the monkey tactile receptive field, the response appeared. The responses disappeared again, if the experimenter moved away (179).

This study is of great interest because it shows a way in which individuals might encode the body of others. Note that, although Ishida et al. (179) have not studied the motor responses of the recorded neurons, area VIP is strictly connected with area F4 (see above), where peripersonal space is encoded in terms of reaching movements. It is likely therefore that the observed visual responses actually represent potential motor acts directed towards specific body parts (123, 142).

E. “Mirror-like” Neurons in Areas F2 and F1

There is evidence that there is a set of neurons located in the dorsal premotor cortex (PMd or F2) that are active when a monkey performs a conditioned task (moving a cursor on a computer screen) and when it observes the same task executed by the experimenter. These neurons, unlike “classical” mirror neurons, did not need to be activated the observation of a hand acting on an object. The observation of goal achievement is sufficient (76).

Dushanova and Donoghue (104) and Tkach et al. (380) extended this observation. In particular, Tkach et al. (380) trained monkeys to move repetitively a cursor to targets randomly presented. There were two phases in the experiment. In the first phase (active movement phase), the monkey moved the cursor, and in the second phase (observation phase), the monkey observed the replayed movements of the first phase. The observation phase had three conditions: 1) cursor and targets visible, 2) only the replayed targets visible, and 3) only the moving cursor visible. It was found that, in both PMd and F1 there were neurons that discharged in a similar way during the execution and the observation of the task. No responses or weak responses were found when the monkey saw the cursor without targets without cursor. The authors concluded that these neurons (“mirror-like” neurons) respond to the goal of the motor act.

VII. THE MIRROR NEURON SYSTEM IN HUMANS

The possibility to record single neurons in humans is limited to preoperative recordings in patients undergoing surgery for intractable epilepsy. In such cases single neurons have been recorded, but, for technical reasons, exclusively from the medial wall of the hemispheres. As a consequence, the cortical regions in which mirror neurons are expected to be (the convexity of the parietal and frontal lobes) have not been explored. A group of researchers tested single neurons from the medial temporal cortex and the medial frontal cortex for mirror properties. They reported neurons that discharged during both execution and observation of congruent actions (271).

A. Brain Imaging

Brain imaging techniques (PET, fMRI) are the gold standard in present-day neuroscience studies for topographical localization of brain functions. However, two great limitations are intrinsic to these methods, namely, the lack of temporal resolution and the correlative nature of the results. In spite of this, a large number of experiments using these techniques demonstrated a strikingly consistent pattern of cortical activity evoked by the observation of others’ actions, overlapping with the cortical network that is recruited during action execution. The bulk of studies have been recently reviewed in several meta-analyses (63, 157, 268) (see FIGURE 14).

These reviews confirmed the early PET and fMRI studies (46, 152, 156, 174, 176, 209, 210, 247, 304, 331) showing that the executed and observed goal-directed grasping movements are encoded in a circuit formed by the IPL and by the ventral premotor cortex (PMv) plus the caudal part of the inferior frontal gyrus (IFGc). It has been also reported that PMd and the SPL could be active during action observation and execution. It is possible that these activations are due to mirror mechanism. It is equally possible, however, that they reflect motor preparation. Monkey single neuron data showing that these areas play an important role in covert motor preparation support the last possibility (84, 194).

The issue of areas that are activated both during action observation and execution was addressed by Gazzola and Keysers (139), using single-subject analyses of unsmoothed fMRI data.
The data showed that voxels shared between action observation and action execution were located, in addition to the classical parieto-premotor circuit, also in various other cortical areas, namely, dorsal premotor, middle cingulate, somatosensory, superior parietal, and middle temporal cortex. It is plausible that the activations outside the classical mirror circuit reflect sensory predictions from internal models. These activations would enrich the information about other individuals’ actions that the mirror mechanism provides.

1. Organization of the representation of observed movements: reaching and grasping

A classical distinction in motor organization is the one between the two parallel “modules” of reaching and grasping (see Ref. 187). In agreement with the notion of the mirror mechanism, observed proximal reaching movements are typically associated with the activation of dorsal parieto-frontal circuit linking the convexity of the superior parietal lobule to the dorsal premotor cortex. However, only few studies (97, 118, 245) investigated the representation of observed reaching motor acts isolated from the distal component of grasping. These studies found activations in a dorsal parieto-frontal circuit spatially overlapping with the areas activated during execution of reaching. A study addressed this issue categorizing the observed movements in distal limb, proximal limb, and axial movements (348). It was found that axial movements activated the medial premotor cortex (SMA), proximal limb movements activated the dorsal part of the convexity of the premotor cortex and, finally, distal limb movements activated ventral premotor cortex.

The bulk of studies on action observation investigated object grasping (63, 157, 268). These studies confirmed the monkey data that the execution of object-centered visually guided hand actions relies on a ventral parieto-frontal circuit including the anterior intraparietal area (AIP) and the IPL caudally and the ventral premotor cortex plus the posterior part of the IFG rostrally. Observing distal motor acts activated voxels that consistently overlap with the ones recruited by active grasping.

2. Representation of goals: decoupling movements from motor acts

As already discussed, motor representations in the cerebral cortex of the monkey range from representations of joint displacements (i.e., movements) to representations of goals (motor acts), to representations of motor intention. Evidence for representation of goals in human motor areas comes from a series of fMRI studies.

First evidence in this sense derives from the study of movements performed by artificial effectors. Video-clips of a human or a robot arm grasping objects were presented to normal volunteers by Gazzola et al. (140). The data showed that in spite of shape and kinematics differences, the parieto-frontal mirror network became active in both conditions. This study was extended by Peeters et al. (301) who studies the cortical activations during the observation of motor acts executed by a human being, by a robot or performed with a tool. The results showed bilateral activation of the mirror network independently of the effector used. Most interestingly, tool action observation determined activation of a specific rostral sector of the left anterior supramarginal gyrus (FIGURE 15). Shimada (360) investigated the congruency between the shape of the acting effector (human vs. robot) and movement kinematics (human vs. robot). His results showed that there was an interaction between these factors, with strong “deactivations” in sensorimotor areas when the individuals saw a human agent performing actions with robotic kinematics.

Second evidence in favor of goal coding is provided by aplasic subjects. Two individuals born without arms and hands and normal controls were scanned while they were watching videos showing hand actions. In addition, the two aplasic individuals also made actions using their feet and mouth. It was found that in the aplasic individuals the parieto-frontal mirror circuit active during the execution of foot and mouth movements was also active when they observed hand motor acts that they had never executed but the goals of which they could obtain using their feet or mouth (141). Similar observations on individuals with limb amputations were provided by Aziz-Zadeh et al. (234).

Third evidence that confirmed goal coding in the mirror circuit is based on presentation of stimuli in a sensory modality different from the visual one. An early study showed that listening to piano tunes activated the parieto-frontal mirror system in expert pianists (161). More recently, Lewis et al. (228) demonstrated that the middle portion of the STG was activated bilaterally during listening and categorization of animal vocalizations while, in contrast, during listening and categorization of sounds of tools manipulated by humans, the activated areas were those forming the pa-
riero-frontal mirror network. The same network was also found to be activated by Gazzola et al. (138) by presentation of sound of hand and mouth actions. The activation was somatotopically organized.

3. Somatotopy or actotopy?

It is a well-established that the cortical motor system of primates contains a double coding of motor behavior. In the primary motor cortex, neurons code mostly movements and they are organized in a somatotopic fashion with lower limb movements located medially, followed in the lateral direction by the upper limb and by the face/head movements. In contrast, as mentioned above, the premotor cortex encodes mostly motor acts, largely independent of individual movements, but still maintaining a certain somatotopic organization, congruent with that of the primary motor cortex. This double coding has produced apparently contradictory results in imaging studies that addressed the issue of whether observed motor acts are encoded in a somatotopic (following the spatial representation of a body map) or actotopic way (clustering together different motor acts with the same goal, irrespective of the body part used).

In a pioneer study, Buccino et al. (46) presented normal volunteers with video clips showing transitive motor acts performed with the mouth, hand, and foot. The activations during the observation of these motor acts were contrasted with those obtained during the observation of the same stimuli presented statically. They found a trend towards a somatotopic organization both in the parietal and in the frontal lobes, although with considerable overlap. A subsequent study (401) used meaningless intransitive movements of the face, hand, or leg and found a similar somatotopic arrangement in the frontal and parietal lobes, but present only in the right hemisphere. Note that also Buccino et al. (46) found a prevalence of mouth movements (ingestive) on the right premotor cortex. Recently, Abdollahi et al. (1) investigated the cortical representation of manipulation, locomotion, and climbing. The result showed that observation of climbing activated the rostro-dorsal part of SPL, locomotion the same region, although weakly, and finally, manipulation AIP.

A subsequent, more detailed, study addressed specifically the issue of somatotopy versus actotopy (182). Volunteers were presented with video clips showing four different motor acts (dragging, dropping, grasping, and pushing) performed with three different effectors (foot, hand, and mouth). The results showed that the general picture of motor act representation was in favor of goal coding. In the frontal lobe a mixed picture was evident in which, although a clear somatotopy was not found, there was some spatial segregation of the three effectors, with foot being more represented dorsally and the other two effectors overlapping one with the others. In the parietal lobe no clear distribution according to effectors was found. In the IPL, the motor acts clustered according to the valence of the motor act, regardless of the effector. Grasping and dragging (the two motor acts bringing the object toward the agent) produced activation in the ventral part of the putative human AIP (phAIP), whereas pushing and dropping (the two motor acts moving the object away from the agent) produced activation dorsally within the same area. This result suggests a specialization of the parietal lobe in representing action goals according to their behavioral valence, while the premotor cortex encoding follows a certain degree of somato-
topy probably functional to the actualization of the motor acts into movements.

4. Motor knowledge and the mirror mechanism

Is there a relation between personal expertise in performing some specific actions and the mirror responses to the observation of the same acts? Evidence for this was provided by Buccino et al. (47) who investigated in an fMRI experiment the differences between observed motor acts performed by different species: human, monkey, and dog. Two types of actions were shown: biting or oral communicative actions (speaking, lip-smacking, barking). Biting, regardless of whom was the agent of the actions, produced bilateral activations in the IPL-IFG circuit, virtually identical for three species especially in the left hemisphere. Communicative actions produced activation in the left caudal IFG that was dependent on species. Speech produced a strong activation in Broca’s area and related areas, while barking produced none. These data show that owned motor behavior (in this case, biting) is represented in the observer’s motor system via a mirror mechanism even when performed by non-con specifics. On the contrary, behavior that does not belong to one’s own repertoire (as is the case of barking) does not produce mirror activations.

In a further study, Calvo-Merino et al. (56) investigated the mirror responses of three different groups of participants: classical dancers, teachers of Capoeira, and people naive to dancing. Stimuli consisted in videos of either Capoeira or classical dance steps. A clear double dissociation was found between the two expert groups. Mirror responses to Capoeira steps were stronger in the Capoeira experts, and vice versa, mirror responses to classical dance steps were stronger in ballet experts. In a further experiment the same researchers (57) tried to disentangle the visual familiarity with the dance steps from the motor expertise. They studied classical ballet and examined the activation in men and women determined by the observation of steps done by dancers of the same and different gender. They found that the mirror system was activated more strongly by steps executed by individuals of the same gender of the observer. This finding indicates that the motor expertise and not visual experience is crucial in activating the mirror system. The data by Calvo-Merino were extended by Cross et al. (87). In their study expert dancers learned new dance sequences for 5 wk. fMRI was weekly recorded while dancers observed the new dance sequences. The results showed that the observation of another dancer’s movements activated the mirror circuit. Critically, the activation of IPL and premotor cortex correlated with dancers’ ratings of their ability to perform the new learned dance sequences.

5. Understanding actions without using the mirror mechanism

The claim that the mirror mechanism plays a crucial role in understanding the behavior of others does not imply that there are no other mechanisms involved in this function. Some mechanisms may rely on the association between a given stimulus and its effect. For example, one can understand a gesture conveying a threat, without necessarily transforming it into a motor format. A monkey is scared when it sees the experimenter throwing a stone towards it even when the way in which the stone is thrown does not correspond to the way in which the monkey would throw it (404, 405). This is not surprising because what counts here is the painful effect of being hit by the stone rather than the precise gesture mirroring.

On the other hand, there is a long tradition that accounts for action understanding by referring to the capability of individuals to “read” the mind of others, that is, to attribute a causal role to their mental states (e.g., beliefs and desires) in executing actions. The nature and the format of this “mindreading” are still a matter of controversy (see Refs. 61, 246). There is, however, no doubt that human beings have this capability. There, however, is a fundamental difference between the mirror-based action understanding and the understanding of others’ behavior relying either on a lower-order associative mechanism or on a higher-order meta-representational capability. The mirror mechanism is, in fact, the only mechanism that allows understanding the actions of others by activating the same circuits that the individuals use when executing the observed action. This kind of understanding has been referred to as “understanding from the inside” (337). The experiment by Buccino et al. (47) that demonstrated the difference between action understanding belonging to human motor repertoire and that of only other species clearly illustrates these different types of action understanding.

6. fMRI and repetition suppression technique

Some studies used the repetition suppression technique during action observation and action execution in an attempt to characterize the proprieties of the mirror neuron system in humans. This technique assumes that stimulus repetition reflects neuronal adaptation and that this effect can be detected using fMRI. One has to make a fundamental distinction between fMRI experiments in which adaptation was investigated by showing two visual actions in sequence (intra-modal testing) and those in which the presentation of an action was either preceded or followed by an active execution of that action by the participant (trans-modal testing).

The results of intra-modal testing were reported in detail in three studies. In one, the stimuli consisted of a series of intransitive motor acts (235). The results showed adaptation in the left lateral occipital lobe and the left extrastriate body area. None of the areas of the parietal and frontal lobe known to be endowed with the mirror mechanism showed repetition suppression. The main aim of the second study (363) was to establish functional dissociations between the dorsal and ventral visual pathways. It was tested whether
the repetitive presentation of object gasping would decrease the hemodynamic responses of the areas in the dorsal stream (anterior intraparietal sulcus and premotor cortex) related to action observation, while object identify those in the ventral stream regions as the fusiform gyrus. The results supported the classical dichotomy between the two streams. As far as the dorsal stream is concerned, they showed clear adaptation in the condition “same object–same grasp,” but a much weaker one in the condition “different object–same grasp.” There are rich connections between inferior temporal lobe and areas of the inferior parietal lobule (37, 282). Thus it is plausible that the described fMRI adaptation effect might have depended essentially on information on objects and took place before information reached the parietal lobe. In the third paper (99) in which adaptation paradigm was employed, the participants played a game (the “rock-paper-scissor” game) in the scanner, against a videotaped opponent. A variety of visual and visuomotor areas were found to decrease their activity with repetition of the same stimulus. It is not obvious, however, why these adaptation effects should be attributed to the activity of mirror neurons. What counts in the “rock-paper-scissor” game is not the kinematics of the observed movements or the observed goal of the motor act (e.g., grasping), but only the final static hand shape (rock, scissor, or paper). Shape discrimination tasks have nothing to do with the “transformation” of observed motor acts or observed visual movements into a motor format, the core feature of the mirror mechanism.

Rather surprisingly, all fMRI studies aiming at demonstrating the “existence” of mirror neurons employing adaptation have claimed that mirror neurons, if they exist, should show “trans-modal adaptation.” For example, Lingnau et al. (235) wrote: “Direct evidence for the existence of mirror neurons would require finding adaptation in the condition in which execution is followed by observation.” This statement is rather curious because it postulates that the physiological basis of the adaptation mechanism is cellular fatigue, i.e., a decrease in the capacity of neurons to generate action potentials. Aside from the fact that cellular fatigue is a rather unlikely event in the case of a presentation of natural stimuli, the data by Sawamura et al. (350) showed that after repetitive presentation of the same stimulus, another stimulus only slightly different from the first one is able to excite the putatively “fatigued” neuron. These findings are utterly incompatible with the assumption of the hypothesis of cellular fatigue. The mechanism leading to adaptation is synaptic fatigue of a specific input to a given neurons rather than the general incapacity of neurons to respond to any stimulus. Hence, fMRI experiments trying to reveal the existence of mirror neurons by resorting to trans-modal adaptation paradigms should be considered very cautiously. Note that the findings of the existence of trans-modal adaptation in human areas endowed with the mirror mechanism (202), although very interesting, are far from being easy to explain. Finally, it is worth stressing the lack of adaptation of visual responses in monkey F5 mirror as recently shown by Caggiano et al. (55).

7. Imitation

Is the mirror system involved in imitation? A recent meta-analysis of 139 imaging experiments (63) addressed this issue. The authors compared the parieto-frontal activations produced by passive observation of actions with those produced by observing them to imitate. A largely overlapping circuit emerged, comprising the “classical” mirror areas AIP/IPL in the parietal lobe and the premotor cortex and caudal IFG in the frontal lobe.

Note that there is ambiguity in the term imitation and, as a consequence, heterogeneity in the experimental tasks devised to investigate its neural basis (see Ref. 172). One main distinction to be made is between immediate imitative behavior and imitation learning. Immediate imitation refers to online replication of an observed behavior. In contrast, imitation learning consists in building new motor memories, based on action observation. A second relevant distinction is that between imitation of action outcomes (also called emulation, see Ref. 381) compared with imitation of the precise movements used to produce a given outcome. A final distinction is that between anatomical imitation and specular imitation.

Prinz and co-workers (316, 318) extensively studied imitation of simple motor acts. They found that tendency to repeat a motor act is greater when the motor act to be copied is well represented in the observer’s motor repertoire. They proposed that there is a “common representational domain” for action perception and execution. The discovery of mirror neurons suggested an alternative explanation for their findings, namely, that a motor mechanism, rather than an abstract, amodal domain is activated during the observed actions that have to imitated (317).

As already mentioned, the human mirror system encodes movements as well as goal-directed motor acts. Evidence on this point was provided by Iacoboni et al. (176). They carried out an fMRI study in which there were two experimental conditions: “observation only” and “observation execution.” In the first condition, participants were shown a moving finger, a cross on a stationary finger, or a cross on empty background. They were instructed to observe passively the stimuli. In the second condition, the same stimuli were presented, but the participants were instructed to lift the right finger in response to their presentation. The fundamental comparison was between trials in which the subjects performed the movement in response to an observed action (“imitation”) and trials in which the movement was triggered by the cross (a “nonimitative” behavior). Activation of the mirror system was significantly stronger during “imitation” than during nonimitative behavior and stimuli pas-
The mirror mechanism is also involved in imitation learning. Some years ago Byrne (51) proposed an interesting model based on his studies of ape behavior. According to his model, two distinct processes are at the basis of learning by imitation. First, the observer segments the action to be imitated into its individual elements, transforming it into a string of motor acts already present in the observer’s motor repertoire. Then, the observer organizes these motor acts into a sequence that replicates the observed one. It is plausible that an analogous process is also at the basis of learning nonsequential motor patterns.

Buccino et al. (48) investigated the neural basis of imitation learning experimentally. In a fMRI study, participants who never played guitar before were asked to imitate guitar chords played by an expert guitarist. The analysis was carried out on four epochs: 1) observation of the chords made by the teacher, 2) pause, 3) execution of the observed chords, and 4) rest. During passive observation there was activation of IPL, PMv, plus the pars opercularis of IFG. During pause, the same circuit as during observation was activated but, most interestingly, there was also blood flow increase in the middle frontal cortex (area 46) and in the anterior mesial cortex. Following Byrne (51), the authors proposed a two-step processing in imitation learning: first, “mirror” activation of motor act representations in the parietal and frontal lobe; second, the recombination, thanks to prefrontal lobe (area 46), of these motor acts, so to fit the observed model. The same authors carried out a subsequent fMRI study in expert and naive guitarists. This new study confirmed the previous data. In particular, the data showed again the fundamental role of area 46 in combining different motor acts in a new motor pattern (48).

The issue of specular imitation versus anatomical imitation was thoroughly addressed by Shmuelof and Zohary in two papers in which it was clearly shown that in AIP the identity of the observed hand determines which of the two hemispheres is predominantly activated (364, 365). The matching between actor and observer is in this case strictly anatomical, since the vision of a right hand activates systematically the left AIP, and vice versa, regardless of the left or right field of presentation. Visual areas encoding body parts, but devoid of motor properties such as the occipito-temporal cortex and the posterior superior temporal cortex, on the contrary, showed a laterality of activation that is related to the visual field in which the hand is presented, irrespective of the hand identity.

8. Intention understanding

As in the monkey, the mirror system of humans is involved in understanding the intention of others. Evidence in favor of this conclusion was first provided by Iacoboni et al. (175). They carried out an fMRI study consisting of three conditions: 1) “context”; 2) “action”; and 3) “intention.” In the first condition participants were presented with pictures of objects arranged as if a person was either ready to have breakfast or had just finished it; in the second condition, the participants saw the picture of a hand grasping a mug without any context; in the third, the participants saw a picture of the same hand grasping a mug within the two contexts. The context in which the action was performed allowed the participants to understand the agent’s intention. The data indicated that in both “action” and “intention” conditions the mirror system became active. The comparison between conditions showed that the intention understanding determined the strongest increase in the activity of the mirror system.

The neural substrate underlying our capacity to disentangle between actions that reflect the intention of the agent (intended actions) and actions that did not reflect it (nonintended actions) was assessed in a fMRI study. Video clips showing a series of actions were shown to normal participants in a double version each. In the first version, the actor achieved the goal of his/her action (e.g., pour the wine); in the other, the actor failed to achieve it because of a motor slip or a clumsy movement (e.g., spill the wine) (45). It turned out that the mirror circuits become active in both conditions. However, if the activations present during the intended actions were subtracted from those present in the nonintended actions, increase of blood flow was found in the right temporoparietal junction, left supramarginal gyrus, and mesial prefrontal cortex. The opposite contrast did not show any significant activation. The authors concluded that the understanding of nonintended action depends on the activation, besides the mirror circuit, of attention-related areas signaling unexpected events in temporal and spatial domains.

B. EEG Studies and Mirror Neurons

The activity of human sensorimotor cortex is characterized by a specific EEG rhythm called mu rhythm (136). This rhythm belongs to the alpha frequency band (8–13Hz) and exhibits a characteristic archlike appearance. The characterizing functional property of mu rhythm is its reactivity to active movements (136). Furthermore, mu rhythm is blocked during action observation (137) and during motor imagery (309). Because of its functional properties, it was proposed that mu rhythm could be used as an electrophysiological marker of the mirror mechanism in humans. This possibility was first tested by Altschuler et al. (9) and thereafter by many other researchers. These investigations supported the hypothesis that mu rhythm dynamics reflect the activity of human mirror system. A strong confirmation of this hypothesis was also provided by an fMRI study in which a clear correlation was found between mu desynchronization and blood flow increase in the motor region (15).
1. The reactivity of the mu rhythm: studies in adults

There is vast literature on reactivity of mu rhythm to the observation of motor behavior. Before reviewing some (not all for space reason) of these studies, it is important to have a global picture of the time course of Rolandic cortical rhythms modifications during action observation. **FIGURE 16** shows this picture based on a recent study by Avanzini et al. (18). Four types of hand movements were presented to normal adults: two were target-directed motor acts (grasping and pointing), and two were no-target directed movement (supinating and clenching). **FIGURE 16** shows the results of the study. All stimuli determined a desynchronization of alpha and beta rhythm in central and parietal regions. Note also the large poststimulus power rebound present for all bands. Note also the correlation between the velocity profile of the observed movement and beta band modulation, a finding indicating a direct matching of the stimulus parameter on motor activity.

A very interesting EEG research branch concerns the effect of social interactions on Rolandic reactivity. Oberman et al. (290) collected data while subjects viewed videos showing three actions: 1) an individual tossed a ball up in the air to themselves, 2) individuals tossed a ball to each other, and 3) individuals tossed, occasionally, a ball toward the viewer. The result showed that the mu rhythm was modulated by the degree of social interaction. Actions where the ball was tossed towards the viewer produced the strongest desynchronization. Similar effects of social stimuli were also found by Perry et al. (307). A related issue was addressed by Kilner et al. (201) using MEG. They recorded cortical activity of subjects while they watched a series of videos of an actor making a movement recorded from different viewpoints. They showed that the cortical response to action observation was modulated by the spatial relationship between the observer and the actor. According to them, this modulation reflects a mechanism that filters information into the mirror system allowing socially relevant information to pass.

Two issues, addressed with fMRI technique, were also investigated using EEG: the effect of motor practice on mirror activity and that of actions describing sounds. As shown in fMRI studies, motor expertise of a given motor behavior produces, during the observation of that behavior, increased blood flow in the areas that belong to the mirror system. Orgs et al. (292) addressed this issue presenting professional dancers and nondancers with videos showing dance movements and movements of everyday life. The results showed that power in alpha and beta frequency bands was reduced when dancers watched dance movements, but not when nondancers watched the same movements. During observation of everyday movements, no group difference was evident. De Lucia et al. (91) recorded auditory evoked potentials in response to sounds of man-made objects and in response of sounds that were not linked to motor actions. Analysis of source estimation identified differential activity within premotor and inferior frontal region in response to sounds of actions typically cueing a responsive action.

2. Further EEG/MEG studies

Another issue that was addressed using electrophysiological methods is imitation. In a pioneer work on this issue, Nishitani and Hari performed two studies in which they investigated MEG activation during imitation of hand-grasping actions and facial movements, respectively. The first study (285) showed the importance of the left IFG in imitation. In the second study (286), volunteers were asked to observe still pictures of lip forms, to imitate them, or to make similar lip forms spontaneously. The mere observation activated sequentially a circuit formed by the visual cortex, STS, IPL,
The results revealed four sequential temporal steps during individuals instructed to understand the agent’s intention. Brain activations following observation of motor acts in Ortigue et al. (293) examined the temporal dynamics of movement is sufficient to excite one’s own motor system. These data indicate that the knowledge of an upcoming observation and that they appear before action execution. The results showed that readiness potentials occur during action observation and that they appear before action execution. These data indicate that the knowledge of an upcoming movement is sufficient to excite one’s own motor system.

In a recent EEG study, based on microstates analysis (220), Ortigue et al. (293) examined the temporal dynamics of brain activations following observation of motor acts in individuals instructed to understand the agent’s intention. The results revealed four sequential temporal steps during intention understanding: 1) bilateral posterior cortical activations, 2) strong activation of the left posterior temporal and inferior parietal cortices with almost a complete disappearance of activations in the right hemisphere, 3) a significant increase of the activations of the right temporo-parietal region, and 4) a global decrease of cortical activity with appearance of activation in the orbito-frontal cortex. The authors concluded that the early activation of the left hemisphere reflects the engagement of a lateralized mirror network mediating goal understanding, while the subsequent later activation of the right hemisphere is due to the role that this hemisphere plays in others’ intention understanding.

3. The reactivity of the cortical motor rhythm: studies in infants

A very interesting field in the research on mirror mechanism is that concerning the reactivity of the Rolandic rhythms to action observation and execution in infants. Relatively to other imaging technique, EEG appears to be a very suitable and also easily available technique. There is, however, a preliminary problem. Are the rhythms recorded over cortical central sites in children functionally homologous to those recorded on the same sites in adults?

Early studies of the developing EEG have documented that an alpha-like rhythm is present in children Rolandic areas. Its frequency is lower than that in adults and has the same frequency range as that of the infant alpha rhythm (6–9 Hz) (217; see also Ref. 371) A systematic investigation of the infant mu rhythm was carried out by Marshall et al. (252) who examined the development of the EEG signal from infancy to early childhood in a longitudinal study comparing periods of quiet attention with periods of abstract visual stimulus. During quiet visual attention, a prominent central rhythm was present at the age of 10, 14, and 24 mo with a peak frequency of 7–8 Hz. By 51 mo of age, the peak frequency of the central rhythm had shifted to 9 Hz.

The problem of the age at which infant mu rhythms respond to hand actions was addressed by Nystrom (287). He presented 6-mo-old infants and adults with videos of a person carrying out goal-directed actions (reaching and grasping an object). While, as expected, adults showed greater mu rhythm desynchronization to the observation of these stimuli compared with the observation of an inanimate moving stimulus, there was no evidence of a similar differential response in the infant EEG. More recently, Nystrom et al. (288) investigated EEG responses in 8-mo-old infants during the observation of an experimenter performing a grasping action. Compared with the observation of a hand movement not directed toward a particular goal, grasping observation produced a significant desynchronization in the 5- to 9-Hz frequency band. The desynchronization occurred around the time that the object was grasped.

Van Elk et al. (393) addressed the issue of mu reactivity in infants using another approach. Instead of showing hand action, they presented to 14- to 16-mo-old infants videos of infants who were crawling or walking. Spectral power in the 7- to 9-Hz band desynchronized more during the observation of crawling than walking (FIGURE 17). These findings clearly indicate that the motor experience has a significant influence on the mirror system responses. A well-practiced motor behavior as crawling has much stronger effect than the not yet learned walking behavior. Compelling evidence that infants are able to link sound to motor activity was provided by Paulus et al. (299). They trained 8-mo-old infants to use a novel rattle that produced a specific sound when shaken. Infants were also presented with another sound not related to an action. EEG responses to the two sounds were recorded. The results showed a stronger mu desynchronization during listening to the action-related sound.

The just reviewed studies provide an important insight into the reactivity of the infant EEG to action observation. Their experimental design did not include, however, an active condition. Two studies addressed this point. Fecteau et al. (113) used a subdural electrode grid to record EEG from a 36-mo-old child with epilepsy who was awaiting neurosurgery. They examined two conditions: in one the child made a drawing, in the other, the child watched an adult carrying out a similar action. The main finding was that alpha-range power at the electrodes over somatosensory cortex showed significant decreases in both conditions relative to a resting baseline. The second study that investigated action execution was carried out by Lepage and Theoret (227). These authors recorded EEG during observation of repetitive hand actions either goal-directed (hand grasping) or not...
goal-directed (moving a hand kept flat) as well as during active hand grasping. Observation of grasping was associated with greater mu rhythm desynchronization at central sites compared with observation of flat hand movements. Action execution was also associated with a significant desynchronization of the mu rhythm over central sites. The magnitude of mu desynchronization during action execution was greater than during action observation.

An attempt to investigate the effects of social interactions on Rolandic reactivity in infants was done by Saby et al. (345). They explored the neural processes related to tendency of infants to prefer others who act like the self in 14-mo-old infants. EEG was recorded while infants were observing actions that either matched or mismatched the action the infant had just executed. Desynchronization of the EEG mu rhythm was greater when infants observed an action that matched their own executed action. This effect was strongest immediately prior to the culmination of the goal of the observed action.

C. Transcranial Magnetic Stimulation and Mirror Neurons

Magnetic stimulation transcranially applied (TMS) to the motor cortex evokes a volley of action potentials along the corticospinal pathways ultimately resulting in a contraction of the muscles controlled by the stimulated cortical area. The electrical activity recorded from the activated muscles is referred to as motor evoked potential (MEP). Fadiga et al. (111) showed that the observation of motor acts done by another individual increases the excitability of the motor cortex. This excitability increase was interpreted as due to the activation of mirror neurons located in the premotor areas and connected with neurons of the motor cortex.

1. Cortical origin of the mirror responses

The demonstration that the effects of action observation on corticospinal excitability occurs at cortical level has been provided by paired-pulse paradigms, which specifically test the intracortical circuitry. In paired-pulse paradigms, the conditioning stimulus (“cond-TMS”) and the test stimulus (“test-TMS”) are delivered through the same coil on the motor cortex. Several different paradigms based on the same principle were employed. The classical one, originally described by Kujirai et al. (212), investigated the effects of a sub-motor threshold “cond-TMS” on a suprathreshold test-TMS. At interstimulus intervals (ISIs) below 5 ms “cond-TMS” produce short-latency intracortical inhibition (SICI). At ISIs above 7 ms, “cond-TMS” produces short-latency intracortical facilitation (SICF). Another paradigm is the “long-latency paired pulse paradigm” (279). In this paradigm both “cond-TMS” and “test-TMS” are delivered through the same coil on the motor cortex. Several different paradigms based on the same principle were employed. The classical one, originally described by Kujirai et al. (212), investigated the effects of a sub-motor threshold “cond-TMS” on a suprathreshold test-TMS. At interstimulus intervals (ISIs) below 5 ms “cond-TMS” produce short-latency intracortical inhibition (SICI). At ISIs above 7 ms, “cond-TMS” produces short-latency intracortical facilitation (SICF). Another paradigm is the “long-latency paired pulse paradigm” (279). In this paradigm both “cond-TMS” and “test-TMS” are suprathreshold. At ISIs around 100 ms, “cond-TMS” exerts long-latency intracortical inhibition (LICI). Finally, the “I-wave facilitation” paradigm (411) consists in stimulating the motor cortex with a suprathreshold “cond-TMS” followed by a subthreshold test-TMS at ISIs from 1 to 5 ms at submillisecond steps. The interaction between the two pulses produces peaks of facilitation that test the interneurons that produce indirect waves (I-waves). For a review, see Reference 410.
The first application of a paired-pulse paradigm to test the motor cortex during action observation was carried out by Strafella and Paus (370) who used both the short-latency and long-latency paradigms. Participants received TMS while they were watching ongoing actions involving distal muscles or proximal muscles. Recordings were made from an intrinsic hand muscle (1DI) and from a proximal muscle (the biceps brachii). The results showed that MEP amplitudes from test-TMS pulses alone were modulated by action observation with an effector specific pattern. The most interesting result came from the effects of the “cond-TMS.” An effector-specific change in short-latency intracortical inhibition and facilitation was observed, thus showing that action mirroring is an exquisitely cortical phenomenon.

A further study (205) found specific cortical effects of action observation using the “I-wave facilitation” paradigm. The results showed a clear increase in the second I-wave facilitatory peak. Modulations of this peak reflect intrahemispheric corticocortical connections to the motor cortex (72), presumably from the premotor cortex. Taken together, these results unequivocally indicate that the site of modulation of the corticospinal system during action observation is intracortical. The question of whether also a modulation at spinal level exists has been explored in a very limited number of studies and no definitive conclusions can be drawn at the moment (39, 298). Also the issue of hemispheric specialization for action observation has been the object of few studies. They all point at a predominant role of the left motor cortex (20, 21, 114).

2. Single pulse TMS of the motor cortex

A) THE BODILY AND SPATIAL FRAMES OF REFERENCE OF MIRROR ACTIVATION. As mentioned above, the modulation of the observer’s motor system mimics the muscular pattern used by the agent to perform the movements. The range of muscle specificity varies depending on the experimental paradigms. One study found an exact replica of the observed muscular pattern in hand and forearm muscles (244). Other studies reported a less strict observation-execution picture. They showed that motor mirroring was muscle specific, but the effect of movement observation was not limited exclusively on the “prime mover” muscle but also involved other muscles along a gradient of functional proximity to the observed movement (251). Finally, a TMS study by Gangitano et al. (134) showed that the observers’ motor cortex is modulated with a muscle-specific pattern when observing different phases of a reach-to-grasp act.

A more complex issue is whether motor resonance reflects the observed behavior in terms of movements or in terms of action goal. There is evidence that in certain conditions, namely, during the observation of intransitive movements, the net output of the observer’s motor system is expression of the observed movements rather than of the spatial end point of the motor act (4, 5, 390). In these studies the significant experimental manipulation consisted in contrasting factors as “movement type,” “spatial end point,” and “observer’s posture.” In Urgesi et al. (390), participants were shown movements of the index finger or of the little finger of actors with their palm down or palm up, so that each of the two fingers could be on the left side or on the right side of the hand. The subjects’ muscular activity was recorded from the muscles that contribute to the movements of the index or of the little finger, namely, the first intersosseus and the abductor digiti minimi muscles. A similar manipulation was used in Alaerts et al. (4, 5) but, in their protocol, the movements consisted in flexion or extension of the wrist, in a palm-up or palm-down position. In this way, the extrinsic spatial end point was the same for all acts, and it was positioned along a far-near axis. The spatial endpoints of the movements were therefore not defined in terms of retinotopic space (left or right to the body part). All these studies obtained similar results, namely, the predominance of muscle-specific encoding of observed actions, with a minimal or no contribution of spatial and postural features.

A different picture emerges from studies in which the observation of transitive (goal-directed) actions was investigated. These studies showed that, as in the monkey, human motor cortex encodes motor acts (68, 70, 101, 105, 106). An experimental paradigm that has helped to disentangle the goal of the motor act from the movements used to achieve it has been the observation of actions done using tools. This paradigm, derived from monkey experiments (387), was adopted in humans in a study with single-pulse TMS over M1 (68). The experimental setup involved two types of tools (“direct” and “inverse” pliers, FIGURE 18) that required opposite movements to achieve the same goal (grasping and releasing). The results showed that when observing goal-directed grasping, the observers’ motor system encoded its goal regardless of the tool used and, therefore, irrespective of the movements performed to achieve it (FIGURE 18). These results were not found when observing intransitive movements. In this case the observer’s motor system mirrored the activity of single muscles, irrespective of the tool used. These findings were recently confirmed in a second study employing a similar “inverse pliers” paradigm (70).

A related topic is that of self-attribution of observed stimuli that produce motor mirroring. It was shown that the observer’s sense of ownership of an observed body part reduced and even turned into inhibition the phenomenon of motor mirroring (354, 355).

B) MOTOR IMAGERY AND MIRROR ACTIVATION. There are two types of mental imagery of actions (13): visual and motor imagery. In the first case, one imagines seeing himself or another person performing actions from an “external viewpoint.” In the second case, one imagines himself performing
actions. In both cases mental imagery of actions is a voluntary process. This must be kept distinguished from the automatic motor mirroring that occurs during action observation (185).

Various studies using TMS over the motor cortex showed that observing or imagining the same acts produces a variety of different patterns of motor modulation in the observer/imaginer (117, 226, 232, 384, 385). A crucial demonstration of such difference was provided by Cattaneo et al. (68). Employing the inverse pliers paradigm (see above), they reported a clear difference between imagery and observation of the same goal-directed actions. The observation of goal-directed actions produced a motor response that mimicked the goal of the action. On the contrary, the imagination of the same goal-directed actions produced a motor facilitation that mimicked the muscular activity required to perform the task. These data indicate that motor imagery is essentially a covert preparation of movement and, as such, is more closely linked to motor execution than motor observation.

C) CHRONOMETRY OF MIRROR RESPONSES. TMS has a temporal resolution of submillisecond magnitude (411). It is therefore an optimal tool for establishing the chronometry of cortical processes. This advantage of TMS has been exploited to investigate the precise time course of motor modulation from the onset of an observed movement. What is the delay between visual presentation of an action and motor system activation? Convergent data on this issue come from four independent studies. In the first, Catmur et al. (64) showed that mirror activation occurs 200 ms from the onset of the observed movement and is still present at 300 ms. In the second, Barchiesi et al. (26) reported that motor facilitation, absent at 150 ms from stimulus onset, was present at 250 ms as well as 320 ms. The above-mentioned works tested the observers’ motor systems during passive observation of actions. A recent work (386) showed that if the mirror phenomenon is probed during a task that requires a hand response to observed actions, a response can be evident as early as 150 ms from the observed movement onset.

**FIGURE 18.** Evidence for action goal coding by the mirror mechanism. Participants watched the experimenter grasping objects with two types of pliers: direct pliers and reverse pliers (left panel). Finger flexion produced closure of the direct pliers, but opening of the reverse ones (right part of the left panel). Finger extension produced opening of the direct pliers, but closing of the reverse ones (left part of the left panel). The right panel shows MEP amplitudes obtained from the opponens pollicis muscle during the observation of different movement phases. Right panel, top: MEPs during the observation of grasping with direct pliers. Right panel, bottom: MEPs during the observation of grasping with reverse pliers. The observers’ motor systems encode the goal of the action, regardless of whether it is achieved by closing or opening the hand. [Modified from Cattaneo et al. (68).]
The knowledge of time of occurrence of mirror responses during action observation is of great importance for studies that investigate whether mirror responses might be modified by the so called “counter-mirror” training. This training consists of instructing subjects to respond as fast as possible to an observed movement with a different movement. In the first study with this task (65), it was found that motor responses to action observation, evaluated the day after the counter-mirror training, displayed an inverted mapping relative to the original response. A subsequent study by Catmur et al. (64) confirmed these findings. In this study, the motor responses were recorded 300 ms following the onset of the stimulus presentation (64). Barchiesi and Cattaneo (26) tested the “reconfiguration” hypothesis applying stimuli early and late following stimulus onset. They found that in an early time segment corresponding to 250 ms from the onset of the observed movement, the participants’ responses were not influenced by training. Only in a later time segment (at 320 ms) the participant’s responses became “counter-mirror” (FIGURE 19, top). These data show that two neural systems concur in producing responses to action observation: a fast and stable system (the mirror system) that is not influenced by recent visuomotor experience and a slower system (most likely related to cognitive decisions) that has the capacity to establish arbitrary associations between visual cues and motor responses (FIGURE 19, bottom). The timing of appearance of motor responses following action presentation would therefore be an important physiological signature that identifies which of the two systems is recruited.

Ubaldi et al. (386) recently confirmed the existence of the biphasic response pattern in the observer’s motor system during action observation. In this work, rather than the after-effects of counter mirror training, the authors tested the motor modulations to action observation during counter-mirror training. The results confirmed that a mirror response, independent of the arbitrary visuomotor rule, was evident in an early time window (150 ms) from the onset of an observed movement, while rule-dependent responses appeared at 300 ms from movement onset. The authors further extended the concept that the early stimulus-driven (mirror) response and the late rule-driven (counter-mirror) response are two independent phenomena by applying repetitive TMS (rTMS) to the posterior parietal cortex and to the prefrontal cortex in two separate groups of subjects. A clear double dissociation was found between the target of rTMS and the early and late components of the motor re-

**FIGURE 19.** Early and late motor responses to action observation. A: TMS-evoked accelerations obtained from participants while watching a hand rotating a lid clockwise (CW) or counter-clockwise (CCW). In baseline (without training) conditions (red segments), a mirror response (CW accelerations when observing a CW movement and CCW accelerations when observing a CCW movement) is present at 250 and 320 ms from the onset of the observed movement. After the “counter-mirror” associative training (blue segments), the mirror responses persist at 250 ms from movement onset but become “counter-mirror” at 320 ms. B: model explaining the time course of motor responses to action observation after the “counter-mirror” training. Two separate processes interact and compete for the motor output. A fast automatic process (referred to as mirror function, dotted line) occurs earlier than 250 ms from stimulus onset and produces mirror responses regardless of the training. An associative process due to the training determines the counter-mirror response. This response (executive function response, dashed line) occurs later and overcomes the mirror function response. The arithmetic summation of the two functions produces a net motor output (solid line) that has a biphasic time course as the one observed in the empirical data described in A. [Modified from Barchiesi and Cattaneo (26), by permission of Oxford University Press.]
response. Parietal rTMS influenced only the early stimulus-driven response; prefrontal rTMS affected only the late rule-driven response.

In a related topic, several studies investigated whether mirror responses recorded during predictable on-going naturalistic movements anticipate the observed movements or if they lag passively behind the observed action. All studies employing on-going observed actions obtained a clear indication that whenever the action is predictable, the motor activation has anticipatory dynamics. One of these studies employed cyclic intransitive wrist movements (270). Motor responses recorded from the observer’s wrist extensors and flexors fitted into a sinusoidal function that matched the sinusoidal variations of the observed wrist angle. More interestingly, when comparing the observer’s and the agent’s sinusoidal functions, a phase shift was evident. The observer’s sinusoidal function anticipated that of the agent by 60° to 90° of a full oscillatory cycle. In another experiment, the time course of the observers’ mirroring of an actor’s grip force was tested during observation of a reach-grasp-lift sequence. It was shown that the observer’s motor activation predicted the actor’s grip force well before the occurrence of the actual grasp (3). These results further expand the findings by Gangitano et al. (133) who showed that the MEPs recorded during observation of predictable actions actually mirror the predicted trajectory of the observed hand rather than the movement that is actually happening.

D) MOTOR EXPERIENCE AND MOTOR RESONANCE. Experience of a certain motor skill appears to be of importance in influencing the mirror responses to observation of actions requiring that skill. In the literature, two different experimental approaches have been taken to handle this problem. The first is to investigate populations of experts, (e.g., dancers, elite sportsmen) who are skilled in determinate actions. Experiments dealing with mirroring in hyperspecialized populations have to disentangle the contribution of motor and visual expertise. The results from the literature show that both these trainings can induce long-term changes in mirroring (2, 119, 191).

The second approach is to investigate the effects of brief sessions of motor training in specific tasks that were previously unknown to participants. Motor practice is known to induce online effects and short-latency aftereffects on action observation (27, 62, 67; for a review, see Ref. 356). Such effects are generally attributed to the mirror neuron mechanism. One study investigated the evolution in time of practice-induced changes in action mirroring in a population of amateur piano players after a short practice of a piano composition. Participants exhibited a consistently greater activation of their motor system when listening to the rehearsed piano tunes relative to nonrehearsed piano tunes. Such auditory-motor facilitation occurred early after rehearsal and increased over days with consolidation of the motor expertise (88). Stefan and co-workers (368, 369) investigated the issue of motor memory formation by execution alone, observation alone, or simultaneous observation and execution. It was shown that a training period in which participants simultaneously performed and observed congruent movements potentiated motor cortex plasticity with respect to motor training alone, as shown by the kinematics of the movement evoked by TMS (see FIGURE 20).

E) ARTICULATORY RESONANCE TO SPEECH SOUNDS. TMS studies showed that the hand-related motor system responds to sounds produced by manual actions (20, 88). A particular case of motor activation to sounds is that occurring in the articulatory system when people listen to speech sounds.

In adults exposed to verbal-related sounds, there is a fast automatic activation of a corresponding orofacial motor program. Articulatory resonance to speech has been described in several papers by recording changes in MEPs to single-pulse TMS applied to the representation of tongue movements towards the trained direction (open columns, baseline; closed column, training effect). The results indicate that action observation has a direct access to the motor system. [Modified from Stefan et al. (369).]

FIGURE 20. Formation of motor memory by action observation. Participants were tested with single-pulse TMS over the motor cortex (first panel: baseline conditions; thumb extension). They underwent subsequently either a motor training or an observational training in which they had to perform or to observe movements opposite to the baseline motor tuning, respectively (second panel: thumb flexion). After training, the participants’ motor cortex tuning was assessed by single-pulse TMS over the motor cortex. Both movement and observation produced a shift of TMS-evoked movements towards the trained direction (open columns, baseline; closed column, training effect). The results indicate that action observation has a direct access to the motor system. [Modified from Stefan et al. (369).]
movements (110, 342) and of lip movements (372, 399, 400). Speech motor resonance is effector specific, i.e., it matches the articulatory gestures that are required to produce the heard sounds. It occurs very early during speech processing, and evidence indicates that this early resonance (100–200 ms) does not require semantic comprehension of the verbal material (342), nor does it reflect the final perceptual stage. Finally, motor responsiveness correlates negatively with the perceptual clarity of the phonological stimuli (89, 274), i.e., it is enhanced by adding noise to the stimuli.

3. Beyond the motor cortex: definition of the mirror network with TMS

The experimental approach of measuring MEPs to TMS on the motor cortex offers the great advantage of unequivocally probing visuomotor integration. However, it cannot provide any information on the neural circuits outside the motor cortex. One possible way to overcome this problem is to apply TMS to other cortical areas so to condition the motor cortex. One possible way to overcome this problem is to apply TMS to other cortical areas so to condition the response of the motor cortex to single-pulse TMS. In these paradigms, an effect of the conditioning stimuli on the MEPs is considered as an index of functional connectivity between the stimulated area and the motor cortex. Furthermore, TMS can be used to stimulate areas different from the motor cortex with a subsequent measurement of the behavioral effects of such interventions.

A) THE “DUAL COIL” TMS PARADIGMS: TESTING CORTICO-MOTOR CONNECTIVITY DURING ACTION OBSERVATION. The “dual coil” paradigms investigate the effect of a “cond-TMS” pulse, delivered with one coil to one cortical site, on the responses to a “test-TMS” pulse delivered with another coil to the motor cortex. This paradigm tests direct cortico-cortical pathways from the site of “cond-TMS” to the motor cortex. The ISIs, commonly employed, are between 4 and 8 ms when intrahemispheric pathways are tested (66) and around 10 ms when transcallosal pathways are investigated (115). A study using this paradigm examined the effects of a “cond-TMS” applied to the ventral premotor cortex or to the anterior intraparietal sulcus on “test-TMS” applied to the motor cortex during action observation (205). Participants were shown movies of a hand grasping either a small or a large object. In half of the movies the hand shape was appropriate to the object size, while in the other half it was not. In those cases in which the hand shape was appropriate to the object size, there was a specific activation of the cortico-cortical pathways, while there was no effect when there was an inappropriate hand shape.

B) VIRTUAL LESION PARADIGMS: IFG, PMV AND MOTOR CORTEX. Avenanti et al. (19) applied prolonged repetitive 1-Hz TMS (rTMS) over the caudal sector of IFG and the somatosensory cortex (S1). Subjects were subsequently tested with TMS of the motor cortex while watching biomechanically possible or impossible movements. The main finding of the study was that virtual lesions of IFG produced by rTMS suppressed mirror facilitation of MEPs when observing possible movements, thus establishing a causal role between the IFG and the mirror-related motor activation. A similar approach was used in another experiment (198) in which the authors investigated the effects of rTMS, applied over the IFG, on the reactivity of the mu rhythm to action observation. The results showed that rTMS reduced the suppression of the cortical rhythm to action observation.

The role of the IFG and of PMv in the genesis of mirror responses has been also investigated in a study in which rTMS was applied to the pars opercularis of the IFG bilaterally. The results showed that rTMS impaired an imitative task but not a nonimitative visuomotor task (165). Pobric and Hamilton (310) performed a study in which participants were asked to make a weight judgment task on a box that was lifted by an actor with different kinematics or on a ball bouncing in the absence of a biological agent. It was shown that rTMS on the IFG produced a deficit in inferring the object’s weight from the kinematics of the hand movements. On the contrary, the judgment on the kinematics of the bouncing ball remained unaffected. Along the same line, another study found that rTMS of left BA44 impaired individual performance in evaluating only biological actions, and more specifically object-oriented actions (78). Stimulation of PMv produced deficits in an action matching task (391) but, interestingly, did not impair a body-form matching task.

C) VIRTUAL LESION PARADIGMS: POSTERIOR TEMPORAL CORTEX. The posterior superior temporal cortex, and in particular the cortex in the banks of the posterior superior temporal sulcus (pSTS), contains cells that encode biological motion (see above). Coherently with these data, TMS applied to the pSTS region disrupts the processing of upright point-light displays of whole bodies moving (158). Because the pSTS region is the main source of visual information feeding into the parieto-frontal mirror system, TMS applied to the pSTS modulates the parieto-frontal mirror mechanism (60). One paper explored the functional connections between the pSTS and the parietal-premotor regions by temporarily perturbing the activity in the pSTS cortex with 1-Hz rTMS and measuring the hemodynamic responses to action observation (14). The data showed that the effects of rTMS over the pSTS were evident in 1) the lateral occipito-temporal cortex, 2) in the anterior intraparietal cortex, and 3) in the premotor cortex, thus confirming that the pSTS occupies a hub position between the early visual areas and the parieto-frontal mirror circuit.

D) TMS-ADAPTATION PARADIGMS. TMS-adaptation paradigms are designed to test the presence of subpopulations of neurons that are spatially overlapping but with different func-
tional properties (366). They take advantage of the well-established psychophysical phenomenon of perceptual adaptation. After adaptation, a subject’s perception is biased against the adapted stimulus. A TMS pulse over the adapted neurons enhances selectively the perception of the adapted features. This technique allows one to localize on the cortex the subpopulation of neurons encoding that feature. The neural mechanisms by which TMS produces state-dependent effects are still debated (263, 305, 357).

One study employing a TMS-adaptation paradigm explored the possibility to induce cross-modal motor–visual adaptation (67). Repeated performance of the same motor act produced adaptation-like phenomena in the visual categorization of actions. Event-related TMS applied to the PMv abolished the adaptation effects, while sham stimulation and active TMS over M1 did not. TMS-adaptation paradigms have been also used with purely visual action stimuli, to investigate the tuning properties of the different nodes of the action observation system. In one TMS study (71) participants underwent visual adaptation to observed actions by repeatedly seeing one of two actions (pushing or pulling) that were performed with one of two different effectors. Subjects were subsequently tested in a match-to-sample action recognition task, while they were stimulated over different cortical areas. TMS selectively enhanced the subjects’ performance when judging the adapted action irrespectively of the effector when it was delivered over the left or right PMv or over the left supramarginal gyrus. On the contrary, when TMS was delivered onto the pSTS region, it improved performance only in processing stimuli that shared both the same action and the same effector with the adaptor sequence. It was concluded that the premotor and parietal cortices contain neurons that were adapted (and therefore encode) the actions in an abstract way, irrespective of the effector that performs them. On the contrary, the temporal cortex contains neurons that represent actions only linked to the very same body part that is performing them. It was concluded that action representation is hierarchically organized, with a low-level pictorial representation in the pSTS cortex and a more abstract representation in the parieto-frontal system.

D. Disorders of Mirror Function

1. Acquired disorders of the mirror mechanism

An important issue is whether lesions of the frontal and parietal areas endowed with the mirror mechanism are causative of incapacity to understand actions done by others. In the monkey, the mirror system is equally represented in both the right and the left hemisphere. Lesion studies are therefore impossible to carry out without determining severe cognitive deficits. The same difficulty is present in humans. However, being the mirror mechanism more represented in the left than in the right hemisphere (see above), clinical studies may provide some information about a possible causative link between motor and perceptual deficits following left hemisphere lesions.

Evidence for associations between motor and perceptual disturbances has been reported in patients with diagnosis of apraxia. Apraxia, however, is a higher order cognitive/motor disturbance that only occasionally is associated with perceptual disturbances. Thus it is important to discuss the fundamental characteristics of apraxia and the location of lesions producing perceptual deficits in patients with this syndrome, before concluding a link between the mirror mechanism and apraxic deficits.

The term apraxia designates the impaired ability to perform motor activity, in spite of preserved motor, somatosensory, and coordination functions in the effectors engaged in the action (93, 164). The characterizing feature of apraxia is an automatic-voluntary dissociation. The same gesture that the patient is unable to perform on the examiner’s request is, typically, correctly performed if done in response to a habitual stimulus or context. There are various classifications of apraxias. A fundamental distinction lies between the ideational apraxia (IA) and the ideomotor apraxia (IMA). Patients with IA do not know what to do, i.e., they are unable to retrieve the movement schema typical for certain object; in contrast, patients with IMA are unable to translate the observed or instructed movement into appropriate motor pattern.

The form of apraxia that has gained most attention in the last years as possibly related to dysfunction of the mirror mechanism is IMA (221). The core IMA symptoms are 1) deficits in performing tool-use pantomimes on verbal command or imitation, e.g., pantomiming to hammer a nail or to brush one’s teeth, and 2) deficits in performing symbolic communicative gestures, as in waving good-bye, on verbal command or imitation. Patients can be impaired in pantomime/gesture performance for both verbal command and imitation or for one of this task only (94, 302). The capacity to perform actions on real objects spontaneously or on command is typically spared, although it can be occasionally impaired (49, 183).

Typically, apraxia is not accompanied by disturbances in action recognition (93). Heilman and co-workers (164, 341) described, however, cases of patients with IMA that showed, besides the classical symptoms, also disturbances in recognizing the actions done by others. This observation raises two issues. First, why in most cases apraxia is not accompanied by perceptual deficits? Second, what may be the neural basis of these deficits?

To answer the first question, let us examine what is the core deficit in apraxia. Regardless of whether the required action
is elicited by a verbal command or by imitation, the initial operation that the patient has to do is that of forming a motor imagery of the requested behavior. Motor imagery is not a mere visual copy of an action, but includes the concept of self (“I am doing the action”). This profoundly differentiates motor imagery from visual imagery (see also above). Once the motor imagery is generated, it has to be translated into an overt behavior. Evidence from fMRI studies showed that when an individual is required to generate motor imagery of symbolic, mimed, or meaningless gestures, there is a strong activation of Broca’s area and of the anterior pole of the temporal lobe (FIGURE 21). These activations are accompanied by activation of the ventrocaudal part of the supramarginal gyrus. In addition, there is an activation of the dorsal part of supramarginal gyrus around the intraparietal sulcus and of the premotor cortex. Note that, unlike the ventrocaudal parietal activation, the dorsal supramarginal activation, as well as the premotor one, are also present when the individuals simply observe the same gestures without any further behavioral request.

On the basis of these findings, the following hypothesis on the genesis of IMA can be advanced. The deficit in IMA patient resides in the incapacity to produce the motor imagery of the requested action or to translate the imagined actions into related motor program. Lesions of Broca’s region would be responsible for the incapacity to generate motor imagery, while damage to the ventrocaudal part of the supramarginal gyrus, or, as already postulated by Liepmann (233), disconnections between Broca’s area and the parietal lobe, would be the cause of the incapacity to translate motor imagery into a motor program. This explanation is valid not only for action elicited on verbal command, but also in the case of imitation. Also, in this case the patient tends, before executing the action, to imaging himself doing it. As stated by Jeannerod (185), motor imagery is nothing else but implicit motor preparation.

The hypothesis about the circuits underlying IMA well explains why in this syndrome only deficits in the motor sphere are typically observed. Deficits in action understanding should appear only when lesions in IMA patients would extend beyond IMA core circuit. If we disregard, now, the apraxia framework and consider more simply the presence or the absence of association of motor and perceptual deficits in patients with parietal or frontal lesions, there is clear evidence that such an association does exist. A correlation, in fact, has been repeatedly found between deficits in gesture/pantomime understanding and gesture/pantomime production (50, 281, 300). In particular, Pazzaglia et al. (300) examined an action recognition task (hand and mouth action-related sound) in patients with limb or buccofacial apraxia. The analysis of the lesion showed that left frontoparietal cortex has a fundamental role in the recognition of the sound due to limb movements. On the contrary, left IFG and the adjacent insular cortex were causatively associated with recognition of sounds generated by the buccofacial apparatus. This double dissociation demonstrates that different sites endowed with the mirror mechanism encode limb and mouth action-related sounds and that these sites are also involved in limb and mouth execution.

In conclusion, IMA is a syndrome related to the incapacity to elicit a motor imagery of the requested action and to execute it. Automatic-voluntary dissociation is its hallmark, as already stressed by Liepmann (233). The presence of perceptual deficits (e.g., action understanding) are not related to apraxia itself, but rather to an extension of the lesion to parietal and premotor areas endowed

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**FIGURE 21.** Activation during motor imagery. Maps of cortical areas during imaging meaningless intransitive action, symbolic gesture, and pantomime of goal-directed action. Top panel indicates the activations obtained pulling together the activation of the three conditions mentioned above.
with the mirror mechanism. Thus the deficit in action understanding and action production, described in patients with parietal and frontal damage, represent clear evidence for a causative relation between action production and action recognition in humans.

2) HYPERACTIVITY OF THE MIRROR MECHANISM. The potential motor acts resulting from activation of the mirror mechanism ought to be subject to an inhibitory control. Otherwise, movements triggered by the observation of motor acts done by others should appear. Evidence for the existence of a top-down executive control on the mirror mechanism comes from experiments on healthy volunteers (40, 135, 269, 386), but the most compelling evidence for such control derives from clinical observations of the release of automatic imitative behaviors. In such conditions, motor mirroring becomes an overt, uncontrollable response that is automatically elicited by seeing other people acting.

Patients with damage to the prefrontal lobes may exhibit behavioral disturbances characterized by the appearance of forced motor behavior triggered by external stimuli. This condition is broadly referred to as “environmental dependency syndrome” (230, 231). A manifestation of it is the “imitation behavior.” Typically this symptom is observed in patients with unilateral or, more frequently, bilateral prefrontal lesions (92, 169, 231, 374) but has also been described in patients with different lesion topography (148, 266). Echopraxia is a similar, but distinct clinical phenomenon. It consists of forced and uncritical imitation of others’ movements sustained through endogenous mechanisms and resulting in its perseveration. Imitation behavior in broad sense is not a frequent symptom. The few descriptions, however, seem to agree on the fact that it contains a spectrum of manifestations according to how much the behavior is voluntary or automatic. While some forms of imitation behavior could seem to be dependent somehow on the patient’s will, other forms, including echopraxia, appear to be totally involuntary (92, 362, 374).

An interesting clinical phenomenon related to a release of motor plans from an executive control is the so-called “anarchic hand.” It consists in the appearance of unintended complex movements of one hand that are directed towards a goal. Interestingly, the awareness of the patients of the movements is preserved. What is lost is the sense of agency of the limb that behaves as if it had “a will of its own” (96, 213). The anarchic hand is associated with lesions of the anterior corpus callosum or the mesial frontal cortex (249). The anarchic hand should be kept distinct from the so-called “alien hand,” which is characterized by a degraded sense of ownership of the affected body part and is typically associated with parietal rather than frontal lesions (249, 294).

2. Developmental disorders of mirror function: autistic spectrum disorders

Autistic spectrum disorder (ASD) refers to a wide continuum of associated cognitive and neurobehavioral disorders characterized by impairment in communication and social interactions, and restricted repetitive and stereotyped behaviors (10, 17, 195). In ASD, a variety of nervous structures are affected, ranging from brain stem to cerebellum and cerebral cortex (42, 83, 124, 273). As far as the cortical abnormalities are concerned, of particular interest is the connectivity deficit found in the parieto-frontal network, i.e., in the circuit whose areas are endowed with the mirror mechanism (159). It has been proposed that a malfunctioning of the mirror mechanism is one of the factors underlying the cognitive aspects of the deficit (402).

Most studies on the relationship between mirror mechanism and autism have employed EEG and MEG techniques. They revealed that the cortical rhythms that desynchronize in typically developing children (TD) during both execution and observation of hand movements do desynchronize in children with autism only during active hand movements (255, 289, 321).

Recently, in a MEG study, Honaga et al. (170) explored neural activity in ASD focusing on power increase in beta frequency band (see EEG section, beta “rebound”) rather than the rhythm desynchronization. ASD and control children were asked to observe and later execute object-related hand actions. They found significantly reduced rebound in ASD only during the observation condition. The absence of motor cortex activation during the observation of movements done by others strongly suggests a deficit of mirror system.

Oberman et al. (291) investigated the sensitivity of mu rhythm desynchronization in relation to the familiarity of the agent performing the observed action. There were four conditions: an unfamiliar hand grasping an object (“stranger”), the hand of the child’s relatives performing the same action (“familiar”), the participant’s own hand (“own”), and, finally, bouncing balls (“control condition”). Both TD and ASD children showed greater suppression to the observation of grasping made by familiar hand compared with that of strangers. The desynchronization appeared to be absent in ASD children, but only with unfamiliar stimuli.

Imitation ability has been frequently found to be impaired in individuals with autism (see Refs. 339, 402). It was suggested that a dysfunction of mirror mechanism might account for this impairment (see above). In a study performed on ASD individuals and age-matched typical adults, Bernier et al. (33) found that while both groups showed a clear attenuation of the mu rhythm during action execution, TD individuals, but not ASD individuals, also showed signifi-
cant attenuation during action observation. The degree of mu wave attenuation during observation correlated with imitation capacities. A deficit in imitation was also found in a MEG study on adults with ASD (284). In contrast to these findings, Raymaekers et al. (326) were unable to find differential mu suppression between ASD and TD children. These results are surprising because they used the same paradigm and stimuli employed by Oberman et al. (289). The authors explained this discrepancy highlighting the heterogeneity of ASD population.

The possibility of abnormalities of mirror mechanism in ASD children was also investigated with fMRI. In a highly cited study, Dapretto et al. (90) studied brain activations in high-functioning children with ASD and in TD children while they observed and imitated emotional facial expressions. The results showed that ASD children, in contrast to TD children, presented poor activation in the frontal mirror node (pars opercularis of IFG). Furthermore, the activation of IFG was inversely related to the severity of symptoms in the social domain. A dysfunctional mirror neuron mechanism was also reported by Martineau et al. (254). In contrast, no abnormalities in the parieto-frontal circuit was found by Dinseit et al. (100) in adults with ASD during the observation and execution of intransitive hand movements.

Another technique that was used for studying the mirror mechanism in autism is TMS. Theoret et al. (378) investigated the neural mechanism matching action observation and execution in adults with ASD and normal controls. They applied TMS over the primary motor cortex (M1) during observation of intransitive, meaningless finger movements. They showed that overall modulation of M1 excitability during action observation was significantly lower in individuals with ASD compared with matched controls. A more recent TMS study tested the cortico-spinal excitability in adults during the observation of transitive hand gesture, relative to observation of the static hand. They found a significantly reduced cortical excitability in ASD relative to controls. Interestingly, among the ASD group there was a negative association between the activity of the mirror mechanism and self-reported social impairments (107). An original approach to the study of autism was used by Puzzo et al. (320). Instead of testing individuals with ASD, they investigated the cortico-spinal excitability in individuals with high and low traits of autism assessed with the autistic quotient (AQ) test (29). Videos of hand and mouth actions and static images with hand or mouth were used as stimuli. The results showed that individuals with low trait of autism presented large MEPs during the observation of the hand and mouth actions compared with MEPs obtained during the observation of static stimuli. In contrast, participants with high traits of autism showed MEPs with similar amplitude during the observation of both static and dynamic stimuli.

A different approach to the problem of possible impairment of the mirror mechanism in ASD was employed by Cattaneo et al. (69). They recorded electromyogram (EMG) from mylohyoideus muscle (MH), one of the muscles involved in the mouth opening, in TD and ASD children during the execution and observation of two actions. One action consisted of grasping a piece of chocolate and bringing it to the mouth (eating action), while the second consisted of grasping a piece of paper and putting it into a container (placing action). It was found that during eating action, the MH muscle became active as soon as the action starts in TD children, while no early activation was observed in children with ASD [FIGURE 22]. In TD children, MH muscle was also active during the observation of the eating action. In contrast, in children with ASD, the observation of another child grasping and eating chocolate did not activate MH muscle. In other terms, the observation of actions of others did not “intrude” into the motor system of ASD children. The authors proposed that a basic deficit in ASD consists of impairment of the motor system, which in turn prevents the organization of intentional motor action. This last deficit is responsible for impaired capacity of children with ASD in understanding others’ intention.

Additional evidence in favor of a deficit of the intention understanding in ASD based on the mirror mechanism has been provided by Boria et al. (36). They tested the capacity of TD and ASD children to report the goal of the observed motor acts, i.e., what the actor was doing, and the intention underlying it, i.e., why he/she was doing it. It was found that children with ASD recognize the what of the motor acts, but they fail to recognize the why, i.e., the intention behind the observed action.

Evidence that children with ASD have motor impairment in action organization was provided by Fabbri-Destro et al. (109). TD and ASD children were asked to perform two actions consisting each of two motor acts, the first identical in both actions, the second varying in its difficulty. It was found that the task difficulty modulates the kinematics of the first motor act, in TD children (190, 253), while it did not affect it in children with ASD.

The data of Boria et al. (36) show that ASD children are able to recognize the what of the motor act was confirmed by Hamilton et al. (160). These authors, however, considered this finding as evidence against a role of mirror neurons in autism deficit. This criticism does not take into consideration that the what of an action can be recognized in different ways even without the involvement of the mirror mechanism (see above).

E. Conclusions

In this review we summarized the present state of our knowledge concerning the mirror mechanism. This
The mirror mechanism appears to play a fundamental role in understanding actions and intentions of others. This conclusion is corroborated by the presence of the mirror mechanism also in species, evolutionarily distant from primates, like birds (197, 314). But what about mammals? Is the mirror mechanism limited to primates, or is it also present in other mammalian families? Future research will clarify this issue. Of particular interest would be to establish the presence of the mirror mechanism in rodents. If the mirror mechanism is present in these species, this will open the possibility to characterize the mirror mechanism at a biochemical level and to establish its genetic bases. Both these approaches are hardly achievable in primates.

Another fundamental development of mirror neuron research should be that of defining the relationships between the basic mirror circuits and other circuits related to it and in particular those that could exert a top-down control on it. Even more fascinating will be to establish the anatomical and functional relationship between the areas endowed with the mirror mechanism and the areas involved, according to fMRI studies, in mentalizing. The study of Yoshida et al. (409) that showed mirror neurons in the monkey medial frontal cortex, an area part of the mentalizing network, appears to be a first step in this direction.

It will be also of great interest to continue the pioneer work by Mukhamel et al. (271) on the properties of single neurons in humans. The technology used in that and other studies on human single neurons enables single neurons recording only from the mesial brain structures (see Ref. 272). It is likely, however, that in the near future electrodes will be available for recording single neuron activity from neural structure located in other parts of the cerebral cortex. This possibility will be instrumental in solving the present dichotomy between the mirror neuron-based cognition and mentalizing.

Finally, as shown in this review, the mirror mechanism is the only mechanism that allows us to understand others “from inside” (337), as individuals similar to ourselves. It is very likely that malfunctioning of this mechanism should be responsible for symptoms of psychiatric disorders characterized by what Baron-Cohen called “zero degrees of empathy” (28). Psychiatry will be, most likely, one of the most important “mirror fields” of the future. The discovery of relations between impairment in the mirror mechanism and...
some autistic symptoms has been an encouraging beginning.

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