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NEW FRONTIERS IN  
**mirror neuron  
research**



PIER FRANCESCO FERRARI  
& GIACOMO RIZZOLATTI

# **New Frontiers in Mirror Neurons Research**



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Edited by

Pier Francesco Ferrari and Giacomo Rizzolatti

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# Preface

When, more than 20 years ago, a group of researchers working in Parma discovered a distinct set of visuomotor neurons in the monkey brain—the mirror neurons—nobody could have imagined the impact that this discovery would have, not only on neuroscience but also on psychology, ethology, sociology, and even philosophy.

The early studies on mirror neurons were mainly focused on determining which stimuli were most appropriate for triggering the neurons and on the relationships between the observed and executed actions. Already in these studies, it was reported that mirror neurons could be modulated by factors such as the direction of the observed action or its spatial location. Yet these aspects were not investigated in detail. A series of recent studies, performed in a collaboration between Parma and Tübingen researchers, have revealed a much more complex picture, showing in particular that location in space (see Chapter 18), context, and even the subjective value of the observed actions are important factors for modulating or even determining the mirror neuron responses.

Another feature that has emerged from recent neurophysiological studies is the link between the mirror premotor neurons and the cortical descending pathways originating from F5 and even F1 (primary motor cortex). Chapters 2, 13, and 18 discuss these data and present theoretical interpretations of these findings. A fundamental aspect of these new findings is that they indicate that action recognition depends not only on the activity of parieto-premotor circuits but also on the activation of other motor structures, including even the primary motor cortex. Thus, understanding actions made by others is based on the occurrence, in the observer's brain, of motor schemas that are almost replicas of those underlying the observed motor act.

Another important contribution made in the last few years has been the interpretation of functional MRI (fMRI) activation during action observation in humans, first explaining fMRI activation in the monkey using the properties of monkey mirror neuron activity and then using this information to interpret human brain imaging data. Chapter 7 offers an extended review based on this approach and an exhaustive discussion of the possible homologies between the human and monkey neural substrates of action observation.

The techniques that have mostly contributed to our knowledge of the mirror mechanism in humans have been magnetoencephalography, EEG, and fMRI. At present, there are hundreds of studies that have used these techniques to show that the main nodes of the action-execution/action-observation circuit for goal-directed hand actions are the superior temporal sulcus region, the inferior parietal lobule, and the premotor cortex. Chapters 4 and 5 discuss the impact that brain imaging techniques have had on mirror mechanism research, while at the same time outlining the limitations of these techniques, especially when the results are used to give cognitive interpretation beyond function localization.

The use of fMRI to infer the areas involved in mentalizing allows one to show which areas contribute to these functions, but it does not provide any mechanistic explanation of how these functions are implemented in the brain.

Another example is the use that has been made of fMRI repetition suppression to infer the activity of mirror neurons in the parietofrontal circuit. Experiments using this approach have led some scholars to even cast doubt on the possible existence of mirror neurons in humans, thus neglecting the neurophysiological basis of this approach and its limitations, which have clearly been underlined by various authors (e.g., Sawamura et al. 2006; see Bartels et al. 2008). It is worth noting that the use of repetition suppression to directly investigate mirror neuron responses in the monkey premotor cortex have shown no or minimal effect (Caggiano et al. 2013; Kilner et al. 2014). This finding indicates that using data from brain imaging to explain neuronal mechanisms is not always possible and, even when feasible, the data must be interpreted with extreme caution.

In spite of these limitations, there is no doubt that brain imaging techniques have played a fundamental role in revealing the importance of the mirror mechanism in another field: emotion. Thanks to these techniques, we know that emotions are recognized not only through cognitive mentalizing processes but also through direct activation of the same brain structures that respond to natural stimuli and mediate the autonomic/motor responses associated with emotions. These data have greatly expanded the horizon of mirror neuron research, showing that the mirror mechanism plays an important role not only in understanding “cold” actions, that is, actions devoid of an emotional content, but also in understanding and sharing emotions felt by others (“understanding from inside”). The description of the neurophysiological mechanisms underlying emotions boosted research into empathy, the study of which is nowadays one of the most flourishing and exciting fields in animal and human behavior.

Technological developments in EEG recording and analysis have made it possible to investigate the mirror mechanism in infants (see Chapter 14) and have enabled experimenters to track the neural changes that occur in ontogeny during the transition away from the behavioral and cognitive phases. Furthermore, studies of the mirror mechanism during development have indicated that the motor system is crucial not only for understanding the behavior of others but also for acquiring new behaviors. These studies, reviewed in Chapters 15 and 17, offer a deep, critical overview of child development at both the behavioral and the electrophysiological levels.

Some of the chapters in this volume are devoted to an investigation of the evolution of the mirror mechanism. Clearly we lack information about whether all social species or only some of them are endowed with this mechanism and, if the latter case, which ones. The species in which the mirror mechanism has been demonstrated include macaques (four species), humans, marmosets, and, outside the primate family, two different species of songbirds. The presence of the mirror mechanism in birds has received great attention for various reasons. First, it is present in a brain center (HVC) that is thought to play a role similar to that of the mammalian motor cortex in the control of sound emission and learning. Second, it is involved in communication. Third, similarly to the language center

in humans, the organization of the HVC is dependent on early experience in order to fully develop.

It has been a matter of debate for a long time as to whether human language was derived from communicative sounds made by our primate ancestors or from gestures. Chapter 8 presents data from Gentilucci and colleagues on this issue, namely, on the relation between actions and communicative sounds. These data illustrate the close link that exists between the production of syllables and the control of hand movements and show, conversely, the modulation of sounds in relation to the type of performed action. These data support the hypothesis for a gestural origin of language, a hypothesis re-proposed some years ago by Rizzolatti and Arbib (1998) on the basis of mirror neuron properties.

Interestingly, previous studies on the mirror mechanism have focused on apes, and the link between monkey and human mirror experiments was lacking. However, recently PET studies have been carried out to investigate which areas in the chimpanzee brain are involved in the observation of actions of others. In agreement with human and monkey data, a temporo-parietal-premotor network was found to be active in chimpanzees during the task. However, unlike in macaques but similar to the case in humans, in chimpanzees the mirror network is also active during the observation of intransitive gestures. Chapter 9 discusses these data within an evolutionary framework, maintaining that the control of progressively more complex actions has been the key for important cognitive advances, such as the capacity to imitate, in the evolution of apes as well as humans.

Studies on the mirror mechanism have had also a profound impact in rehabilitation practice, through the idea that action observation, by activating visually cortical motor representations, could facilitate the recovery of motor functions that have been previously compromised. This approach (called action observation therapy) has started to accompany traditional rehabilitative techniques in patients with stroke, has been used for the treatment of Parkinson's disease patients, and has been applied to aphasic patients and to children with cerebral palsy. More recently, encouraging results have been reported in non-neurological patients undergoing rehabilitation following orthopedic interventions

Lastly, some of the chapters in this volume are devoted to exploring relations between the mirror mechanism and those neurodevelopmental disorders in which social aspects are compromised. These relations have been particularly studied and debated with respect to their ability to explain the social and communicative deficits that are symptoms of autism. Chapter 21 reviews the evidence in favor of and against this hypothesis and provides a critical account of how different sets of data could be reconciled.

This book is an attempt to integrate our knowledge about the mirror mechanism, from physiology to development, as well as its role in different psychological functions. The contributors of this volume have exhaustively addressed the most recent issues concerning mirror neurons, using a comparative and interdisciplinary approach. It is likely that the reader will be surprised by the number of topics covered by this book, but the breadth of the subject matter reflects a process well known in the history of science: a key discovery, like a stone thrown on the water, produces waves that subsequently expand to touch borders far from the origin.

The book is directed at a broad audience, from college and university students to researchers in different fields, and from those who want to have the most up-to-date information about the mirror mechanism to those who wish to enter the field and expand those areas that so far have been little studied. We would like to thank the volume's contributors, who with great enthusiasm have agreed to join us in this adventure, as well as the Ettore Majorana Foundation and Centre for Scientific Culture, which in 2012 hosted and supported a memorable workshop held in Erice and for which the object was to promote an understanding of the new frontiers in mirror neuron research, 20 years after the first discovery of these neurons. This volume is the updated outcome of that event.

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## References

- Bartels, A., Logothetis, N. K., and Moutoussis, K. (2008) fMRI and its interpretations: An illustration on directional selectivity in area V5/MT. *Trends in Neuroscience*, **31**, 444–53.
- Caggiano, V., Pomper, J. K., Fleischer, F., Fogassi, L., Giese, M., and Thier, P. (2013) Mirror neurons in monkey area F5 do not adapt to the observation of repeated actions. *Nature Communications*, **4**, 1433.
- Kilner, J. M., Crskov, A., and Lemon, R. N. (2014) Do monkey F5 mirror neurons show changes in firing rate during repeated observation of natural actions? *Journal of Neurophysiology*, **111**, 1214–26.
- Rizzolatti, G., and Arbib, M. A. (1998) Language within our grasp. *Trends in Neuroscience*, **21**, 188–94.
- Sawamura, H., Orban, G. A., and Vogels, R. (2006) Selectivity of neuronal adaptation does not match response selectivity: A single-cell study of the fMRI adaptation paradigm. *Neuron*, **49**, 307–18.

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Section 1

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# **Basic findings and concepts in action-perception theory**



## Chapter 1

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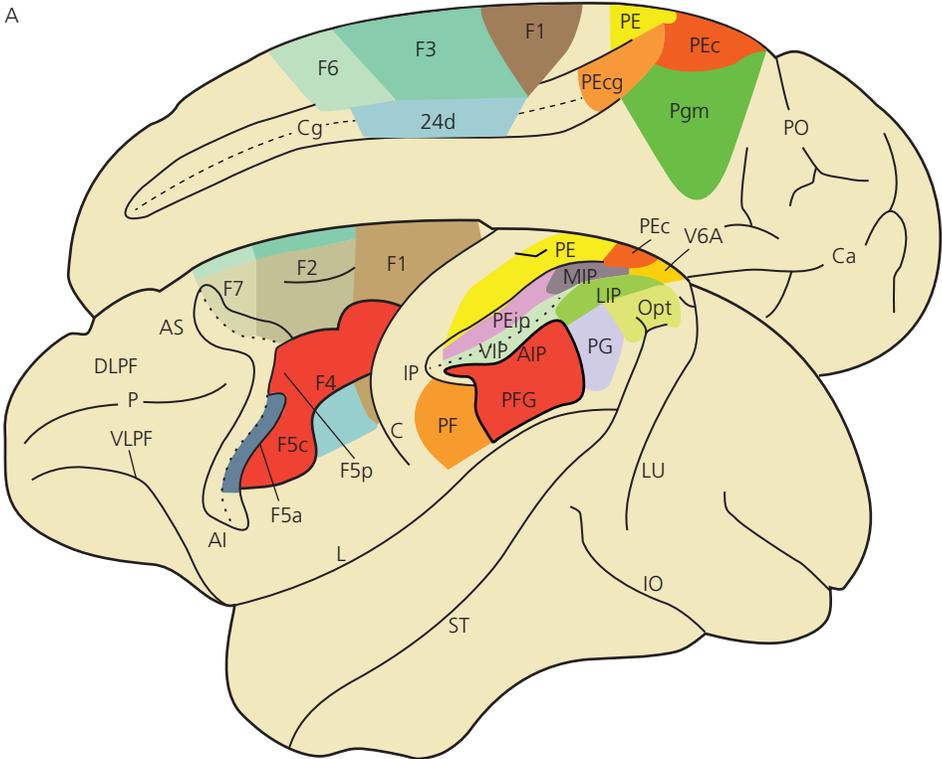
# The neuroanatomy of the mirror neuron system

Stefano Rozzi

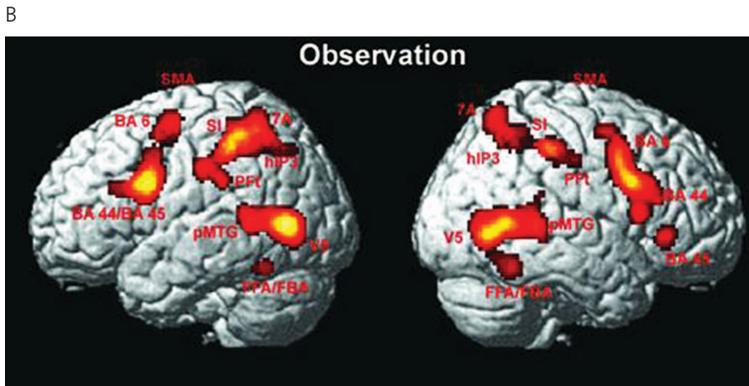
### Introduction

Since the last part of the twentieth century, the general vision of the functional role of the motor cortex has radically changed: nowadays, the motor cortex is no longer considered merely the producer of movements but is also thought to be involved in cognitive functions such as space coding, motor learning, action understanding, and imitation. Particularly important, in this respect, has been the identification of mirror neurons (di Pellegrino et al. 1992; Gallese et al. 1996; Rizzolatti et al. 1996). These neurons, first recorded in monkey premotor cortex, were subsequently also described in other parts of the brain. They discharge both during the execution of specific motor acts and during the observation of similar acts. Thus, the observation of an action produces in the observer a motor activation, as if the observer were actually programming the execution of the observed action. This “mirror mechanism” is thought to be involved in action and intention understanding (see Rizzolatti and Sinigaglia 2010; Rizzolatti et al. 2014; Rizzolatti and Fogassi 2014).

So far, the mirror mechanism has been described in monkeys, humans, and birds (see Chapters 2, 4, 5, 7, and 10). In monkeys and humans, the mirror system includes not only cortical areas controlling hand or mouth actions (Gallese et al. 1996; Fogassi et al. 2005) and eye movements (Shepherd et al. 2009) but also centers involved in space coding (Hishida et al. 2010) and emotions (Gallese et al. 2004; Singer et al. 2004). In birds, on the other hand, the mirror system includes motor centers contributing to song production and learning (Prather et al. 2008; Keller and Hahnloser 2009). These findings indicate that the mirror mechanism can encompass a wide variety of functions, depending on its anatomical location and, in particular, on the type of motor representations that become active because of different sensory inputs. From this perspective, central to the mirror system are the motor areas involved. Interestingly, two cortical sectors involved in programming and executing actions, the ventral premotor cortex (PMv) and the inferior parietal lobule (IPL), are also active during action observation, in both monkeys and humans (Fig. 1.1). However, some caution should be taken when comparing the mirror system in the two species: in the monkey most data have been obtained using single-neuron recordings, while in humans most investigations have involved noninvasive brain imaging techniques (see Chapters 5 and 7). In spite of these technical differences, it is clear, however, that the



**Fig. 1.1** (A) Lateral and mesial views of the monkey brain showing the parcellation of the agranular frontal and posterior parietal cortices. The regions where mirror neurons have been recorded are indicated by squared shaded areas. Intraparietal, arcuate, and cingulate sulci are shown unfolded. For the nomenclature and definition of the areas of agranular frontal and posterior parietal cortices, see the text; AI, inferior arcuate sulcus; AS, superior arcuate sulcus; C, central sulcus; Ca, calcarine fissure; Cg, cingulate sulcus; DLPP, dorsolateral prefrontal cortex; IO, inferior occipital sulcus; L, lateral fissure; Lu, lunate sulcus; P, principal sulcus; PO, parieto-occipital sulcus; ST, superior temporal sulcus; VLPF, ventrolateral prefrontal cortex. (B) Cortical areas active during action observation in humans. Three main regions are active: a portion of the superior temporal sulcus, the inferior parietal lobule, including the intraparietal sulcus and a small part of superior parietal lobule, and the premotor cortex, mainly in its ventral part, plus the posterior part of the inferior frontal gyrus. The activated regions depicted on the left and right hemispheres represent the results from a meta-analysis performed on 104 studies; BA, Brodmann area; FBA, fusiform body area; FFA, fusiform face area; hIP3, human intraparietal area 3; pMTG, posterior temporal cortex; SI, primary somatosensory cortex; SMA, supplementary motor area. Reprinted from *NeuroImage*, 50 (3), Svenja Caspers, Karl Zilles, Angela R. Laird, and Simon B. Eickhoff, ALE meta-analysis of action observation and imitation in the human brain, pp. 1148–67, doi:10.1016/j.neuroimage.2009.12.112, Copyright (2010), with permission from Elsevier.



**Fig. 1.1** (continued)

regions in which a large part of the human networks responding during action observation are located are similar to action observation–responsive regions described in the monkey.

In this chapter, the anatomy of the parieto-premotor mirror system will be described, and evidence will be provided to show that a larger network underpinning this system is possibly at work. Given the above-mentioned centrality of the motor areas for the mirror mechanism, the anatomy of the motor system in the monkey will be first reviewed, with particular emphasis on area F5, in which mirror neurons were first recorded. Then it will be shown that, through a multimodal anatomical and functional approach, a more detailed description of the system can be made. Finally, the anatomical properties of monkey motor and mirror systems will be compared with those of humans.

## The agranular frontal cortex: a mosaic of areas

The first architectonic map of the human cerebral cortex was provided by Campbell (1905). The cortex located in front of the central sulcus (the “precentral” cortex) can clearly be distinguished from that located rostral to it and caudal to the prefrontal lobe (the “intermediate precentral cortex”). In Campbell’s view, the precentral cortex was involved in motor control, while the intermediate sector was implicated in higher-order motor functions. Brodmann (1909) agreed with the view that there are two motor areas, area 4 and area 6, and provided a more detailed map of the frontal lobe in monkeys and humans. The idea that architectonic parcellations reflect functional differences was strongly supported by Fulton (1935), who showed that lesions of area 6 (the premotor cortex) produce specific deficits in the execution of skilled movements. However, the existence of a high-order motor area rostral to area 4 was brought into question by electrophysiological studies employing electrical stimulation. In particular, Woolsey and colleagues (1952) identified two complete somatotopic motor representations in the agranular frontal cortex of the monkey: one on the lateral surface of the cortex, including area 4 and the caudal part of area 6 (the primary motor cortex, or M1), and the other located on the mesial surface of area 6 (the supplementary motor area [SMA]). They concluded that area 4 and posterior

area 6 together form a functional entity, while the rostral part of area 6 was not part of the motor cortex, as electrical stimulation of that area did not produce movements.

Brodmann's definition of area 6 as a single entity was challenged by numerous subsequent architectonic studies. In particular, different authors divided this cortical sector into different subareas (e.g., Vogt and Vogt 1919; Bonin and Bailey 1947). Recently, a more objective assessment of areal borders was provided by combining cytoarchitectonic and neurochemical techniques (see Geyer et al. 2000; Belmalih et al. 2007). The use of this multiarchitectonic approach to analyzing the motor cortex of the monkey resulted in the map first proposed by Matelli et al. (1985) and further developed by others (Matelli et al. 1991; Belmalih et al. 2009). In this map, shown in Fig. 1.1A, area F1 roughly corresponds to area 4 (primary motor cortex, or M1), and the mesial, dorsal, and ventral sectors of area 6 are each composed of a caudal region and a rostral region.

This map has been further validated by converging evidence demonstrating that each architectonic subdivision is also different in terms of connections as well as neuronal properties (Rizzolatti et al. 1998; Rizzolatti and Luppino 2001).

## Connections of the motor areas in the monkey

Tract tracing studies have been used to identify the anatomical connections of each motor area to subcortical structures and cortical areas and represent an invaluable tool for the interpretation of the functional roles of these areas. These studies showed that each motor area has a specific pattern of connections characterizing it. However, on the basis of their general pattern of connectivity, the different premotor areas have been grouped into two major classes (Rizzolatti and Luppino 2001): the caudal premotor areas F2, F3, F4, F5p, and F5c and the rostral premotor areas F5a, F6, and F7.

## Connections with the spinal cord and intrinsic motor connections: a possible pathway for inhibiting action execution during action observation

As a whole, the motor cortex is a source of different descending motor pathways, which provide the motor cortex with access to brainstem and spinal motor centers. The organization of the corticospinal and corticobulbar connections supports the subdivision of the premotor areas into two classes. Strick and coworkers (Dum and Strick 1991; He et al. 1993, 1995) extensively studied the origin of the corticospinal tract and showed that corticospinal projections originate both from the primary motor area and from all the caudal premotor areas. These projections are somatotopically organized: hindlimb and forelimb motor fields project to the lumbar and cervical spinal cord, respectively, while face and mouth cortical representations are sources of corticobulbar projections (Morecraft et al. 2001). All these areas are mostly connected with the intermediate zone of the spinal cord, but F1 is also a source of monosynaptic projections to spinal motoneurons and is thus considered the final common pathway, at the cortical level, for controlling skilled hand movements. In line with this view, it is known that all the caudal premotor areas are

somatotopically connected to F1. However, the presence of corticospinal projections from caudal premotor areas clearly indicates that they could participate in the generation and control of movements not only through F1 but also in parallel with it.

In contrast, the rostral premotor areas do not project directly to the spinal cord. Instead, their descending projections reach different parts of the brainstem (Keizer and Kuypers 1989). Furthermore, these areas are not connected with F1 and generally have widespread connections with numerous motor areas. These data indicate that rostral premotor areas can be involved in the generation of motor behavior only indirectly, through their subcortical relays or their connections with the caudal premotor areas.

The description of mirror neurons in the posterior premotor area F5c and in area F1 raises the question, why don't we automatically move when we observe an action? One possible explanation may be as follows. In a recent single-neuron experiment, it was shown that the activity of a significant portion of pyramidal tract neurons (PTNs) in area F5 was modulated by action observation (Kraskov et al. 2009), which acted either to increase or decrease discharge. This finding demonstrates that mirror neuron activity can be transmitted to the spinal cord. Considering that more than one-fourth of PTNs showed suppression of discharge during action observation but fired during active grasping, the authors of this study suggested that this inhibitory effect might play a role in preventing movement generation during action observation.

The same authors also recorded PTN mirror neurons in F1 (Vigneswaran et al. 2013). The majority of these neurons increased their discharge during action observation, while others showed a reduced firing rate. Interestingly, the first class of neurons were only half as active for action observation as for action execution, and the second class of neurons had the opposite activity pattern, increasing their firing rate during action execution. Thus, although many F1 PTNs discharge during action observation, their output to the spinal cord might be suppressed or insufficient to produce overt muscle activity.

These findings suggest that the output of mirror system is not strictly limited to other cortical areas but also reaches the spinal cord. The role of PTN mirror neurons could be crucial in the inhibition of unwanted self-movements during action observation. Up to now, however, there have been no studies specifically investigating in humans or other primates whether mirror neurons are also present in the spinal cord or in other brainstem nuclei involved in motor execution.

### **Cortical connections of the agranular frontal cortex**

Cortical afferents to the frontal motor areas mainly derive from three regions: the parietal cortex (the primary somatosensory cortex and the posterior parietal cortex), the prefrontal cortex, and the agranular cingulate cortex (see Rizzolatti and Luppino 2001).

The reciprocal connections with the parietal cortex are very strong and represent the major source of input to area F1 and the caudal premotor areas. Anatomical and functional evidence indicates that, like the agranular frontal cortex, the posterior parietal cortex consists of a mosaic of distinct areas (Fig. 1.1). Each of these areas is involved in specific aspects of sensory information processing and in the control of specific effectors

(mouth, hand, arm, and eyes). Both the IPL and the superior parietal lobule (SPL) receive both somatosensory and visual inputs (Colby 1998; Rizzolatti and Matelli 2003). In general, almost all IPL areas and the posterior areas of the SPL process either only visual or both somatosensory and visual information, while the rostral areas of the SPL deal mainly with somatosensory information (Caminiti et al. 1996; Rizzolatti et al. 1997; Rozzi et al. 2008).

Examining the organization of parieto-frontal connections in more detail, it emerges that each motor area is reciprocally connected with a specific set of parietal areas. Typically, within the set of parietal areas connecting to a specific motor area, some have much stronger connections (predominant connections), and others have weaker connections (additional connections). Within this general framework, it is possible to describe a series of largely segregated circuits constituted by parietal and motor areas linked by predominant connections (e.g., the ventral intraparietal area [VIP] to F4, the anterior intraparietal area [AIP] to F5, and the medial intraparietal area/V6A to F2; see Rizzolatti et al. 1998). Interestingly, functional evidence indicates that the parietal and frontal areas that form each of these circuits share common functional properties. An example of this type of circuit is that connecting the parietal area VIP and the premotor area F4. These two areas are strongly anatomically connected (Luppino et al. 1999), and both contain bimodal, visual, and tactile neurons (Colby et al. 1993; Fogassi et al. 1996). The tactile receptive fields of these neurons are large and generally located on the face, the arms, and the upper part of the body, while the visual receptive fields are located in the peripersonal space, in register with the tactile receptive fields. In most cases, the visually responsive neurons respond preferentially to stimuli directed toward the tactile receptive fields. The functional properties of the VIP–F4 circuit indicate that this circuit plays a role in encoding the peripersonal space and in transforming object locations into appropriate movements toward them. The functional correlate of this anatomical organization is that each of these circuits is differently involved in transforming sensory stimuli into motor terms. This implies, first, that the posterior parietal cortex is actually part of the motor system and, second, that the parieto-frontal circuits, and not the single motor areas, should be considered the functional units of the cortical motor system (Rizzolatti et al. 1998; Rizzolatti and Luppino 2001).

Prefrontal projections to the motor cortex are mainly directed to rostral premotor areas (Luppino et al. 1993; Lu et al. 1994; Gerbella et al. 2010; Borra et al. 2011; Gerbella et al. 2013). Prefrontal input to the dorsal premotor area F7 originates only from the dorso-lateral prefrontal cortex (DLPF), that to the mesial premotor area F6 from both the DLPF and the ventrolateral prefrontal cortex (VLPF), and that to the ventral premotor area F5a only from the VLPF. Area F6 also receives strong afferences from the rostral cingulate cortex (area 24c). Cingulate connections are considerably weaker for F7 and F5a than for F6. However, F5a is densely connected with rostral opercular frontal areas.

These anatomical data indicate that the caudal premotor areas are involved in transforming sensory information into potential motor acts, while the rostral areas play a hierarchically higher role by conveying information related to high-order action organization,

working memory, and motivation from the prefrontal, cingulate, and opercular frontal cortex to the caudal premotor areas. This information can be used by the caudal premotor areas for determining which motor acts will be executed and when, according to external and internal contingencies.

The features of the parieto-frontal and prefronto-frontal circuits involving area F5 will be discussed in the following sections.

## The mirror network in monkeys

### Area F5: anatomical subdivisions

F5 is the premotor area where mirror neurons were first described. Since then, this area has been deemed to be crucially involved in goal coding and action understanding, as well as motor control. In this section, the anatomical and functional properties of this area will be described, with particular emphasis on its involvement in the mirror system.

Electrophysiological studies indicated that there is a motor representation of the hand and the mouth in area F5 (Kurata and Tanji 1986; Gentilucci et al. 1988; Rizzolatti et al. 1990; Hepp-Reymond et al. 1994; Maranesi et al. 2012) and that this area plays a crucial role in the generation and control of goal-directed distal motor acts such as grasping (Gentilucci et al. 1988; Rizzolatti et al. 1988; Umiltà et al. 2008).

Subsequent anatomical studies revealed that F5, originally thought to be a single entity, is not homogeneous. Luppino and coworkers provided data indicating that F5 is constituted by three sectors, each with a distinct architectonic structure and characterized by a peculiar pattern of connections (Belmalih et al. 2009; Borra et al. 2010; Gerbella et al. 2011). One of them, F5c, for “convexity” F5, extends along the convexity of the postarcuate cortex, adjacent to the inferior arcuate sulcus. The other two, F5p, for “posterior” F5, and F5a, for “anterior” F5, lie within the posterior bank of the inferior arcuate sulcus, at different anteroposterior levels.

Though precise correlation of electrophysiological data with architectonic data is still lacking, F5p and F5c appear to represent two different sectors in F5, hosting neurons with partially different functional properties (see Rizzolatti et al. 1998; Rizzolatti and Luppino 2001), as will be explained in the following section.

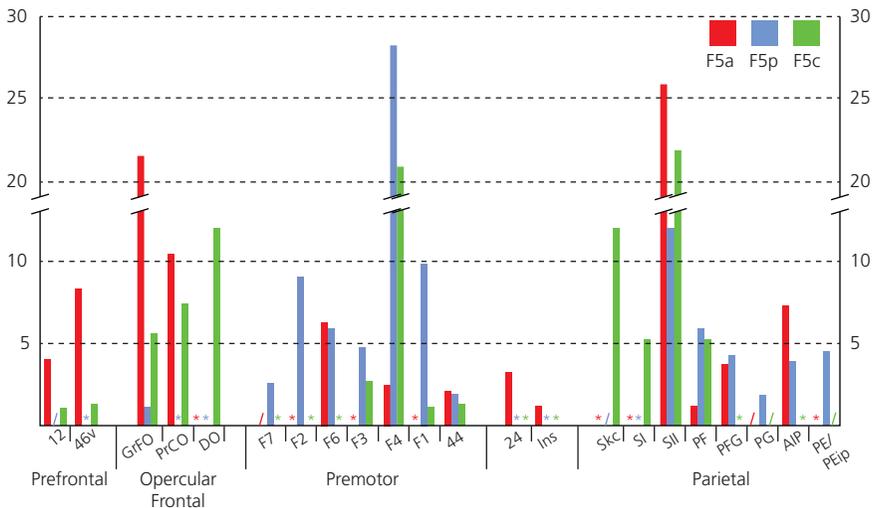
### The cortical circuits involving the F5 sectors, and their functional role in action execution and observation

*F5p* corresponds to a hand-related field whose neurons code specific goal-directed motor acts. Some of these neurons are also responsive to the observation of objects (“canonical” neurons; Murata et al. 1997; Raos et al. 2006). Thus, F5p is involved in the selection of distal motor acts appropriate for hand–object interactions, based on the analysis of the object physical characteristics (Jeannerod et al. 1995). In order to elicit movements, the output of this process of visuomotor transformations has to reach the spinal cord (see “Connections with the spinal cord and intrinsic motor connections: a possible pathway for inhibiting action execution during action observation”).

*F5c* largely corresponds to a hand and mouth-related field (Gentilucci et al. 1988; Maranesi et al. 2012), hosting motor neurons and mirror neurons (see Rizzolatti et al. 2014). Besides being part of the mirror system, *F5c* is also involved in other aspects of cognitive motor functions, such as the evaluation and comparison of current and remembered sensory information for perceptual decisions (Romo et al. 2004; Lemus et al. 2009) and the monitoring of the outcomes of these decisions for learning and adaptation of future behavior (Pardo-Vazquez et al. 2008, 2009).

*F5p* and *F5c* are both strongly connected with the parietal areas *AIP* and *PFG* and the secondary somatosensory cortex (*SII*; Fig. 1.2).

Area *AIP* is a hand-related field located in the rostral part of the lateral bank of the intraparietal sulcus (Sakata et al. 1995; Murata et al. 2000). *AIP* neurons typically discharge during the execution of grasping motor acts. Furthermore, some of these neurons also discharge when objects are simply observed. In these neurons, the visual responses appear to represent specific intrinsic properties (e.g., size, orientation) of the objects. The identification of tight connections between the *AIP* and the inferotemporal areas located at the highest levels of the ventral visual stream (Borra et al. 2008) suggests that information on object identity can reach the *AIP*. Thus, the *AIP*–*F5p* circuit could use information about



**Fig 1.2** The relative strengths of cortical connections made by *F5a*, *F5p*, and *F5c*, shown in terms of mean percent distribution of retrograde labeling; *AIP*, anterior intraparietal area; *DO*, dorsal opercular area; *GrFO*, granular frontal opercular area; *Ins*, insular cortex; *PEip*, the intraparietal sector of area *PE*; *PrCO*, precentral opercular area; *SI*, primary somatosensory cortex; *SII*, secondary somatosensory cortex; *Skc*, somatic koniocortex; / = no labeling; \* = labeling < 1%. Adapted from Marzio Gerbella, Abdelouahed Belmalih, Elena Borra, Stefano Rozzi, Giuseppe Luppino, Cortical Connections of the Macaque Caudal Ventrolateral Prefrontal Areas 45A and 45B, *Cerebral Cortex*, 20 (1), pp. 141–168, Figure 20, doi: 10.1093/cercor/bhp087 © 2010, Oxford University Press.

both the physical features and the functions of the target object to generate visuomotor transformations for grasping.

Furthermore, functional magnetic resonance (fMRI) data in awake macaques (Nelissen et al. 2011) have shown that area AIP is active during action observation. The authors of this study hypothesized that the activation is most likely due to the presence of mirror neurons in this area. A recent electrophysiological study (Pani et al. 2014) confirmed this hypothesis at the single-neuron level, showing that the AIP contains neurons that are active both during action execution and observation. Thus, AIP–F5p connections could also represent a component of the mirror system and possibly may be related to the description of hand–object interactions.

Area *PFG*, located in the IPL convexity, is mostly a hand-related field which contains neurons coding goal-directed motor acts as well as mirror neurons (Fogassi et al. 2005; Rozzi et al. 2008). Interestingly, the activity of a large proportion of grasping and mirror neurons is modulated by the overarching goal of the action in which the motor act is embedded (Fogassi et al. 2005; Bonini et al. 2010, 2011) and appears to be involved in higher-order aspects of action organization and related to the motor intention of the agent (Rizzolatti and Fogassi 2014). Similar neuronal properties have been recorded in area F5 as well (Bonini et al. 2010, 2011). By matching sensory information about action to an intentional-motor representation, the mirror mechanism located in these areas might be important for understanding other individuals' intentions (Fogassi et al. 2005; see Rizzolatti and Sinigaglia 2010; Rizzolatti et al. 2014).

Area *SII*, in the parietal operculum, is considered a higher-order somatosensory area involved in tactile object recognition and in coding tactile expectancies about the contact with objects (Carlsson et al. 2000; Reed et al. 2004). *SII* could feed this information to the F5 sectors, contributing to the update and selection of premotor grasping motor programs or enabling the precise control of fingertip forces for grasping stability (Gentilucci et al. 1995; Ehrsson et al. 2003). Presently, no monkey data are available about the possible involvement of this area in action coding and the mirror system.

*F5a* shares with the other F5 subdivisions some connections to parietal areas such as AIP, PFG, and *SII* but is also characterized by dense connections with ventrolateral prefrontal area 12, ventral area 46, and the rostral opercular frontal sectors (Fig. 1.2; Gerbella et al. 2010) and is thus part of the rostral premotor areas. While there has not been a detailed investigation of the presence of mirror neurons in *F5a*, this F5 sector yielded significant fMRI responses to action observation in the monkey (Nelissen et al. 2005). In particular, *F5a* seems to be a site of integration of sensory–motor parietal signals with higher-order information originating from prefrontal and rostral frontal opercular areas. The results of this integration can be sent to *F5p* and *F5c*, providing them with contextual and mnemonic information. This input could modulate the activity of mirror neurons observed when actions are not visible, but can be inferred by their sound, or when the motor intention of the observed agent is not immediately available, but can be inferred by the context (Umiltà et al. 2001; Kohler et al. 2002; Bonini et al. 2010).

## Distinct anatomofunctional temporo-parieto-premotor mirror pathways

Most of the functional data described in this chapter are based on single-neuron recording experiments. While this technique is the only one capable of demonstrating that the same neuron is discharging during both movement execution and observation, it cannot identify the whole set of areas involved in action observation. Such information is crucial for validating the functional hypotheses proposed in the first part of the chapter and which are based on anatomical studies. To this end, brain imaging techniques are of invaluable help. The first study employing fMRI in the monkey to identify areas active during the observation of motor acts focused on the frontal lobe areas (Nelissen et al. 2005). By using anatomically defined regions of interest (ROIs), the authors found that observation of video clips showing a hand grasping an object activates the PMv areas F5a and F5p and the prefrontal areas 45A, 45B, and 46. When, instead of an isolated hand, the video clip showed an individual grasping an object, significant magnetic resonance responses were also found in F5c. These data show that the frontal lobe of the monkey hosts multiple representations of others' actions. More specifically, the representation located in F5c seems context dependent, being activated only when the agent is seen in the scene, whereas the representations located in F5a, F5p, and the prefrontal areas appear to code the action as such.

A subsequent study investigated how visual responses related to action observation might reach the premotor areas, by using fMRI to examine activation in the monkeys' superior temporal sulcus (STS) and posterior parietal lobule during the observation of grasping acts and then correlating the functional data with connectional data (Nelissen et al. 2011). Videos showing an object being grasped by either a person or just the person's hand activated areas in the depths of the lower and upper banks of the STS as well as in the inferior parietal cortex. A further ROI analysis showed that observation of grasping acts activates three areas in the IPL: the PFG, the AIP, and the anterior portion of the lateral intraparietal cortex (LIPa). In the STS, five regions were consistently more active during action observation than during control conditions: middle temporal (MT)/V5, the lower superior temporal region (LST), and a more rostral region tentatively named lower bank 2 (LB2), all of which are in the lower bank of the STS; the fundal area of the STS (FST); and the middle part of the superior temporal polysensory area (STPm), which is in the upper bank of the STS.

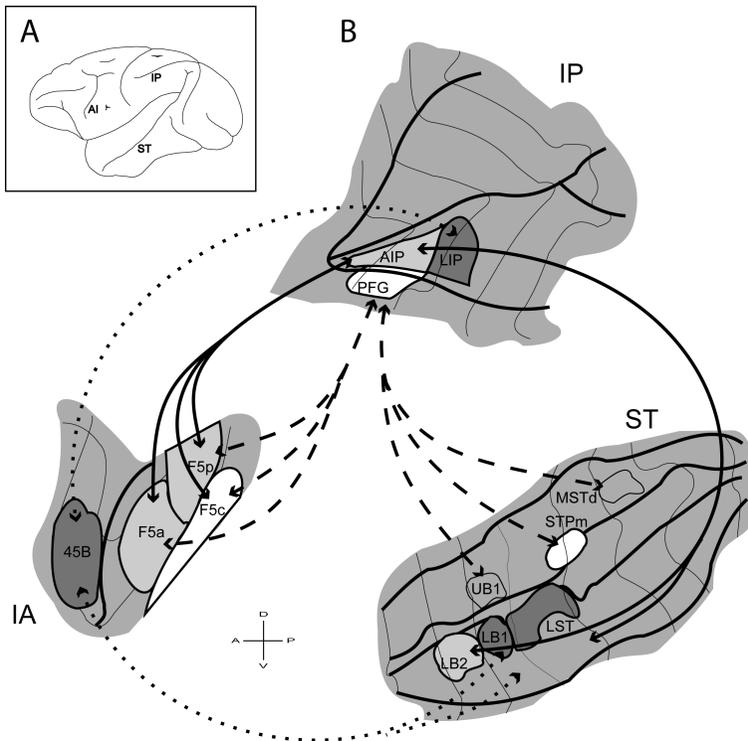
In order to assess which of these STS areas that are active during action observation might send information to the parietal areas involved in coding for grasping, retrograde tracers were injected into areas AIP and PFG. Injections in AIP yielded widespread STS labeling. However, a consistency analysis indicated that the most consistent labeling in all studied monkeys was present only in LB2 and laterally in the inferior temporal cortex near the lip of the STS. Injections in PFG produced consistent labeling in three sectors of the upper bank of the STS: the dorsal medial superior temporal cortex, STPm, and upper bank 1. Note that, of these three sectors, only STPm was consistently active during action observation.

Altogether, these data indicate that two distinct functional pathways might convey action information between the STS, the IPL, and the PMv (Fig. 1.3, dashed and continuous arrows). One pathway links the STPm in the STS with the parietal PFG, which, in turn, projects to F5c; the other pathway connects LB2 with the parietal AIP, which, in turn, is connected to F5a and F5p. Both pathways transmit information necessary for understanding the observed motor act, but each of them seems to provide a different type of information; thus, they may play different roles in the process of understanding the intention underlying a motor act. More specifically, the STPm–PFG–F5c pathway seems concerned with the agent of the motor act, while the LB2–AIP–F5a/p pathway is more concerned with the details of hand grip and object semantics and may aid in understanding motor acts with respect to these factors.

In the same study, a third pathway that linked the prearcuate area 45B with lower bank 1 and LST in the lower bank of the STS and with LIPa in the lateral bank of the intraparietal sulcus was described (Fig. 1.3, dotted arrows). These areas are active during action observation, but mirror neurons have never been recorded in any of them. Note, however, that mirror-like responses for allocating attention to a certain position have been demonstrated in the oculomotor parietal area, the lateral intraparietal cortex (Shepherd et al. 2009). Furthermore, LIPa and 45B are known to be involved in generating and controlling eye movements; thus, the authors suggest that action observation signals could reach the prefrontal area 45B for oculomotor control (Gerbella et al. 2010; Nelissen et al. 2011).

### Possible involvement of the prefrontal cortex in the mirror network

Another area that yielded significant action observation-related fMRI responses in Nelissen et al. (2011) was prefrontal area 46. No electrophysiological data are available at the moment about the possible presence of mirror neurons in this area. However, movement-related activity in the VLPF has previously been described (Tanila et al. 1992; Hoshi et al. 1998). Furthermore, recent connectional studies on the VLPF have shown that specific sectors of ventral area 46 (the rostral part of 46VC) and of area 12 (intermediate 12r) are reciprocally connected with numerous nodes of the mirror pathways described above, including the PMv area F5a, the IPL areas PFG and AIP, and a sector of the ventral bank of the rostral STS sector, and correspond with fMRI sites that are active during action observation. These observations suggest that certain portions of the prefrontal cortex may also be part of the mirror system, although electrophysiological recordings will be necessary to confirm this hypothesis. A possible role of the prefrontal cortex in the mirror system could be to provide the motor representations of the parietal and motor areas with contextual information, thus allowing action understanding when the whole action is not visible (Umiltà et al. 2001), or enabling intention understanding (Fogassi et al. 2005). Furthermore, the prefrontal cortex could play a role in recombining the observed motor acts captured by the mirror system in order to produce an act fitting the observed model, thus allowing imitative learning, as suggested by studies on humans (Buccino et al. 2004; see “Anatomy of the mirror system in humans”). However, further studies are needed in order to verify



**Fig. 1.3** Temporo-parieto-frontal grasping observation networks in the monkey. (A) Lateral view of a macaque brain showing the locations of the three regions involved in action observation: the inferior arcuate sulcus (IAS), the intraparietal sulcus and inferior parietal lobule (IPS/IPL), and the superior temporal sulcus (STS). (B) Flattened representation of the inferior arcuate, intraparietal, and superior temporal sulci; AIP, anterior intraparietal area; F5a, F5 anterior; F5c, F5 convexity; F5p, F5 posterior; FEF, frontal eye fields; FST, fundal area of the superior temporal sulcus; LB1, lower bank 1; LB2, lower bank 2; LIPa, anterior portion of the lateral intraparietal cortex; LST, lower superior temporal region; MSTd, dorsal medial superior temporal cortex; MT, middle temporal cortex; MTp, middle temporal cortex peripheral; STPm, middle part of the superior temporal polysensory area; UB1, upper bank 1; UB2, upper bank 2. Visual information on observed actions can be sent forward from the STS through the parietal cortex to area F5 along two functional pathways: an STPm-PFG-F5c pathway and an LB2-AIP-F5a/p pathway, indicated with dashed and continuous lines, respectively. Area 45B receives parietal input from LIPa and also has direct connections with the lower bank of the STS (dotted lines). The arrows specify the functional pathways. Adapted from Koen Nelissen, Elena Borra, Marzio Gerbella, Stefano Rozzi, Giuseppe Luppino, Wim Vanduffel, Giacomo Rizzolatti, and Guy A. Orban, Action Observation Circuits in the Macaque Monkey Cortex, *The Journal of Neuroscience*, 31 (10), pp. 3743–3756, Figure 13, doi: 10.1523/JNEUROSCI.4803-10.2011 © 2011, The Society for Neuroscience.

this hypothesis and assess the specific contribution of these prefrontal areas, which are classically considered to exert a top-down control on sensory and motor areas, to the mirror system.

## The motor cortex in humans

The data reviewed above show that a multidisciplinary approach based on multimodal architectonic, functional, and connectional techniques has been crucial for describing the network of areas involved in the mirror mechanism and for identifying or hypothesizing about (when insufficient functional data have been available) the functional role of the different pathways forming it. The much lower resolution of the connectional and functional techniques currently available for studies in humans still precludes a detailed description of the organization of the human motor cortex and the human mirror system. However, connectivity studies in humans have suggested that the general connectional features of different premotor regions are similar to those described in monkeys, and brain imaging studies have indicated that motor tasks activate different parietal and frontal areas (Cavina-Pratesi et al. 2010; see Culham and Valyear 2006). Furthermore, noninvasive perturbation studies based on transcranial magnetic stimulation have demonstrated that the parietal cortex (area AIP) is directly involved in motor control in humans as well (Davare et al. 2010), strongly contributing to our current understanding of the functional organization of the motor system in humans. Altogether, these findings are suggestive of a clear homology between the organization of the macaque cortex and that of the human motor cortex.

The general organization of the agranular frontal cortex in humans is very similar to that in the macaque (Bonin and Bailey 1947). In particular, the human motor cortex is also composed of a mosaic of areas; the primary motor cortex is located caudally, mostly buried inside the central sulcus, and the mesial cortical surface consists of two cortical areas: SMA/F3 and the pre-SMA/F6 (see Zilles et al. 1996). Furthermore, in both species the lateral convexity is formed by two main regions: the dorsal premotor region and the ventral premotor region; this observation was recently supported by diffusion tractography data in humans (Tomassini et al. 2007; Schubotz et al. 2010; Mars et al. 2011).

Functionally, the primary motor cortex in humans is also somatotopically organized, with the motor representations for the leg, arm, and face disposed in dorsoventral order in area 4. This map does not extend rostrally into area 6, as described in pioneering macroelectrode surface stimulation studies (Penfield and Welch 1951). Finally, as in the monkey, the various areas forming area 6 are independent functional entities involved in different aspects of sensory-motor transformations and in motor control. Broca's region, generally considered to be formed by architectonic areas 44 and 45, is located rostral to the PMv. While a clear anatomical and functional homology is recognizable between the frontal motor areas of monkeys and humans, such a homology is difficult to draw for Broca's area. Functional data indicate that Broca's region is involved not only in speech but also in communicative actions (Clos et al. 2013), like F5 in monkeys (Ferrari et al. 2003; Coudé

et al. 2011). This prompted the hypothesis that some functions represented in area F5 in monkeys may have moved to the evolutionary new Broca's region in humans. Clos and coworkers (2013), using meta-analytic connectivity-based parcellation, revealed the existence of five functional clusters in area 44. The two posterior clusters are related to action processes, while the three anterior clusters are primarily associated with language and cognition. Notably, their "cluster 4," located in the posterioventral part of area 44, is involved in the observation of hand actions and in action imagery and could be thus part of the human mirror system. From the anatomical point of view, on the basis of receptor–architectonic data, areas 44 and 45 seem to be clustered together with the opercular and ventral premotor areas (Amunts et al. 2010; Amunts and Zilles 2012). Furthermore, Amunts and Zilles (2012) have proposed that the monkey F5a may correspond to the human area 6r1, which is considered to be part of Broca's region. Altogether, these data support the idea that some of the functions of the monkey mirror system were incorporated into Broca's region in humans.

## Anatomy of the mirror system in humans

A large number of experiments using brain imaging techniques in humans have demonstrated a consistent pattern of cortical activity during action observation (see Rizzolatti et al. 2014; also see Chapter 5). In a recent meta-analysis, Caspers and coworkers (2010) analyzed 104 action observation experiments and identified several brain regions that showed consistent activation during action observation (Fig. 1.1B). In particular, these action observation networks encompassed the following areas across both hemispheres symmetrically: Brodmann area 44/45 (located in the frontal cortex), the lateral dorsal premotor cortex, the SMA, the rostral IPL, the primary somatosensory cortex, the superior parietal cortex, the intraparietal cortex, the posterior middle temporal gyrus at the transition to visual area V5, and the fusiform face/fusiform body area.

Interestingly, a large part of this network overlaps with the one described in the monkey; thus, observation of goal-directed motor acts activates areas located in the IPL, the PMv, and the caudal part of the inferior frontal gyrus in humans as well. However, numerous other areas are also activated in humans during action observation. This observation may be due to several factors. First, it is possible that the full extent of the mirror system in the monkey has not yet been mapped. Recent demonstrations of the presence of mirror neurons in additional regions such as the parietal AIP (Pani et al. 2014) support this hypothesis. Second, the mirror system in humans might have expanded into additional cortical areas, probably acquiring new functions. Third, the activation seen during action observation could be independent of the presence of mirror neurons but related to different aspects of visual processing or to motor preparation. All these hypotheses are plausible, but none have been so far empirically tested. An attempt has been made in a recent fMRI study aimed to precisely identify regions activated by both action observation and action execution and thus likely to contain mirror neurons (Gazzola and Keysers 2009). The authors performed a single-subject analysis of unsmoothed fMRI data. They showed that

voxels shared between action observation and action execution were present not only in the classical parieto-premotor circuit but also in the dorsal premotor cortex, the middle cingulate cortex, the somatosensory cortex, the superior parietal cortex, and the middle temporal cortex. The activation of areas outside the classical mirror system could reflect sensory predictions from internal models. Such activation would enrich the information that the mirror mechanism provides about other individuals' actions. This study, however, only infers and does not directly demonstrate the presence of mirror neurons in these areas. Parallel human and monkey fMRI studies on action observation and execution, followed by electrophysiology recordings in the monkey, will be important to investigate the outstanding issues raised above.

Interestingly, the set of areas active during action observation extends beyond the "classical" mirror system when the observation is aimed at producing a novel motor pattern. Buccino and coworkers (2004) specifically investigated the role of the mirror system in imitation learning, using fMRI. In this study, naive participants were asked to observe images depicting the hand of an expert guitarist playing chords and, after a delay, to imitate them. As expected, during action observation the IPL, the PMv, and the pars opercularis of the inferior frontal gyrus were active. Interestingly, during the delay epoch preceding movement execution, in addition to this circuit, prefrontal area 46, which is located in the middle frontal cortex, and the anterior mesial cortex were active. The authors of this study proposed that area 46 could recombine the observed motor acts captured by the mirror system, in order to produce an act fitting the observed model.

## Conclusions

The data reviewed in this chapter provide an updated view of the organization of the monkey motor cortex, using a multidisciplinary anatomical and functional approach. A similar level of detail in the description of the organization of the human motor cortex is currently unavailable, because of the lower resolution of the techniques at hand. However, clear homologies in the organization of the macaque motor cortex and the human motor cortex can be demonstrated. The description of the anatomy of the motor system has proven to be crucial for understanding the neural mechanisms underpinning the cognitive functions deeply embedded in motor organization. In particular, the mirror mechanism, one of the mechanisms considered to be involved in action recognition, relies on potential motor acts that originally evolved for motor behavior and subsequently became the substrate for understanding other individuals. Indeed, such a complex psychological function cannot be carried out by an individual area but results from the specific contribution of several different areas linked together by cortical connections and forming functionally specialized networks. This is true also for the mirror system. In particular, it is clear that specific sets of temporal, parietal, and motor areas contribute to different aspects of the mirror system functions in both monkeys and humans.

Finally, it has been shown that this network extends to other regions, including specific areas of the prefrontal cortex. A deeper investigation of this issue will be crucial for

defining the relationships between the basic mirror circuits and other circuits possibly exerting a top-down control on them.

## References

- Amunts, K., Lenzen, M., Friederici, A. D., Schleicher, A., Morosan, P., Palomero-Gallagher, N., et al. (2010) Broca's region: Novel organizational principles and multiple receptor mapping. *PLoS Biology*, **8**, e1000489.
- Amunts, K., and Zilles, K. (2012) Architecture and organizational principles of Broca's region. *Trends in Cognitive Sciences*, **16**, 418–26.
- Belmalih, A., Borra, E., Contini, M., Gerbella, M., Rozzi, S., and Luppino, G. (2007) A multiarchitectonic approach for the definition of functionally distinct areas and domains in the monkey frontal lobe. *Journal of Anatomy*, **211**, 199–211.
- Belmalih, A., Borra, E., Contini, M., Gerbella, M., Rozzi, S., and Luppino, G. (2009) Multimodal architectonic subdivision of the rostral part (area F5) of the macaque ventral premotor cortex. *Journal of Comparative Neurology*, **512**, 183–217.
- Bonin, G. von, and Bailey, P. (1947) *The Neocortex of Macaca mulatta*. University of Illinois Press, Urbana, IL.
- Bonini, L., Rozzi, S., Serventi, F. U., Simone, L., Ferrari, P. F., and Fogassi, L. (2010) Ventral premotor and inferior parietal cortices make distinct contribution to action organization and intention understanding. *Cerebral Cortex*, **20**, 1372–85.
- Bonini, L., Serventi, F. U., Simone, L., Rozzi, S., Ferrari, P. F., and Fogassi, L. (2011) Grasping neurons of monkey parietal and premotor cortices encode action goals at distinct levels of abstraction during complex action sequences. *Journal of Neuroscience*, **31**, 5876–86.
- Borra, E., Belmalih, A., Calzavara, R., Gerbella, M., Murata, A., Rozzi, S., and Luppino, G. (2008) Cortical connections of the macaque anterior intraparietal (AIP) area. *Cerebral Cortex*, **18**, 1094–111.
- Borra, E., Belmalih, A., Gerbella, M., Rozzi, S., and Luppino, G. (2010) Projections of the hand field of the macaque ventral premotor area F5 to the brainstem and spinal cord. *Journal of Comparative Neurology*, **518**, 2570–91.
- Borra, E., Gerbella, M., Rozzi, S., and Luppino, G. (2011) Anatomical evidence for the involvement of the macaque ventrolateral prefrontal area 12r in controlling goal-directed actions. *Journal of Neuroscience*, **31**, 12351–63.
- Brodmann, K. (1909) *Vergleichende Lokalisationslehre der Großhirnrinde*, Leipzig, Barth.
- Buccino, G., Vogt, S., Ritzl, A., Fink, G. R., Zilles, K., Freund, H. J., et al. (2004) Neural circuits underlying imitation learning of hand actions: An event-related fMRI study. *Neuron*, **42**, 323–34.
- Caminiti, R., Ferraina, S., and Johnson, P. B. (1996) The sources of visual information to the primate frontal lobe: A novel role for the superior parietal lobule. *Cerebral Cortex*, **6**, 319–28.
- Campbell, A. (1905) *Histological Studies on the Localization of Cerebral Function*. Cambridge University Press, Cambridge.
- Carlsson, K., Petrovic, P., Skare, S., Petersson, K. M., and Ingvar, M. (2000) Tickling expectations: Neural processing in anticipation of a sensory stimulus. *Journal of Cognitive Neuroscience*, **12**, 691–703.
- Caspers, S., Zilles, K., Laird, A. R., and Eickhoff, S. B. (2010) ALE meta-analysis of action observation and imitation in the human brain. *NeuroImage*, **50**, 1148–67.
- Cavina-Pratesi, C., Monaco, S., Fattori, P., Galletti, C., McAdam, T. D., Quinlan, D. J., et al. (2010) Functional magnetic resonance imaging reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions in humans. *Journal of Neuroscience*, **30**, 10306–23.

- Clos, M., Amunts, K., Laird, A. R., Fox, P. T., and Eickhoff, S. B. (2013) Tackling the multifunctional nature of Broca's region meta-analytically: Co-activation-based parcellation of area 44. *NeuroImage*, **83**, 174–88.
- Colby, C. L. (1998) Action-oriented spatial reference frames in cortex. *Neuron*, **20**, 15–24.
- Colby, C. L., Duhamel, J.-R., and Goldberg, M. E. (1993) Ventral intraparietal area of the macaque: Anatomic location and visual response properties. *Journal of Neurophysiology*, **69**, 902–14.
- Coudé, G., Ferrari, P. F., Rodà, F., Maranesi, M., Borelli, E., Veroni, V., et al. (2011) Neurons controlling voluntary vocalization in the macaque ventral premotor cortex. *PLoS ONE*, **6**, e26822.
- Culham, J. C., and Valyear, K. F. (2006) Human parietal cortex in action. *Current Opinion in Neurobiology*, **16**, 205–12.
- Davare, M., Rothwell, J. C., and Lemon, R. N. (2010) Causal connectivity between the human anterior intraparietal area and premotor cortex during grasp. *Current Biology*, **20**, 176–81.
- di Pellegrino, G., Fadiga, L., Gallese, V., and Rizzolatti, G. (1992) Understanding motor events: A neurophysiological study. *Experimental Brain Research*, **91**, 176–80.
- Dum, R. P., and Strick, P. L. (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. *Journal of Neuroscience*, **11**, 667–89.
- Ehrsson, H. H., Fagergren, A., Johansson, R. S., and Forssberg, H. (2003) Evidence for the involvement of the posterior parietal cortex in coordination of fingertip forces for grasp stability in manipulation. *Journal of Neurophysiology*, **90**, 2978–86.
- Ferrari, P. F., Gallese, V., Rizzolatti, G., and Fogassi, L. (2003) Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. *European Journal of Neuroscience*, **17**, 1703–14.
- Fogassi, L., Gallese, V., Fadiga, L., Luppino, G., Matelli, M., and Rizzolatti, G. (1996) Coding of peripersonal space in inferior premotor cortex (area F4). *Journal of Neurophysiology*, **76**, 141–57.
- Fogassi, L., Ferrari, P. F., Gesierich, B., Rozzi, S., Chersi, F., and Rizzolatti, G. (2005) Parietal lobe: From action organization to intention understanding. *Science*, **308**, 662–7.
- Fulton, J. (1935) A note on the definition of the “motor” and “premotor” areas. *Brain*, **58**, 311–16.
- Gallese, V., Fadiga, L., Fogassi, L., and Rizzolatti, G. (1996) Action recognition in the premotor cortex. *Brain*, **119**, 593–609.
- Gallese, V., Keysers, C., and Rizzolatti, G. (2004) A unifying view of the basis of social cognition. *Trends in Cognitive Sciences*, **8**, 396–403.
- Gazzola, V., and Keysers, C. (2009) The observation and execution of actions share motor and somatosensory voxels in all tested subjects: Single-subject analyses of unsmoothed fMRI data. *Cerebral Cortex*, **19**, 1239–55.
- Gentilucci, M., Fogassi, L., Luppino, G., Matelli, M., Camarda, R., and Rizzolatti, G. (1988) Functional organization of inferior area 6 in the macaque monkey. I. Somatotopy and the control of proximal movements. *Experimental Brain Research*, **71**, 475–90.
- Gentilucci, M., Daprati, E., Toni, I., Chieffi, S., and Saetti, M. C. (1995) Unconscious updating of grasp motor program. *Experimental Brain Research*, **105**, 291–303.
- Gerbella, M., Belmalih, A., Borra, E., Rozzi, S., and Luppino, G. (2010) Cortical connections of the macaque caudal ventrolateral prefrontal areas 45A and 45B. *Cerebral Cortex*, **20**, 141–68.
- Gerbella, M., Belmalih, A., Borra, E., Rozzi, S., and Luppino, G. (2011) Cortical connections of the anterior (F5a) subdivision of the macaque ventral premotor area F5. *Brain Structure and Function*, **216**, 43–65.
- Gerbella, M., Borra, E., Tonelli, S., Rozzi, S., and Luppino, G. (2013) Connectional heterogeneity of the ventral part of the macaque area 46. *Cerebral Cortex*, **23**, 967–87.
- Geyer, S., Matelli, M., Luppino, G., and Zilles, K. (2000) Functional neuroanatomy of the primate isocortical motor system. *Anatomy and Embryology*, **202**, 443–74.

- He, S. Q., Dum, R. P., and Strick, P. L. (1993) Topographic organization of corticospinal projections from the frontal lobe: Motor areas on the lateral surface of the hemisphere. *Journal of Neuroscience*, **13**, 952–80.
- He, S. Q., Dum, R. P., and Strick, P. L. (1995) Topographic organization of corticospinal projections from the frontal lobe: Motor areas on the medial surface of the hemisphere. *Journal of Neuroscience*, **15**, 3284–306.
- Hepp-Reymond, M. C., Hüsler, E. J., Maier, M. A., and Qi, H. X. (1994) Force-related neuronal activity in two regions of the primate ventral premotor cortex. *Canadian Journal of Physiology and Pharmacology*, **72**, 571–9.
- Hoshi, E., Shima, K., and Tanji, J. (1998) Task-dependent selectivity of movement-related neuronal activity in the primate prefrontal cortex. *Journal of Neurophysiology*, **80**, 3392–7.
- Ishida, H., Nakajima, K., Inase, M., and Murata, A. (2010) Shared mapping of own and others' bodies in visuotactile bimodal area of monkey parietal cortex. *Journal of Cognitive Neuroscience*, **22**, 83–96.
- Jeannerod, M., Arbib, M. A., Rizzolatti, G., and Sakata, H. (1995) Grasping objects: The cortical mechanisms of visuomotor transformation. *Trends in Neurosciences*, **18**, 314–20.
- Keizer, K., and Kuypers, H. G. (1989) Distribution of corticospinal neurons with collaterals to the lower brain stem reticular formation in monkey (*Macaca fascicularis*). *Experimental Brain Research*, **74**, 311–18.
- Keller, G. B., and Hahnloser, R. H. R. (2009) Neural processing of auditory feedback during vocal practice in a songbird. *Nature*, **457**, 187–90.
- Kohler, E., Keysers, C., Umiltà, M. A., Fogassi, L., Gallese, V., and Rizzolatti, G. (2002) Hearing sounds, understanding actions: Action representation in mirror neurons. *Science*, **297**, 846–8.
- Kraskov, A., Dancause, N., Quallo, M. M., Shepherd, S., and Lemon, R. N. (2009) Corticospinal neurons in macaque ventral premotor cortex with mirror properties: A potential mechanism for action suppression? *Neuron*, **64**, 922–30.
- Kurata, K., and Tanji, J. (1986) Premotor cortex neurons in macaques: Activity before distal and proximal forelimb movements. *Journal of Neuroscience*, **6**, 403–11.
- Lemus, L., Hernández, A., and Romo, R. (2009) Neural encoding of auditory discrimination in ventral premotor cortex. *Proceedings of the National Academy of Sciences of the United States of America*, **106**, 14640–5.
- Lu, M. T., Preston, J. B., and Strick, P. L. (1994) Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. *Journal of Comparative Neurology*, **341**, 375–92.
- Luppino, G., Matelli, M., Camarda, R., and Rizzolatti, G. (1993) Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *Journal of Comparative Neurology*, **338**, 114–40.
- Luppino, G., Murata, A., Govoni, P., and Matelli, M. (1999) Largely segregated parietofrontal connections linking rostral intraparietal cortex (areas AIP and VIP) and the ventral premotor cortex (areas F5 and F4). *Experimental Brain Research*, **128**, 181–7.
- Maranesi, M., Rodà, F., Bonini, L., Rozzi, S., Ferrari, P. F., Fogassi, L., et al. (2012) Anatomic-functional organization of the ventral primary motor and premotor cortex in the macaque monkey. *European Journal of Neuroscience*, **36**, 3376–87.
- Mars, R. B., Jbabdi, S., Sallet, J., O'Reilly, J. X., Croxson, P. L., Olivier, E., et al. (2011) Diffusion-weighted imaging tractography-based parcellation of the human parietal cortex and comparison with human and macaque resting-state functional connectivity. *Journal of Neuroscience*, **31**, 4087–4100.
- Matelli, M., Luppino, G., and Rizzolatti, G. (1985) Patterns of cytochrome oxidase activity in the frontal agranular cortex of the macaque monkey. *Behavioural Brain Research*, **18**, 125–36.

- Matelli, M., Luppino, G., and Rizzolatti, G. (1991) Architecture of superior and mesial area 6 and the adjacent cingulate cortex in the macaque monkey. *Journal of Comparative Neurology*, **311**, 445–62.
- Morecraft, R. J., Louie, J. L., Herrick, J. L., and Stilwell-Morecraft, K. S. (2001) Cortical innervation of the facial nucleus in the non-human primate: A new interpretation of the effects of stroke and related subtotal brain trauma on the muscles of facial expression. *Brain*, **124**, 176–208.
- Murata, A., Fadiga, L., Fogassi, L., Gallese, V., Raos, V., and Rizzolatti, G. (1997) Object representation in the ventral premotor cortex (area F5) of the monkey. *Journal of Neurophysiology*, **78**, 2226–30.
- Murata, A., Gallese, V., Luppino, G., Kaseda, M., and Sakata, H. (2000) Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. *Journal of Neurophysiology*, **83**, 2580–601.
- Nelissen, K., Luppino, G., Vanduffel, W., Rizzolatti, G., and Orban, G. A. (2005) Observing others: Multiple action representation in the frontal lobe. *Science*, **310**, 332–6.
- Nelissen, K., Borra, E., Gerbella, M., Rozzi, S., Luppino, G., Vanduffel, W., et al. (2011) Action observation circuits in the macaque monkey cortex. *Journal of Neuroscience*, **31**, 3743–56.
- Pani, P., Theys, T., Romero, M. C., and Janssen, P. (2014) Grasping execution and grasping observation activity of single neurons in the macaque anterior intraparietal area. *Journal of Cognitive Neuroscience*, **26**, 2342–55.
- Pardo-Vazquez, J. L., Leboran, V., and Acuña, C. (2008) Neural correlates of decisions and their outcomes in the ventral premotor cortex. *Journal of Neuroscience*, **28**, 12396–408.
- Pardo-Vazquez, J. L., Leboran, V., and Acuña, C. (2009) A role for the ventral premotor cortex beyond performance monitoring. *Proceedings of the National Academy of Sciences of the United States of America*, **106**, 18815–19.
- Penfield, W., and Welch, K. (1951) The supplementary motor area of the cerebral cortex: A clinical and experimental study. *Archives of Neurology and Psychiatry*, **66**, 289–317.
- Prather, J. F., Peters, S., Nowicki, S., and Mooney, R. (2008) Precise auditory-vocal mirroring in neurons for learned vocal communication. *Nature*, **451**, 305–10.
- Raos, V., Umiltà, M. A., Murata, A., Fogassi, L., and Gallese, V. (2006) Functional properties of grasping-related neurons in the ventral premotor area F5 of the macaque monkey. *Journal of Neurophysiology*, **95**, 709–29.
- Reed, C. L., Shoham, S., and Halgren, E. (2004) Neural substrates of tactile object recognition: An fMRI study. *Human Brain Mapping*, **21**, 236–46.
- Rizzolatti, G., Camarda, R., Fogassi, L., Gentilucci, M., Luppino, G., and Matelli, M. (1988) Functional organization of inferior area 6 in the macaque monkey. II. Area F5 and the control of distal movements. *Experimental Brain Research*, **71**, 491–507.
- Rizzolatti, G., Gentilucci, M., Camarda, R. M., Gallese, V., Luppino, G., Matelli, M., et al. (1990) Neurons related to reaching-grasping arm movements in the rostral part of area 6 (area 6a beta). *Experimental Brain Research*, **82**, 337–50.
- Rizzolatti, G., Gentilucci, M., Camarda, R. M., Gallese, V., Luppino, G., Matelli, M., and Fogassi, L. (1996) Premotor cortex and the recognition of motor actions. *Cognitive Brain Research*, **3**, 131–41.
- Rizzolatti, G., Cattaneo, L., Fabbri-Destro, M., and Rozzi, S. (2014) Cortical mechanisms underlying the organization of goal-directed actions and mirror neuron-based action understanding. *Physiological Reviews*, **94**, 655–706.
- Rizzolatti, G., and Fogassi, L. (2014) The mirror mechanism: Recent findings and perspectives. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, **369**, 20130420.
- Rizzolatti, G., Fogassi, L., and Gallese, V. (1997) Parietal cortex: From sight to action. *Current Opinion in Neurobiology*, **7**, 562–7.

- Rizzolatti, G., and Luppino, G. (2001) The cortical motor system. *Neuron*, **31**, 889–901.
- Rizzolatti, G., Luppino, G., and Matelli, M. (1998) The organization of the cortical motor system: New concepts. *Electroencephalography and Clinical Neurophysiology*, **106**, 283–96.
- Rizzolatti, G., and Matelli, M. (2003) Two different streams form the dorsal visual system: Anatomy and functions. *Experimental Brain Research*, **153**, 146–57.
- Rizzolatti, G., and Sinigaglia, C. (2010) The functional role of the parieto-frontal mirror circuit: Interpretations and misinterpretations. *Nature Reviews Neuroscience*, **11**, 264–74.
- Romo, R., Hernández, A., and Zainos, A. (2004) Neuronal correlates of a perceptual decision in ventral premotor cortex. *Neuron*, **41**, 165–73.
- Rozzi, S., Ferrari, P. F., Bonini, L., Rizzolatti, G., and Fogassi, L. (2008) Functional organization of inferior parietal lobule convexity in the macaque monkey: Electrophysiological characterization of motor, sensory and mirror responses and their correlation with cytoarchitectonic areas. *European Journal of Neuroscience*, **28**, 1569–88.
- Sakata, H., Taira, M., Murata, A., and Mine, S. (1995) Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. *Cerebral Cortex*, **5**, 429–38.
- Schubotz, R. I., Anwander, A., Knösche, T. R., Cramon, D. Y. von, and Tittgemeyer, M. (2010) Anatomical and functional parcellation of the human lateral premotor cortex. *NeuroImage*, **50**, 396–408.
- Shepherd, S. V., Klein, J. T., Deaner, R. O., and Platt, M. L. (2009) Mirroring of attention by neurons in macaque parietal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, **106**, 9489–94.
- Singer, T., Seymour, B., O’Doherty, J., Kaube, H., Dolan, R. J., and Frith, C. D. (2004) Empathy for pain involves the affective but not sensory components of pain. *Science*, **303**, 1157–62.
- Tanila, H., Carlson, S., Linnankoski, I., Lindroos, F., and Kahila, H. (1992) Functional properties of dorsolateral prefrontal cortical neurons in awake monkey. *Behavioural Brain Research*, **47**, 169–80.
- Tomassini, V., Jbabdi, S., Klein, J. C., Behrens, T. E., Pozzilli, C., Matthews, P. M., et al. (2007) Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. *Journal of Neuroscience*, **27**, 10259–69.
- Umiltà, M. A., Kohler, E., Gallese, V., Fogassi, L., Fadiga, L., Keysers, C., et al. (2001) I know what you are doing: A neurophysiological study. *Neuron*, **31**, 155–65.
- Umiltà, M., Escola, L., Intskirveli, I., Grammont, F., Rochat, M., Caruana, F., et al. (2008) When pliers become fingers in the monkey motor system. *Proceedings of the National Academy of Sciences of the United States of America*, **105**, 2209–13.
- Vigneswaran, G., Philipp, R., Lemon, R. N., and Kraskov, A. (2013) M1 corticospinal mirror neurons and their role in movement suppression during action observation. *Current Biology*, **23**, 236–43.
- Vogt, C., and Vogt, O. (1919) Allgemeinere Ergebnisse unserer Hirnforschung. *Journal für Psychologie und Neurologie*, **25**, 279–461.
- Woolsey, C., Settlage, P. H., Meyer, D. R., Sencer, W., Pinto Hamuy, T., and Travis, A. M. (1952) Patterns of localization in precentral and “supplementary” motor areas and their relation to the concept of a premotor area. *Research Publications of the Association for Research in Nervous and Mental Disease*, **30**, 238–64.
- Zilles, K., Schlaug, G., Geyer, S., Luppino, G., Matelli, M., Qü, M., et al. (1996) Anatomy and transmitter receptors of the supplementary motor areas in the human and nonhuman primate brain. *Advances in Neurology*, **70**, 29–43.

# The role of mirror neurons in goal coding and intention understanding

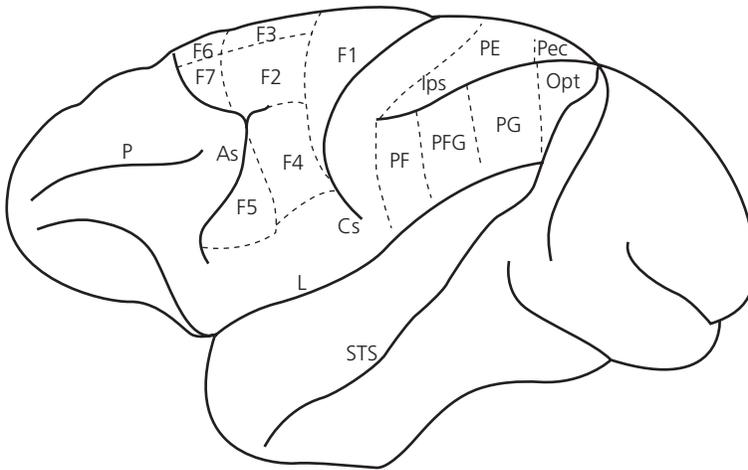
Leonardo Fogassi and Luca Bonini

### Introduction

One of the most debated issues prompted by the discovery of mirror neurons concerns whether their response properties can account for specific cognitive functions or whether their activation is simply the byproduct of top-down effects exerted on motor areas by higher-order “cognitive” cortical regions. For example, according to some authors (see Csibra 2007; Csibra and Gergely 2007), the understanding of others’ actions and intentions is achieved outside the motor system, and action mirroring is the consequence, rather than the cause, of these sociocognitive functions. This debate is fueled by the persistence of the traditional view, which considers cognitive functions to be the result of higher-order processes independent from the mechanisms and circuits of the motor system. Furthermore, the widely accepted relationship between high-order cognitive capacities and language in humans further emphasizes the dichotomy between cognition and action.

However, in the last 30 years there has been a radical change in the conceptualization of the organization and function of the cortical motor system. Novel neuroanatomical data have been reported in the monkey, leading to the idea of an extended motor system that includes parietal regions as well as frontal motor areas (see Fig. 2.1). In addition, functional studies have led to a deeper understanding of the neuronal mechanisms operating within these circuits. Altogether, these findings have prompted new theoretical views on the role and relevance of the motor system in perceptual and cognitive functions.

One of these views focuses on the idea that “goals” (Rizzolatti et al. 1988) are the major operating code used by the motor system. Previous scholars (see Bernstein 1996) defined actions as “whole sequences of movements that together solve a motor problem [...] and all the movements parts of such a chain are related to each other by the meaning of the problem.” In this definition “motor problem” clearly refers to what we usually identify with the concept of motor goal; but, since even very simple discrete movements such as arm reaches, saccades, or the extension/flexion of a finger can be considered as being goal directed depending on the situation (see Bonini et al. 2013), it is clear that a hierarchy of goals, rather than a single level of goal coding, does exist. Accepting this idea, it is possible to exploit the concept of goal to explain the functional relevance of the reciprocal connections between the nodes of the cortical motor system, in which a store of different goals



**Fig. 2.1** Lateral view of the monkey brain, showing the subdivisions of the agranular frontal and posterior parietal cortices. Agranular frontal areas have been labeled according to Matelli et al. (1985, 1991). Posterior parietal areas are defined according to Pandya and Seltzer (1982) and Gregoriou et al. (2006). Abbreviations: As, arcuate sulcus; Cs, central sulcus; Ips, intraparietal sulcus; L, lateral sulcus; P, principal sulcus; STS, superior temporal sulcus. Data from M. Matelli, G. Luppino, and G. Rizzolatti, Patterns of cytochrome oxidase activity in the frontal agranular cortex of the macaque monkey. *Behavioral Brain Research* 18, p. 125–136, 1985, M. Matelli, G. Luppino, and G. Rizzolatti, Architecture of superior and mesial area 6 and the adjacent cingulate cortex in the macaque monkey, *Journal of Comparative Neurology*, 311, p. 445–462, 1991, D. N. Pandya and B. Seltzer, Intrinsic connections and architectonics of posterior parietal cortex in the rhesus monkey, *Journal of Comparative Neurology*, 204, p. 196–210, 1982, and G. G. Gregoriou, E. Borra, M. Matelli, and G. Luppino, Architectonic organization of the inferior parietal convexity of the macaque monkey, *Journal of Comparative Neurology*, 496, p. 422–451, 2006.

is available both for the organization of one's own intentional actions and for the understanding of other's behavior.

In the present chapter, we will try initially to clarify the relevance of the concept of goal for understanding the anatomo-functional organization of the cortical motor system. Then, we will apply this concept to the interpretation of the properties of mirror neurons present in several cortical motor areas. We will show that higher levels of goal representation in some regions of the “extended” cortical motor system can underlie the organization of one's own intentional actions, as well as the decoding of others' intentions.

## The motor system and the concept of goal

There is no doubt that all animals endowed with a nervous system, even those that possess only a few dozens of neurons, can express active movements to reach specific objectives or to avoid potentially dangerous stimuli (Llinas 2002). Of course, as the achievement of specific objectives occurs through the interaction with the external environment, the

organism needs good neural control of its movements as well as some kind of sensory–motor transformation, in order to flexibly adapt its behavior to environmental changes.

It has been thought for a long time that this latter capacity mainly relies on a unidirectional information flow, from sensory to motor brain structures; consequently, the idea that the achievement of an organism's own motor objectives is one of the most crucial tasks it has to deal with, has been neglected. As a consequence, the evolution and implementation of cognitive properties by a nervous system was mainly conceived as being the result of sensory processing. This view was in line with the observation that perceptual deficits appeared following damage to posterior brain areas, which were considered responsible for high-level sensory processing and multimodal association. Indeed, in agreement with the two-visual-pathways model proposed by Ungerleider and Mishkin (1982), patients with lesions in the ventral pathway (occipito-inferotemporal cortex) showed impaired object recognition capacities, being unable to identify “what” an object was, while those with posterior parietal lesions showed essentially spatial deficits, being unable to localize “where” objects were located. In this model, the “visual” brain was conceived as being completely segregated from the “motor” brain. Goodale and Milner (1992) re-conceptualized the two-pathway model but retained a dichotomy between “vision for perception” and “vision for action.” This picture changes significantly, however, if one recognizes the leading role of the motor system in many aspects of cortical processing, well beyond its purely motor functions. This is certainly not to downplay the relevance of this system in movement control and execution. Instead, it makes it possible to investigate the issue of which functions stem from the organization of the cortical motor system.

Until the 1980s, it was believed that goal coding was a property of higher-order (called associative) cortical areas, while the command and implementation of the motor synergies necessary to achieve a given goal was carried out by the motor system. After the 1980s, however, there was a radical change in the way of looking at cortical information processing, mainly because of the discoveries and advances from different areas of neuroscience.

The first contribution was derived from neuroanatomy. In particular, with the introduction of new tracing and anatomical methods, scientists could discern whether a projection was a feed-forward or feed-back one, depending on the source and termination of the fibers (Felleman and Van Essen 1991). Nevertheless, most anatomical studies showed that cortical circuits are formed by reciprocally connected regions that play mutual roles in similar functions. A classic example of this integration is the one between sensory and motor information, assuming that the former comes from posterior cortical areas and the latter from anterior ones.

The second contribution came from neurophysiology. After the classical single-neuron studies demonstrating that motor neuron discharge encodes movement parameters such as force (Evarts 1968) or direction (Georgopoulos et al. 1982), many studies demonstrated that single neurons in premotor (and, although to a lesser extent, primary motor) cortex can discharge largely independently of actual movement execution (Alexander and Crutcher 1990; Kakei et al. 2001). In other words, their activation provides the representation of a potential motor goal triggered by a stimulus in the environment, even when that

goal does not necessarily need to be attained through the organization of an appropriate (overt) motor action. The properties of premotor neurons have been widely described in previous reviews (see, e.g., Rizzolatti et al. 2000, 2014), and the most important hallmark feature of most neurons in the premotor cortex appears to be the encoding of the goal of motor acts. For example, neurons in the monkey ventral premotor area F5 (see Fig. 2.1) discharge during grasping of a piece of food, independently of whether this act is executed with the hand, with the mouth (Rizzolatti et al. 1988), or even with a tool the monkey has been trained to use in place of the hand for grasping (Umiltà et al. 2008). Similarly, neurons in the ventral premotor area F4 can discharge during arm extension, but only if this act is performed for reaching and grasping an object, not when it is used to push away an obstacle (Rizzolatti et al. 1988). Neurons in the dorsal premotor cortex share similar properties in terms of goal coding: for example, they can code a space location independently of the arm used to reach it (Hoshi and Tanji 2000). Interestingly, although goal coding appears to be a typical property of premotor neurons, it has been ascribed also to some neurons of the primary motor cortex (Alexander and Crutcher 1990; Umiltà et al. 2008).

Anatomo-functional studies of inferior parietal areas (see Rozzi et al. 2008), which are strongly and reciprocally connected with the ventral premotor cortex (Rozzi et al. 2006), showed that goal coding is a widespread feature of the neurons belonging to the extended cortical motor system. In particular, it has been shown that the whole inferior parietal lobule (see Fig. 2.1) contains neurons with motor properties, which are organized in a gross somatotopic arrangement, with mouth motor acts represented in the rostralmost part of the lobule, mainly in area PF, while hand and arm motor acts are represented in areas PFG and PG, respectively, and all these neurons mainly code the goal of motor acts, rather than simple movements. Taken together, these findings support the view that the motor system is constituted not only by areas of the agranular frontal cortex but also by parietal regions anatomically connected with the frontal ones (Rizzolatti and Luppino 2001). The main task of this “extended” motor system is that of coding the goal of motor acts and thus providing an articulated set of motor representations that constitute the individual’s motor repertoire. Crucially, representing motor acts in terms of “potential” motor goals, that is, independently of whether and how they are actually turned into action, makes it possible to easily activate these motor representations not only when an individual needs to act but also when the representation of this act is elicited by stimuli of the outside world, such as during the observation of graspable objects (Murata et al. 1997) or of another individual’s motor acts (Gallese et al. 1996).

## Mirror neurons and goal coding

In order to interpret what mirror neurons are coding when they activate during the observation of others’ actions, a reasonable approach appears to be that of starting from the general coding properties of the areas where they have been found. Indeed, studies on ventral premotor cortex performed in parallel to those describing mirror neurons showed that a motor representation of reaching could be activated even when the monkey remained still; such studies indicate

that a pragmatic meaning can be attributed to the location of objects in the peripersonal (reachable) space (Fogassi et al. 1992, 1996; Rizzolatti et al. 1997). In addition, a motor representation of grasping can be activated, in the absence of any monkey active movement, by the so-called canonical neurons, which encode the potential grip types afforded by a visually presented (graspable) object (Murata et al. 1997). Specific parieto-premotor circuits subserve the sensory-motor transformations required to exploit motor representations for these perceptual and motor functions (Rizzolatti et al. 1998; Rizzolatti and Luppino 2001), and a similar mechanism is very likely at the basis of mirror neuron responses, the main difference being the type of visual stimulus activating them.

Besides activating when the monkey performs a certain hand or mouth motor act, mirror neurons also respond to the observation of the same act performed by another individual (Gallese et al. 1996; Rizzolatti et al. 1996). The importance of mirror neurons is not simply related to their complex and unexpected visual response: after all, neurons with similar visual properties had been previously described in other brain regions such as the superior temporal sulcus (Perrett et al. 1989; Jellema et al. 2000). The crucial issue, which offers a more intriguing interpretation of their properties, is the presence of a motor response, as well as the type of sensorimotor transformation they operate. Like the other cells in the ventral premotor cortex, mirror neurons are basically motor neurons: they represent specific goals and can generate the representation of a goal even when the monkey does not move but simply observes another agent moving to reach that goal. On this basis, it has been proposed that the activation of one's own motor representations during the observation of other's action endows the observer with a peculiar form of understanding of that action, that is, "from the inside" (Rizzolatti and Sinigaglia 2010). Two studies on the properties of ventral premotor mirror neurons clearly demonstrate this point.

In the first study, mirror neuron responses were recorded while the monkey observed grasping motor acts performed by an experimenter, but in one condition the final part of the grasping act, that is, the hand-object interaction, occurred behind an opaque screen and was thus not visible to the monkey (Umiltà et al. 2001). The results of this study showed that mirror neurons could still code the invisible grasping, provided that the monkey was aware of the presence of a target object behind the screen. Indeed, when no object was present, they did not fire during mimicked actions, even if the available visual information was exactly the same as in the hidden action condition. This response can be thus considered as a "mental operation," since it is possible only by retrieving a representation of the target object from memory and by internally reconstructing the hidden motor act on the basis of its stored motor representation. The second study showed that a subset of mirror neurons, called "audiovisual" mirror neurons, respond not only to the execution and observation of a motor act, such as peanut breaking or paper ripping, but also to the sound of that motor act (Kohler et al. 2002). This type of activation is conceivable only by accepting that the representation of a specific motor goal can be accessed and retrieved by multiple sensory modalities. In addition, two separate investigations showed that mirror neurons can respond to the observation of motor acts performed with tools known to the observing monkey (Ferrari et al. 2005; Umiltà et al. 2008); these results suggest that

the crucial factor for mirror neuron visual response is the match between the goal of the observed act, regardless of how it is attained, and the goal represented motorically by the same neuron.

As mentioned above, the match between visual representations of observed motor acts (in visual areas) and their motor representation (in the observer's premotor cortex) is likely based on a mechanism very similar to the one proposed for canonical and peripersonal neurons. Indeed, canonical and mirror neurons are indistinguishable from the motor point of view: in both types of neurons, the representation of a motor goal constitutes the content to which two different sets of visual stimuli, that is, the observed objects and the others' actions, are matched. Although the two classes of neurons are clearly distinguished on the basis of the visual input to which they respond, a recent study in which neurons in area F5 were tested during action execution, object presentation, and action observation showed that a further category of neurons, called "canonical-mirror" neurons, does exist. Canonical-mirror neurons exhibit the interesting property of encoding both observed objects, when they are presented within the monkey's peripersonal space, and others' observed actions (Bonini et al. 2014a). The existence of these neurons indicates that the previously hypothesized categorical segregation of different types of neurons (canonical and mirror) was at least too rigid. In addition, it constitutes a further demonstration of the importance of representing movement in terms of goals for attributing meaning to different types of visual information. In other words, a motor representation of grasping can be recruited both when perceiving a grasping act done by another agent and when perceiving the "graspability" of an object presented in the observer's peripersonal space.

Altogether, these studies support the idea that, by describing observed motor events in terms of the very same motor goals associated with the observer's own actions, mirror neurons play a crucial role in action understanding. Thus, these studies provide a clear example of how a cognitive function can emerge from motor organization. A recent study extended this view (Bonini et al. 2014b). In this study, monkeys were trained to perform a go/no-go grasping task, requiring them to do ("action" condition) or to refrain from doing ("inaction" condition) grasping/pulling actions on different target objects as well as to observe the same action and inaction conditions performed by an experimenter. The most interesting result of this experiment was that, while all the neurons recorded from the ventral premotor area F5 responded during the action condition, almost 16% of them also responded during the inaction condition. However, the great majority responded when either the monkey or the experimenter refrained from grasping, and not in both cases. This finding clearly indicates that specific representations of our own or another's action can be recruited not only when we perform or observe that action but also when we need to represent its negation. Thus, it seems reasonable to conclude that at least some ventral premotor neurons encode representations of grasping at a "conceptual" level, thus allowing such representations to be used both when the monkey actively grasps or observes another agent grasping an object and when it intentionally refrains from grasping or observes another agent refraining from doing so.