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The macaque lateral grasping network: A neural substrate for generating purposeful hand actions.

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Abstract

In primates, neural mechanisms for controlling skilled hand actions primarily rely on sensorimotor transformations. These transformations are mediated by circuits linking specific inferior parietal with ventral premotor areas in which sensory coding of objects' features automatically trigger appropriate hand motor programs. Recently, connectional studies in macaques showed that these parietal and premotor areas are nodes of a large-scale cortical network, designated as "lateral grasping network," including specific temporal and prefrontal sectors involved in object recognition and executive functions, respectively. These data extend grasping models so far proposed in providing a possible substrate for interfacing perceptual, cognitive, and hand-related sensorimotor processes for controlling hand actions based on object identity, goals, and memory-based or contextual information and for the contribution of motor signals to cognitive motor functions. Human studies provided evidence for a possible counterpart of the macaque lateral grasping network, suggesting that in primate evolution the neural mechanisms for controlling hand actions described in the macaque have been retained and exploited for the emergence of human-specific motor and cognitive motor capacities.

Keywords	Sensorimotor transformations; Executive functions; Motor control; Hand-object interactions; Affordances extraction; Parieto-frontal circuits; Ventral visual stream; Prefrontal cortex
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Suggested reviewers	Roger Lemon, Eiji Hoshi, Marc Schieber, Eric Rouiller

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Dear Dr. Chamberlain,

We are herewith submitting a revised version of the manuscript NEUBIOREV_2016_514 "The macaque lateral grasping network: a neural substrate for generating purposeful hand actions" for publication in Neuroscience & Biobehavioral Reviews.

We have been very pleased that the Reviewers liked our manuscript. All their comments and suggestions have been welcomed and accommodated in revising the manuscript. We found them very helpful for improving the coverage of the topic of the present review and for highlighting some aspects that were underestimated in the previous version. The manuscript has been also checked for typographical errors and has been revised by a professional company for editing and proofreading.

In the Responses to Reviewer section, we describe in details the way in which we have responded to the comments of the referees.

We hope that, after these revisions, the present manuscript can be considered acceptable for publication in Neuroscience & Biobehavioral Reviews.

Sincerely yours,

Giuseppe Luppino

We sincerely thank the Reviewers for taking their time in reviewing our manuscript and for their positive comments. Their comments and suggestions have been very helpful for improving the coverage of the topic of the present review and for highlighting some aspects that were underestimated in the previous version.

The following is the detailed description of the way in which the comments of the Reviewers have been addressed.

Reviewer #2:

Comment

P5 para 1. I think this para reads as if the authors are of the opinion that the sole function of M1 is in the execution of actions processed through the lateral network. I think this impression needs to be corrected. We know, for example, that it is possible to dissociate motor cortex activity from muscle activity (Fetz, Schieber) and that motor imagery/motor rehearsal can activate M1 without any sign of motor execution, that M1 in macaques can host mirror neurons, all suggesting that M1 does more than act as the executive.

Response

We fully agree on the notion that the primate M1 is not just involved in controlling movements execution and we acknowledge that in the original version of the manuscript we could have given the impression that this was our opinion. Thus, we have added a paragraph (page 5, third para) in which we have noted that "….F1 is not just an essential step of the output of the lateral grasping network and might have a role in motor control more complex than the emission of signals driving muscles activity" and briefly reviewed experimental evidence supporting this statement.

Comment

P6 bottom of para 2. In the macaque, stimulation of PMv with single shocks rarely evokes motor responses in hand muscles, but can modulate responses evoked from M1. This may be different in humans, since direct electrical stimulation of the ventrolateral division of PMv in human patients undergoing awake mapping prior to tumour surgery do show such motor responses, although these are all significantly delayed compared to those evoked from M1 (see Fornia et al Cerebral Cortex 2016).

Response

We thank the Reviewer for highlighting this very recent and interesting study. The results of this study and their relevance to the issue of the possible homologies between the human and the macaque PMv have been mentioned in Section 5.1 (Page 23). Data from electrical stimulation of the cortical surface, as those of Fornia et al., are difficult to compare with data from intracortical microstimulation, as those from macaque studies, in terms of cortical excitability. However, in the context of our review article, it is interesting noting that Fornia et al have suggested that, as for the macaque F5p, the dorsal hand sector of the human PMv could act via a slower and possibly more indirect route to the spinal cord than M1, either through connections to M1 or through corticospinal projections.

Comment

P7 para 2 Is it not true that the distinction between 'canonical' and 'mirror' neurons in F5 is no longer considered to be absolute? (Bonini)

Response

Actually, Bonini et al (2014) have described a third class of visuomotor F5 neurons, which activate during the observation of either objects or actions and were referred to as "canonical-mirror neurons". In revising the manuscript, we have expanded in Section 2.3 (page 8, second and third para) the description of the various classes of visuomotor F5 neurons and of their distribution in the various subdivisions of this area.

Comment

P12 para 2. I could not understand the phrase "……not only how an object is made…to …action is". This needs to be rewritten…do the authors mean how the grasp of the object is made?

Response

This sentence has been rewritten

Comment

P12 para 2. For me a key feature of activity in the IT areas is that neurons there do not respond during execution of self-movement. I think that is still correct? Could the authors make that explicit in this section?

Response

This issue has been addressed in Section 2.4 (page 13). Specifically, we have noted that there is no evidence for modulation of IT neurons by hand motor signals, though it, to our knowledge, has never been explicitly investigated.

Comment

P18 para 3. Please give some idea of what is meant by 'relatively fast' at the bottom of p18.
P19 top. Likewise what does 'slightly slower' mean in terms of actual time?

Response

In Section 2.4 (page 13), we have indicated the latencies of the visual responses of 3D selective AIP and IT neurons. Then, in Section 3 (page 20), the text has been modified in order to clarify the timing of the various inputs to AIP.

Comment

P19/20. The overriding impression here is that this network is largely driven by online sensory information, entering the network at different nodes through different pathways. However, there seems to be little mention of the fact that in many cases most of the drive may come from internal models of intended action. Of course, these models have been constructed over time with the help of sensory information about objects etc, but it is surely the case that much of the immediate sensory input is needed to recruit these models rather than provide moment-to-moment guidance of the action? Could this be made clearer?

Response

We fully agree with the reviewer. In Section 3 (page 19) we have revised the description of the model in order to make more explicit that visuomotor transformations for grasping actually consist in recruitment of internal motor representations for feedforward control of grasping. The same network could also take care of monitoring and, if needed, adjusting movement execution based on sensory feedback.

Comment

P22 para 2. "…….area 44…is involved in both hand action execution and observation" but the authors should cite Cerri et al (2014, Human Brain Mapping) which reports that Broca does not respond to action observation and evokes no motor output in either hand or phonoarticulatory muscles.

Response

This negative result has been mentioned in the text (Section 5.1, page 24).

Reviewer #3:

Comment

In section 2.2 the authors focus on area F5p, concluding with their thoughts on its role. What about F5a and F5c? Although F5a is mentioned repeatedly after this point, F5c is not. It would be useful to add a paragraph or two at this point comparing and contrasting the roles of F5a and F5c with that of F5p

Response

This section has been revised (Section 2.2, page 5) in order to describe more in detail the somatotopy and the characterizing connectional features of the various F5 subdivisions.

Minor comments:

The manuscript would benefit from careful proofreading by a native English speaker, ideally someone familiar with this material because identifying some of the errors will be beyond the standard grammar check. Here are just a few examples:

Page 3--"outmost" probably should be "utmost"

Page 11--"Specifically, this visual pathway, as a whole, is a "vision for action" pathway involved in visuomotor transformations, meant as a fast, automatic, and unconscious process carried out independently from perceptual processes, considered as an exclusive province of the occipito-temporal "ventral visual stream".

probably should be something like:

"Specifically, this visual pathway, as a whole, is a "vision for action" pathway involved in visuomotor transformations, meant as a fast, automatic, and unconscious process carried out independently from perceptual processes that are considered to be the exclusive province of the occipito-temporal "ventral visual stream"."

Page 12--"is broadcasted" should be "is broadcast"

Response

The manuscript has been revised for proofreading by a professional specialized company

The macaque lateral grasping network: a neural substrate for generating purposeful hand actions

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Abstract

In primates, neural mechanisms for controlling skilled hand actions primarily rely on sensorimotor transformations. These transformations are mediated by circuits linking specific inferior parietal with ventral premotor areas in which sensory coding of objects' features automatically trigger appropriate hand motor programs. Recently, connectional studies in macaques showed that these parietal and premotor areas are nodes of a large-scale cortical network, designated as "*lateral grasping network,*" including specific temporal and prefrontal sectors involved in object recognition and executive functions, respectively. These data extend grasping models so far proposed in providing a possible substrate for interfacing perceptual, cognitive, and hand-related sensorimotor processes for controlling hand actions based on object identity, goals, and memory-based or contextual information and for the contribution of motor signals to cognitive motor functions. Human studies provided evidence for a possible counterpart of the macaque *lateral grasping network,* suggesting that in primate evolution the neural mechanisms for controlling hand actions described in the macaque have been retained and exploited for the emergence of human-specific motor and cognitive motor capacities.

1. Introduction

In our everyday lives, we routinely interact with different objects in several different ways and for different purposes, thanks to highly evolved neural mechanisms enabling us to generate–in a remarkably fast, effortless, and reliable way–hand actions appropriate to behavioral goals, an object's properties, and external contingencies. A full description of these mechanisms and the underpinning neural substrate is still today a major issue in integrative neuroscience, of utmost relevance also for supporting theoretically sound, research-based clinical practices and the relatively recently developed fields of neuroprosthetics and brain-machine interfaces.

In the last two to three decades, research carried out mostly in non-human primates has clearly pointed out that cortical control of motor behavior primarily relies on integration of sensory with motor information, mediated by strong and reciprocal connections linking agranular frontal (motor and premotor) with posterior parietal areas (see, e.g., Caminiti et al., 2015; Rizzolatti et al., 1998). This integration is the basis of the so-called sensorimotor transformations, in which sensory information processing automatically leads to the activation, in the motor cortex, of representations of "potential actions" (Cisek and Kalaska, 2010; Cisek, 2007; Rizzolatti and Luppino, 2001).

Within this general framework, in the macaque brain there are areas in the inferior parietal lobule (IPL) and in the ventral premotor (PMv) cortex forming parieto-frontal circuits crucially involved in selecting and controlling appropriate object-oriented hand actions. One of these circuits, linking the IPL anterior intraparietal (AIP) area and the PMv area F5, plays a primary role in visuomotor transformations for grasping, in which visual coding of the object's physical properties (e.g., size, shape, orientation) automatically leads to the activation of distal movement representations appropriate for hand-object interactions (Jeannerod et al., 1995). This process has also been referred to as "affordances extraction" (see, e.g., Fagg and Arbib, 1998). According to Gibson (1979), affordances are all the motor possibilities that an object offers an individual, and they depend on the motor capabilities of the observer. Thus, virtually every object typically can offer us several affordances. The selection of one of the several possibilities will then depend upon several different factors, such as object identity, memorized information on object properties, contextual information, or behavioral goals. The neural pathways mediating these aspects of perceptual and cognitive control on the selection and execution of hand actions have been until recently relatively poorly explored and still represent a relatively open issue in even more recent reviews on grasping control (e.g., Castiello, 2005; Grafton, 2010; Janssen and Scherberger, 2014). In recent years, connectional studies in macaques have shown that IPL and PMv areas involved in sensorimotor transformations for grasping are at the core of a large-scale cortical network that includes temporal

and prefrontal areas involved in object recognition and executive control of behavior, respectively (Borra et al., 2011, 2008; Gerbella et al., 2013, 2011; Rozzi et al., 2006). This network has been designated as the "*lateral grasping network*" (Borra et al., 2014b).

In this review article, we will first provide a comprehensive description of the anatomical and functional organization of the macaque *lateral grasping network* and suggest that this network is a possible substrate for integration of perceptual and cognitive with hand-related sensorimotor processes for generating purposeful hand actions. We will then review evidence suggesting that, in the evolution of the human lineage, the basic neural mechanisms for controlling hand actions described in the macaque have been retained and involve cortical sectors putatively homologous to the nodes of the macaque *lateral grasping network*. Finally, we will address the issue of the relationship of the *lateral grasping network* with the cortical network involving the caudal superior parietal lobule (SPL) and the dorsal premotor (PMd) cortex, involved in controlling reaching-to-grasp movements.

2. The macaque *lateral grasping network*

2.1. The ventral premotor area F5 and cortical representations of hand motor acts

Area F5, located in the rostral part of the macaque PMv (Fig. 1), is a major hub of the *lateral grasping network*. This area hosts a motor representation of the hand, more dorsally, and the mouth, more ventrally, which overlap to a considerable extent (Gentilucci et al., 1988; Hepp-Reymond et al., 1994; Kurata and Tanji, 1986; Maranesi et al., 2012; Rizzolatti et al., 1988). Neurons in this area typically encode specific hand, mouth, or both hand and mouth motor acts, such as grasping, breaking, and holding, rather than the single movements forming them (Rizzolatti et al., 1988). Furthermore, the activity of many hand-grasping neurons is tuned for the execution of specific hand-grasping configurations (e.g., Bonini et al., 2012; Fluet et al., 2010; Rizzolatti et al., 1988; Schaffelhofer and Scherberger, 2016; Spinks et al., 2008). Finally, while some neurons discharge during the execution of the whole motor act, others fire only during a certain part of it. It is noteworthy that many of these neurons appear to encode the goal of the motor act and not the motor act, per se. Thus, for example, they activate when a given motor goal (e.g., grasping) is achieved either using different effectors (e.g., the right hand, the left hand, or the mouth), or even opposite movements of the same effector (Kakei et al., 2001; Rizzolatti et al., 1988; Umiltà et al., 2008). Based on these findings, it was suggested that F5 contains a storage or "vocabulary" of internal representations of goal-directed hand, mouth, or hand and mouth motor acts. Each "word" of this

vocabulary is represented by populations of F5 neurons coding motor acts at different levels of abstraction (see Rizzolatti and Luppino, 2001; Rizzolatti et al., 2014). The presence in the premotor cortex, which is only one step away from the primary motor cortex, of a vocabulary of goal-directed motor acts enormously facilitates the complex neural mechanisms underlying the selection of the effectors and acts most appropriate for achieving a given motor goal. Thus, F5 occupies a key position in the *lateral grasping network*, representing the place where neural processes carried out upstream and related to the selection of appropriate hand and mouth motor acts merge with processes carried out downstream and related to their execution.

2.2. The posterior (F5p) subdivision of F5 and execution of hand motor acts

Though F5 has usually been considered a single cortical entity, architectonic data have suggested that this area is actually a complex of three different subdivisions (Fig. 1): the "anterior" (F5a) and "posterior" (F5p), located at different antero-posterior levels of the posterior bank of the inferior arcuate sulcus, and the "convexity" (F5c), located on the postarcuate convexity cortex (Belmalih et al., 2009). Connectional data (Gerbella et al., 2011) have shown that these three subdivisions are tightly interconnected and share several common connections, especially with posterior parietal areas, but also display some characterizing features suggesting a differential role in controlling hand, mouth, or hand and mouth motor acts. In the F5 sector corresponding to F5p, neural activity is almost completely hand related (e.g., Fluet et al., 2010; Gentilucci et al., 1988; Maranesi et al., 2012; Nelissen and Vanduffel, 2011; Theys et al., 2013, 2012), and intracortical microstimulation is effective in evoking hand movements at relatively low current thresholds, albeit higher than those effective in the primary motor area F1 (e.g., Godschalk et al., 1995; Maranesi et al., 2012). Furthermore, F5p is connected to several arm/hand premotor fields and is unique among the F5 subdivisions in being robustly and extensively connected to the hand field of F1 and a source of projections to the cervical spinal cord (Fig. 2; Borra et al., 2010; Gerbella et al., 2011). In the F5 sector corresponding to F5c, mouth or hand and mouth motor acts are mostly represented, and intracortical microstimulation is less effective than in F5p and mostly evokes mouth movements (e.g., Godschalk et al., 1995; Maranesi et al., 2012). The lateral portion of this sector also hosts neurons discharging selectively during monkey vocalization (Coudé et al., 2011). Furthermore, F5c is mostly connected to adjacent mouth-related frontal opercular and caudal PMv (ventral area F4) fields, is more weakly connected to the mouth fields of F3/SMA and F1 (Gerbella et al., 2011), and is a source of projections to the facial nucleus (Morecraft et al., 2001). Finally, the more recently defined F5a appears to host, as F5p, mostly a hand motor representation (Fluet et al., 2010; Nelissen

and Vanduffel, 2011; Schaffelhofer and Scherberger, 2016; Theys et al., 2012). However, the possible involvement of this sector in controlling mouth actions has not yet been systematically investigated. As described in detail in Section 2.5, converging projections from posterior parietal, ventrolateral prefrontal, and rostral frontal opercular areas characterize the connectional features of this F5 sector. Among these three F5 subdivisions, F5p, based on its motor representation and connectivity with the hand field of F1, could be the node of the *lateral grasping network* more directly involved in putting hand motor acts into action, once selected.

Indeed, the primary motor area F1, where hand movements are represented in terms of highly restricted muscle synergies, plays a fundamental role in primates in controlling dexterous hand actions, based on rich projections to the spinal cord that, in part, directly target motorneuronal pools of distal muscles (Lemon, 2008; Rathelot and Strick, 2009, 2006; Schieber, 2001). The projections from F5p to F1 could then represent the substrate for the selection and generation of the muscle synergies (movements) necessary for the execution of a motor act coded by a specific population of F5 neurons. In fact, electrophysiological studies have provided evidence for a hierarchical model in which area F5 influences the activity of distal muscles through cortico-cortical interactions with F1 (Cerri et al., 2003; Prabhu et al., 2009; Shimazu et al., 2004; Umilta et al., 2007).

Note, however, that F1 should not be considered as just an essential step of the output of the lateral grasping network, as it might have a role in motor control more complex than the emission of signals driving muscle activity. There is ample evidence that neurons in F1 are not necessarily always coactivated with limb muscles (see, for review, Schieber, 2011). For example, their activity can be associated with the direction of the movement rather than the patterns of muscle contraction (Kakei et al., 1999), or can reflect the goal of a motor act as F5p neurons (Umiltà et al., 2008; Maranesi et al., 2012). Furthermore, F1 is a target of projections from several premotor and somatosensory parietal areas (e.g., Hatanaka et al., 2001) and there is evidence for a caudal phylogenetically "new" subdivision that displays cortico-motorneuronal projections and a rostral phylogenetically "older" subdivision lacking these projections (Rathelot and Strick, 2009). Though F5p appears to project to both these subdivisions (Borra et al., 2010), there is evidence in new world monkeys for a differential distribution of the various input to F1, providing the substrate for different modules in the arm/hand field of this area involved in different cortical networks (Dea et al., 2016).

The more caudal premotor areas connected to F1 (F3/SMA, F2, F4, F5p) are also sources of projections to the spinal cord (e.g., Dum and Strick, 1991; He et al., 1993) and to the reticular formation (Keizer and Kuypers, 1989). These descending motor projections could mediate a role of these areas in motor execution in parallel with the primary motor cortex. Specifically, area F5p is a

source of projections to the mesencephalic, pontine, and bulbar reticular formations (Borra et al., 2010), which in turn can monosynaptically excite the motorneurons controlling intrinsic hand muscles (Riddle et al., 2009). Furthermore, area F5p, or at least a sector largely corresponding to it, is a source of corticospinal projections to the intermediate zone of the cervical spinal cord (Borra et al., 2010; Dum and Strick, 1991; He et al., 1993). These projections are weaker to the C6-T1 segments, where motorneuronal pools of hand muscles are located, and denser to the C2-C5 segments, where there are propriospinal neurons mediating disynaptic pyramidal excitation to forelimb motorneurons (Isa et al., 2007, 2006). Thus, F5p has access, albeit mostly indirect (via brainstem or upper cervical segments), to spinal segments where hand muscle motorneurons are located, suggesting a contribution of this area to the generation and control of hand movements in parallel with the hand field of F1. How these connections specifically contribute to the control of hand movements remains to be assessed. Indeed, though corticospinal F5 neurons display grasping-related activity (Kraskov et al., 2014, 2009), motor effects evoked by intracortical microstimulation in F5 appear to depend, at least in part, on cortico-cortical interactions with F1 (Schmidlin et al., 2008). However, there is evidence suggesting that the descending pathways originating from F5p can play an important role in the functional recovery of hand dexterity after lesions of F1 or its descending projections. Indeed, after lesion of the arm/hand field of the primary motor area, non-human primates can recover hand dexterity, including relatively independent finger movements and precision grip (Darling et al., 2014; Frost et al., 2003; Liu and Rouiller, 1999; Murata et al., 2008). Increased activity, expansion of the hand movement representation, neurochemical changes, and development of new cortical connections have suggested a crucial role of F5p, or of its new world monkey homolog, in this recovery (see Dancause et al., 2006, 2005; Frost et al., 2003; Higo et al., 2009; Murata et al., 2015; Nishimura et al., 2007; Nudo, 2007, 2006).

2.3. Parieto-frontal circuits and sensorimotor transformations for grasping

As noted in the introduction, one primary mechanism leading to the activation of appropriate motor representations of hand motor acts is based on sensorimotor transformations mediated by the strong and reciprocal connections of the PMv with the IPL. Particularly important are visuomotor transformations that enable us to select appropriate hand motor acts simply based on target object observation, thus to pre-shape the hand during the reaching phase of the action (Jeannerod, 1981). This mechanism is reflected in the properties of a major class of visuomotor F5 neurons, designated as "canonical" (Rizzolatti and Fadiga, 1998). These neurons activate as soon as objects of a certain size, shape, and orientation, congruent with its motor specificity, become visible, even when they

are simply observed and no hand–object interaction is requested (Fluet et al., 2010; Murata et al., 1997; Raos et al., 2006; Umilta et al., 2007; Vargas-Irwin et al., 2015). This neural activity can be interpreted as the result of visuomotor transformations in which extraction of objects affordances automatically produces the activation of potential motor acts for hand–object interactions (see, Rizzolatti and Luppino, 2001).

Area F5 also hosts another class of visuomotor neurons that could contribute to the control of hand actions. These neurons, designated as "mirror neurons," activate during the execution of hand motor acts, as well as during the observation of similar acts done by others (Gallese et al., 1996; Rizzolatti et al., 1996). This neural activity has been interpreted as the result of visuomotor transformations in which observed actions are mapped on their corresponding internal motor representations. It has been suggested that these neurons are part of an observation–execution matching system (mirror system) at the basis of the ability to recognizing others' goal-directed motor acts (Rizzolatti et al., 2014).

Canonical and mirror neurons were originally identified in F5p and F5c, respectively (Gallese et al., 1996; Murata et al., 1997), suggesting a preferential engagement of F5p in visuomotor control of grasping and of F5c in cognitive motor functions. However, the anatomical segregation of these two classes of neurons is not clear cut (Bonini et al., 2014), and even corticospinal F5 neurons can be modulated by action observation (Kraskov et al., 2009; 2014). Furthermore, both F5p and F5c host a third class of visuomotor neurons coding either objects or actions (canonical-mirror neurons, Bonini et al., 2014) Interestingly, a proportion of visuomotor F5 neurons activate selectively or preferentially when hand actions are observed from a first-person perspective (Caggiano et al., 2011) and appears to encode the visual feedback of a monkey's own hand during action execution, suggesting that a possible additional function of the mirror system consists of self-action monitoring (Maranesi et al., 2015).

The hand-related F5 territory involving F5a, F5p, and dorsal F5c is richly and reciprocally connected to two hand-related areas of the IPL—AIP and PFG—and with the hand field of the SII region of the opercular parietal cortex (Gerbella et al., 2011; Gharbawie et al., 2011; Gregoriou et al., 2006; Luppino et al., 1999; Tanné-Gariépy et al., 2002). Additional connections involve the mouth-related area PF and the arm-related area PG of the IPL. AIP, PFG, and the hand field of SII are richly connected with one another (Borra et al., 2008; Rozzi et al., 2006) and differentially contribute to sensorimotor transformations for grasping as described below.

Area AIP was originally defined by Sakata and colleagues (Taira et al., 1990) as a sector of the lateral bank of the intraparietal sulcus hosting neurons active during the execution of object-oriented hand actions. This hand-related sector, as electrophysiologically defined, corresponds well

to that sector of the lateral bank of the intraparietal sulcus connected to F5 (Borra et al., 2008; Luppino et al., 1999). Hand-related AIP neurons display functional properties for several aspects similar to those of F5 and were classified by Sakata and colleagues (Murata et al., 2000, 1996; Sakata et al., 1995; Taira et al., 1990) into three main classes: "motor-dominant neurons" firing equally well during grasping in both light and darkness, "visual and motor neurons" discharging stronger during grasping in light than in darkness, and "visual-dominant" neurons discharging during grasping in light but not in darkness. Motor activity of these neurons tends to be more selectively tuned for the type of grip (Baumann et al., 2009; Murata et al., 2000; Sakata et al., 1995). Visual responses of AIP neurons fall in two different categories, designated as object- and non-object type, respectively (Murata et al., 2000; Sakata et al., 1995). Object-type visually responsive neurons, similarly to canonical F5 neurons, activate as soon as an object becomes visible, even when the object is simply observed. These visual responses appear to precede those in F5 (Schaffelhofer and Scherberger, 2016) and show selectivity for common geometric features shared by similar objects, suggesting involvement in coding physical properties of the objects (Baumann et al., 2009; Murata et al., 2000; Sakata et al., 1995; Schaffelhofer and Scherberger, 2016). Indeed, studies by Janssen and colleagues (Romero et al., 2013; Srivastava et al., 2009; Theys et al., 2013, 2012) have shown that AIP neurons can extract or have access to 3D object information defined by binocular disparity. Non-object type neurons are not active during simple object fixation. It was suggested that their responses could be dependent on the sight of that particular hand action or the interaction of hand and object during manipulation (Murata et al., 2000; Sakata et al., 1995). Recent studies showed that AIP neurons can activate during grasping observation also from a first-person perspective, even when the object has been removed from a video (Maeda et al., 2015; Pani et al., 2014) suggesting involvement in both action understanding and in monitoring of a subject's own hand actions. Since early studies it has been suggested that AIP is a target of a dorsal visual stream pathway dedicated to the analysis of the object's intrinsic properties (size, shape, orientation, etc) and finalized to the extraction of object affordances, ultimately mediated by the AIP-F5 circuit (Jeannerod et al., 1995; Sakata et al., 1997). Strong evidence for a selective and crucial role of the AIP-F5 circuit in visuomotor transformations for grasping has been provided by studies showing that inactivation of either AIP or F5 (mostly F5p) severely affects grasping (Fogassi et al., 2001; Gallese et al., 1994). Specifically, the deficit mostly consisted in a mismatch between the intrinsic properties of the object to be grasped and the hand shaping necessary to grasp it, resulting in awkward grasping or even complete grasping failure. The selectivity of this deficit of visuomotor transformations for grasping was demonstrated by the observation that reaching and movement time were not clearly affected and that objects could be

grasped after tactile exploration. Furthermore, recent modeling studies have shown that AIP and F5 grasping-related activity can be successfully used for decoding appropriate hand–object interactions, suggesting that these two areas represent potentially reliable sources of signals for guiding functional neural interfaces for hand grasping (Carpaneto et al., 2011; Janssen and Scherberger, 2014; Schaffelhofer et al., 2015; Townsend et al., 2011).

Area PFG is an architectonically distinct area located in the mid-rostral part of the IPL convexity cortex adjacent to AIP (Fig. 1; Gregoriou et al., 2006). Neurons in this area display mostly hand-, but also mouth- or hand- and mouth-related activity (Gardner et al., 2007; Hyvärinen, 1981; Rozzi et al., 2008; Yokochi et al., 2003). PFG neurons also display somatosensory and/or visual responses confined to the peripersonal space and visual responses to object presentation (Gallese et al., 2002; Hyvärinen, 1981; Rozzi et al., 2008). Most hand-related neurons activate during the execution of object-oriented hand actions (Gardner et al., 2007; Rozzi et al., 2008), often showing selectivity for the grip type (Bonini et al., 2012). They also appear to encode instantaneous force variation and to keep in memory force signals for guiding hand actions (Ferrari-Toniolo et al., 2015). These data suggest involvement of this area in the cortical network for fine control of object grasping and manipulation. Furthermore, more than half of PFG grasping neurons (but also nearly half of those in F5) can be differentially activated depending on the goal of the action (e.g., grasp-to-eat or grasp-to-place) in which the coded act is embedded (Fogassi et al., 2005; Bonini et al., 2010; 2011; 2012). Thus, the activity of these PFG and F5 "action goal-related" neurons appears to be influenced by the context in which the action is performed and to reflect sequential action organization according to its goal or motor intention (Bonini et al., 2012, 2011, 2010; Fogassi et al., 2005). Furthermore, the finding that PFG grasping neurons can integrate information on both grip type and action goal suggests that this IPL area encodes information about both "how" and "why" each motor act has to be done (Bonini et al., 2012). Finally, as many PFG neurons also display mirror properties (Bonini et al., 2010; Gallese et al, 2002; Rozzi et al., 2008), this area has been considered the main parietal node of the "mirror system" (Rizzolatti et al., 2014). Interestingly, there are PFG mirror neurons active during the observation of grasping when embedded within a sequential action with a specific goal, thus suggesting a role in coding motor intention of others (Bonini et al., 2010; Fogassi et al., 2005).

The so called "SII region" corresponds to a somatosensory responsive sector of the parietal operculum (Fig. 1) originally considered to host a single topographic map of the body surface (Friedman et al., 1980; Robinson and Burton, 1980a; Woolsey, 1943). Later studies have subdivided this region into two distinct areas, designated as "parietal ventral" (PV) and SII (Krubitzer et al., 1995), or the hand field into three distinct sectors, located at different rostrocaudal

levels (Fitzgerald et al., 2004). Several studies have provided evidence for a role of this region in higher-order aspects of somatosensory processing (Hsiao et al., 1993; Robinson and Burton, 1980b; Romo et al., 2002). However, Fitzgerald et al. (2004) showed that neurons in the rostral and caudal parts of the SII hand field are preferentially responsive to proprioceptive input and many of them respond well to active movement, especially when grasping objects. Other studies have shown that the SII region hosts neurons firing during the execution of hand and mouth actions (Taoka et al., 2013) or object-oriented hand actions (Hihara et al., 2015; Ishida et al., 2013), many of them not responsive to passive somatosensory stimulation. These data, as well as connectional data showing robust connectivity of almost the entire extent of the SII hand field with F5, AIP, and PFG (Fig. 4; Borra et al., 2008; Gerbella et al., 2011; Rozzi et al., 2006), suggest a role of the SII region in somatomotor transformations for object-oriented hand actions and for haptic processing of object shape. Ishida et al. (2013) have hypothesized that the motor activity of SII hand-related neurons could reflect efference copy of selected motor commands from F5, used to make first a prediction of the sensory consequences of the movement and then a comparison with the actual sensory feedback. In turn, SII could be a source of somatosensory feedback information used in F5 and IPL hand-related areas for the timing of the hand–object interaction sequence and for monitoring and updating hand motor programs. Finally, a recent study (Hihara et al., 2015) showed that the SII region also hosts visually responsive neurons, responding to stimulation in the peripersonal space of the monkey to observation of human actions or of moving objects, suggesting a role of this area in multisensory integration for motor control.

2.4. Temporal connections of IPL hand-related areas and interaction of sensorimotor with perceptual processes

As reviewed in Section 2.3, in the macaque brain there is a parieto-frontal circuit linking areas AIP and F5 that is crucially involved in extracting object affordances, based on pragmatic, automatic visual analysis of object shapes. This circuit is at the core of virtually all models of cortical control of grasping so far proposed (Castiello and Begliomini, 2008; Castiello, 2005; Fagg and Arbib, 1998; Grafton, 2010; Janssen and Scherberger, 2014; Jeannerod et al., 1995; Rizzolatti and Luppino, 2001; Sakata et al., 1997) and has been considered a paradigmatic example of a "vision for action" pathway. As originally proposed by Milner and Goodale (1995, 1993), the dorsal visual stream—the visual information processing pathway that reaches from the extrastriate cortex to the IPL and the caudal part of the SPL—is not involved in space perception, as proposed by Ungerleider and Miskin (1982). Specifically, this visual pathway, as a whole, is a "vision for

action" pathway involved in visuomotor transformations, meant as a fast, automatic, and unconscious process carried out independently from perceptual processes that are considered to be the exclusive province of the occipito-temporal "ventral visual stream." This view leaves open the question of how and where perceptual and cognitive processes modulate or steer sensorimotor processes. A different model of the general organization of visual information processing in the macaque posterior parietal cortex has been subsequently proposed by Rizzolatti and Matelli (2003), based on the available connectional and functional data. According to this model, the various parieto-frontal circuits, fed by the dorsal visual stream, can be grouped into two anatomically and functionally distinct main components: the dorso-dorsal stream, formed by circuits linking SPL with dorsal premotor (PMd) areas, and the ventro-dorsal stream, formed by circuits linking IPL with PMv areas and the FEF. One important characterizing connectional feature distinguishing the v-d from the d-d stream is that the IPL, but not the SPL, displays robust connectivity with the temporal cortex. Accordingly, the macaque IPL is a region where visual information originating from both the dorsal and the ventral visual streams is integrated with information on motor programs. This type of integration could provide the neural substrate for a role of the v-d stream in what could be defined as a "perception-based" control of motor behavior (see also Fogassi and Luppino, 2005). In this context, the rostral IPL areas AIP and PFG are mostly involved in controlling hand movements, while the more caudal IPL convexity areas PG and Opt are mostly involved in controlling arm and coordinated arm and eye movements (Battaglia-Mayer et al., 2005, 2001; Hyvärinen, 1981; Mountcastle et al., 1975; Rozzi et al., 2008) and the more caudal intraparietal area LIP in controlling eye movements (Gnadt and Andersen, 1988).

Systematic analysis of the cortical connectivity of visuomotor areas of the macaque IPL has shown that its connections with the temporal cortex are topographically organized (see Borra and Luppino, 2017). Specifically, visuomotor IPL convexity areas (PFG, PG, Opt) are mostly connected with sectors of the upper bank of the superior temporal sulcus (STS), whereas AIP (but also LIP, Blatt et al., 1990; Cavada and Goldman-Rakic, 1989a; personal observations) displays temporal connections mostly with inferotemporal areas located at the highest hierarchical levels of the ventral visual stream and involved in object discrimination and recognition (see, e.g., Tanaka, 1996). Specifically, area AIP, though extensively connected to several inferotemporal areas, is very strongly connected to an intermediate sector of area TEa/m, located in the lower bank of the STS (Fig. 5; Borra et al., 2008). Functional imaging and electrophysiological data have provided clear evidence for a role of this inferotemporal sector in 3D shape coding (Denys et al., 2004; Janssen et al., 2001; Sereno et al., 2002; Uka et al., 2000; Yamane et al., 2008), and neurons in this sector appear to be involved in 3D shape perception (Verhoef et al., 2012). This same inferotemporal

sector also appears to be involved in visual coding of hand–object interactions (Nelissen et al., 2011; Perrett et al., 1989). Thus, it has been recently proposed that the lower bank of the STS is part of a component of the ventral visual stream specifically dedicated to 3D shape and action processing (Orban et al., 2014). The connections between AIP and intermediate area TEa/m provide the substrate for possible interaction and exchange of visual and motor signals between these two areas. Indeed, there is evidence for synchronization of neural activity in intermediate TEa/m and AIP during 3D shape discrimination (Verhoef et al., 2011) and for a contribution of AIP neurons to 3D shape perception (Verhoef et al., 2015a, 2015b). Thus, it is possible that ventral visual stream information on object identity is broadcast from inferotemporal areas directly to AIP. Accordingly, extraction of object affordances carried out by the AIP–F5 circuit would rely on information related not only to the intrinsic properties but also to the identity of the object target of the action. As the latency of 3D shape selectivity in AIP and TEa/m is about 70 ms and 130 ms, respectively, after the stimulus onset (Janssen et al., 1999; Srivastava et al., 2009), it is possible that information on object identity from TEa/m intervenes in AIP in biasing the selection of some of the affordances previously extracted based on visual coding of the object's physical properties. The projections from inferotemporal areas to AIP could also broadcast information related to visual coding of object-oriented actions. This information could contribute to the possible role of AIP in both monitoring one's own hand actions and action recognition, providing visual descriptions of type and immediate goal of hand actions made by others (Nelissen et al., 2011). The connectivity between AIP and inferotemporal cortex raises the question of the possible nature of the information sent by AIP to TEa/m. In theory, this connection could provide a direct link between components of the hand motor system and areas responsible for object recognition, that is, an access of signals related to motor and haptic representations of hand actions to the representations of object identity. If this is the case, then these connections could play a crucial role in the neural mechanisms underlying tactile object recognition. To our knowledge, there is no evidence for modulation of inferotemporal neurons by motor or haptic hand signals, though apparently it has never been explicitly examined. A recent functional fMRI study (Ward et al., 2015) found activation of several STS areas during different types of eye movements, including sectors of the lower bank, possibly corresponding to those connected to frontal and parietal oculomotor areas (Cavada and Goldmann-Rakic, 1989b; Blatt et al., 1990; Gerbella et al., 2010; Nelissen et al., 2011). Thus, the possibility that neural activity in intermediate TEa/m could be modulated by motor or haptic signals cannot be ruled out, though still needs to be empirically demonstrated.

In contrast to the AIP, the temporal connections of area PFG mostly involve sectors of the upper bank of the STS, corresponding to the so-called superior temporal polysensory (STP) area, a site of

convergent projections from somatosensory, auditory, and visual areas (Cusick, 1997; Felleman and Van Essen, 1991). Early studies suggested a role of this area in integrating information within and across modalities, subserving orienting behavior to novel stimuli (Baylis et al., 1987; Bruce et al., 1981). Furthermore, area STP hosts visually responsive neurons (see, Carey et al., 1997) coding biological motion, differentiating between self-produced actions and actions made by others, and coding intentionality of actions (Jellema and Perrett, 2003; Jellema et al., 2000). Finally, a sector of area STP connected to PFG activates during observation of object-oriented hand actions (Nelissen et al., 2011). All together, these data suggest that STP could be a source of visual action information that could contribute to the possible role of PFG mirror neurons in extracting the intention behind the observed motor act. The possible contribution of these connections to the neural mechanisms for controlling goal-directed hand actions still remains to be investigated.

2.5. Prefrontal cortex and executive control of hand actions

Selection and control of appropriate hand–object interactions cannot rely exclusively on sensorimotor transformations mediated by parieto-frontal circuits. For example, a cup will very likely be grasped differently according to whether we want to drink from it or move it into the sink. Furthermore, in any case, grip force and finger posturing will be influenced by learned visual and context-related cues about, for example, its possible weight and temperature. In other circumstances, the selection of a specific hand–object interaction will be dictated by conventional rules, for example when a knob is rotated clockwise or counterclockwise according to the desired effect.

Indeed, electrophysiological data in macaques have shown that, when waiting in darkness for a go signal, AIP neurons can show sustained activity reflecting encoding in working memory of objects' 3D features (Murata et al., 1996). Furthermore, grasp-selective neurons in both AIP and F5 can activate also when the way in which a given object has to be grasped is instructed by an arbitrary cue, for example an LED of a specific color (Baumann et al., 2009; Fluet et al., 2010), thus reflecting encoding of abstract information previously associated with a specific grip. Finally, as mentioned above, PFG and F5 "action goal-related" neurons show selectivity depending on the action context (Bonini et al., 2012, 2011, 2010). In F5, "action goal-related" neurons show selectivity for the action goal based not only on the context but also on the identity of the object, coded visually or haptically, thus providing evidence for multimodal processing of pragmatic and semantic information on potential targets of manual actions (Bruni et al., 2015b). These data strongly suggest that affordances extraction and selection processing carried out by IPL–PMv

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circuits is under a direct influence of executive control of motor behavior, in which the prefrontal cortex very likely plays a primary role. Furthermore, in the location of F5 there are neurons displaying memory-related activity used for perceptual decisions (Lemus et al., 2009; Romo et al., 2004) and evaluation of their outcomes (Pardo-Vazquez et al., 2009, 2008), suggesting involvement in decision-making processes together with the prefrontal cortex.

The prefrontal cortex is a large, heterogeneous region considered as a whole to be critically involved in the so-called *executive functions*, a term that, in general, refers to those mechanisms by which behavioral performance is optimized in situations requiring cognitive processes (see, Tanji and Hoshi, 2008). Non-human primate studies have shown that the prefrontal cortex consists of several connectionally and functionally distinct areas or domains. These areas/domains, originally described in terms of higher-order processing of different aspects of sensory information and its encoding into different domains of working memory (Goldman-Rakic, 1987; Levy and Goldman-Rakic, 2000), have been subsequently associated to the control of different aspects of behavioral planning (see, Miller and Cohen, 2001; Tanji and Hoshi, 2008).

The exact way in which prefrontal areas act on parietofrontal circuits for executive control of purposeful hand actions and the underpinning neural substrate have been until recently relatively poorly explored. Based on the available connectional data, it was suggested that the prefrontal cortex—specifically the ventral area 46 (46v)—could control the activity of the AIP–F5 circuit mostly through direct connections to AIP or through indirect (via pre-SMA/F6) connections to F5 (Fagg and Arbib, 1998; Grafton, 2010; Rizzolatti and Luppino, 2001). However, recent connectional and functional evidence has provided new insight on this issue.

One important finding has been the identification of area F5a, located ventrally in the postarcuate bank (Belmalih et al., 2009). This subdivision hosts grasping-related and 3D shapes selective visual dominant and visuomotor neurons (Fluet et al., 2010; Schaffelhofer and Scherberger, 2016; Theys et al., 2012) and activates during the analysis of stereoscopic 3D shape information (Joly et al., 2009) and the execution of object-oriented hand action (Nelissen and Vanduffel, 2011). These data strongly suggest involvement of this sector in visuomotor transformations for grasping. A recent study (Schaffelhofer and Scherberger, 2016) in which AIP, F5a, and F5p neurons have been simultaneously recorded during the execution of object-oriented hand actions showed that while movement-related activity was represented in both F5a and F5p, visual and visuomotor activity was considerably more represented in F5a so that activity in F5a tended to precede that in F5p. Like F5p, F5a is strongly connected to AIP, PFG, and the hand field of SII, but one characterizing feature of this area is the robust connectivity with ventrolateral prefrontal (VLPF) areas 46v and 12r (Gerbella et al., 2011; Figs. 3 and 4). Based on these data, it has been suggested that F5a is a pre-

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PMv area, a privileged site of integration of hand-related sensory-motor signals originating from inferior and opercular parietal areas with higher-order information originating from specific VLPF areas (Gerbella et al., 2011).

The observation that the prefrontal territories connected to either F5a or AIP appear to largely overlap suggested that in the VLPF there are sectors involved in the cortical circuits for controlling hand actions. Systematic analysis of the cortical connectivity of areas 12r (Borra et al., 2011) and 46v (Gerbella et al., 2013) showed that this is indeed the case (Fig. 6). Specifically, an intermediate sector of area 12r, an area classically considered as a prefrontal target of the inferotemporal cortex (e.g., Webster et al., 1994), showed connections with both F5a and AIP and with the hand field of SII (Borra et al., 2011). Interestingly, the inferotemporal connections of this sector involved most densely the same intermediate sector of area TEa/m, which is connected to AIP (Fig. 5). Furthermore, a dorsally adjacent VLPF sector, located rostrally in the caudal half of area 46v (rostral 46vc), displayed connections to F5a and the hand field of SII and topographically organized connections to AIP and PFG (Gerbella et al., 2013). These two VLPF "hand-related" sectors were found to border caudally with sectors of areas 12r and 46v connected to frontal and parietal oculomotor areas and rostrally with sectors displaying mostly intraprefrontal connectivity (Borra et al., 2011; Gerbella et al., 2013). All together, these data suggested a modular organization of the caudal VLPF in which executive functions are finalized to the control of oculomotor behavior more caudally and of skeletomotor behavior more rostrally. Functional studies have indeed shown that cells active in tasks requiring oculomotor responses (e.g., Averbeck et al., 2006; Boch and Goldberg, 1989; Ichihara-Takeda and Funahashi, 2007) and the execution of arm/hand responses (Hoshi et al., 2000, 1998; Requin et al., 1990) tended to be located more caudally and more rostrally in the VLPF, respectively. The involvement of the anatomically "hand-related" sectors of areas 12r and 46v in the neural mechanisms for controlling hand actions has been recently evidenced by data showing that both these sectors host neurons active during the execution of object-oriented hand actions (Bruni et al., 2015a; Simone et al., 2015). These data largely extend previously proposed models of grasping control, providing evidence for VLPF sectors that could be the specific substrate for interfacing perceptual, cognitive, and sensorimotor hand-related processes.

Area 12r hosts visual neurons tuned to the identity or features of objects (Asaad et al., 1998; Wilson et al., 1993) and is critically involved in behavioral tasks in which information about object identity plays a key role (Mishkin and Manning, 1978; Passingham, 1975; Wang et al., 2000). Accordingly, this area has been considered to play a role in working memory for objects and shapes (Wilson et al., 1993), conditional learning based on object identity (Passingham, 1993; Passingham et al., 2000), and encoding category membership (Freedman et al., 2002; Miller et al., 2002).

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However, the above mentioned connectional data suggest that intermediate area 12r is also an integral part of the cortical network for controlling hand actions centered on the AIP–SII–F5 circuitry. Thus, this sector is a possible substrate for integration of ventral visual stream with sensorimotor hand-related information in the prefrontal cortex. These data, in addition to those on the temporal connectivity of area AIP, provide strong support to the idea argued by Cisek and Kalaska (2010) that the properties of ventral stream processing may not have originally evolved for a role in pure perception, but may instead reveal its earlier and more fundamental role in collecting information useful for action selection. Thus, in the intermediate part of area 12r, retrieval, retention, and manipulation of information on objects or hand–object interactions could be finalized to the control of object-oriented hand actions. Accordingly, information on object identity and on object properties (e.g., weight, center of mass, fragility, texture) deriving from object manipulation or explicit knowledge could be used for grasping selection, anticipatory force control, or updating motor programs (Johansson and Cole, 1992; Loh et al., 2010; Lukos et al., 2007, 2008). This field could also contribute to tactile object recognition, which requires retrieval of memorized information and working memory about object properties and identity. Finally, the robust connectivity with orbitofrontal areas suggests that object information processing in this field also reflects affective properties, or the "value" of objects (Schultz, 2000). This information could be then used in area 46v, densely connected to intermediate area 12r, for intentional selection of actions (Tanji and Hoshi, 2008).

Area 46v appears to be involved in using context-related information for learning and applying behavioral guiding rules for action selection (e.g., Hoshi et al., 1998; Murray et al., 2000; Wallis et al., 2001; White and Wise, 1999). Indeed, lesions involving the VLPF cortex, lead to impairment of new associations between arbitrary visual cues and forelimb movements (Bussey et al., 2001). Neurons in this area also appear to encode representations of the final goal of a sequential action, suggesting a role in governing goal-oriented sequential behavior (Saito et al., 2005), events that occur as a consequence of behavioral actions rather than the intended movements (Mushiake et al., 2006), and information representing multiple phases of behavioral events (Saga et al., 2011). Furthermore, area 46v (but also area 12r) hosts neurons coding contextual information for selecting and guiding object-oriented hand actions and neurons providing multimodal representations of the intended goal of a forthcoming action, thus encoding a behavioral decision independently from the sensory information allowing the subject to make it (Bruni et al., 2015a). Accordingly, the area 46v sector connected to F5a, SII, and AIP, in parallel and in cooperation with area 12r, could be involved in selecting, monitoring, and updating object-oriented hand actions based on behavioral goals, behavioral guiding rules, and current, memorized, or working memory information on motor

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programs and object properties. Furthermore, the area 46v sector connected to F5a, SII, and PFG could be preferentially involved in intentional action selection, in organizing motor acts into action sequences, and in keeping active internal representations of an individual's motor intentions.

2.6. The granular opercular frontal (GrFO) area and evaluation of values and costs in selecting hand actions.

Very often the decision of which action to perform is based on computation of values and costs, that is, the integration of information on the value of sensory stimuli with motivational, cognitive, and contextual variables. The orbitofrontal cortex appears to play a primary role in encoding the significance of stimuli within an emotional context and in the computation of good identities and subjective values in an abstract representation (see, Grabenhorst and Rolls, 2011; Padoa-Schioppa and Cai, 2011). The exact way in which value-based information guides decisions between actions is still a matter of active research. It is largely agreed that the strong connectivity between orbitofrontal and lateral prefrontal areas could represent one major pathway mediating the influence of this information on executive functions. Indeed, electrophysiological studies have shown involvement of area 46 in the neural mechanisms underlying the transformation of value-based information into actions (good-to-action transformations; Cai and Padoa-Schioppa, 2014). Furthermore, it has been argued that decision between actions needs computation of action costs based on integration of value-based information with sensorimotor signals (Cisek, 2012). Lateral prefrontal areas, including the hand-related sectors of area 12r and 46v, thanks to their connectivity with both orbitofrontal and premotor and parietal areas, could contribute to this process.

Recent data provided evidence for an additional pathway linking the orbitofrontal with the PMv area F5a, running through the newly identified granular frontal opercular (GrFO) area (Gerbella et al., 2016b). Area GrFO is an architectonic area located rostrally in the frontal operculum, just ventral to F5a (Fig. 1; Belmalih et al., 2009). Though virtually unexplored in electrophysiological studies, the strong connectivity with F5a and the hand field of SII (Gerbella et al., 2016b) and functional imaging data showing activation during the execution of object-oriented hand actions (Nelissen and Vanduffel, 2011) suggest affiliation of this area to the cortical network for controlling hand actions. However, connectivity with the SII mouth field and with the neighboring opercular frontal areas suggests a role also in controlling mouth motor behavior. Area GrFO also displays robust connectivity with the hand-related VLPF sectors of areas 12r and 46v and with several cortical and subcortical structures affiliated to the limbic system, including orbitofrontal areas, rostral cingulate area 24, agranular and dysgranular insula, and the amygdala (Gerbella et al.,

2016b). These data suggest that area GrFO is a site of integration of diverse types of limbic information which could then be conveyed mostly to area F5a, thus providing the neural substrate for a relatively direct contribution of signals, possibly related to subjective values, emotional significance of stimuli, or internal states, to the selection of appropriate goal-directed hand actions. This hypothesis, however, needs empirical demonstration.

2.7. The dysgranular insula and modulation of hand actions by internal states

The primate insula is an anatomically and functionally heterogeneous integrative limbic region (Augustine, 1996; Kurth et al., 2010; Mesulam and Mufson, 1982a) considered to play a fundamental and integrative role in the coordination between internal and external information through emotional subjective awareness (Ibañez et al., 2010). Based on functional and clinical evidence, it has been suggested that this region could be involved in a large variety of functions, including, for example, basal subjective states mediating action preparation (Ibañez et al. 2010) and evaluating intentional action outcomes (Brass and Haggard, 2010). Indirect connectional evidence (Borra et al., 2011, 2008; Gerbella et al., 2013, 2011, 2016b; Jezzini et al., 2015; Rozzi et al., 2006) indicates that IPL (AIP, PFG), PMv (F5a, F5p), frontal opercular (GrFO), and VLPF (intermediate area 12r, rostral part of 46vc) hand-related areas are all connected with a specific sector located relatively dorsally in the dysgranular insula (Fig. 4). This sector appears to overlap, at least in part, with an insular zone from which intracortical microstimulation evokes hand movements (Jezzini et al., 2012). Thus, this specific sector of the dysgranular insula is a possible source of signals related to internal states modulating the control of hand actions.

3. The *lateral grasping network* in action

Data so far reviewed provide evidence for a large-scale, functionally specialized cortical network—*lateral grasping network*—in which internal representations of hand motor acts, recruited by sensory (most often visual) information are selected and put into action for feed-forward control of purposeful object-oriented actions and in which the execution of these actions is monitored and, if needed, adjusted based on sensory feed-back and memorized information. Based on these data, it is then possible to imagine an anatomically plausible model of grasping control that largely extends previously proposed models.

As summarized in Figure 7, the grasping model here imagined, as most previously proposed models (e.g., Castiello, 2005; Fagg and Arbib, 1998; Grafton, 2010; Rizzolatti and Luppino, 2001),

is centered on the parieto-frontal circuit linking AIP with F5 subdivisions (mostly F5p and F5a). The primary role of this circuit is to extract object affordances. This process primarily relies on visual coding of the object physical properties, carried out along a dorsal visual stream pathway running through areas V3A and CIP (Sakata et al., 1997) and leading to activation of visually responsive, 3D shape-selective AIP neurons at about 70 ms after the stimulus onset (Sivrastava et al., 2009). The joint activity of AIP and F5 (at least initially, mostly F5a) then results in the activation in F5 of the internal representations of all the various potential actions that could be used for interacting with an object (Fagg and Arbib, 1998; Rizzolatti and Luppino, 2001). In parallel with this fast dorsal visual stream processing, there is a ventral visual stream analysis of object features (Janssen et al., 1999) that, through the IT–AIP connections, molds the activity of the AIP–F5 circuit, pruning the wide range of formerly activated potential actions for privileging those more congruent with the identity of the specific target object.

Object-related ventral visual stream information is broadcast, in addition to AIP, to the intermediate part of area 12r. Meanwhile, sensorimotor signals related to the activated hand motor programs are sent from AIP and F5a to the same sector of area 12r and to the adjacent hand-related sector of area 46vc. Area 12r, based on integration of object-related information coming from the inferotemporal and orbitofrontal cortex with sensorimotor hand-related signals, could then contribute to the advance specification of some aspects of the motor program (e.g., force, finger posturing) based on retrieval of explicit and/or implicit memorized information on object properties. In area 46vc, convergence of sensorimotor signals related to potential hand-object interactions, object-related and contextual information, and higher-order information from rostral prefrontal areas, possibly related to behavioral goals, could result in encoding of action goals. Projections from this area, via AIP, PFG, and F5a, then mediate the selection of the populations of action goal-related and grasping selective F5p neurons most appropriate for achieving the action goal. In this context, the projections from the insula to virtually all the nodes of the network could be responsible for modulating selection and control of hand actions according to the internal state of the individual. Furthermore, future studies will shed light on the possible role of area GrFO in modulating hand-action selection based on subjective values and emotional significance of stimuli. Once the processes related to action selection are completed, the appropriate hand motor act coded by specific populations of F5p neurons is then put into action through the projections of F5p to F1 and to subcortical motor centers, thus assuring feed-forward control of grasping. During movement execution, the whole network is involved in feedback monitoring and adjustments of the ongoing motor program, based on visual and haptic information on hand actions and hand–object interactions. This information could be used in area 12r for building up sensorimotor memories to

obtain optimal finger posturing and grip force based on certain object properties and for learning to handle unfamiliar objects and new hand–object interactions. Furthermore, sensorimotor signals could be used in area 46vc for monitoring and, if needed, updating the execution of object-oriented hand actions according to internal representations of an individual's motor intentions.

This extended version of the grasping model fits very well with general models of action selection and specification in which information arriving from the world is continuously used to specify several currently available potential actions and, among them, the one that will be turned into overt execution (Cisek and Kalaska, 2010; Cisek, 2007; Klaes et al., 2011).

The grasping model here proposed is certainly still not exhaustive. First there is connectional evidence for the participation of other components to the *lateral grasping network* (see Section 4), and second, other networks could contribute in parallel to some aspects of this motor behavior (see Section 6). Furthermore, it should be noted that the *lateral grasping network*, or parts of it, could be involved in other functions, such as other's action understanding and tactile object recognition.

4. Possible additional contributors to the *lateral grasping network*

Based on connectional data, it is expected that several neural centers could be more or less directly involved in the *lateral grasping network*, though their exact functional contributions still remain to be fully elucidated.

One of these centers is the medial premotor area F6/pre-SMA, an arm-related area located rostrally to the supplementary motor area (Luppino et al., 1991; Matsuzaka et al., 1992; Picard and Strick, 1996). This area is densely connected with the dorsal and ventral area 46, the rostral cingulate area 24c, and dorsal and ventral premotor arm/hand fields, especially the location of F5a and more weakly with arm/hand IPL areas PG and PFG (Luppino et al., 1993; Wang et al., 2005). It is largely agreed that this area is involved in higher-order aspects of motor control (see, e.g., Nachev et al., 2008; Picard and Strick, 2001), including updating of motor plans (Shima et al., 1996), selecting effector-independent actions (Fujii et al., 2002), organizing complex motor sequences (Tanji and Shima, 1994; Tanji, 2001), learning sequential actions (Nakamura et al., 1998), controlling interval timing (Mita et al., 2009), and performance monitoring (Scangos et al., 2013). Altogether, these data have suggested a general role of this area in forwarding signals transforming potential actions into actual movements, thus determining movement onset based on contextual and motivational information, and in controlling the temporal organization of motor programs (Ridderinkhof et al., 2011; Rizzolatti et al., 2014). This role could be exerted through the widespread connections of this area with all the various arm/hand premotor fields, including F5a. A

recent study (Lanzilotto et al., 2016) showing that in F6 there are motor and visuomotor neurons firing during the execution of reaching grasping neurons has provided evidence for a contribution of this area to the *lateral grasping network* and has started in shedding light on its possible role in generating object-oriented actions.

Furthermore, the IPL, PMv, and VLPF areas of the *lateral grasping network* are sources of corticostriatal projections and targets of transthalamic pallidal or nigral projections (Clower et al., 2005; Gerbella et al., 2016a; Ishida et al., 2016; Kelly and Strick, 2004; Middleton and Strick, 2002, 2000). The IPL and PMv areas of the network are also sources of corticopontine projections and targets of transthalamic cerebellar projections (Strick et al., 2009). The involvement of basal ganglia and cerebellum in controlling hand actions is well-known from electrophysiological, functional imaging, and clinical evidence (see, e.g., Bodranghien et al., 2016; Glickstein et al., 2005; Prodoehl et al., 2008). However, to better understand the mode of information processing in these two structures, more detailed connectional information is needed on the way in which signals from the hand-related cortical areas are sent to, and sent back from, the basal ganglia and cerebellar circuitries. Interestingly, recent data showed an overlap of corticostriatal projections from areas of the *lateral grasping network* in correspondence of two putaminal zones, distinct from the putaminal zone target of projections from the primary motor area (Gerbella et al., 2016a), suggesting the presence of multiple hand-related basal ganglia loops. Future studies will clarify the possible differential contribution of these newly identified hand-related striatal zones to the neural mechanisms for controlling purposeful hand actions in light of the well-established general role of the basal ganglia in action selection and motor learning (DeLong and Wichmann, 2009).

5. A putative human *lateral grasping network*

It is generally assumed in neuroscience research that experimental data obtained from non-human primate studies can be very helpful for understanding the human brain functions in normal and pathological conditions (see, e.g., Passingham, 2009). Old world monkeys, such as macaques, are the primates most closely related to humans in which invasive experiments can be carried out to obtain highly detailed anatomical and physiological information on the neural pathways and mechanisms underlying sensory, motor, and cognitive functions. One potential challenge to the generalization of these data to the human brain is that about 30 million years of independent evolution resulted in significant differences between the brains of monkeys and humans, for example the disproportionate enlargement in the human brain of some cortical regions considered the neural basis of the outstanding cognitive capabilities of humans (see, e.g., Chaplin et al., 2013;

Passingham, 2009; Rilling et al., 2012; Sereno and Tootell, 2005). However, based on comparative observations, it is largely agreed that the monkey and human brain share a common plan of anatomical and functional organization of sensory, motor, and association cortical areas (see, e.g., Caminiti et al., 2015; Geyer et al., 2000; Mars et al., 2016). Furthermore, it is largely accepted that evolutionary processes have more commonly involved the modification of existing anatomical structures than the addition of new structures, so that novel functions have mostly evolved from the adaptation of existing neural mechanisms (de Waal and Ferrari, 2010; Passingham, 2009; Rilling et al., 2012). Accordingly, the macaque model could be essential for understanding the mechanisms of the brain even in cases where humans have cognitive abilities that have not developed in other animals. This is what appears to be the case for the neural mechanisms underlying selection and control of goal-directed hand actions.

5.1. *Putative human homologs of the macaque parietal and premotor nodes of the lateral grasping network*

Since from early functional imaging studies (Binkofski et al., 1998; Culham et al., 2003; Ehrsson et al., 2000; Frey et al., 2005; Johnson-Frey, 2004; Toni et al., 2001), it has been shown that the execution of object-oriented hand actions activates cortical zones located both in the PMv and the IPL. Transcranial magnetic stimulation (TMS) studies showed an interaction of the dorsal part of the PMv hand-related zone with the primary motor cortex, modulated during grasping execution, and that virtual lesion of this PMv sector impairs grasping execution (Davare et al., 2009, 2008, 2006). Furthermore, a recent study (Fornia et al., 2016) showed that short-train or single-pulse electrical stimulation of the cortical surface along the dorso-ventral extent of the PMv is effective in evoking hand, orofacial, and combined orofacial and hand motor responses from the dorsal, ventral, and intermediate part, respectively, providing evidence for a somatotopic arrangement of this region similar to that of the macaque F5. This study also showed that current intensities needed to elicit hand responses and the latencies of these responses were higher than those observed for the primary motor area, suggesting that, as for the macaque F5p, this dorsal PMv hand sector acts via a slower and possibly more indirect route to the spinal cord than the primary motor area. All together, these data provide clear evidence for homologies between the human and the macaque PMv, specifically of the human dorsal PMv with the macaque F5p. More ventrally, the hand-related zone extends from the precentral gyrus into the inferior frontal gyrys (IFG), involving Brodmann's architectonic area 44 (Brodmann, 1909), which is the caudal part of Broca's region, crucially involved in various aspects of language (see, e.g., Friederici, 2011). Several studies (Caspers et al., 2010; Fadiga et al.,

2009; Grosbras et al., 2012; Johnson-Frey, 2004; Rizzolatti et al., 2014; however, see Cerri et al., 2014) have shown that Broca's region, or at least its caudal part, is involved in both hand-action execution and observation and in higher-order aspects of motor control, such as action understanding, motor imagery, tool use, and imitation. Based on these data, it has been suggested that the functions of this region, including language processing, have evolved, at least in part, from the adaptation of neural mechanisms taking place in the macaque area F5 (see, e.g., Fabbri-Destro and Rizzolatti, 2008; Fogassi and Ferrari, 2012; Rizzolatti and Arbib, 1998; Rizzolatti and Craighero, 2004). According to Sanides (1964; see also Amunts and Zilles, 2012) the "fronto-opercular zone," corresponding to Broca's region, has in part evolved from the differentiation, along a caudo−rostral gradation stream, of phylogenetically older areas of the PMv. Furthermore, a multimodal architectonic study (Amunts et al., 2010) has shown that Broca's region can be subdivided into more than a dozen areas, making the issue of the possible homologies of the human PMv/IFG with the corresponding region of the macaque brain quite difficult to address. The finding that, based on architectonic similarities, one newly defined area of Broca's region (area 6r1) could be the putative human homolog of the macaque area F5a (Amunts et al., 2010; Amunts and Zilles 2012), appears in line with the Sanides' proposal. Based on mere topological considerations, it is expected that the constellation of areas forming Broca's region also includes a possible homolog of the macaque frontal opercular area GrFO. Indeed, Amunts et al. (2010) provided evidence for several opercular areas, two of them—op6 and op8—located ventral to a subdivision of ventral area 6 and to area 44, respectively. There is evidence for involvement of the frontal opercular cortex in performance monitoring (Amiez et al., 2016) and, in the left hemisphere, in some aspects of language processing (Friederici et al., 2006). A possible involvement of this region in controlling hand actions still remains to be explored.

In the rostral IPL, the execution of object-oriented actions activates both the rostral part of the lateral bank of the IPS and the supramarginal gyrys (SMG). The lateral bank of the IPS also activates during object exploration and modelling (Jäncke et al., 2001), surface orientation discrimination and subsequent related spatial adjustment of finger position (Shikata et al., 2003), and as well as PMv, when grasping tools (Jacobs et al., 2010). Recent electrophysiological data have shown that this region hosts neurons selectively tuned for motor imagery of specific hand shapes (Klaes et al., 2015). This same region is also involved in 3D shape processing from disparity (Georgieva et al., 2009) and in coding intrinsic object properties (Monaco et al., 2015), and it activates during the observation of object-oriented actions (e.g., Biagi et al., 2010; Caspers et al., 2010; Jastorff et al., 2010). TMS studies have shown that virtual lesions of this zone affect hand shaping, scaling of grip force (Dafotakis et al., 2008; Davare et al., 2007), and online adjustments of

goal-directed hand actions (Rice et al., 2006; Tunik et al., 2005). Based on these data, it is largely agreed that this rostral IPS zone is the putative homolog of the macaque area AIP. Furthermore, the increase in effective connectivity between the human AIP and PMv when grasping small objects (Grol et al., 2007) and the reduction in PMv–M1 interactions during grasping preparation after virtual lesion of the human AIP (Davare et al., 2010) suggest a parieto-frontal circuit for visual control of hand actions homologous to the macaque AIP/F5 circuit.

Execution (Grèzes and Decety, 2001) and observation (Caspers et al., 2010; Gazzola and Keysers, 2009; Grosbras et al., 2012; Molenberghs et al., 2012) of object-oriented actions also activate the SMG, mostly in correspondence of architectonic area PFt (Caspers et al., 2013, 2010, 2006). SMG activation has also been observed after unpredicted changes of the grasped object weight, suggesting, as for the macaque area PFG, involvement in comparing predicted and actual sensory input during object manipulation and updating of sensorimotor memories (Jenmalm et al., 2006). Furthermore, TMS of this region (but also of the caudal IFG) affects planning of sequential goal-directed hand actions in which object grasping is embedded in actions with different goals (Tunik et al., 2008). Area PFt is part of a rostral cluster of IPL areas (Caspers et al., 2013, 2008, 2006) that, based on tractographic observations, appears to share with the macaque rostral IPL areas several connectional features (Caspers et al., 2011; Ruschel et al., 2014). Accordingly, this area has been considered the putative homolog of the macaque area PF/PFG (Caspers et al., 2011). However, in the left hemisphere, the SMG is clearly involved also in cognitive abilities unique or almost unique to humans, such as higher-order aspects of organization of object-oriented actions, including tool use (Johnson-Frey et al., 2005; Peeters et al., 2009, 2013; Ramayya et al., 2010) and imitation learning (Buccino et al., 2004). Furthermore, lesions affecting this region are often associated with ideomotor apraxia, a higher-order motor deficit consisting of a failure in implementing the internal representation of a gesture into the appropriate motor actions (De Renzi and Faglioni, 1999). Based on comparative observations in humans and macaques, Peeters et al. (2009, 2013) have concluded that the left rostral SMG includes an evolutionarily new human-specific zone devoted to tool use, which could have differentiated from phylogenetically older rostral IPL areas. Thus, the remarkable ability of humans in tool use could have resulted from the exploitation and adaptation of the neural mechanisms underlying goal-related action organization and grip selection based on object shape and identity, taking place in macaque IPL areas AIP and PFG (see, e.g., Orban and Caruana, 2014).

There is also clear evidence for a putative human homolog of the macaque SII region. Specifically, the human parietal operculum hosts two architectonically distinct somatosensory areas, designated as OP1 and OP4, which based on their location and somatotopy could represent the putative homologs of the two subdivisions (PV and SII, respectively) of the macaque SII region

(Eickhoff et al., 2007, 2006a, 2006b). Tractographic data suggested connectivity of these two areas with rostral IPL and PMv areas and with Broca's region (Eickhoff et al., 2010). Functional imaging data showed that this region activates during both tactile stimulation (Burton et al., 2008; Disbrow et al., 2000; Eickhoff et al., 2007) and movement execution (Gazzola and Keysers, 2009; Hinkley et al., 2007). Other studies showed involvement of this region in tactile object recognition (Reed et al., 2004) and in coding tactile expectancies about the contact with objects, based on previous experience and contextual cues (Carlsson et al., 2000). Furthermore, the SII region activates during observation of actions (Gazzola and Keysers 2009) and of interpersonal touch (Ebisch et al., 2008; Keysers et al., 2004), suggesting multisensory integration. Finally, TMS studies provided evidence for a causal role of the SII region in haptic working memory of object properties and grasping motor programs (Cattaneo et al., 2015; Maule et al., 2015). These data are fully in line with a role of this region, as it can be predicted based on its connectivity in the macaque brain in haptic control of hand actions and in building up and maintaining sensorimotor memories for selecting and updating grasping motor programs and for controlling fingertip forces.

After the development of non-invasive tractographic techniques, several studies (Hecht et al., 2013; Ramayya et al., 2010; Rushworth et al., 2006; Schubotz et al., 2010) have provided evidence for anatomical connectivity between the rostral IPL and the PMv/IFG. Unfortunately, technical limitations intrinsic to MR-based connectional approaches (Reveley et al., 2015; Thomas et al., 2014) still prevent reliable definition of point to point anatomical connectivity in the human brain as it can be obtained in the macaque based on neural tracer injections. In both macaques and humans, the frontal connectivity of the rostral IPL is largely supported by the third branch of the superior longitudinal fasciculus (Schmahmann et al., 2007; Thiebaut de Schotten et al., 2012). Comparative observations have suggested expansion of this connectivity in primate evolution (Hecht et al., 2013).

In sum, converging evidence clearly indicates that the human brain hosts a network of IPL, opercular parietal, and PMv areas, homologous to the core of the macaque *lateral grasping network*, involved in sensorimotor transformations for controlling hand actions (Fig. 8). However, this network also incorporates novel components evolved from the phylogenetically older nodes of the *lateral grasping network*.

5.2. Putative human homologs of the macaque temporal nodes of the lateral grasping network

Increasing evidence (see, van Polanen and Davare, 2015) clearly supports the notion that in the human brain, the dorsal and the ventral visual streams are not functionally independent but interact in several aspects of visual and motor processing.

For example, Verhagen et al. (2008) have shown that grasping objects based on processing of pictorial depth cues increases the activity of the human AIP and its functional connectivity with the PMv and the Lateral Occipital complex (LOC), a region considered together with the neighboring fusiform gyrus as the putative human homolog of the macaque inferotemporal cortex (see, e.g., Orban et al., 2014). Verhagen et al. (2012) have also shown that the human AIP is necessary for the fast generation of new motor plans based on both spatial and pictorial cues. Other studies have shown that LOC activates when grasping requires processing of volumetric information (Majdandžić et al., 2007) and when predicting the weight of an object based on sensorimotor signals (Gallivan et al., 2014). Furthermore, when planning object-oriented actions, there are activity patterns in LOC reflecting the type of hand action (Gallivan et al., 2013a), and the organization of visual objects representation in this region reflects action-related properties of the objects (Bracci and Peelen, 2013; Bracci et al., 2012; Mahon et al., 2007; Peelen et al., 2013). Finally, visual and haptic coding of objects activates the human AIP (Grefkes et al., 2002) and a part of the LOC (Amedi et al., 2002; James et al., 2002; Reed et al., 2004), providing evidence for multimodal representation of objects in the human ventral visual stream and suggesting interaction between AIP and LOC for tactile object recognition (Lacey et al., 2009; Tal and Amedi, 2009).

Altogether these findings indicate that visuomotor processing for selecting and controlling hand actions carried out in the human AIP is influenced by processing taking place in ventral visual stream areas and that the human AIP is a possible source of motor and haptic information contributing to build up multimodal representations of objects in LOC. Temporal connectivity of the IPL can be supported, as in macaques (Schmahmann et al., 2007), by the middle and the inferior longitudinal fasciculus (Hecht et al., 2013; Makris et al., 2013). Comparative tractographic observations have suggested that in humans the temporal connectivity of at least the SMG is much stronger and more extensive than in macaques, especially in the left hemisphere (Hecht et al., 2013). Specifically, these connections appear to involve both the putative human homolog of the macaque IT and regions of the superior temporal sulcus putatively homologous of the macaque STP involved in coding biological motion (Grosbras et al., 2012; Jastorff and Orban, 2009) and important for social cognition (see, e.g., Allison et al., 2000; Frith and Frith, 2010). Furthermore, they involve regions of the middle temporal gyrus where semantic information about tools and tool-use actions appears to be stored (Johnson-Frey, 2004; Johnson-Frey et al., 2005; Orban and Caruana, 2014; Ramayya et al., 2010).

5.3. Putative human homologs of the macaque prefrontal nodes of the lateral grasping network

As expected from functional and connectional data from non-human primate studies, there is evidence that, in humans, activity in the IPL and PMv hand-related regions is modulated by cognitive processes likely involving the prefrontal cortex. For example, when grasping is performed without visual feedback, after a delay from the object presentation, there is a sustained activation of human AIP (Fiehler et al., 2011; Singhal et al., 2013), and TMS of this area appears to affect both immediate and delayed grasping (Cohen et al., 2009). These data suggest involvement of human AIP in maintaining target information in working memory used for an upcoming grasping action. Furthermore, there is evidence for integration in human AIP not only of spatial and pictorial object-related information but also of learned knowledge of object configurations (Verhagen et al., 2012). Finally, grasping-related activity in rostral IPL (including human AIP) and in PMv increases when subjects select the way in which an object is grasped based on contextual information, thus suggesting context-sensitivity of grasp representations in these regions (Marangon et al., 2011).

The issue of the possible homologies between the macaque and the human prefrontal cortex is still matter of debate (e.g., Fuster, 2015; Smaers et al., 2011). Some authors have suggested that in the course of evolution, the prefrontal cortex has undergone more expansion than the rest of the cortex and its relative size has reached a maximum in the human brain (e.g., Blinkov and Glezer, 1968; Brodmann, 1912; Passingham, 1973). This disproportionate expansion has been considered to be largely responsible for the uniqueness of human cognitive specialization (e.g., Deacon, 1997). However, other authors have concluded that the human frontal cortex is not disproportionately larger compared to that in other primates (Bush and Allman, 2004; Semendeferi et al., 2002; Uylings and van Eden, 1990). Nevertheless, different lines of evidence suggest that the human and the macaque prefrontal cortex share common general anatomical and functional organizational features. Specifically, comparative studies suggested that the basic architectonic organization of this region is similar in the two species (see, Petrides, 2005). Furthermore, recent models of executive functions in the human prefrontal cortex have emphasized a rostrocaudal hierarchical organization of cognitive processing (Badre, 2008; Botvinick, 2008; Koechlin and Summerfield, 2007) that could be based on rostrocaudal connectional gradients similar to those observed in the macaque VLPF (Borra et al., 2011; Gerbella et al., 2013).

In this context, there is clear clinical, electrophysiological, and imaging evidence for the involvement of the human middle frontal gyrus (MFG)—for the most part the putative homolog of the macaque ventral area 46 (Petrides, 2005)—in different aspects of executive control of motor

behavior. Activation of the MFG is prominent during action selection, particularly in tasks in which participants are required to freely select their movement (Rowe et al., 2005). Furthermore, TMS over this region affects free selection of hand actions (Hadland et al., 2001) and modulates the excitability of the primary motor cortex, showing temporally and spatially selective interaction between these two areas (Hasan et al., 2013). Clinical observations also indicate that lesions involving the MFG can be associated to limb apraxia (Goldenberg and Spatt, 2009; Haaland et al., 2000), and functional imaging evidence showed involvement of this region during the preparation of contralateral and ipsilateral hand actions (Gallivan et al., 2013b) and in higher-order aspects of hand-action control, such as tool use (Brandi et al., 2014; Choi et al., 2001; Johnson-Frey et al., 2005; Moll et al., 2000) and imitation learning of hand actions (Buccino et al., 2004; Higuchi et al., 2012; Vogt et al., 2007). Finally, the MFG displays visual object-related activation (Denys et al., 2004), activates during texture recognition (Stylianou-Korsnes et al., 2010), and appears to be involved also in tactile object recognition (Lacey et al., 2010; Reed et al., 2004; Savini et al., 2010). Cieslik et al. (2013) have suggested a rostrocaudal subdivision of the MFG into 2 distinct subregions in which the caudal one is characterized by functional connectivity with bilateral intraparietal sulci, including the location of the human AIP, and appears to be more strongly related to action execution and working memory. Altogether, data showing that the human MFG hosts areas/fields relatively directly involved in executive control of hand actions, as well as architectonic observations, suggest an homology of at least part of this region with the macaque VLPF hand-related sectors of areas 46v and 12r. The second and the third branch of the superior longitudinal fasciculus connecting the IPL with the frontal lobe (Thiebaut de Schotten et al., 2012), and the frontal inferior longitudinal tract connecting the precentral gyrus to the MFG (Catani et al., 2012) could provide the substrate for the participation of this region to the putative human homolog of the *lateral grasping network*. The possible MFG connectivity with hand-related PMv and IPL areas has not been yet explored in DTI studies, except for observations showing connectivity of this region with the caudal part of the SMG (Caspers et al., 2011).

5.4. Putative human homolog of the macaque insular node of the lateral grasping network

Recent functional imaging studies (Di Cesare et al., 2015, 2014) have provided evidence for a putative human homolog of the hand-related sector of the macaque insula and shed light on the possible contribution of this field to the control of hand actions. Specifically, the execution of object-oriented hand actions performed with a vitality form (e.g., gently or rudely) determined a specific activation, relative to control actions, of a sector located in the dorsocentral insula. This

same insular sector also became active during motor imagery and vitality forms observation. Based on these data, it has been suggested that during action execution, the insula modulate the cortical circuits for controlling hand actions, determining different vitality forms according to the internal state of the individual. This proposal fits well with the proposed general role of the insula in integrating information coming from the external context with that encoding the internal state of the individual (Craig, 2002) and in representing current emotional states and predicting emotional states relevant to the self and others (Lamm and Singer, 2010). Tractographic observations have provided evidence for connectivity of the insula with the PMv, the IFG, the MFG, and the IPL (Cerliani et al., 2012; Ghaziri et al., 2015).

In sum, there is clear functional evidence suggesting that in the evolution of the human lineage, the neural mechanisms for controlling hand actions described in the macaque have been retained and involve cortical sectors likely homologous to the nodes of the macaque *lateral grasping network* (Fig. 8). Furthermore, thanks to the differentiation of novel temporal, SMG, and IFG areas from phylogenetically older areas of the *lateral grasping network* and to the strengthening of the temporal-IPL-IFG connectivity, these basic neural mechanisms could have been also exploited for the development of higher-order cognitive functions unique to humans, such as tool use (Ramayya et al., 2010), social learning (Hecht et al., 2013), and high-order communicative behavior including language (see, e.g., Rizzolatti and Arbib, 1998).

6. Lateral grasping network vs. dorso-dorsal stream

One challenging question raised by research in recent years that appears to be crucial for better understanding the neural mechanism for generating hand actions concerns the potential division of labor between the *lateral grasping network* and the cortical circuits linking the caudal SPL with the PMd, forming the dorso-dorsal (Rizzolatti and Matelli, 2003) or dorso-medial (Galletti et al., 2003) stream. The caudal SPL hosts several visuomotor areas, such as V6A, PGm, PEc, and MIP, differentially connected with the PMd areas F7 and F2 (Bakola et al., 2010; Gamberini et al., 2009; Johnson et al., 1996, 1993; Marconi et al., 2001; Matelli et al., 1998; Tanné-Gariépy et al., 2002). These caudal SPL areas, in general, combine visuospatial information with gaze- and arm-related signals for visuomotor control of arm reaching movements (Battaglia-Mayer et al., 2001, 2000; Ferraina et al., 1997a, 1997b; Galletti et al., 2003, 1999, 1997, 1996; Marconi et al., 2001), thus supporting the notion that the dorso-dorsal stream is primarily involved in visuomotor control of reaching behavior (e.g., Battaglia-Mayer et al., 2003; Wise et al., 1997). The finding that neurons in one of these areas—V6A—show grasping-related activity (Fattori et al., 2010, 2009) has led to a

partial reinterpretation of the role of this stream in motor control. Area V6A is a major target of the motion-sensitive extrastriate area V6 (Galletti and Fattori, 2003; Galletti et al., 1996), the major source of visual information to the dorso-dorsal stream (Galletti et al., 2001). Extensive study by Galletti and colleagues (for a recent throughout review, see Fattori et al., 2015) has shown that in this area there is a high proportion of visual neurons responsive to the contralateral visual field with emphasis on the lower visual field from the fovea to the far periphery (Gamberini et al., 2011) and a smaller proportion of somatosensory neurons, mostly responding to displacement of proximal upper limb joints (Breveglieri et al., 2002). Many V6A neurons also display gaze- or saccade-related activity (Galletti et al., 1995; Kutz et al., 2003) or are active during the execution of reaching movement (Galletti et al., 1997), showing encoding of target depth and direction based on arm- and gaze-related signals (Hadjidimitrakis et al., 2014). However, the large majority of V6A reaching neurons also display grasping-related activity modulated by wrist orientation and grip type (Fattori et al., 2010, 2009), respond to visual presentation of real objects (Fattori et al., 2012), and appear to be involved in computation of object affordances (Breveglieri et al., 2015). These findings suggest encoding of signals related to both reaching and grasping behavior, even at the level of individual neurons, which differentiate area V6A from AIP, where purely distal motor acts are represented. A lesion of area V6A produces misreaching in visually guided movements with the arm contralateral to the lesion and deficits in wrist orientation and grasping movements (Battaglini et al., 2002). Area V6A is connected to the rostral PMd area F7 and to the rostro-ventral part of the caudal PMd area F2 (F2vr; Gamberini et al., 2009; Marconi et al., 2001; Matelli et al., 1998). Area F7 hosts neurons showing eye- and arm-related activity (Fujii et al., 2000) and coding position in space of targets for reaching movements (Vaadia et al., 1986), whereas F2vr hosts visuomotor grasping neurons encoding object features (Raos et al., 2004) and specifying object location relative to the monkey's peri- or extrapersonal space (Fogassi et al., 1999; see also Maranesi et al., 2014). Thus, the functional properties of this PMd sector appear in many aspects similar to those of F5p. Areas V6A (Gamberini et al., 2009) and both F7 and F2vr (Luppino et al., 2003) are also connected to the dorsal part of area 46 (46d), a region originally considered to be involved in encoding visuospatial information in working memory (see, Levy and Goldman-Rakic, 2000) but also involved in abstract representations and categorizations of complex motor sequences (Shima et al., 2007). Preliminary data (Borra et al., 2014a) show that there is a specific mid-caudal sector of area 46d displaying connections with PMd areas F7 and F2vr and caudal SPL areas V6A and PGm, thus providing evidence for a cortical network involving caudal SPL, PMd, and dorsal prefrontal areas, here tentatively designated as "*dorsal reaching–grasping network*". Note that F2vr, which is the premotor hand-related field involved in this network, does not appear to have a direct access to the

caudal part of the primary motor area where highly restricted hand muscle synergies are represented (Luppino et al., 2003; Tokuno and Tanji, 1993).

Human patients with lesions including the caudal SPL show optic ataxia (Perenin and Vighetto, 1988), characterized by misreaching in visually guided movements and deficit in adjusting hand orienting and shaping during prehension of objects under visual guidance, thus suggesting involvement of a putative human homolog of the macaque area V6A (Battaglia-Mayer et al., 2006; Galletti et al., 2004). Recent functional data (reviewed by Pitzalis et al., 2015) have provided clear evidence for a putative human homolog of the macaque area V6A that activates during pointing (e.g., Cavina-Pratesi et al., 2010; Galati et al., 2011) and appears to be involved in processing of object intrinsic and extrinsic properties (Monaco et al., 2015, 2014), wrist orientation, and grasping (Gallivan et al., 2011; Monaco et al., 2011). Furthermore, functional connectivity data have suggested (Tosoni et al., 2015) a linkage of this area with the PMd that could be supported by the first branch of the SLF (Thiebaut de Schotten et al., 2012). Finally, TMS of the PMd impairs the proper coupling between grasping and lifting an object, delaying the recruitment of proximal muscles responsible for the lifting phase (Davare et al., 2006). These data fit well with a possible role of the human homolog of the macaque dorso-dorsal stream in controlling combined proximal and distal movements.

Based on data from both macaque and human studies, Pitzalis et al. (2015) have suggested that the caudal SPL area V6A, thanks to visual input from V6, can compute object location even in dynamic conditions, such as those created by self-motion, which is crucial for orchestrating the eye and arm movements necessary to reach or avoid static and moving objects in the environment. This information, combined with information on object intrinsic properties, gaze, and arm-related somatosensory and motor signals, is then used along the SPL–PMd circuits (and, possibly, by the *dorsal reaching–grasping network*) for relatively fast feed-forward guidance and online monitoring of reach-to-grasp actions (Fattori et al., 2015; Maranesi et al., 2014).

The picture emerging from these relatively recent data goes beyond the proposed dichotomy between a dorso-dorsal and a ventro-dorsal stream primarily involved in visuomotor control of reaching and grasping, respectively (see, e.g., Culham et al., 2006; Karl and Whishaw, 2013), raising the challenging question of which is the relative contribution of the ventro-dorsal stream/*lateral grasping network* and the dorso-dorsal stream in controlling object-oriented hand actions. In the last few years, a series of functional studies in human subjects by Toni and colleagues (Grol et al., 2007; Verhagen et al., 2013, 2012, 2008) has contributed considerably in shedding light on this issue, at least at the macroscale level. These studies have first shown that the execution of object-oriented hand actions engages both a lateral pathway, running through the

putative human AIP and PMv, and a dorsal pathway, running through the putative human V6A and PMd. However, increase in activity and in functional connectivity was stronger in the lateral than in the dorsal pathway when grasping relatively smaller objects (Grol et al., 2007) and when planning object prehension required the processing of pictorial depth cues (Verhagen et al., 2008). These data suggest a primary role of the *lateral grasping network* when object-oriented actions require skilled control of hand movements or rely on perceptual information provided by the ventral stream. Moreover, as already noted above, Verhagen et al. (2012) provided evidence for a role of human AIP in the fast generation of motor plans of object-oriented actions based on both spatial and pictorial cues and learned object knowledge. Finally, there is evidence from TMS interference data that, when grasping objects, neural activity in the lateral pathway precedes that in the dorsal pathway (Davare et al., 2006; Taubert et al., 2010). Indeed, Verhagen et al. (2013) have shown that the dorso-dorsal stream is temporally dependent on AIP and that the ventro-dorsal stream can compensate for transient perturbations of V6A. These authors have then proposed a hierarchical organization between ventro-dorsal and dorso-dorsal circuits during planning and executing object-oriented actions, reflecting their temporal dependencies and the different levels of abstraction at which those circuits operate. Accordingly, first, the ventro-dorsal stream (we would say the *lateral grasping network*) computes an initial structure of the motor plan on the basis of object knowledge gathered from both dorsal and ventral visual streams and constructs an object-based action prior; then, the dorso-dorsal stream uses this movement structure as a prior for guiding the accurate parameterization.

The picture emerging from these human studies clearly suggests interaction between these two largely anatomically segregated networks when object-oriented actions are planned and put into action. Indeed, connectional data from macaque studies have shown that area V6A is reciprocally connected to caudal arm- and arm/eye-related IPL areas PG and Opt (Gamberini et al., 2009; Rozzi et al., 2006), respectively, and with area AIP (Borra et al., 2008; Gamberini et al., 2009). Furthermore, there is evidence for reciprocal connectivity between F2vr and F5p (Gerbella et al., 2011; Marconi et al., 2001). Thus, these data provide the substrate for interaction of the two streams at both the parietal and the frontal levels.

7. Concluding remarks

In the present article we have reviewed evidence from macaque and human studies to conclude that the primate brain is endowed with a large-scale cortical network, functionally specialized for controlling purposeful hand actions and designated as *lateral grasping network*. This network is

centered on the AIP–F5 circuit (or its homolog in the human brain) involved in visuomotor transformations for grasping and gathers information from both dorsal and ventral visual stream areas, prefrontal areas involved in executive functions, and orbitofrontal and insular areas affiliated to the limbic system. This network appears to have a leading role in controlling hand actions whenever the accomplishment of a given goal requires dexterous hand actions and management of pictorial cues, learned object knowledge, sensorimotor memories, and contextual information and the integration of specific hand motor acts within sequential actions. The *lateral grasping network* has two possible major outputs. First, it has a more direct motor output through projections to the primary motor cortex, which is fundamental for the execution of dexterous hand actions. Second, it has an output on the dorso-dorsal stream/*dorsal reaching-grasping network*, where visuospatial processing can guarantee appropriate guidance and monitoring of all the phases of the prehension movements. It is possible, however, that when there is no need of highly dexterous hand movements and temporal constraints are imposed, especially in a dynamic environment of self- or object motion, the dorso-dorsal-stream is primarily in charge of object-oriented actions. In this case, the engagement of the *lateral grasping network* would be minimized and mostly limited in providing the dorso-dorsal stream with information on object features resulting from fast visuomotor transformations of object intrinsic properties, carried out along the ventro-dorsal stream.

This possible unitary view of the cortical mechanisms for controlling object-oriented actions still needs firm empirical demonstration and pushes forward future research aiming to define the exact way in which these two main networks interact at both the parietal and the premotor levels in order to obtain a coherent orchestration of this important aspect of motor behavior that has been one major winning card in primate evolution.

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Figure legends

Figure 1. Schematic view of the lateral cortical surface of the macaque brain showing the areal subdivision of the frontal, parietal, insular and inferotemporal cortex. Cortical areas/fields taking part in the *lateral grasping network* are highlighted in gray. The superior (SA) and inferior (IA) arcuate, intraparietal (IP), lateral (L) and superior temporal (ST) sulci are shown unfolded to display the location of cortical areas buried in their banks. C, Lu and P indicate the central, the lunate and the principal sulcus, respectively. In the frontal lobe, prefrontal areas are defined according to Carmichael and Price (1994), Gerbella et al. (2007), and Saleem et al. (2014) and agranular frontal (motor) areas to Matelli et al. (1991) and Belmalih et al. (2009). Parietal areas are defined according to Pandya and Seltzer (1982) and Gregoriou et al. (2006) and insular subdivisions according to Mesulam and Mufson (1982b). Areas of the superior temporal sulcus and inferotemporal convexity cortex are defined according to Seltzer and Pandya (1978) and Boussaoud et al. (1990).

Figure 2. Projections from F5p to the hand field of the primary motor area F1 and the spinal cord. Distribution of retrogradely labeled neurons observed in the hemisphere of a macaque monkey after tracer injections in the hand field of the primary motor area F1 (A) and in the contralateral lateral funiculus of the spinal cord at the upper cervical levels (B). The labeling is shown on dorsolateral views of the hemisphere and in drawings of coronal sections through the posterior bank of the inferior arcuate sulcus, taken at the levels indicated on the dorsolateral view of the hemisphere. Section drawings through the central sulcus (a) and the spinal cord at level C4 (a') show the location of the injection sites. The labeling in F5p located in the posterior part of the postarcuate bank shows that this area projects to both the hand field of F1 and the spinal cord. Data from Borra et al. (2010). Abbreviations as in Figure 1.

Figure 3. Parietal and prefrontal afferents to F5p and F5a. Distribution of retrogradely labeled neurons in the hemispheres of two macaque monkeys observed after tracer injections in F5p (A) and F5a (B), respectively. Sections d and c' show the location the injection site in F5p and F5a, respectively. Parietal labeling in sections a, b, a' and b' shows that SII, PFG, and AIP are major sources of parietal afferents to both F5p and F5a. Connections of F5p with F1 (section c) and connections of F5a with the intermediate part of area 12r and the rostral part of the caudal half of area 46v (sections d' and e') are distinguishing features of the connectivity patterns of these two areas. Data from Gerbella et al. (2011).

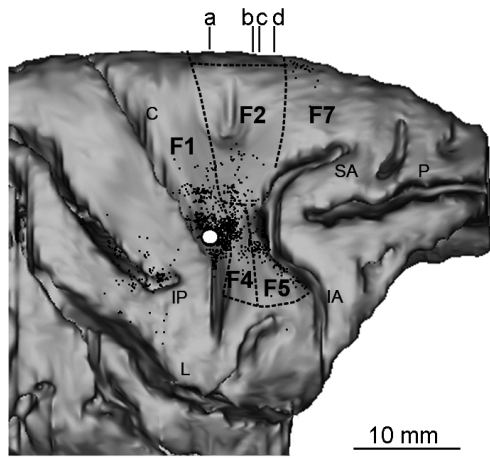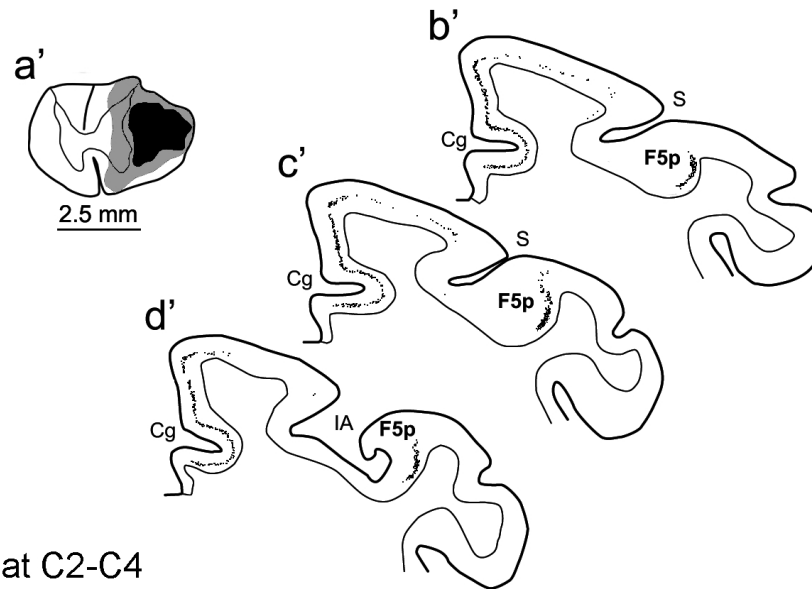**Figure 4.** Involvement of SII and dysgranular insula in the *lateral grasping network*. Distribution of retrogradely labeled neurons in the lateral sulcus, observed after tracer injections in areas PFG (A), AIP (B), F5a (C), 46v (D), and 12r (E). Each panel displays the results from two

different cases, shown in black and grey, respectively. To facilitate comparisons across cases, the distribution of the labeling in each individual case has been warped to a template 2D reconstruction of the upper bank of the lateral sulcus and of the insula, aligned to correspond with the fundus of the bank, indicated by a straight line. Rostral is on the right. Arrows mark the levels of AP 0 and of the rostralmost levels of the intraparietal (IP) and central sulcus (C). Panel F shows the location of the hand field of SII in a similar 2D reconstruction of the lateral sulcus and its anterior and posterior limit (indicated by arrows) on a lateral view of the hemisphere (modified from Fitzgerald et al., 2004). The rich labeling involving in all cases the SII hand field and the dysgranular insula shows that both these fields project to VLPF, PMv, and IPL nodes of the *lateral grasping network*. Reanalysis of data from Rozzi et al. (2006), Borra et al. (2011; 2008) and Gerbella et al. (2013; 2011).

Figure 5. Involvement of inferotemporal area TEa/m in the *lateral grasping network*. Distribution of retrogradely labeled neurons in the superior temporal sulcus, observed after tracer injections in areas AIP (A) and 12r (B). Each panel displays the results from two different cases, shown in black and grey, respectively, warped to a template 2D reconstruction of the superior temporal sulcus aligned to correspond with the fundus and middle of the floor. Arrows mark AP levels 0 and 12. The rich labeling involving in all cases the intermediate part of area TEa/m, between AP 8 and AP 12, shows that this sector projects to both areas AIP and 12r. Reanalysis of data from Borra et al. (2011; 2008).

Figure 6. Involvement of the intermediate part of area 12r and the rostral part of caudal 46v (46vc) in the *lateral grasping network*. Distribution of anterogradely labeled terminals in the hemispheres of two macaque monkeys observed after retro-anterograde tracer injections in the intermediate part of area 12r (A) and in the rostral part of area 46vc (B), respectively. Sections a and a' show the location the injection site in intermediate 12r and rostral 46vc, respectively. Anterograde labeling in PMv (sections b and b'), in the parietal operculum (section c and c'), in the IPL (sections d and d' and lateral view of the hemisphere in B) and in the inferotemporal cortex (section c) shows that intermediate 12r and rostral 46vc both project to F5a, SII, and AIP, intermediate area 12r projects also to the intermediate part of area TEa/m, and rostral 46vc projects also to PFG. Data from Borra et al. (2011) and Gerbella et al. (2013).

Figure 7. Summary view of the nodes and connections of the macaque *lateral grasping network*. Text boxes shortly indicate the possible contribution of each node to the generation of hand actions.

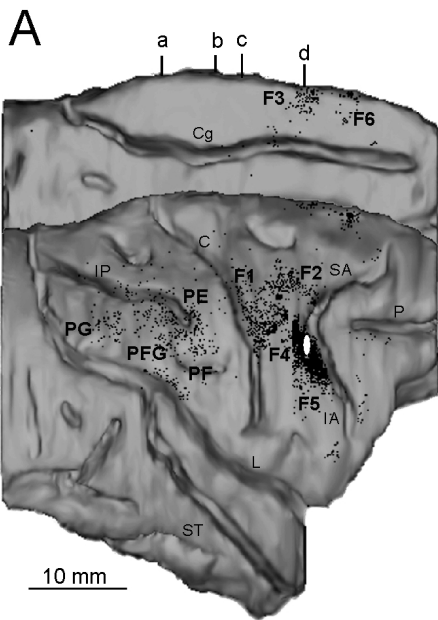**Figure 8.** Summary view of the possible human counterparts of the nodes of the macaque *lateral grasping network*.
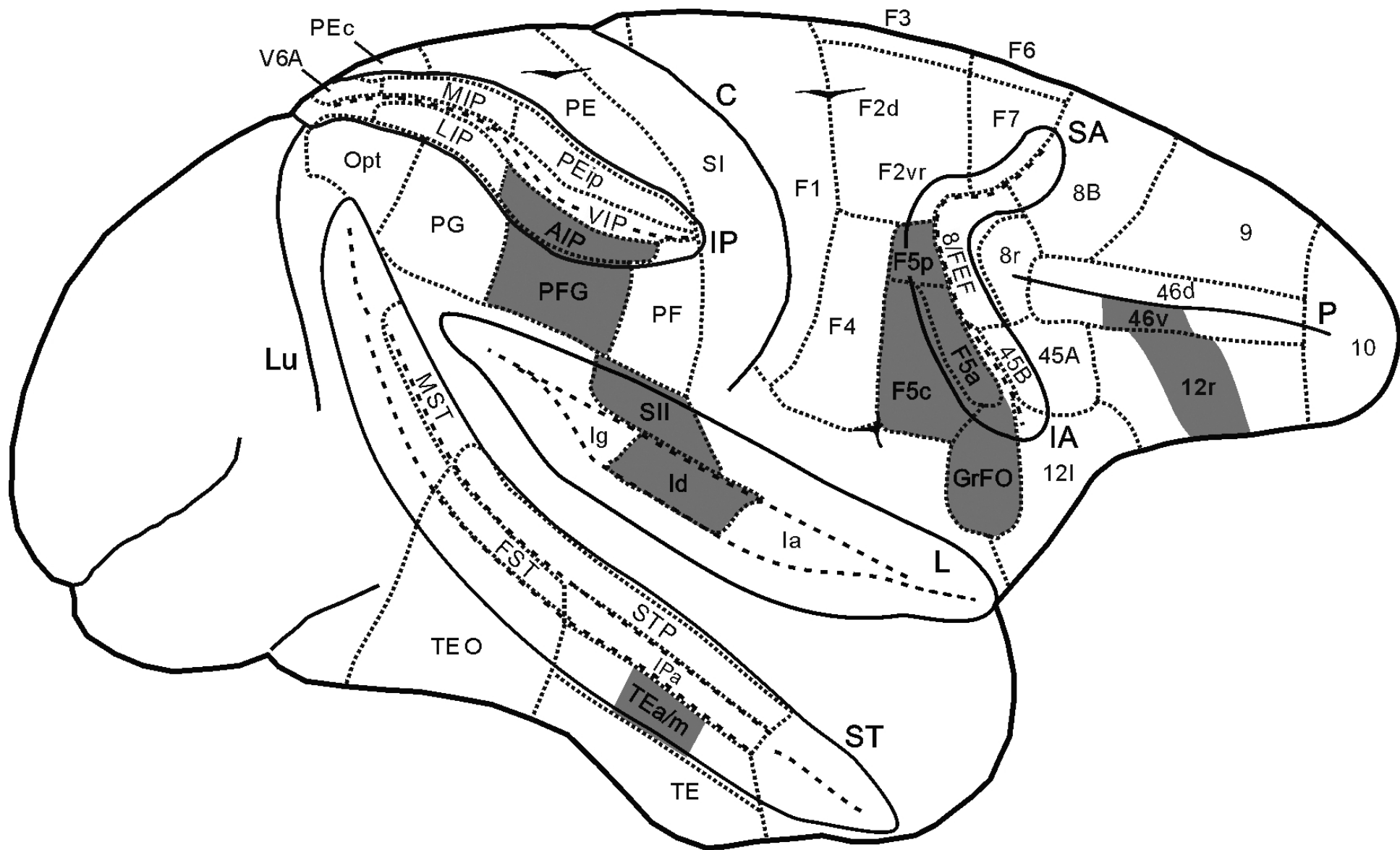
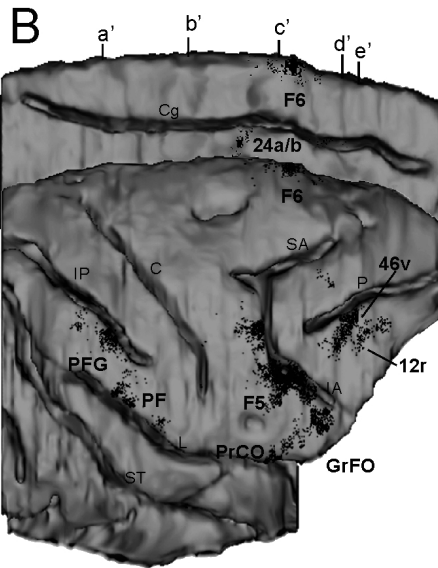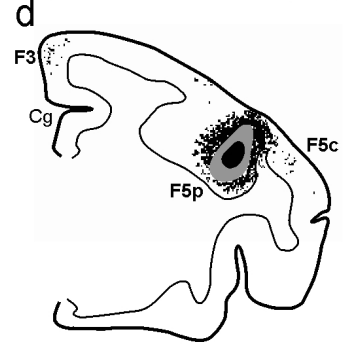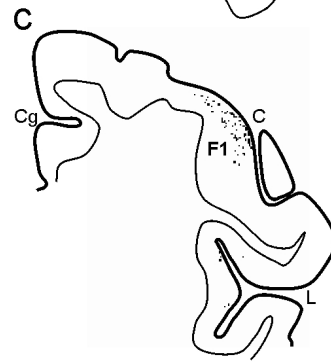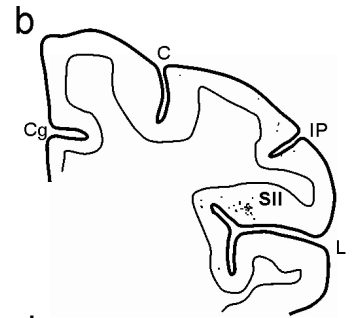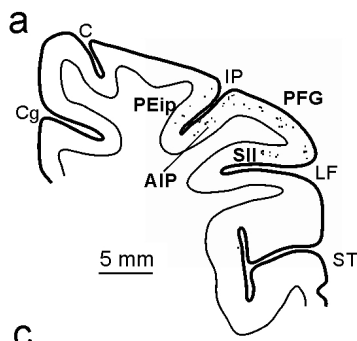A — Injection in the hand field of F1
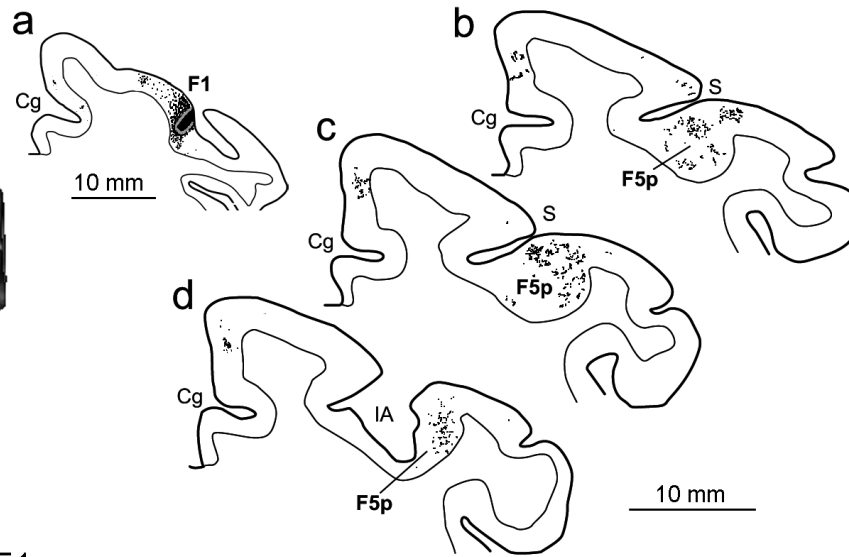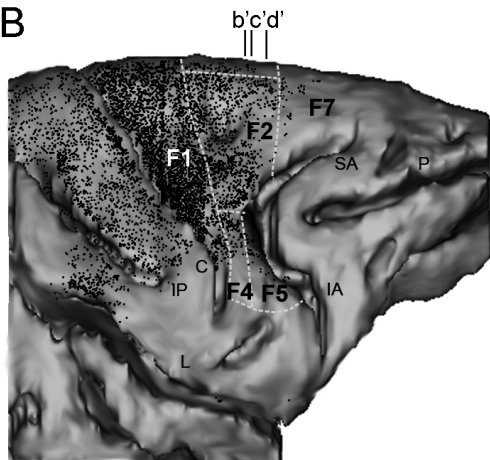
B — Injection in the lateral funiculus at C2-C4

A

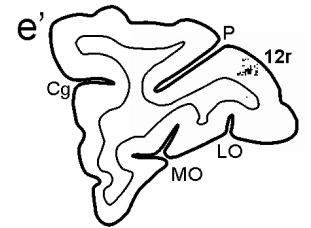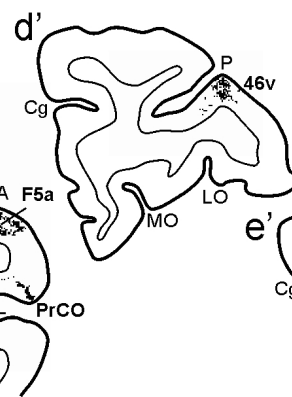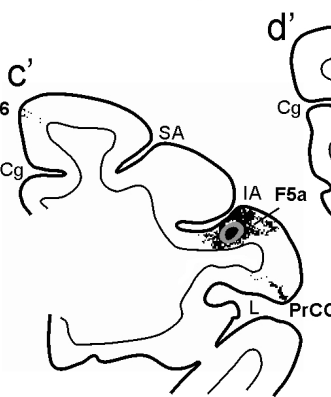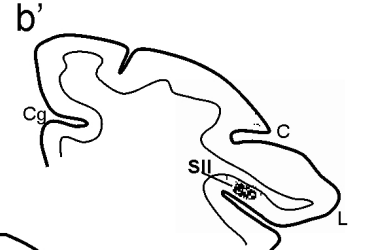F3
F6
Cg
C
IP
F1
F2
SA
PE
PG
PFG
PF
F4
F5
IA
P
L
ST

10 mm

Injection in F5p

a

C
Cg
PEip
IP
PFG
AIP
SII
LF
ST

5 mm

b

Cg
C
IP
SII
L

c

Cg
F1
C
L

d

F3
Cg
F5p
F5c

B

a'
b'
c'
d' e'
Cg
F6
24a/b
F6
SA
IP
C
P
46v
PFG
12r
PF
F5
IA
L
PrCO
GrFO
ST

Injection in F5a

a'

C
Cg
IP
PFG
AIP
L

b'

Cg
C
SII
L

c'

F6
SA
Cg
IA
F5a
L
PrCO

d'

P
46v
Cg
LO
MO

e'

P
12r
Cg
LO
MO

A **PFG** 0 IP C SII UBL PGop Ig Id Insula 10 mm

B **AIP** 0 IP C SII UBL PGop PrCO Insula Id

C **F5a** 0 IP C SII PrCO UBL Insula Id

D **46v** 0 IP C SII PrCO UBL Insula Id

E **12r** 0 IP C SII UBL PrCO Insula Id Ia

F **SII hand field** from Fitzgerald et al. 2004
A M A M Digits M A M UBL A Palm D1 M Trunk A Palm D5 M A Palm Digits M HL A M HL HL A A Trunk
LBL Insula
IP SA C P Lu IA L ST

A AIP

B 12r

0

12

MST

STP

UBST

fundus

IPa

TEa/m

TEO

LBST

10 mm

0

12

UBST

fundus

IPa

TEa/m

LBST

A

F6

Cg

24a

SA

IP

C

P   46v

Lu

SII

F5a   IA

GrFO

IO   L   PrCO   12l

ST

10 mm

Injection in intermediate 12r

B

Cg

F6

24a/b

IP

C   SA

PFG   P

46d

PF

Lu   L   12r

F5a   IA

PrCO   GrFO

IO

ST
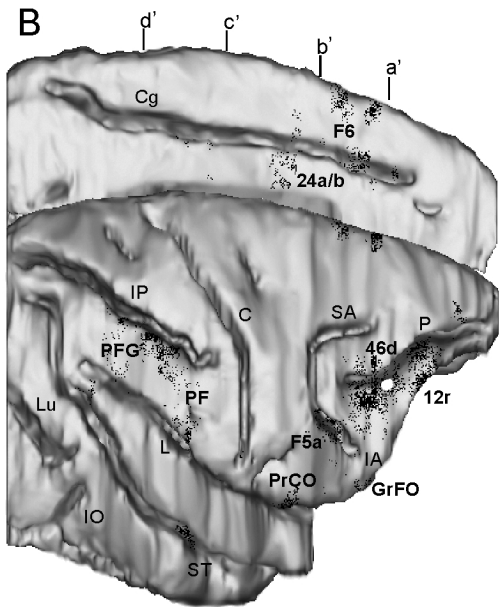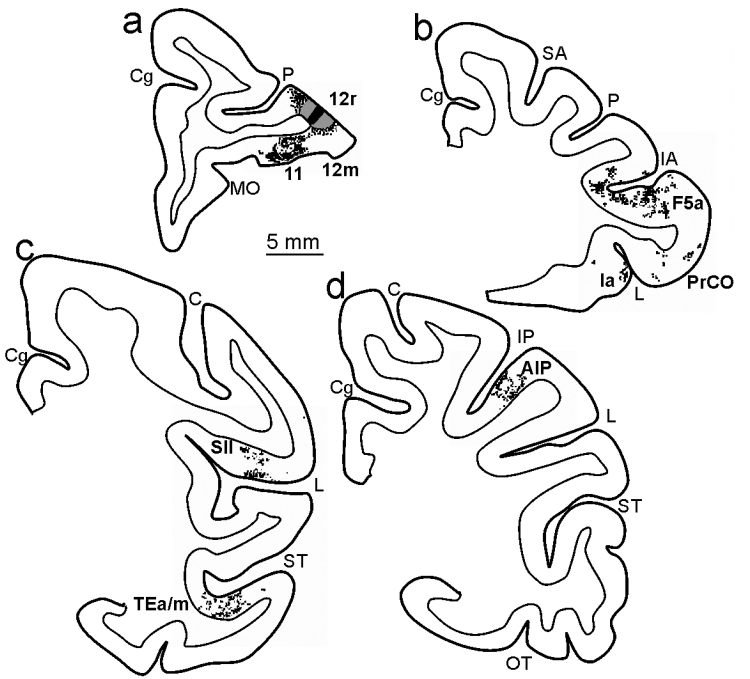
Injection in rostral 46vc

a

Cg   P   12r

MO   11   12m

5 mm

b

SA

Cg   P

IA

F5a

Ia   L   PrCO

c

C

Cg

SII

L

TEa/m   ST

d

C

IP   AIP

Cg

L

ST

OT

a'

Cg   P   46vc

12r

MO

b'

SA

Cg   IA

F5a

c'

C

Cg

Id   SII

L

d'

C

Cg   IP

AIP   L
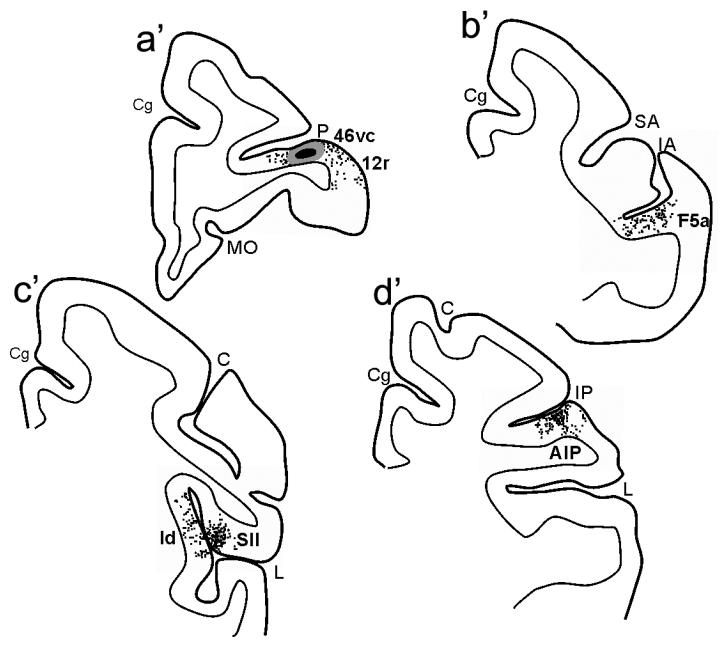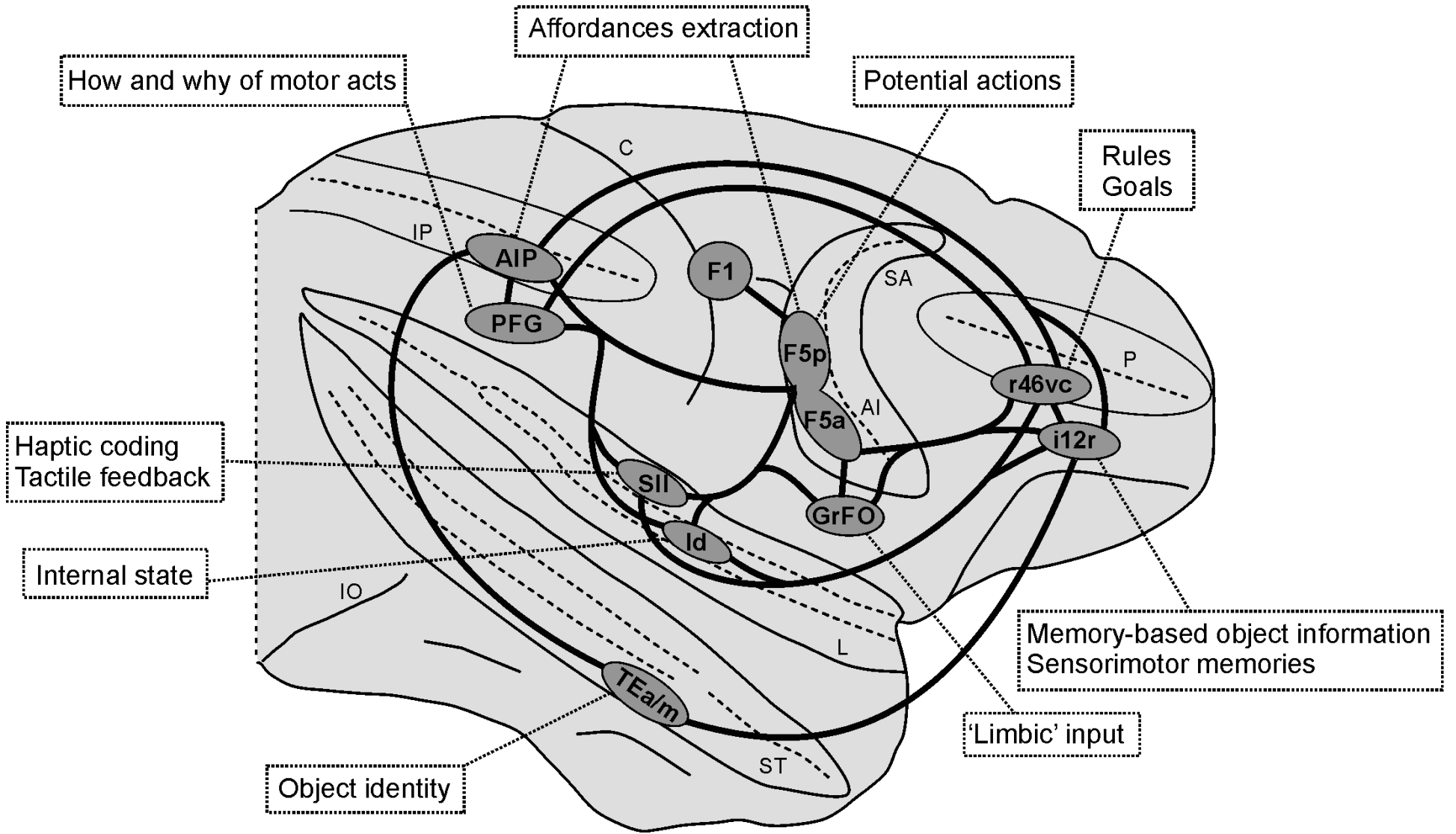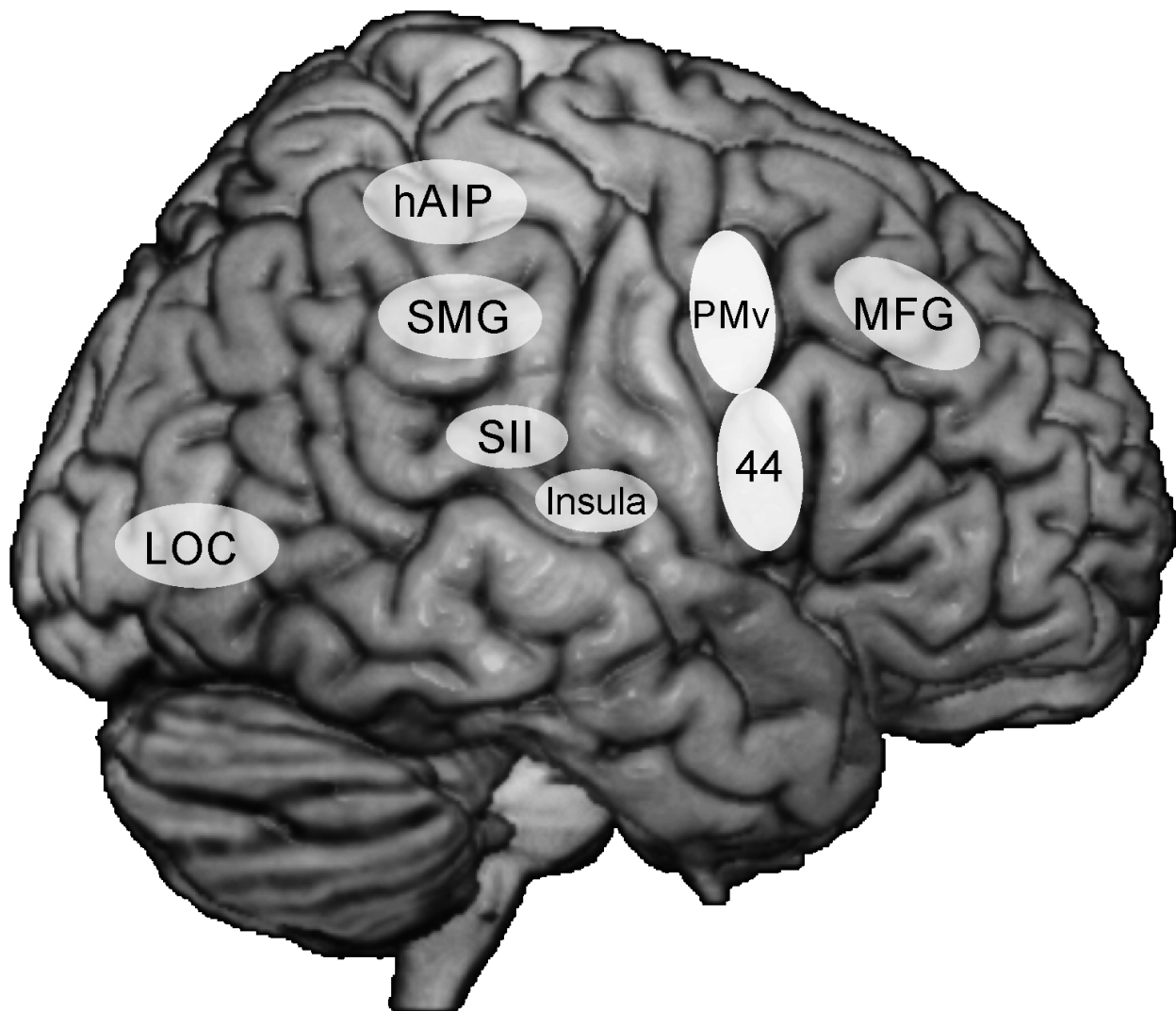
Highlights

Inferior parietal–ventral premotor macaque circuits crucially involved in visuomotor transformations for grasping are at the core of a large-scale cortical network

This network –the *lateral grasping network*– includes sectors of the parietal and frontal operculum and of the inferotemporal, ventrolateral prefrontal, and insular cortex

The *lateral grasping network* is a possible substrate for interfacing perceptual, cognitive, limbic and hand-related sensorimotor processes, extending grasping models so far proposed

This network could play a primary role whenever dexterous hand actions require management of pictorial cues, learned object knowledge, sensorimotor memories and contextual information

There is evidence for a possible human counterpart of the macaque *lateral grasping network*