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Coding of grip type and action goal in premotor and parietal grasping neurons

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INTRODUCTION

1.1 Movements, motor acts and action.

From neurophysiological point of view, *movement* could be defined as the activation of a single muscular district that allows the displacement in the space of joints, such as thumb flexion, wrist rotation etc.

Conversely, *motor acts* are composed by synergy of movements and different joints organized in order to achieve their own goal. Reaching, grasping, bringing to the mouth, and biting represent distinct motor acts, each of which is endowed with its specific motor goal (e.g.: the goal of grasping is that of taking possessions of an object).

Planning and executing an a*ction*, such as "grasping and eating an apple", implies having a final goal (e.g., "to eat the apple") that leads to the selection of an appropriate sequence of "motor acts" (Rizzolatti et al., 1988; Bonini et al., 2010).

From a neurophysiological perspective (Fogassi et al., 2005; Iacoboni et al., 2005) the final action goal is considered to be an internal representation that determines the selection of the motor acts and the organization of the action itself. This final action goal can be identified as the *motor intention* of the acting individual.

According to this view, action goal defines not only *why* we perform an action but also *what* kind of motor acts are necessary to achieve that goal and *how* doing them. For example, the vision of a steaming cup of tea is a sensory cue that could suggest to an observer to drink it. Otherwise, the empty cup after the teatime could suggest to clean it. The motor acts that allow the accomplishment of the actions "drink" or "clean" the cup are essentially the same: reaching the cup, grasping and bringing it to the mouth or to the sink. Note that the way in which they are performed could be different depending on the final goal of the action in which the motor acts are embedded. If agent's motor intention is drinking the tea, he performs grasping motor act using the index and the thumb (precision grip). On the contrary, moving the cup in order to clean it induces the agent to grasp it using another type of grip for example a whole hand prehension.

1.2 Cortical control of voluntary movement

Traditionally, the frontal lobe of primates is anatomically formed by two main sectors: a rostral one (prefrontal cortex) endowed with higher order cognitive functions such as working memory (Wilson et al., 1993), planning goal direct behaviours and problem solving (Matsumoti and Tanaka, 2004), and a caudal one that is related to the control of movements. Experimental evidence on the motor role of this caudal sector has been firstly assigned by electrophysiological studies (Ferrier, 1874; Fritsch and Hitzig, 1870) showing that the electrical stimulation of the surface of this cortical region could evoke muscle twitches. Over the next several decades different studies confirmed and extended these findings identifying a primary motor map that contained a relatively clear separation among body part representation, and an adjacent premotor area that contained more overlap among body part representations (Fulton, 1935; Vogt and Vogt, 1919). In line with these functional data, anatomical studies pointed out that the caudal frontal sector, that completely lacked of granular cells (agranular frontal cortex), can be subdivided into two cytoarchitectonic areas: area 4 and area 6, respectively the primary motor and premotor cortex (Broadmann 1909). However, the role of area 6 has been matter of debate for years. A central issue of this debate has been the relationship between area 6 and area 4. According to Fulton (1934), who more than anyone popularized the concept of a premotor cortex, area 6 was functionally separated from and functionally higher than area 4. In this line, premotor cortex had a unique role in programming movements and in particular sequence of movements whereas primary motor cortex was involved in movement execution. On the other hand, Penfield and Welch (1951) and Woosley et al. (1952), using as evidence the results of their electrical stimulation experiments respectively on human and monkey brain, proposed that there was no premotor cortex anterior to the primary motor cortex. Instead, they proposed that motor cortex was divisible into a lateral motor cortex (M1) and medial motor cortex (M2 or supplementary motor area, SMA) both containing a map of the body that was used to control movements. According to them, the rostral part of area 6 is not involved in movement control. This data strongly supported the hypothesis that perception and action were separate and hierarchically organized psychological functions. In this view, the information was processed following a serial order, starting from associative regions such as posterior parietal cortex (PPC) where afferents from different sensory modalities were integrated in order to provide the basis of perceptual processes. In the associative cortex a motor plan was elaborated and subsequently send to motor cortex that had the unique function to execute it.

Premotor cortex

The ideas of Woosley have been a dogma in the physiology of the motor system for almost three decades.

In the mid-eighties of the 19th century, a convergent series of data coming from anatomical and functional studies reveal that Brodmann'area 6 is functionally different from area 4 and includes architectonically distinct areas (Matelli et al., 1985). These various motor areas have specific different afferent and efferent connections and appear to play different functional role in motor control. Comparing this parcellation with the classical map of Brodmann, F1 correspond to Brodmann area 4 while the others areas (F2-F7) lie inside Broadmann area 6 or premotor cortex. In particular, it is possible to distinguish three main premotor cortical sectors: the ventral premotor cortex (area F4 and F5), the dorsal premotor cortex (area F2 and F7) and the mesial premotor cortex (area F3 and F6). In accord to their extrinsic connections, the anterior premotor areas (F6-F7) receive their main cortical input from prefrontal cortex ("prefronto-dependent"motor areas) which plays a role in "high-order" functions such as working memory, temporal planning of actions and motivation (Luppino and Rizzolatti 2000). The caudal premotor areas (F2-F5) receive their main connections from parietal cortex, also formed by a multiplicity of independent areas, each of which appears to deal with specific aspects of sensory information.

Moreover, the subdivision of premotor areas by cortico-cortical projections is in accord with their connections with the spinal cord (Rizzolatti and Luppino, 2001). In the frontal lobe, corticospinal tract originates from the caudal motor areas that is from F1, F2, F3 and part of F4 and F5. An important difference between corticospinal projection originating from F1 and those arising from premotor areas consists in their different terminal territory in the spinal cord. Fibres originating from F1 end in the intermediate regions of the spinal cord (laminae VI, VII, and VIII) and in lamina IX, where motor neurons are located. Projections from premotor areas conveyed through corticospinal tract mostly terminate in the spinal cord intermediate region. The functional interpretation proposed by Luppino and Rizzolatti (2000) is that spinal projections from F2, F3, F4 and F5 activate preformed medullar circuits, determining the global frame of the movement. In contrast, projections originating from F1 break innate synergies by ending directly on motor neurons and in this way determine the fine morphology of the movement. All premotor areas but F6 and F7, are involved in movement execution directly by means of projections to spinal cord or indirectly through projections to F1.

These anatomical data are also supported by lesion studies in primates. Lesions involving the hand representation of the primary motor cortex or its projections to the spinal cord cause a severe loss of manual dexterity, especially the ability to make independent finger movements that are controlled by direct cortico-motoneuronal projections. A remarkable recovery is possible when premotor cortex is undamaged. Recent studies (Borra et al., 2010) suggest that the hand field of monkey's area F5 has an important role in the functional recovery of manual dexterity after lesions of F1 by its cortico-spinal projections which terminate in the upper segments (C3-C4) of the spinal cord. At this spinal level propiospinal system mediates effective di-synaptic or oligo-synaptic pyramidal excitation to hand muscle motoneurons (Isa et al., 2007).

Posterior parietal cortex

Parietal cortex is subdivided in two main regions: the primary somatosensory cortex and, caudally, the posterior parietal cortex (PPC). The intraparietal sulcus is a fundamental landmark in the parietal lobe of primates, since it subdivides the PPC in two main sectors: superior parietal lobule (SPL) localized above the intraparietal sulcus and inferior parietal lobule (IPL), localized below to it.

Classically, the posterior parietal cortex (PPC) of primates has been considered as a large associative cortical region whose functional role was to integrate afferents originated from different sensory modalities in order to provide the basis for perceptual processes such as space perception and perception of the body schema (Critchley, 1953). Thus, perception and action were defined as two separate, different domains that were processed by different cortical areas.

In contrast to this view, various lines of evidence have shown that PPC is not only involved in higher order sensory analysis but also plays an important role in motor control. Similarly to the frontal cortex, anatomical studies identified several areas in SPL and IPL that are strictly connected to frontal areas, providing a more complex scenario. According to Pandya and Seltzer (1982), SPL consists of two main regions, area PE and area Pec, while IPL convexity is formed by 3 areas: a rostral, an intermediate, and a caudal one, defined as PF, PG, and Opt, respectively, plus a transitional area located between areas PF and PG and named PFG. Further citoarchitectonic and odological studies (Gregoriou et al., 2006; Rozzi et. al., 2006), besides confirming the subdivision proposed by Pandya and Seltzer, identified area PFG as an independent area with distinct architectonic features and pattern of connections. Other areas belonging to IPL lie in the ventral bank and in the fundus of the intraparietal sulcus: area AIP, VIP and LIP. Area PEip and MIP that are located in the dorsal bank of the sulculs belong to SPL. Physiological studies in monkeys (Mountcastle et al., 1975; Hyvärinen, 1981) showed that PPC is formed by a mosaic of distinct functional areas, each receiving either visual or both somatosensory and that is involved in the control of sensory guided movements performed with different effectors. This line of evidence is in contrast with the classical view that assigned to PPC the unique role of associative region, and supports the idea of a key role in motor control. Thus, perception and action cannot be considered anymore segregated processes but they derive from the activity of largely independent parallel system.

Particularly influential in this conceptualization of the functional role of PPC was the work of Milner and Goodale (Goodale and Milner,1992; Goodale et al., 1995). They re-examined the proposal of Mishkin and Ungerleider (1982) that the visual cortical areas are functionally organized in two information streams: one centred on area V4 and bringing the information on object properties to the inferior-temporal lobe (ventral stream), the other was centred to MT/V5 and bringing spatial information to the parietal lobule (dorsal stream). The functional difference between these two streams relies in the resulting percept: ventral stream elaborates visual information in order to obtain a perceptual description of objects while dorsal stream elaborates visual information for space perception. The functional value of the anatomical duality proposed by Ungerleider and Mishkin was supported by the effects on monkey behavior following separate lesions of each pathway. Lesion of the ventral stream primarily affected object recognition, whereas lesion of the dorsal system produced disturbances in object localization.

Milner and Goodale (Goodale and Milner, 1992; Milner and Goodale, 1995) reported the case of a patient with visual agnosia: she was unable to recognize objects or to deliberately size her fingers according to the size of visually inspected target objects. On the contrary, when the patient was previously instructed to take the object, she was able to reach object's location and accurately preshape her hand according to the object's size and shape. In agreement to the functional difference between the two steams stressed by Ungerleider and Miskin, Milner and Goodale speculated that the difference in the two systems relies in the use that the individuals make of the visual information. Visual information that reaches different brain regions according to these pathways is the same but it is elaborates in parallel: the ventral stream provides visual information for perception ("what") and the dorsal stream provides information necessary for the control of action ("how").

Rizzolatti and Matelli (2003) proposed further subdivision of the dorsal stream: the dorso-dorsal stream (d-d- stream) formed by area V6 and area V6A and MIP, and the ventro-dorsal stream (v-d stream) formed by area MT and by the visual areas of the inferior parietal lobule. The d-d stream is strongly connected to SPL and the latter to MST and IPL. Although both streams have a role in action organization, the v-d stream plays a crucial role in space perception and action understanding. Monkey electrophysilogical studies have shown that these two perceptual functions depend on specific parieto-premotor circuits, each involved in particular sensory-motor transformation. The first circuit transforms the visual location of an object in an appropriate reaching movement. The second transforms the biological information about a motor act into its motor representation. In the following section another parieto-premotor circuit with a central role in the transformation of object features in motor rapresentatio is described.

1.3 Visumotor transformation for grasping

Skillful objects grasping requires the transformation of intrinsic object properties (size and shape) into a pattern of distal movements (finger and wrist). In humans and in monkeys, different neurophysiological studies identifing in the cortical circuit, comprising the anterior intraparietal area (AIP) and ventral premotor area F5 a visuomotor grasping circuit that allows transformation of an object physical properties into a suitable motor command for grasp.

In monkeys, single-neuron recordings carried out using the naturalistic approach showed that the firing of the majority of neurons of area F5 is related to specific goal-related distal motor acts and not to single movements (Rizzolatti et al., 1988). Execution of distal motor acts such as grasping, holding, manipulating, and tearing are very effective in triggering F5 neuron responses. In addition, most of "grasping neurons" code specific types of hand prehension, such as precision grip, whole hand and finger prehension. A crucial property of F5 neurons is that goal coding is independent of the sequence of movements or, very often, of the effector used to achieve it, showing a high level of motor abstraction. Umiltà and coworkers (2008) provide a strong empirical validation of this proposal. Monkey were trained to grasp food with "normal pliers", opened by the extension of the fingers and closed by their flexion, and with a "reversible pliers" that requires finger opening, instead of closing in order to grasp an object. The results showed that a number of F5 motor neurons that were activated during hand grasping, also discharged during grasping with pliers.

It has been proposed that in area F5 there is a "vocabulary" of elementary motor acts in which each "word" corresponds to a category of motor neurons that represent either the goal of the motor act, or the way in which it is executed, or the temporal segmentation of the action (Rizzolatti et al., 1988).

Besides motor neurons, a considerable part of F5 neurons respond to visual presentation of three-dimentional (3D) objects. Very often there is a strict relationship between the type of prehension coded by a neuron and the physical characteristics of the stimulus effective in triggering its visual responses (Rizzolatti et al., 1988; Murata et al., 1997; Raos et al., 2006).

Experimental paradigms similar to that used to investigate the functional properties of F5 neurons were performed also in monkey anterior intraparietal area (AIP, Murata et al., 2000). Similar to F5, area AIP contains neurons that discharge during grasping in both light or dark conditions but not during the visual fixation of objects ("motor dominant" neurons) or neurons that respond stronger during grasping in light and also during object fixation ("Visual and motor" neurons). A third class of AIP neurons discharge only during grasping in light and during object fixation ("visual dominant" neurons). This last class of neurons is not present in area F5. Likewise to area F5, the visual responses of AIP neurons represent the shape, size and orientation of 3D objects and the activity of "motor dominant" neurons in part represents parameters of hand movements such as shape of the hand, grip size, or hand orientation. Anatomically, area AIP is strictly connected to area F5 (Borra et al., 2008) providing anatomical support to the notion that AIP and F5 form a parieto-frontal circuit dedicated to visuomotor transformation for grasping. Moreover, AIP display strong connections with several sectors of the inferotemporal cortex. The identification of direct anatomical connections with the inferotemporal cortex gives to AIP the unique role of linking the parieto-frontal network of areas involved in sensorimotor transformations for grasping with areas involved in object recognition. It could represent a crucial node in a cortical circuit in which hand related sensory and motor signals have access to representations of object identity for tactile object recognition.

Furthermore, reversible lesion experimenters have shown that inactivation of area AIP (Gallese et al., 1994) or F5 (Fogassi et al., 2001) produces grasping impairment, which results in a mismatch between the actual object shape and the appropriate hand preshaping. Differently from AIP, however, PMv also exerts a strong influence on M1 (Shimazu et al. 2004; Cattaneo et al. 2005; Umiltà et al. 2007; Davare et al. 2009; Prabhu et al. 2009; Buch et al. 2010) and the spinal cord regions (Borra et al. 2010) that are responsible for the generation and control of hand movements. In humans, Davare et cowokers (2010) show that virtual lesions of AIP with theta-burst transcranical magnetic stimulation (cTBS) is associated with a relative loss of the grasp-specific pattern of digit muscle activity. Moreover, the usual muscle-specific PMv-M1 interactions that appeared during grasping preparation were significantly reduced without directly modifying corticospinal excitability. The authors suggest that AIP virtual lesion reduces the amount of visual information about the object that is passed to PMv, and this in turn reduces the extent to which motor programs can be tuned to different graspable objects. Virtual lesion of AIP could affect the precise hand-object relationship and resulting in less accurate motor prototype to shape the hand appropriately around an object.

1.4 Hand grasping neurons: grip type

“ *This diversity (of the prehensile activities of the hand) is in fact not so much an expression of a multiplicity of movements but of the vast range of the purposive actions involving objects of all shapes and size that are handled during every day activity”* (Napier, 1955).

Raos and co-workers (2006) investigated the motor and visual properties of F5 grasping neurons using a controlled paradigm in which monkeys had to grasp or to observe different three dimensional objects. This study shows that all recorded neurons display a preference for grasping and object or a set of objects with a specific type of grip. Moreover, in about half of the neurons the same preference is present also during the visual presentation of the same object. The congruence between the motor and visual discharge is express by the type of grip that is useful to interact with an object or a set of objects.

In the inferior parietal lobule (IPL) of the monkey recent studies (Fogassi et al., 2005; Rozzi et al., 2008; Bonini et al., 2010) show that motor neurons became active in relation to movements having a specific goal. Similarly to F5 neurons, they are active during a specific motor act and not when a similar movement is performed with another purpose, and some of them discharge when the monkey use different effectors to achieve the same motor goal (e.g.: grasping with mouth and grasping with hand). Moreover, functional mapping studies of the convexity of IPL (Hyvärinen, 1981; Rozzi et al., 2008) show a general somatotopy based on the distribution of the type of motor acts and effectors used to achieve their goals. This distribution roughly correspond to the cytoarchitectonic subdivision identified by Gregoriou and coworkers (2006) that allows to consider these cytoarchitectonic fields as three distinct anatomo-functional areas. In the most rostral part of IPL, that is area PF, the most represented motor acts are biting and, to a lesser extent, hand grasping. Area PFG contains hand-related neurons in particular grasping neurons. Area PG is characterized by neurons that are activated during the execution of arm reaching. Finally, in area Opt oculomotor responses are mainly representated.

A considerable number of PFG neurons code how grasping act has to be performed, showing selectivity for a specific type of grip but also respond to visual presentation of objects as shown for AIP and F5 neurons (Rozzi et al., 2008). This functional similarity is strongly supported by strict and reciprocal connections between F5, AIP and PFG, suggesting that IPL convexity should be considered as a part of the motor system.

1.5 Hand grasping neurons: action-goal coding

In the rostral part of the convexity of the inferior parietal cortex Yokochi and co-worker (2003) have identified a class of neurons (face-hand neurons) that respond to somatosensory stimuli applied to the face and hand simultaneously. These neurons were more active during the execution of face and hand actions together. The authors proposed that the rostral part of IPL is a region in which synergism between sensory and motor signal is organized and used for action construction. Recently, it has been demonstrated that the discharge of most IPL hand grasping neurons was influenced by the final goal of the action sequence in which the grasping act was embedded (Fogassi et al., 2005; Bonini et al., 2010). In the study of Fogassi and co-workers (2005), grasping neurons of area PFG were tested in two main conditions. In the grasp-to-eat condition, the monkey reached and grasped a piece of food located in front of it and brought it into its mouth, while in grasp-to-place condition the monkey reached and grasped an object in order to place it into a container. Thus, although in both conditions the first motor act the monkey had to performed was the same, the final goal of the two actions sequence was different. These findings and the properties of IPL neurons (Yokochi et al., 2003) suggest that in this cortical sector neurons are organized in chains, each of which aimed at a specific action goal (Fogassi et al., 2005; Rizzolatti et al. 2006).

Because of the strict anatomical connections between area PFG and area F5, the same paradigm was used by Bonini and co-workers (2010) to record neurons from both premotor area F5 and parietal area PFG. The aim of the study was that of verifying if motor neurons of area F5 discharge differently in accord to the final goal of the action in which the coded act is embedded. A second aim was to understand the possible differential roles of these two areas in coding action goals. The main finding of the study was that also in F5 the discharge of part of hand grasping neurons is influenced by the action goal. However, motor neurons are more frequently and strongly influenced by action goal in area PFG. Although anatomical studies evidence the presence of reciprocal connections between the recorded sector of area PFG and F5 that could explain their functional similarities, it is also known that these two areas are connected with different cortical regions thus showing different functional specificity. Also prefrontal cortex is more strongly connected on area PFG than area F5. This latter area is stronger connected to M1 and others premotor areas. According to this neuroanatomical pattern, the two areas provide a different contribution to action goal coding. Very likely, area PFG plays a more important role in organizing motor acts into actions while F5 appears to be more involved in coding the goal of the single motor acts in a more abstract fashion (Rizzolatti et al., 1988; Umiltà et al., 2008).

1.6 Aims of the study

All together these data have shown that action goal and grip type are different motor aspects that both premotor and parietal hand grasping neurons can reflect in their discharge. Do these variables, grip type and action goal, are integrated at the single neuron level or are they separately encoded by distinct neuronal systems, working in parallel during action unfolding? To address this issue, here we recorded neuronal activity from inferior parietal area PFG and ventral premotor area F5 of three monkeys while they performed simple grasp-to-eat and grasp-to-place natural actions, requiring different types of grip to grasp the target object. This enabled us to clarify the functional relationship between grip types and action goal coding at the single neuron level.

MATERIALS AND METHODS

The study has been carried out on three macaque monkeys (2 female *Macaca nemestrina* and 1 male *Macaca mulatta*), which will be referred to as M1, M2 and M3, respectively.

Before recordings, each monkey was habituated to comfortably sit upright in a primate chair, to interact with the experimenters and to familiarize with the experimental setup. Then, they were trained to perform the motor task described below using the hand contralateral to the hemisphere to be recorded. When the training was completed, a head fixation system and a titanium recording chamber were implanted under general anaesthesia.

All the experimental protocols were approved by the Veterinarian Animal Care and Use Committee of the University of Parma and complied with the European law on the humane care and use of laboratory animals.

2.1 Training session

Monkeys were trained to sit in the primate chair and to receive their daily food. In this way, they got used to interact with the experimenter and grasping the food from his hands. Moreover, monkeys were habituated to receive tactile stimulations or slow and fast mobilization of joints, and to pay attention to the experimenter's actions executed in different regions of space.

When monkeys were completely comfortable with the experimental set up, they were trained to execute the motor task.

Behavioral task and apparatus

The basic motor task employed in this study allowed us to study two different variables: action goal and grip type. In order to study the first variable, monkey had to grasp a piece of food and bring it into the mouth, or to place it into a container located near its mouth (figure 1A). The apparatus used for the task consisted of a square plexiglass table (side=42 cm) attached to the primate chair. A metal cylinder (diameter 28 mm, height 25 mm) was fixed to the table on a virtual line prolonging the monkey body midline, at a distance of 16 cm from it. Monkey held its hand in a fixed starting position while the experimenter positioned a piece of food (apple, carrot or fresh potato) or an object (of the same size and shape of the food) as target in one of the specific devices described below. During these operations, a transparent plastic screen (40 x 23 cm) was interposed between the monkey and the target. The first part of the task was identical in all conditions. When the screen was removed, the monkey detached its hand from the cylinder in order to reach and grasp the target (food or object) to eat the food ('grasp-to-eat') or to place the object into a container located near the mouth ('grasp-to-place') (see Figure 1A, I and II, respectively). After correct accomplishment of grasp-to-place actions, a piece of food identical to that used for grasp-to-eat trials was delivered as a reward.

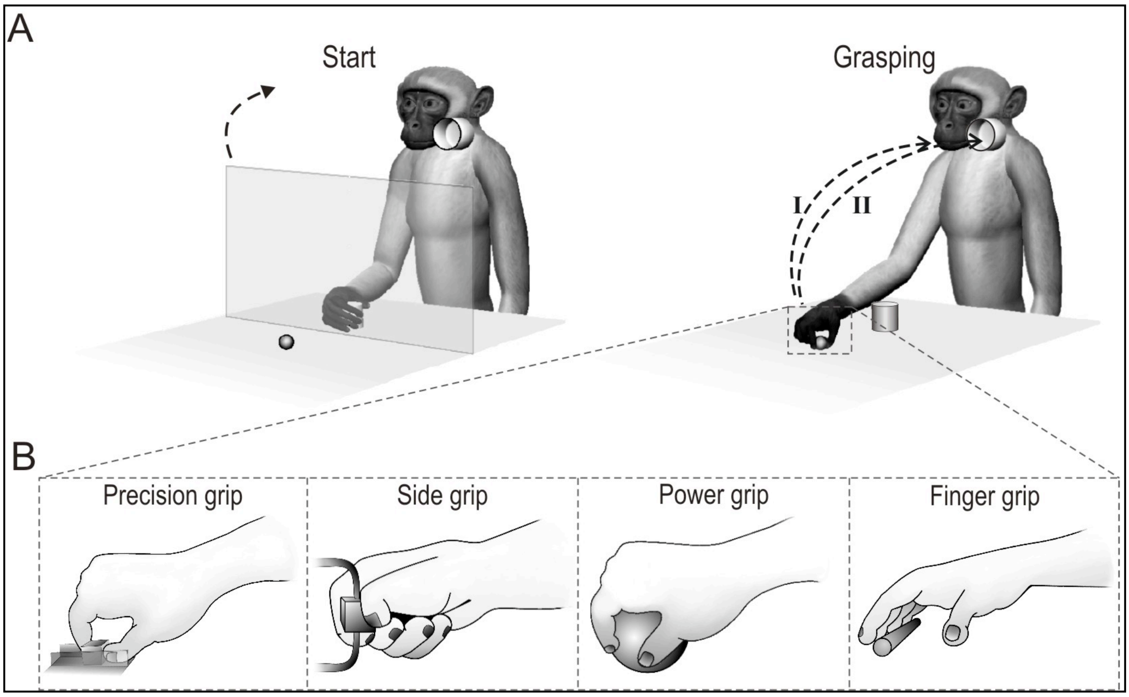

Figure 1. Motor task and types of grip studied. ***A,*** The motor task. The monkey started with its hand from a fixed position (A, left), whit a transparent plastic screen interposed between its hand and the target. When the screen was lifted (Start signal), it reached and grasped a piece

of food (or an object) in order to (*I*) bring the food to the mouth and eating it or (*II*) place it (or the object) into a container located near the mouth. ***B,*** Different types of grip used to grasp the object during the motor task.

Control trials were carried out also by using the same food morsel as target in both grasp-to-eat and grasp-to-place conditions. In this latter case, the monkey was briefly (less than 1 second) visually presented with a more palatable food reward before grasp-to-place trials onset. After a variable delay (2-5 seconds), the screen was lifted and the monkey grasped the food and placed it, in order to receive the more palatable reward.

In order to study possible grip selectivity, monkeys were trained to perform both conditions of the motor task using different grip types. To better achieve this purpose, we used different devices for locating the target of monkeys' grasping acts, in order to force them to employ a specific grip type.

Figure 1B shows the different types of grip employed for studying neuronal activity. Monkeys were trained to perform: a) 'precision grip' (PG), by using the thumb and the pulpar surface of the last phalanx of the index finger, when a small piece of food or an object of the same size and shape (cube, 1x1 cm) had to be grasped from a groove; b) 'side grip' (SG), by using the thumb and the radial surface of the last phalanx of the index finger with half-pronation of the hand, when the same small food or object used for PG had to be grasped from the arms of pliers with vertical orientation (height-0.9 cm; length - 2 cm each one); c) 'finger prehension'(FP), by extending all the fingers but the thumb when a thin cylinder of food or a metallic one (diameter – 0.7 cm and length - 5 cm) had to be grasped from a tray (length - 10 cm; width – 10 cm) positioned in front of the monkey, d) 'whole hand prehension' (WH), by using all fingers, including the thumb in opposition with the hand palmar surface, when a big sphere (4 cm - diameter) or a big piece of food of the same size had to be grasped from a tray positioned in front of the monkey. All target objects were located at a fixed distance of 16 cm from the starting position.

Grasp-to-eat and grasp-to-place trials, performed with different types of grip, were run in a pseudorandom fashion. If monkey detached the hand from the starting cylinder before the go signal or failed to correctly grasp the target, the trial was discarded and not included in the data set. Furthermore, in case of grasp-to-place food morsels, if the monkey ate the food the trial was discarded and it was not rewarded with the preferred food. Deleted trials were repeated in order to collect at least ten correct trials for each experimental condition.

2.2 Surgical procedures for the implantation of the head fixation system and the recording chamber

After completion of the training, a head fixation system and a titanium recording chamber (AlphaOmega Engineering, Nazareth, Israel - inner diameter 18 mm) were implanted under general anaesthesia (ketamine hydrocloride, 5 mg/Kg i.m. and medetomidine hydrocloride, 0.1 mg/Kg i.m.). Upon recovery from anaesthesia the animals were returned to their home cage and continuously monitored. Daxametasone and prophylactic broad-spectrum antibiotics were administered intra and postoperatively (Borra et al., 2010).

The head fixation system was composed by four hollow titanium cylinders. They were positioned in the anterior temporal and occipital regions of each hemisphere and fixed to the skull. Four titanium screws were fixed to the skull each near the cylinder. Cylinders and screws were held together by means of acrylic cement (Antibiotic Simplex©). Once implanted, the head fixation system was not used for a month in order to allow the screws to be embedded into the bone. After this period, four metallic sliding bar fixed to the head holder were inserted into the cylinders in order to keep the monkey head fixed.

During the following month, monkeys had to continue the training sessions receiving food in the chair o during the motor task with the head restrained. When the animals reached good performance in the new situation and in the motor task, the next surgery was performed in order to implant the recording chamber. Each animal was placed in a stereotaxic apparatus and a craniotomy was performed over the region of interest, identified by the stereotaxic coordinates used in previous single neuron recording studies of premotor and parietal areas. The titanium recording chamber was fixed to the skull by at least four screws and the borders of the chamber were sealed to the bone by acrylic antibiotic cement.

At the end of the surgery, a corner of the chamber was measured using stereotaxic coordinates in order to use it as point of reference for the construction of the recording grid.

2.3 Recording techniques

Single-neuron recordings were carried out by using single glass-coated tungsten microelectrodes (impedance 0.5-1 MΩ) inserted through the intact dura, perpendicularly to the cortical surface. The microelectrode was mounted on an electrode-driving terminal fixed onto the recording chamber (MT, Alpha Omega, Nazareth, Israel) with its vertical branch rotated 35° with respect to the vertical axes (0°) in order to penetrate the dura perpendicularly. The electrode was moved into the brain by a computer-controlled micromanipulator (EPS, Alpha Omega, Nazareth, Israel). Neuronal activity was amplified (MCPplus, Alpha Omega, Nazareth, Israel) and monitored on an oscilloscope. The raw analog signal was finally fed to a PC to be recorded, stored, and subsequently analyzed.

Single-neuron action potentials were isolated on-line with a dual voltage-time window discriminator (Bak Electronics, Germantown, MD) for more detailed testing of neuronal properties (see below).

A contact- detecting circuit was used to align neuronal activity with external events by generating TTL (5 V) signals. Whenever the monkey touched a metal surface producing the closure of the circuit, the signal was sent to a PC.

2.4 Recording sites and clinical testing of neuronal activity

The recording chambers were implanted based on stereotaxic coordinates of the target cortical regions. After chamber implantation, the region of interest (the hand regions of parietal area PFG and ventral premotor area F5) was functionally identified by studying single neurons and multiunit activity and through intracortical microstimulation (Fogassi et al., 2005; Raos et al., 2006; Rozzi et al., 2008).

For each recording site, before acquisition of neuronal activity with the motor tasks, clinical testing of single neurons and multiunit activity was carried out. In particular, single and multiunit activity was studied in order to exclude those sites with strong responses during mouth or arm active movements, during passive hand and/or arm displacement, tactil stimulation of the hand and/or arm skin surface, or during simple visual presentation of objects. Only those cortical sites in which neurons responded specifically during hand motor acts were tested with the motor task and included in this study.

Somatosensory responses

Light touch was assessed by lightly touching the skin or bending the hairs with cotton wad or small brushes, or by blowing air puff on restricted body parts. Deep touch responses were assessed by applying pressures to specific spots on the skin with the tip of a stick orfingers. Proprioceptive responses were tested by squeezing muscle bellies or by slow and fast passive mobilization of joints.

Visual responses

Visual properties were studied by presenting the monkey with three dimensional objects of different shape, size and orientation, at different space locations or distances from the monkey. The objects were presented to the free-gazing monkey by removing a screen occluding their vision or by abruptly introducing them into the visual field, holding them by hand or stuck on a wand. In this latter case the experimenter's hand was not visible, in order to exclude that the possible visual response could be due to biological motion. The same stimuli were also moved along tangential planes following linear or circular trajectories at different distances from the monkey, or along trajectories directed toward or away from the different body parts.

Neuronal responses to action observation were tested by presenting different hand and mouth motor acts that the experimenter performed in front of the monkey such as grasping, manipulating, breaking, holding, releasing and taking objects away. Movements of single experimenter's body parts were also presented to the monkeys, by showing the head or the trunk turning towards different directions, displacing arms or legs without any interaction with objects. In order to define visual responses as 'mirror', neuronal activity specifically related to observation of goal-directed motor acts was also tested during monkey active execution of hand or mouth motor acts.

Motor properties

Neuronal activity was tested during the execution of active movements. Active movements consisted of forelimb movements, such as arm reaching or hand acts (e.g. grasping, manipulating, tearing, and breaking). Target objects for the various tested acts were presented in all space sectors, and monkeys could grasp them by using either left or right arm, to evaluate possible bilateral motor responses.

In order to dissociate neural responses related to grasping from those related to reaching, food or object were introduced near the monkey's body, so that they could be grasped without extending the arm. Neurons were classified as distal only when they fired consistently during a particular distal movement, regardless of whether the arm was flexed, extended, adducted or abducted. Neuronal responses were attributed to reaching when they required arm projection and appeared to be absent when simple grasping was performed with the arm restrained. Monkeys performed motor act in light and dark conditions, to evaluate neural properties with or without visual guidance.

2.5 Recording of behavioral events and definition of grasping epochs

Contact detecting electric circuits were used to signal the main behavioral events, subsequently used for aligning neuronal activity and for statistical analysis of neuronal discharge in different epochs. The recorded events were: a) detachment of the hand from the starting point; b) contact of the hand with the food or object target of the action; c) contact of the hand with the border of the container in which the object/food had to be placed.

Neuronal activity was stored from 2 seconds before until 2 seconds after the behavioral event signalling the detachment of monkey hand from the starting point (4 seconds for each trial). Based on digital signals related to the behavioral events described above, we defined two epochs of interest in which neuronal activity was compared: 1) grasping epoch, starting 300 ms before the hand touched the target object (food or metallic solid) and ending 300 ms after this event, and 2) baseline epoch, starting 2 seconds before the hand touched the target and lasting for 600 ms, when the hand was at rest on the starting point. Time intervals of grasping epoch have been chosen on the basis of a largely accepted broad definition of “hand grasping” motor act, which includes both the hand shaping and actual grasping phases (Jeannerod et al., 1988; Mason et al., 2004; Chen et al., 2009), and accordingly with previous studies of our group (Fogassi et al., 2005; Bonini et al., 2010).

2.6 Data analyses

Raw neural data were acquired and stored by means of Lab-View based software, together with the digital events related to the behavioral paradigm, and further analyzed with Matlab R2008B. Single spikes shapes were extracted and sorted off-line using dedicated software (Wave-Cluss, Quian Quiroga et al. 2004).

Only neurons steadily recorded for at least 10 trials for each Grip and Goal tested condition have been included in the data set. Single neuron responses were then statistically assessed by mean of repeated measures ANOVA (factors: grip, action goal and epoch), followed by Bonferroni post-hoc tests. All analysis were performed using a significance criterion of $P<0.05$. All the neurons presented in this study displayed a statistically significant response during grasping as compared to baseline epoch. In order to compare the percentage of neurons in each neuronal category founded in this study, a chi-square test was applied.

Population analysis

Population analyses have been carried out taking into account single neurons response expressed in terms of net-normalized mean activity, calculate as follows. The mean activity was calculated for each 20 ms bin through all the recorded trials of both experimental conditions. For each condition, an off-set procedure was applied, subtracting the mean baseline activity from the value of each bin (net activity). The highest net activity value among those of the compared conditions was taken to divide the value of each single bin (net-normalized mean activity): using this procedure each neuron is characterized by a mean baseline activity equal to 0 and a peak activity value of 1. In order to reliably identify the peack of activity timing a rolling average (period = 60 ms) has been applied to the net normalized mean activity, centered to each single bin. This procedure was aimed at allowing a more reliable identification of the peak of activity (the highest value for each condition).

As far as the action goal is concerned, the preferred and not-preferred conditions were chosen within the grip condition in which the difference in the mean firing rate between preferred and not-preferred action goal conditions was maximal. This procedure was applied whenever statistical analysis revealed a general preference for action goal in all tested grip types. In other cases, statistical analysis clearly indicated the grip in which goal preference was significant.

As far as the type of grip is concerned, the preferred and not-preferred conditions were chosen within the action goal condition in which the difference in the mean firing rate between preferred and not-preferred goal conditions was maximal.This procedure was applied whenever statistical analysis revealed a general preference for type of grips in all tested action goal conditions.

Population responses aligned on the moment when the hand of the monkey touched the target object has been analyzed by considering grasping related activity during three successive periods: baseline activity (600 ms long), pre-contact epoch, starting 300 ms before the contact of monkey's hand and the target, and post-contact epoch, from the contact of monkeys' hand with the target to 300 ms after this event (Bonini et al., 2010).

In order to better identify a possible selectivity during the baseline epoch, in some cases population response was aligned with the moment in which the monkey detach the hand from the starting position and has been analyzed by considering epoch of 500 ms long.

Neuronal population responses were analyzed by ANOVA for repeated measures (factors: Condition and Epoch), followed by Bonferroni post-hoc tests. All analysis were performed using a significance criterion of $P<0.05$.

Normalized differential activity

Some analyses were performed by considering the normalized differential activity in three different periods: baseline, pre and post-contact epochs. In order to calculate the differential activity, the normalized activity in the not preferred condition was subtracted from the normalized activity in the preferred condition. This procedure has been applied for the discharge of F5 and PFG neurons. Then by means of ANOVA for repeated measures (factors: Condition and Epoch), the differential normalized activity was analyzed.

2.7 Intracotrical stimulations

Intracortical microstimulations (ICMS) consisted of trains of cathodal pulses (train duration 50 ms, pulse width 0.2 ms, pulse frequency 330 Hz) generated by a constant current stimulator with a current intensity of 40 μA. They were performed within 2.5-3 mm of cortical depth in a sample of penetrations of both F5 and PFG recording sites.

2.8 Histological reconstruction and identification of the recorded regions

At the end of the experiments in M1 and M2, neuronal tracers were injected in the centre of the premotor and parietal regions where hand-grasping neurons were acquired. Injection sites were identified using stereotaxic coordinates based on the functional maps of the recorded areas. Immediately before tracer injections, a recording session was performed in order to confirm the presence of reliable neural activity and properties coherent with those previously found during the electrophysiological experiments.

In order to directly assess whether the regions containing task-related neurons are anatomically connected, at the end of neurophysiological experiments, neural tracers were injected in the PFG and F5 sectors where motor neurons of this current study were recorded. Immediately before tracer injection, a recording session was performed in order to confirm the presence of reliable neural activity and properties coherent with those previously found during the electrophysiological experiment. Tracers were slowly pressure injected about 1.2--1.8 mm below the cortical surface through a Hamilton microsyringe (Reno, NV). In M1, wheat germ agglutinin (WGA, 4% in saline; Vector Laboratories, Burlingame, CA) was injected in PFG, whereas in M2 cholera toxin B subunit, conjugated with Alexa 594 and Alexa 488 (CTB-A, 1% in phosphate-buffered saline; Molecular Probes) were injected in PFG and F5, respectively. In all cases, the volume of injected tracer was 1 µl. About 1 week before sacrificing the animals (7 days for M1; 10 days for M2), electrolytic lesions (10 µA cathodic pulses per 10 s) were performed at known coordinates at the external borders of the recorded regions. After electrolytic lesions and appropriate survival period for tracers transport (14 days for CTB-A and 2 days for WGA), each animal received an overdose of sodium thiopental and was consecutively perfused through the left cardiac ventricle with saline, 3.5%-4% paraformaldehyde, and 5% glycerol prepared in 0.1 M phosphate buffer and pH7.4. The brain was then extracted, photographed, and cut (slice thickness 60 µm). For M1, the third section of each 5 was processed for WGA immunohistochemistry. For both monkeys, each second and fifth section of a series of 5 were stained using the Nissl method (thionin,0.1% in 0.1 M acetate buffer, pH 3.7). The locations of penetrations were then reconstructed on the basis of electrolytic lesions, stereotaxic coordinates, depths of penetrations, and functional properties. Subsequently, the cytoarchitectonic features of IPL convexity and PMv were identified based on the criteria defined by Luppino and coworkers (Gregoriou et al. 2006; Belmalih et al. 2009). Injection sites were defined according to the criteria previously described for CTB-gold and WGA-horseradish peroxidase (Luppino et al. 2001, 2003) and attributed to the different cytoarchitectonic areas. WGA-labeled neurons were identified in bright field as a black, dense and homogeneous staining in the cytoplasm. CTB-A labeling was analyzed by using standard fluorescein (for CTB-A 488) or rhodamine (for CTB-A 594) sets of filters (see Rozzi et al. 2006). The distribution of retrograde labeling was plotted in coronal sections (600 µm sampling) and related to the outer and inner cortical borders, by using a computer-based charting system.

3. RESULTS

Neuronal activity was recorded from the posterior bank of the inferior arcuate sulcus and adjacent convexity (area F5, Matelli et al., 1985) and the inferior parietal area PFG (Gregoriou et al., 2006). In particular, we recorded 89 grasping neurons from areas F5 in the right hemisphere of M1 and M2 and the left hemisphere of M3. Furthermore, we recorded 90 PFG grasping neurons from the right hemispheres of M2 and M3. Figure 2A shows the anatomical location of the two investigated regions.

Results of single neurons analyses (see Materials and Methods) evidence the existence of 4 main neuronal categories (see Table 1 and 2): “Grip selective” neurons, that activated differently according to the type of grip used for grasping, regardless of the goal (Eating or Placing) of the action in which grasping was embedded; “Goal selective” neurons, that discharged differently during grasping according to the goal of the action, independently of the type of grip employed to grasp the target; “Grip-and-Goal selective” neurons, that were differently activated according to both the type of grip and the action goal. Finally, No preference neurons coded grasping with similar discharge intensity, regardless of both the type of grip and the action goal.

Table 1. Number of F5 neurons classified on the basis of their ‘Grip’ and ‘Goal’ preference.

	Action goal preference				TOTAL
	Eat > Place	Place > Eat	*tot*	No Preference	
Grip Preference	15	9	24	35	
No grip preference	8	5	13	17	
tot	23	14			
TOTAL	37			52	89

Table 2. Number of PFG neurons classified on the basis of their ‘Grip’ and ‘Goal’ preference.

	Action goal preference				TOTAL
	Eat > Place	Place > Eat	*tot*	No Preference	
Grip Preference	9	15	24	38	
No grip preference	5	6	11	17	
tot	14	21			
TOTAL	35			55	90

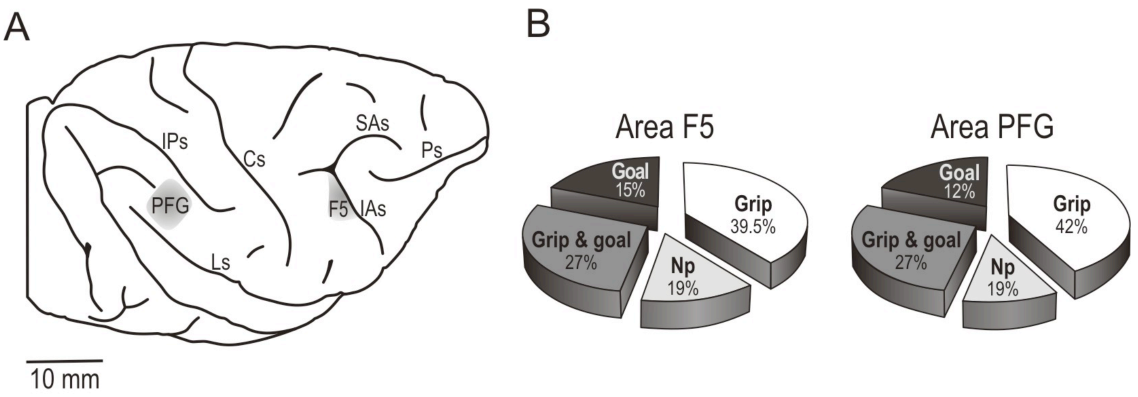

Figure 2. ***A,*** Lateral view of the right hemisphere of monkey 3. The grey shaded regions indicate the sectors of inferior parietal convexity (area PFG) and of the ventral premotor cortex (area F5) from which neuronal recordings were carried out. IAs, inferior arcuate sulcus; SAs, superior arcuate sulcus; Cs, central sulcus; IPs, intraparietal sulcus; Ls, lateral sulcus; Ps, principal sulcus. ***B,*** Proportion of Grip selective , Goal selective, Grip-and-Goal selective and 'No preference' neurons in area F5 and PFG.

The proportion of neurons within the different neuronal categories (Figure 2B) appears to be remarkably similar between the two areas ("Grip selective" neurons: χ^2=0.16, ns; "Goal selective" neurons: χ^2=0.23, ns; "Grip-and-Goal selective" neurons: χ^2=0.0 ns; "No Preference" neurons: χ^2=0.0 ns).

3.1 Grip selectivity during the execution of simple goal directed actions

Almost half of all the recorded neurons (39.5% in F5 and 42% in PFG) show a preference for the type of grip used for grasping the object.

Figure 3 shows examples of "Grip selective" neurons recorded from both areas. Unit 92 (Figure 3A) is a highly selective F5 Grip neuron, activated only during the execution of a finger prehension, both in grasp-to-eat and grasp-to-place conditions. Note that the discharge is absent when grasping is performed using a whole hand prehension or a precision grip. In other cases, the neurons selectivity is broader. Figure 3B shows an example of a PFG neuron (Unit 42) strongly activated during the execution of SG and PG, requiring the control of the index finger used in opposition to the thumb, but not when the monkey perform a finger prehension, involving the use of all the finger but the thumb. Notably, like Unit 92, also this neuron does not show any significant difference in discharge intensity during grasp-to-eat and grasp-to-place conditions.

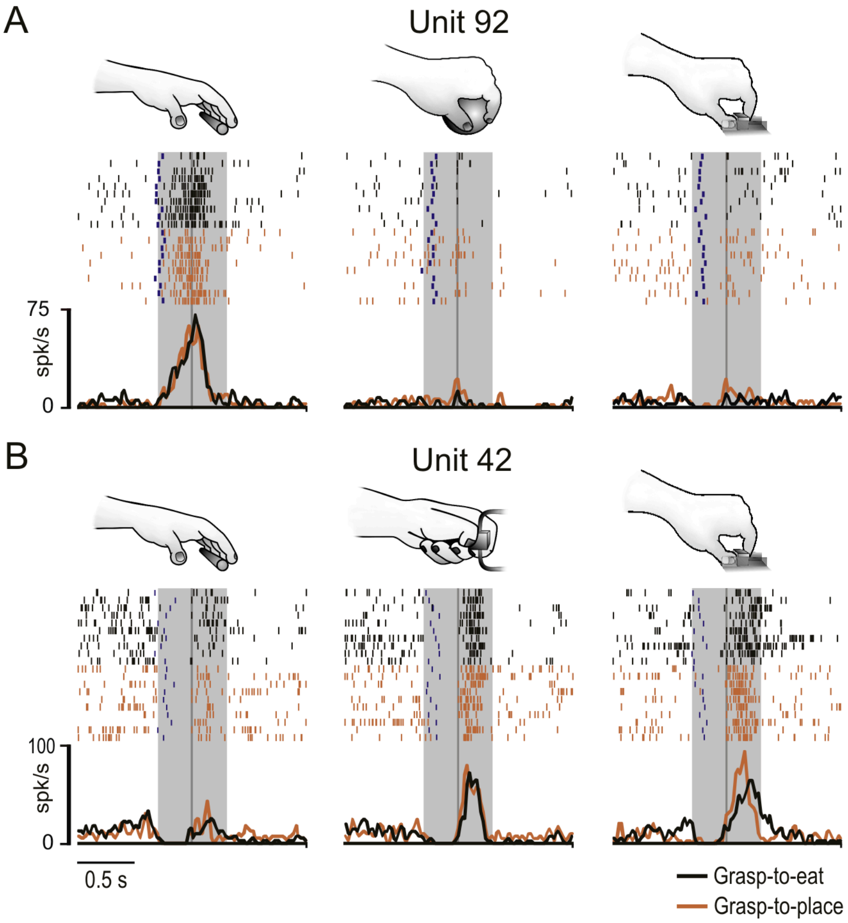

Figure 3. Examples of Grip selective neurons. ***A,*** F5 Grip selective neuron active only during finger prehension. ***B,*** PFG Grip selective neuron discharging stronger during precision and side grip as compared to finger prehesion. Note that in both neurons the discharge is not different between grasp-to-eat (black) and grasp-to-place (red) conditions. The grey shaded regions identify grasping epochs used for statistical analysis. Rasters and histograms are aligned with the moment when monkey's hand touched the target. Blue bars signal the detachment of monkey's hand from the starting position (trigger).

Among the recorded "Grip selective" neurons, 28 showed a clear-cut preference for FP (F5: N=16; PFG: N=12), 25 for SG (F5: N=10; PFG: N=15) and 13 for PG (F5: N=9; PFG: N=4). The remaining neurons (N=7) only founded in area PFG discharged strongly during two different grip types as compared to a third grip, in which the activity was significantly weaker (an example is Unit 42 in Figure 3B). No neuron selective for WH has been found. Figure 4 shows the time course and intensity of the normalized activity of PFG and F5 "Grip selective" neuronal populations, comparing the activity associated to the execution of the preferred grip with that of the not preferred one, during either grasp-to-eat or grasp-to-place condition (see the Materials and Methods section titled "Population analysis", for details about the criteria adopted in order to identify the preferred and not preferred condition). In order to analyze possible grip selectivity prior to movement onset, that is, during resting and pre-movement periods, the normalized activity has been first aligned on the moment when the monkey detached the hand from the starting position, and then subdivided into 4 epochs (each lasting 500 ms). From epoch 1 to 3, the hand was still on the starting position while the monkey was waiting for the go-signal ("Rest" epochs). Kinematics analyses revealed that movement onset occurred during epoch 4 ("Onset" epoch), on average 139 ms ± 20 ms before the detachment of monkey's hand from the starting position (as indicated by the black arrows in Figure 4), with no differences between the three monkeys [F(2,27)=0.12, ns]. Finally, the grasping related response aligned on the moment when the monkey hand touched the target object was considered as a fifth 600 ms epoch (300 ms before plus 300 ms after this event, as for single neurons analyses), that was referred to as "Grasp" epoch.

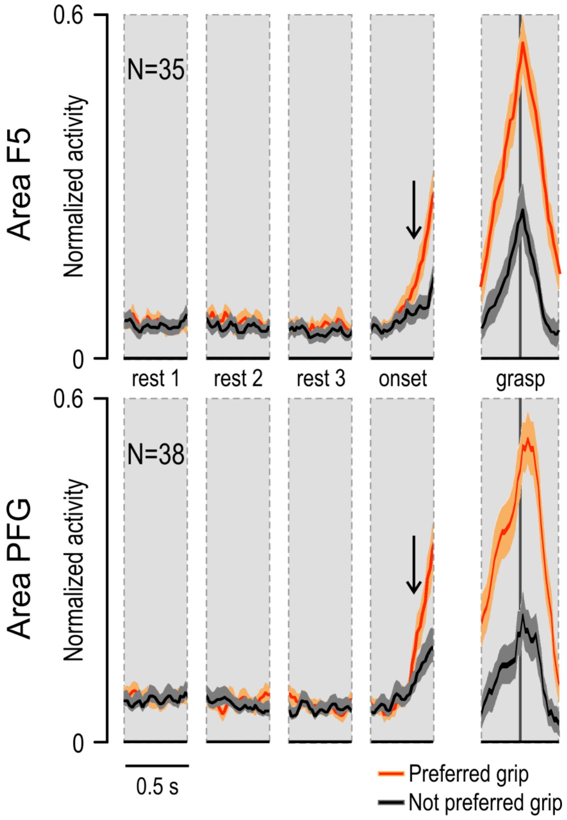

Figure 4. Time course of the response of F5 and PFG 'Grip' neurons in the preferred (red line) and not preferred (black line) grip. From Rest 1 epoch to Onset epoch, the activity is aligned on the moment when monkeys' hand detached from the starting position. Black arrows during Onset epoch indicate the moment when monkey hand movement started. Grasp epoch shows the population response aligned on the moment when monkey hand touched the target object (vertical grey line). Orange and grey shading indicate 1 standard error. Grey shaded regions indicate the time interval considered for each of the five epochs.

A 2 x 2 x 5 factorial ANOVA for repeated measures (factors: Area, Grip and Epoch) has been then applied to both F5 and PFG "Grip selective" neuronal populations. This analysis revealed a significant main effect for both Grip [F(1,71)=116.6, $p<0.001$] and Epoch [F(4,284)=179.84, $p<0.001$] but not for the factor Area [F(1,71)=0.13, $p=0.71$]. Furthermore, it also showed a significant interaction between the three factors [F(4,284)=14.44 $p< 0.001$]. Bonferroni post-hoc tests revealed that grip selectivity is absent during the first three Rest epochs, when monkeys held their hand on the starting position, while it starts to raise significantly during Onset epoch ($p<0.01$ for both areas) and reaches its peak during the successive Grasp epoch ($p<0.001$ for both areas). Thus, neuronal selectivity is absent during the resting epochs and it becomes significant only during actual hand movement, in a similar way in the two areas.

The fact that grip selectivity start rising at the beginning of movement onset enables to exclude that it is due to different tactile feed-back provided by the different target objects. However, since the peak of grip selectivity occurs when monkeys' hand touch the target in both F5 and PFG neuronal populations (F5: 2053 ± 181 ms from the beginning of acquisition; PFG: 2030 ± 257 ms, $t = 0.45$, ns), one might still argue that tactile feed-back may account for at least part of the observed grip selectivity. This latter possibility can be discarded insofar as both single neurons and multiunit activity of all the recorded sites were not modulated by tactile stimuli or joints displacements (see Materials and Methods for details about clinical testing procedures).

3.2 Goal selectivity during the execution of simple goal directed actions

Some of the recorded neurons in both areas (F5: 15%; PFG: 12%), discharged differently during grasp-to-eat and grasp-to-place conditions, regardless of the type of grip used for grasping the target object ("Goal selective" neurons).

Figure 5 shows examples of "Goal selective" neurons. Unit 19 (Figure 5A), is an F5 neurons that discharges stronger during grasp-to-eat than during grasp-to-place an object, regardless of the type of grip performed by the monkey. Unit 56 (Figure 5B) recorded from area PFG, shows the opposite selectivity, being more strongly activated during grasp-to-place than during grasp-to-eat condition, independently of the grip type employed for grasping the target.

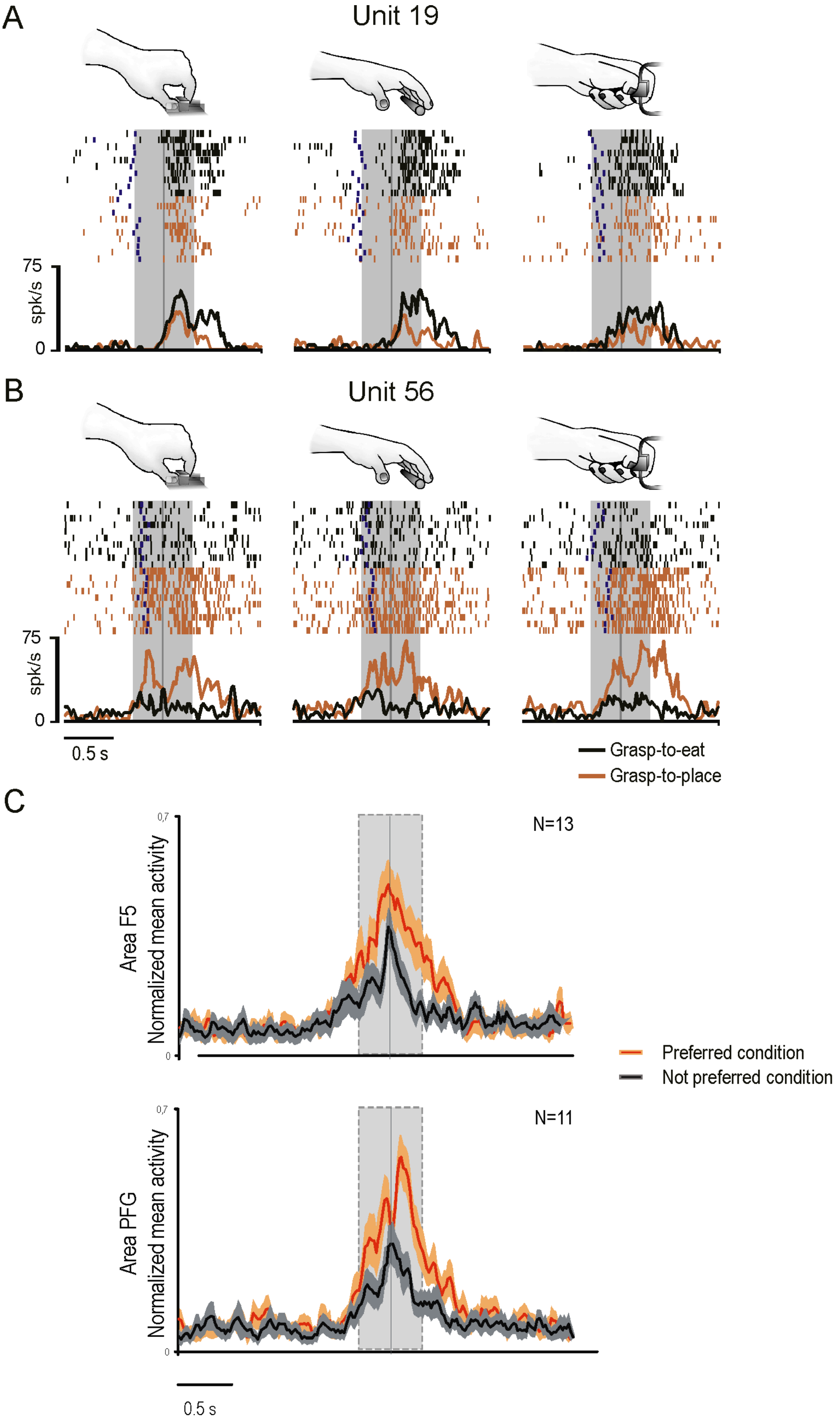

Figure 5. Example of "Goal selective" neurons. ***A,*** F5 "Goal selective" neuron discharging stronger during grasp-to-eat than grasp-to-place condition, regardless of the grip type performed by the monkey. Neuron response is not different between grip conditions. ***B,*** PFG "Goal selective" neuron activated stronger during grasp-to-place than grasp-to-eat condition, regardless of the grip type. Conventions as in figure 3. ***C,*** Time course of the response of F5 and PFG "Goal selective" neuronal population, aligned on the moment when monkey hand touched the target. Conventions as in figure 3 and 5.

Figure 5C shows the time course and intensity of F5 and PFG "Goal selective" neuronal population aligned on the moment when the monkey hand touched the target. A 2 x 3 repeated measures ANOVA (factor: Condition and Epoch) has been carried out by considering grasping related activity during three successive periods: baseline activity (600 ms long), pre-contact epoch, starting 300 ms before the contact of monkey's hand and the target, and post-contact epoch, from the contact of monkey hand with the target to 300 ms after this event. This analysis revealed that in area F5 there is a significant main effect for both Condition [$F(1,12)=95.83$ $p< 0.001$] and Epoch [$F(2,24)=18.95$ $p< 0.001$] and a significant interaction between them [$F(2,24)=11.63$ $p< 0.05$]. As clearly shown in the upper part of figure 5C, the response of F5 neurons is significantly higher in the preferred condition than in the not preferred condition during both grasping epochs (Bonferroni post-hoc tests: $p<0.05$;$p<0.001$). Moreover, in the preferred condition there is no difference in the discharge between pre and post-contact epochs. In area PFG, the same analysis reveal a significant main effect for Condition [$F(1,10)=68.86$ $p< 0.001$] and for Epoch [$F(2,20)=30.51$ $p< 0.001$]. The interaction between these two factors is also significant [$F(2,20)=22.36$ $p< 0.05$]. Similarly to F5, Bonferroni post-hoc tests reveal that the response in the preferred condition is higher than in the not preferred condition in both grasping epochs ($p<0.05$; $p<0.001$). More interesting, in the preferred condition the response of PFG "Goal selective" neuronal population is significantly higher in the post-contact epoch than the response in the pre-contact epochs ($p<0.05$).

3.3 Neuronal selectivity for grip type and action goal

A considerable proportion of the neurons recorded from both area F5 and PFG (27% for both areas) showed a preference for both the investigated variables, namely, grip type and action goal.

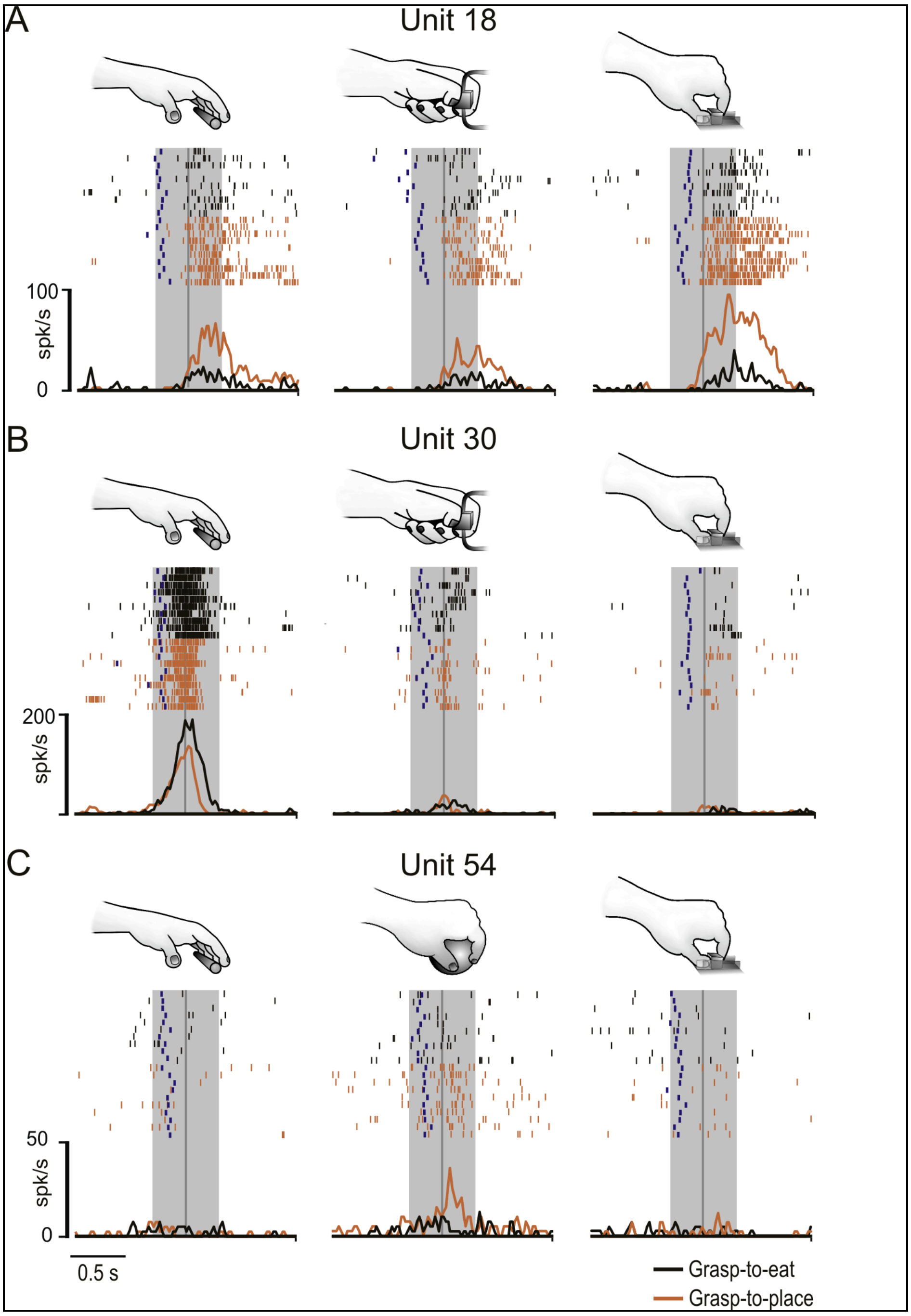

Figure 6. Examples of “Grip-and-Goal selective” neurons. ***A,*** F5 “Grip-and-Goal selective” neuron that discharges stronger in grasp to place condition in all the tested grip. Moreover, its response is higher during grasping performed with PG. ***B,*** Another F5 “Grip-and-Goal selective” neuron that is activated only during grasping with FP and its discharge is stronger in grasp-to-eat than grasp-to-place condition. ***C,*** PFG “Grip-and-Goal selective” neuron that is activates when monkey performs grasping with WH but only when action goal is place the target.

Figure 6 shows examples of the different behaviours of these “Grip-and-goal selective” neurons. Unit 18 (Figure 6A) discharges stronger during grasp-to-place than grasp-to-eat condition during all the grip types employed by the monkey for grasping the target. Nevertheless, the neuron discharge is also overall stronger when grasp-to-eat is performed using a PG as compared with any other of the tested grip types. More then half (62.5%) of F5 “Grip-and-goal selective” neurons and a consistent percentage of those of PFG (44%) shows this behaviour, displaying a modulation of the discharge according with a specific action goal during all grip conditions, in addition to grip selectivity. Figure 6B and 6C exemplify other frequent behaviour of this neuronal category. In 25% of F5 and 48% of PFG “Grip-and-goal selective” neurons, the preference for goal variable is express only when monkey performed grasping act with a specific grip. Both Unit 30 and 54 show a very specific response to only one of the tested grips: Unit 30 is selective for FP, while Unit 54 is selective for WH prehension. Notably, the action goal preference appears in both neurons only when the monkey performed the grasping act with the grip type preferred by the neuron, namely, grasp-to-eat with FP for Unit 30 and grasp-to-place with WH for Unit 54.

Population analyses were carried out in order to compare the preference for the grip type and the action goal expressed by the same PFG and F5 Grip-and-Goal selective neurons. Figure 7A (upper part) shows the time course and the intensity of the response of F5 and PFG neuronal populations during the execution of the motor task in the preferred and not preferred grip. A 2 x 3 ANOVA (factors: Grip and Epoch) revealed a main effect for the factors Grip [F5: $F(1,23)=166.57$, $p<0.001$; PFG: $F(1,23)=234.37$, $p<0.001$] and Epoch [F5: $F(2,46)=52.24$, $p<0.001$; PFG: $F(2,46)=85.97$, $p<0.001$] and a significant interaction between them [F5: $F(2,46)=27.92$, $p<0.001$; PFG: $F(2,46)=69.9$, $p<0.001$]. Bonferroni post-hoc tests revealed that, in both areas, the neuronal response is higher during the execution of the preferred as compared to the not preferred grip during both the pre- and post-contact epochs ($p<0.001$ for both comparisons). Furthermore, the discharge is stronger in post-contact than in the pre-contact grasping epoch ($p<0.001$ for both Preferred and not preferred grip).

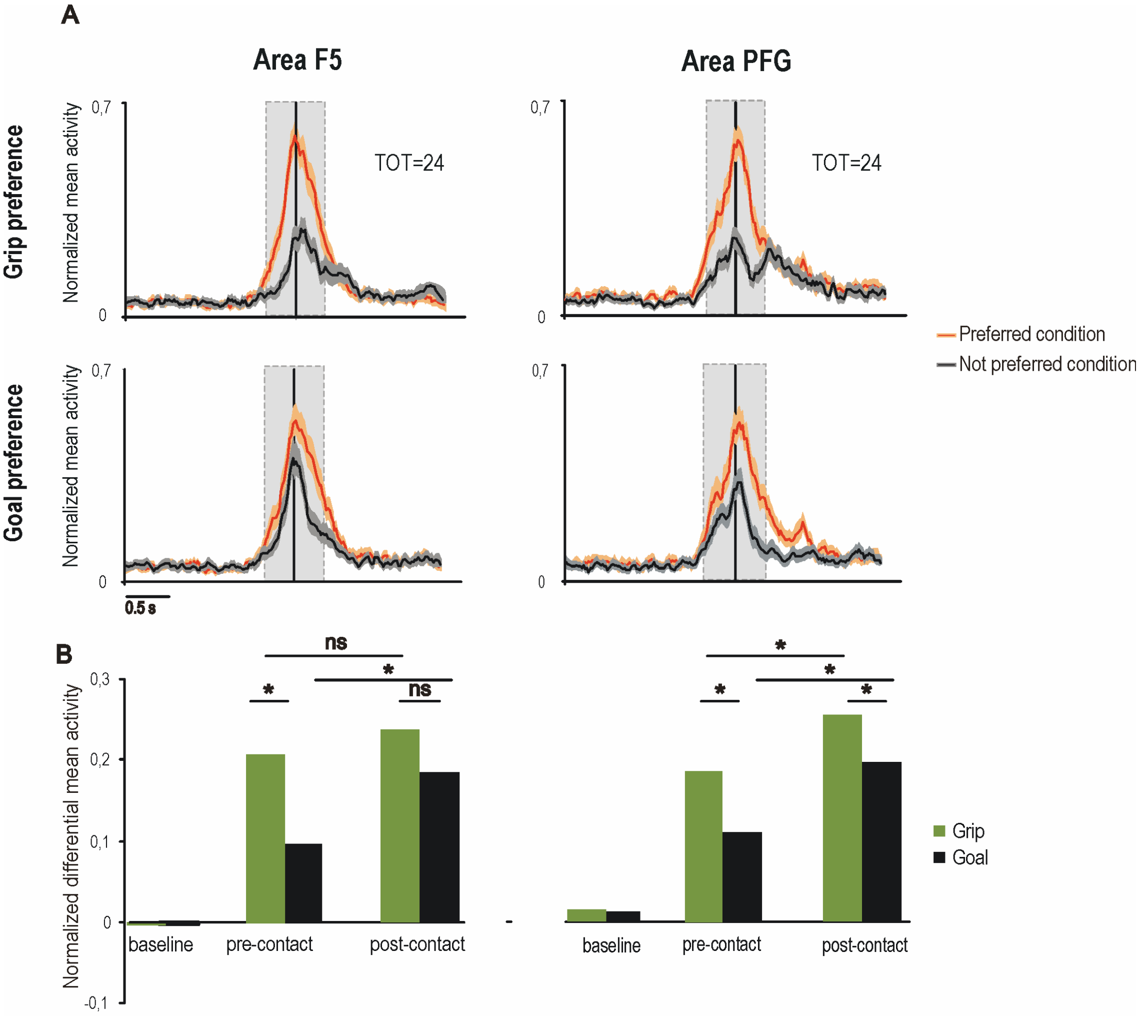

Figure 7. *A*, Temporal profile of the normalized activity of the whole neuronal population of F5 and PFG Grip and goal selective neurons during the execution of the preferred and not preferred grip type (upper part) and action goal (lower part). The response is aligned to the contact of the hand with the target. ***B*,** Comparison between normalized differential activity for grip and goal variables in the baseline, pre and post-contact epochs for F5 and PFG "Grip and goal selective" neurons. The differential response for grip variable is illustrated by green histograms. Black histograms represent the differential activity between action goal preferred and not preferred condition.

Figure 7A (lower part) shows the time course and intensity of the response of the same F5 and PFG grip-and-goal selective neuronal populations during the execution of the motor task in the preferred and not preferred action goal condition. A 2 x 3 ANOVA for repeated measures (factors: Condition and Epoch) revealed a significant main effect for the factor Condition [F5: $F(1,23)=237.42$, $p<0.001$; PFG: $F(1,23)=88.84$, $p<0.001$], Epoch [F5: $F(2,46)=44.96$, $p<0.001$; PFG: $F(2,46)=70.39$,

$p<0.001$] and for their interaction [F5: $F(2,46)=36.49$, $p<0.001$; PFG: $F(2,46)=36.54$, $p<0.001$]. Bonferroni post-hoc tests showed that, in both areas, the response associated to the preferred action goal condition is higher than that for the not preferred condition, during both pre- and post-contact epochs ($p<0.001$ for both comparisons). Furthermore, the discharge in the post-contact epoch is stronger than that in the pre-contact epoch (Bonferroni post-hoc tests, $p<0.001$).

Figure 7B shows the differential mean activity between the preferred and not preferred grip (green histogram) and action goal (black histogram) conditions in F5 Grip-and-Goal selective neurons. A 2 x 3 ANOVA for repeated measures (factors: Condition and Epoch), revealed that there is a main effect for the factor Condition [$F(1,23)=22.52$, $p<0.001$], Epoch [$F(2,46)=40.28$, $p<0.001$] and a significant interaction between the two factors [$F(2,46)=5.98$, $p<0.05$]. It is interesting to note that, in area F5, Bonferroni post-hoc tests revealed that the grip preference is significantly higher than the action goal preference, but only in the pre-contact epoch ($p < 0.05$). This effect seems to be due to an increased preference for the action goal during the post-contact as compared to the pre-contact epoch ($p < 0.05$), while the grip selectivity remains similar. In area PFG (figure 7B), the same analysis evidenced a significant main effect for Condition [$F(1,23)=23.79$, $p<0.001$], Epoch [$F(2,46)=78.52$, $p<0.001$], and for their interaction [$F(2,46)=5,87$, $p<0.05$]. Differently from area F5, Bonferroni post-hoc tests revealed that PFG Grip-and-goal selective neuronal population show a higher preference for grip as compared to action goal during both pre ($p<0.001$) and post-contact ($p<0.05$) epochs. Furthermore, the same analysis also revealed that during post-contact as compared to pre-contact epoch there is a significant increase of the selectivity for both the grip ($p<0.05$) and the action goal ($p<0.001$).

3.4 Stimulation data

In a sample of penetrations located in the investigated regions of the convexity of area F5 (N = 15 in M1; N = 23 in M2) and PFG (N = 18 in M2), intracortical microstimulation (ICMS) was performed (see Material and Methods, section ‘Intracortical stimulations’). The sites of stimulation were located in the recording region of F5 of M1 and M2 and in the left inferior parietal convexity of M2. It’s interesting to note that movements were evoked in the majority of the stimulated penetrations in F5 of both monkeys (65.2% in M1; 66.6% in M2) with a threshold of 40 μA. On the contrary, intracortical microstimulations in area PFG of M2 never evoked any movement.

Evoked movements consisted on fast, short-lasting movements and they could involve single joint (e.g.: thumb or wrist flexion/extension) and displacement of two arm segments (e.g.: hand and wrist together). In few cases when stimulations were performed in more lateral part of F5, hand and mouth movements were correlated to the stimulation.

3.5 Histological reconstruction and cortical connections between F5 and PFG recorded regions

At the end of the recording sessions in the right hemisphere of two monkeys by three, neuronal tracers were injected in the centre of the premotor and parietal recorded regions (figure 9).

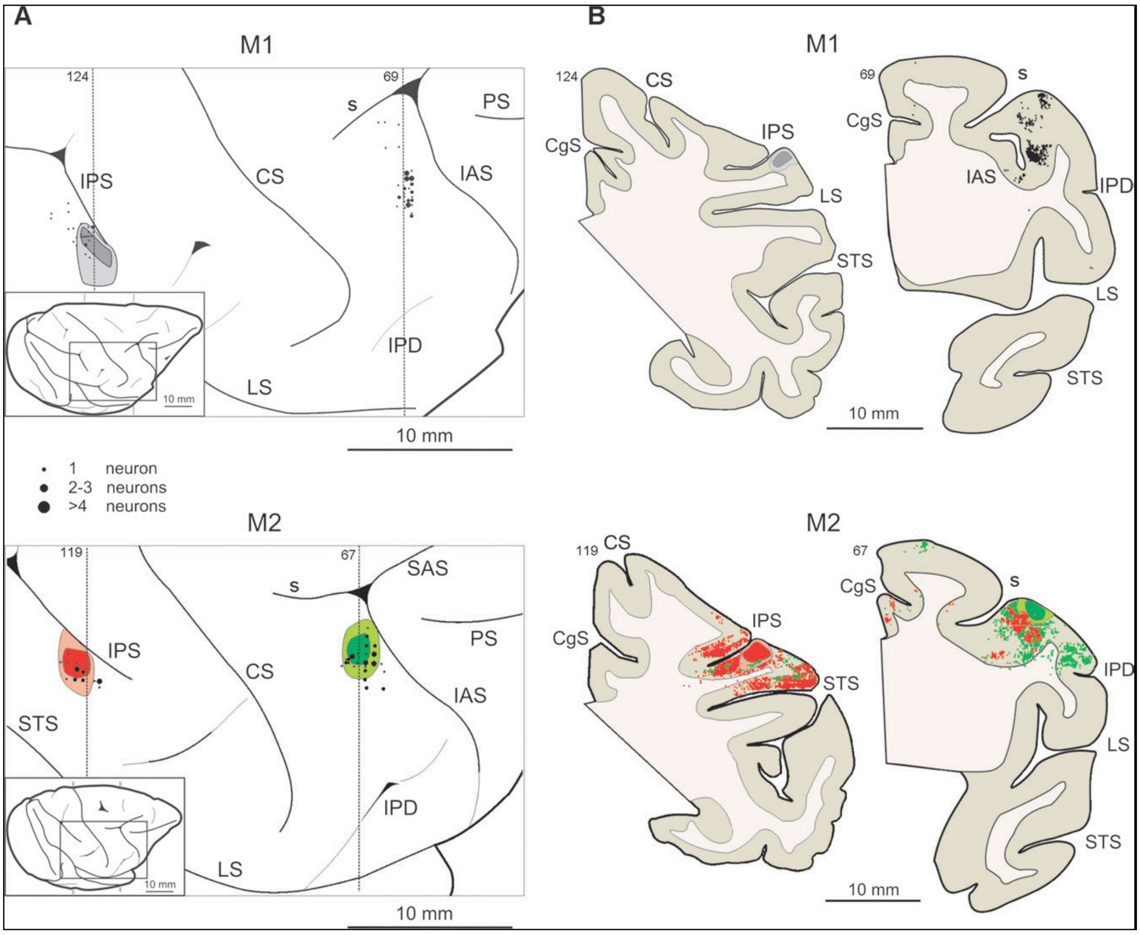

Figure 9. A, Recostruction of penetrations and injection sites in PFG and F5 recorded region in two of the monkeys used in this study. In each brain, the penetrations and the injection sites are represented. The shaded region is the extention of the core (darker color) and halo (ligher color). The dotted lines indicates the level at which the coronal sections, shown in B are thaken. B, Coronal sections of the two recorded regions. In the left part of the figure parietal sites of injection are rapresented. Black dots in section 69 indicate neurons labeled with WGA funded in area F5 of M1. Red and green dots represent neurons labeled in M2 after injection of CTB-Alexa 594 in area PFG and CTB-Alexa 488 in area F5, respectively. CgS, cingulate sulcus; CS, central sulcus; IAS, inferior arcuate sulcus; IPD, inferior precentral dimple; IPS, intraparietal sulcus; s, spur of the arcuate sulcus; SAS, superior arcuate sulcus; STS, superior temporal sulcus.

The anatomical data reveal that the majority of penetrations were located inside the cytoarchitectonic areas F5 and PFG as defined by previous works (Belmalih et al., 2009; Gregoriou et al., 2006). Moreover, after WGA injection in area PFG of M1 and CTB-A 594 injection in the same area of M2 labeled cells were observed in the investigated sector of F5. Moreover, in M2 CTB-A 488 injection (green labelling) was performed in the recorded area F5. This latter finding indicate that the two investigated regions are not only strictly but also reciprocal connected.

4. DISCUSSION

This study was aimed at investigating the possible interaction between neural coding of different aspects crucial for action organization, namely, grip type and action goal. To this purpose, monkeys were trained to perform a motor task consisting of two motorically similar grasping actions, characterized by different final goals (i.e. “eating” or “placing”). In one action the monkey was required to reach and grasp a piece of food in order to eat it, in the other to reach and grasp an object or a piece of food to place it into a container located near its mouth. Depending on the size, shape and the device holding the target, the monkey had to perform the two actions using different grip types such as finger prehension (FP), whole hand prehension (WH), side grip (SG) and precision grip (PG). These grip types have been chosen because they are the most represented in the monkey motor repertoire and they are used without need of any specific motor training. Indeed they are naturally adopted by these animals in their natural environment to grasp and processing food items (Macfarlane and Graziano, 2009).

Our data revealed that most (81%) of the recorded neurons of the inferior parietal area PFG and the ventral premotor area F5 show selectivity for at least one of the investigated variables. In particular, the majority of grasping neurons were selective for the grip type, regardless of the action goal (“Grip” selective neurons). In contrast, a smaller proportion of neurons discharged differently according to the final goal of the action in which grasping was embedded, but did not show any modulation for the grip type required to perform the action (“Goal” selective neurons). More interestingly, the discharge of a third, consistent group of neurons, reflected in different ways both these variables, showing a preference for a certain action goal combined with the selectivity for a specific grip type (“Grip and Goal” selective neurons). Unexpectedly, these three neuronal categories were similarly represented in both areas F5 and PFG.

One of the main technical difficulties of this study, as compared to previous works on similar topics, concerned the necessity of using, as targets, objects or food of different size and shape. On one side, this was necessary in order to induce the monkey to adopt different grip types according to the physical properties of the target. On the other side, food has always to be employed as a target during grasp-to-eat conditions. Both these aspects, the type of target (food or object) and its size, could constitute potential confounding factors. In fact, one may suggest, for example, that both grip and goal selectivity could be at least partially due to the different rewarding value associated to different experimental conditions. Grip selectivity, for example, could be biased by the size of the reward that monkey achieved for the execution of specific grips, such as finger or whole hand prehension, obtained by presenting the monkey with either medium or big food morsels: in both cases, grasp-to-eat condition is necessarily more rewarding than the corresponding grasp-to-place condition. Thus, one could expect a systematically stronger discharge during grasp to eat than during grasp to place conditions when monkey performed an FP or a WH compared with SG or PG conditions. However, 42% of "Grip selective" neurons preferentially discharge during FP in both grasp-to-eat and grasp-to-place conditions (see figure 3A), even if in the second condition the reward consists in a piece of food smaller than the food to be placed. Thus their selectivity is not due to the different amount of reward employed In addition, more than half of "Grip selective" neurons show a clear-cut preference for others grip conditions (SG or PG), in which the amount of the reward is lower. Finally, more controlled experimental studies explicitly investigating the relationship between action goal selectivity and the reward delivered to the monkey for the correct task accomplishment revealed that the amount of reward does not alter action goal selectivity (Bonini et al. under revision).

4.1 Coding of grip type in F5 and PFG grasping neurons

Grasping objects requires that visual information related to their physical properties is transformed into the appropriate hand motor pattern necessary for interacting with them.

As far as grip selectivity is concerned, the greater percentage of premotor (39.5%) and parietal (42%) grasping neurons recorded in this study was selective at least for the grip type performed by the monkeys. In both areas, the preference for complex grips such as finger prehension (F5: 46%; PFG: 38%) is quite equally represented as compared to grips that required the opposition of thumb and index such as side grip and precision grip (F5: 54%; PFG: 62%). No one of the “Grip selective” neurons showed preference for WH.

These data are similar to those found in the neurophysiological studies that employed a naturalistic approach in the investigation of neuronal activity of F5 (Rizzolatti et al. 1988) and PFG (Rozzi et al. 1988). In order to render more natural the two action goal condition, in our experiment monkeys performed mainly four types of grips that are in its motor repertory.

It is well known that most of hand-grasping neurons in area F5 show selectivity for the grip posture used to grasp the objects (Rizzolatti et al., 1988; Raos et al., 2006), particularly those located in the posterior bank of the inferior arcuate sulcus, namely area F5p (Belmalih et al., 2009). This study confirms this view, showing that also a considerable proportion (39.5%) of grasping neurons recorded from the dorsal convexity of area F5 (area F5c, see Belmalih et al., 2009) are selective for the grip type, regardless of the action in which the coded grip was employed.

As far as PFG grasping neurons are concerned, previous studies were mostly based on naturalistic investigation (Rozzi et al., 2008) or used controlled paradigm in which the variable grip was not directly investigated. Here we show that, similarly to F5, 42% of PFG hand grasping neurons encode the grip type that the monkey employed for performing the action. The presence of grip selectivity in area PFG fits well with anatomical data showing strong and reciprocal connections of this area with both areas AIP and F5 (Rozzi et al., 2006; Borra et al., 2008), where grip selective neurons have been classically described using controlled paradigms (Sakata et al., 1995; Murata et al., 2000; Raos et al., 2006). Thus, the cortical circuitry involved in controlling the hand shape for grasping has to be extended to include also this region.

It should be noted that we wilfully restricted our recordings to the convexity of area F5 and to area PFG, and did not overstep the anatomo-functional border with area F5p (Belmalih et al., 2009) and AIP (Borra et al., 2008), respectively. It is well known that a considerable proportion of the neurons in both areas F5p and AIP showed visual, besides motor, grip selectivity during object fixation period (Taira et al. 1990; Murata et al. 1997; 2000; Raos et al., 2006). Notably, this selectivity appears to be due not to the object visual features per se but rather to the type of grip they afford (Jeannerod et al., 1995). In line with this proposal, following reversible inactivation of F5p and area AIP, the monkeys capacity to shape the hand according to the visual features of the object was dramatically impaired (Gallese et al., 1994; Fogassi et al., 2001). Thus, these premotor and parietal sectors seem to have a crucial role in the visuomotor transformations for grasping objects. In contrast, after the inactivation of F5 and PFG convexity, no clear motor impairment was observed (Fogassi et al., 2001; Bonini et al., 2008). Therefore, despite the remarkable similarity of visual properties between PFG and F5c, on one side, and between AIP and F5p, on the other, it is possible that both sectors belong to a parallel parieto-frontal circuit devoted to the organization of different aspects of hand actions.

A further difference between the neuronal grip selectivity of F5c-PFG, on one side, and F5p-AIP, on the other, is that while the latter circuit frequently respond during visual fixation and motor preparation periods (Murata et al., 2000; Raos et al., 2006), we did not find evidences of such a behaviour in the Grip selective neuronal population. In fact, population analyses revealed that in both F5c and PFG “Grip selective” neuronal populations the time course of the activity and neuronal selectivity for the preferred grip increased at the very beginning of movement, but were absent during the resting period. Although our motor task did not include a formal testing of the visual responses to the presentation/visual fixation of the target object, we can exclude that the neurons included in this study have a relevant visual, besides to the motor, selectivity. In fact, during baseline epoch when the monkey was at rest, waiting for the removal of the screen, the activity in the forthcoming preferred and not preferred conditions was not different. Moreover, prior to formal recordings with the motor task, clinical testing of the multiunit activity has been performed in order to verify whether the recorded neurons showed any modulation of the discharge during visual presentation of object or object fixation. This enabled us to exclude that the grip selectivity was due to visual responses related to object features.

4.2 Coding of action goal in premotor and parietal grasping neurons

Simple natural actions are formed by a brief sequence of motor acts (such as reaching, grasping and bringing to the mouth) chained together in order to attain the final goal of the whole action (e.g. eating or placing). Each single motor act is endowed with its specific motor goal (the goal of "grasping" is that of taking possession of an object). The control of the different effectors (such as arm, hand or mouth) requires parallel mechanisms that work together in order to rendering more smooth the sequential execution of the motor acts within an action. During the arm transport phase, the fingers assume the correct shape of three-dimensional graspable object and, simultaneously, the muscles that control mouth opening are already activated during shaping and grasping phase (Cattaneo et al., 2007).

Previous studies extensively investigated the relative contribution of the action final goal on the discharge of PFG and F5 grasping neurons (Fogassi et al., 2005; Bonini et al., 2010), showing that, in both areas, hand-grasping neurons are differently activated according with the goal of the action performed by the monkey. However, as mentioned above, these studies mainly focused on studying neuronal activity during the execution of precision grip, while in this work we employed different types of grip for testing neuronal activity during actions with different goals.

Our data reveal that a small number of neurons, similar in both areas, show a selectivity for the action goal, discharging differently when grasping was performed for either eating or placing, and regardless of the type of grip required to perform the action. Recent findings (Bonini et al., under revision) show that mainly in area PFG there are different types of neurons encoding the action goal at different levels of abstraction. This study demonstrated that during complex action sequences, action goal related neurons could reflect the action goal not only in the late phase of action unfolding (grasping of the target before achieving the final goal) but also during an early phase of the action. It has been hypothesized that this type of neurons reflects the action goal at a higher level of motor abstraction, by keeping active, during the execution of natural actions, higher level representations of the individual motor intention.

These studies suggest that, on one side, action goal related neurons serve for the sequential organization of successive motor acts in an action sequence (Fogassi et al., 2005; Bonini et al., 2010), regardless of the type of grip and motor parameters, that in principle could be specified in parallel by other cortical circuits. On the other side, action goal related neurons could provide an on-line monitoring of the adherence of the current motor program to the final goal of the acting individual, constituting a possible neuronal correlate of motor intention.

Although the percentage of “Goal selective” neurons is not different between areas F5 and area PFG, it is interesting to note that “Goal selective” neuronal population of area PFG has a stronger response in the post-contact epoch than in the pre-contact epochs, while this effect has not been found in area F5. These data are in line with previous studies (Bonini et al. 2010), showing that neuronal activity and action goal preference increase during the actual grasping and holding phase of the grasping action in PFG more than in F5 neuronal populations.

4.3 Coding of grip type and action goal in premotor and parietal cortex

One of the main finding of this study is that single grasping neurons of area F5 and PFG can code both the way in which a certain motor act has to be performed (grip type) and the goal of the action in which the coded act is embedded. Interestingly, the preference for both grip type and action goal can interact in two main ways.

First, neurons could be selective for a specific type of grip, besides showing a modulation of their activity according to a specific action goal in all the tested grip types: more than half (62.5%) of F5 “Grip-and-goal” selective neurons and a consistent portion (44%) of those of PFG showed this behaviour. Second, neurons could show a preference for a specific action goal only when the monkey was grasping the object using a specific grip type: 25% of F5 and 48% of PFG “Grip-and-goal” selective neurons behaved in such a way. The remaining neurons, less frequently found (F5: N=3; PFG: N=2), showed different types of interaction, showing for example the emergence of an action goal preference during the performance of the less preferred grip type.

In the neuronal group showing the first modality of grip-goal interaction, the information on action goal is reflected in all the tested grips, showing an higher level of motor abstraction as compared to neurons belong to the second group. In this latter case, coding of action goal is more constrained to the motor features of the grasping act. The specificity for the different types of grip shown by “Grip-and-goal” selective neurons is similar to that observed for “Grip selective” neurons. Finger prehension (F5: 5; PFG: 9) and grips that require the opposition of thumb and index fingers, such as SG and PG (F5: 9; PFG: 9) were equally represented. Moreover, a few PFG neurons (N=4) showed grip selectivity when monkey performed WH prehension.

It is interesting to note that in F5 “Grip-and-goal” selective neurons the preference for grip type was significantly higher than the preference for action goal in the pre-contact epoch while in the post contact epoch this difference disappeared, mainly because the preference for the action goal increased. This finding is in line with the notion derived from a number of psychophysical and kinematic studies, that reaching for grasping an object implies the activation of the motor process leading to the correct action execution well before movement onset (Jeannerod; Gentilucci 1991 Rosembaum 2007). Neurophysiological studies demonstrated that in area F5 grip selectivity appears already in an early stage of the task to be performed (Murata et al., 1997; Raos et al., 2006; Umiltà 2007). On the contrary, in area PFG the selectivity for the grip type, as compared to that for action goal, was expressed in both grasping epochs.

On the other hand, as action goal preference is concerned, both premotor and parietal “Grip and goal selective” populations showed the differential mean activity already during the pre-contact epoch when the hand approaches the object and preshapes with respect to its features but drastically increased in the post contact epoch. The increased impact of action goal on the latest epoch of grasping neurons activity suggests that neurons coding motor acts recruited earlier in action sequence could facilitate those neurons coding motor acts activated later in the same action.

Intracortical stimulations performed in a sample of penetrations of both premotor and parietal recorded sectors have shown that more than half of the premotor stimulation sites evoked arm movements. On the contrary, stimulations of area PFG did not evoke any observable movement. It is interesting to note that both areas have corticospinal connections, although they are different insofar as PFG targets the dorsal horn of the spinal cord, while F5 projections terminate also in the intermediate interneuronal laminae. This anatomical evidence could justify the difference in the electrical excitability of the two areas. These data underline the different role that could be assumed by motor responses in the two areas besides their functional similarity. Area F5, which is richly connected to primary motor cortex and also to spinal cord, is more involved in the coding of the single motor acts and the execution of them, while area PFG is more involved in the cognitive aspects of movement such as the organization of the different motor acts in specific actions in accord with their final goal.

However, the fact that the two studied variables interact in both studied sectors indicate their role in the selection of specific types of grip as required by the context in which the action is executed. For example, if I want to drink a cup of coffee, I will prefer to use a precision grip to grasp the handle of the cup in order not to touch the hot body of the cup. If, instead, I want to wash the empty cup, I can take it from the body. Thus, different action goals can induce the choice of different grips. Of course, during these actions, in our parieto-premotor circuits several types of grasping neurons will contribute to action organization. In the above example, grasping of the handle will probably involve neurons selective for the goal of drinking during execution of precision grip. However, it is also possible that during this motor act, also neurons specific only for the action goal and for precision grip also activate, to support action implementation.

4.4 Possible network involved in action organization

Neuronal tracer injections in two out of three monkey of the study in the recording PFG and F5 sectors evidenced that both regions are strictly and reciprocally connected. This anatomical pattern underlines the functional similarity between these two sectors that emerge also in the present study and, as previously described, strongly supports the notion that these two sectors form a parieto-frontal circuit involved in action organization. On the other hand, these two areas show specific connections with other cortical areas that could explain the different role they have in action organization. Area PFG is more connected to prefrontal domain (area 12 and 46v) that is a well known target of the inferotemporal areas (Webster et al., 1994). This prefrontal domain is considered to be involved in higher order processing of non spatial information

(Wilson et al., 1993; Passingam et al., 2000; Romanski 2004), where objects are encoded in working memory. Moreover, the prefrontal cortex has a role in sequential aspects of motor cognition, such as the selection of motor sequence (Koechlin et al., 2002). Furthermore, it appears to be involved in coding behavioural goals (Tanji and Hoshi 2008). The stronger connection of this region with area PFG than with area F5 may support the more important role of PFG in organizing motor acts into action based on its final goal. On the contrary, area F5 is strongly connected to primary motor and premotor cortices (Mausakka and Strick 1979; Matelli et al., 1996; Belmalih et al., 2007). This could confirm the more important role of area F5 in coding the goal of single motor acts.

Electroencephalograhic and cortical field potential studies (Wheaton et al, 2005a, 2005b) showed that the parietal cortex becomes active well before the premotor cortex during self-paced voluntary movements. Moreover, Pesaran and coworkers (2008) simultaneously recorded from premotor and parietal cortex during a free-choice reaching task and found that the information initially flows from premotor and parietal cortex but a subsequent bacward activity reflects the final decision process. Taken together, these data support the view that despite remarkably similar functional properties, nevertheless area F5 and PFG process similar information for different purposes. Area PFG, more distant from the motor output, has a leading role in the organization of motor act into action and in monitoring the adherence of action implementation with its behavioral purpose. On the other hand, the strict connections between area F5 and M1 would allow the transformation of the coded motor acts in actual execution (Rizzolatti et al., 1988; Umiltà et al., 2008).

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