

The Extended Mirror Neuron Network: Anatomy, Origin, and Functions

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Abstract

Mirror neurons (MNs) are a fascinating class of cells originally discovered in the ventral premotor cortex (PMv) and, subsequently, in the inferior parietal lobule (IPL) of the macaque, which become active during both the execution and observation of actions. In this review, I will first highlight the mounting evidence indicating that mirroring others' actions engages a broad system of reciprocally connected cortical areas, which extends well beyond the classical IPL-PMv circuit and might even include subcortical regions such as the basal ganglia. Then, I will present the most recent findings supporting the idea that the observation of one's own actions, which might play a role in the ontogenetic origin and tuning of MNs, retains a particular relevance within the adult MN system. Finally, I will propose that both cortical and subcortical mechanisms do exist to decouple MN activity from the motor output, in order to render it exploitable for high-order perceptual, cognitive, and even social functions. The findings reviewed here provide an original framework for envisaging the main challenges and experimental directions of future neurophysiological and neuroanatomical studies of the monkey MN system.

Keywords

action observation, grasping, basal ganglia, social cognition, development

In spite of the heated debate on their origin and functions (Cook and others 2014), mirror neurons (MNs) are well known because of their intriguing capacity to become active not only during action execution but also during the observation of others' actions (see Kilner and Lemon 2013).

Originally discovered in the ventral premotor cortex (PMv) of the macaque (di Pellegrino and others 1992; Gallese and others 1996; Rizzolatti and others 1996), neurons with mirror-like properties have subsequently been found in a network of anatomically connected cortical regions (*cortical MN network*; see Fig. 1A), each of which is endowed with different anatomical pathways conveying visual information regarding others' actions, which is primarily processed in the superior temporal sulcus (STS; Barraclough and others 2009; Jellema and Perrett 2006; Perrett and others 1989). These regions include the inferior parietal areas PFG (Bonini and others 2010; Fogassi and others 2005) and AIP (Maeda and others 2015; Pani and others 2014), the dorsal premotor cortex (Cisek and Kalaska 2004; Tkach and others 2007), and the medial frontal cortex (MFC)—in particular the pre-supplementary motor (pre-SMA) and anterior cingulate cortex (Mukamel and others 2010; Yoshida and others 2011). Neurons with mirror properties have also been described in the primary motor cortex (Dushanova and Donoghue 2010; Tkach and others 2007; Vigneswaran

and others 2013), and convergent anatomical (Borra and others 2011; Gerbella and others 2013) and functional evidence (Nelissen and others 2011) suggests that even the ventrolateral prefrontal cortex (VLPF) may host neurons with mirror-like properties.

Recent anatomical data (Gerbella and others 2015) have also shown that most of the above-mentioned areas forming the cortical MN network for hand actions (i.e., area AIP/PFG, PMv, and VLPF) send convergent projections to specific sectors of the putamen, a nucleus of the basal ganglia with well-established motor properties (BG; see Fig. 1B). Although virtually no study has directly addressed the possible presence of MNs in the BG, these anatomical data and some previous functional evidence in humans (Alegre and others 2010; Kessler and others 2006) strongly suggest that the inclusion of the BG in an extended cortico-subcortical MN network (see Caligiore and others 2013), as well as its possible implications for MN functioning, should be at least carefully considered.

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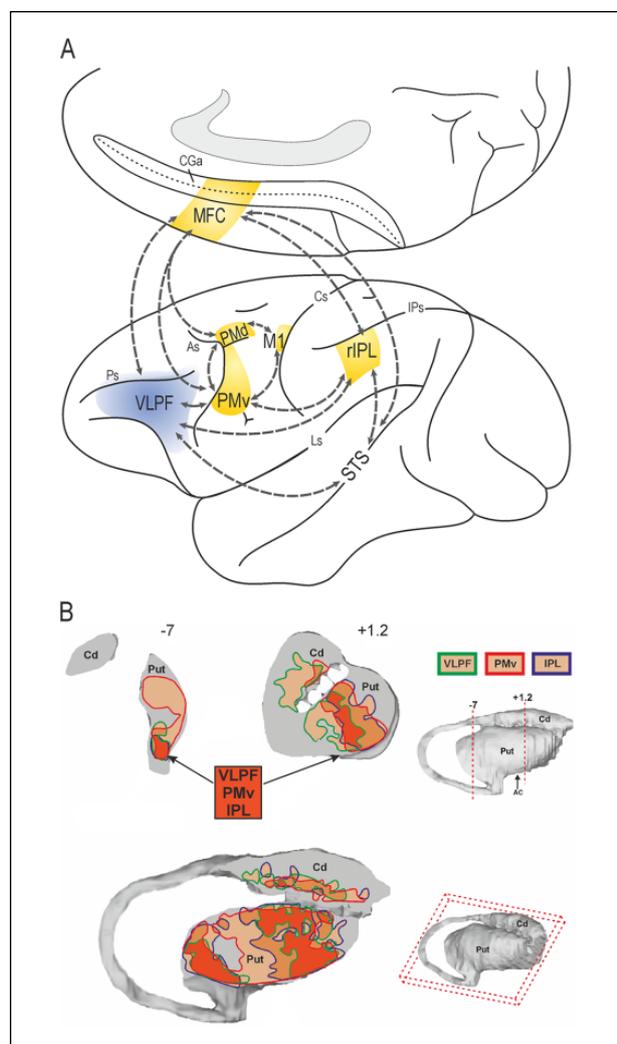


Figure 1. The extended MN network. (A) The cortical MN network includes a set of areas in which the presence of single neurons with mirror properties has been directly demonstrated (yellow) as well as other regions (the ventrolateral prefrontal areas 12 and 46) in which the presence of MNs is supported by anatomical evidence but not yet directly demonstrated (blue). The arrows represent the main anatomical connection between these areas. As = arcuate sulcus; Cs = central sulcus; CGa = anterior cingulate gyrus; IPs = intraparietal sulcus; Ls = lateral sulcus; Ps = principal sulcus. M1 = hand sector of the primary motor cortex; MFC = medial frontal cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; rIPL = rostral inferior parietal lobule; STS = superior temporal sulcus; VLPF = ventrolateral prefrontal cortex. (B) Territories of the basal ganglia (BG) receiving projections from the areas belonging to the cortical MN network, namely, PMv (sector with red borders), IPL (blue borders), or VLPF (green borders). The light and dark orange shadings highlight the BG sectors in which two or even all of these three distinct sources of corticostriatal projections overlap. The coordinates (-7 and +1.2) indicated in the reconstruction on the top right part of the panel show the anteroposterior locations of the two BG slices shown on the left. Put = putamen; Cd = caudate nucleus. Other conventions as in panel A.

In this review, I will first propose that MNs in several nodes of the cortical network play a role in monitoring one's own actions in addition to those of others, a claim that is consistent with ontogenetic models that connect the origin of MNs to sensorimotor representations of self-generated actions, which are progressively generalized during development to the visual description of others' actions. Furthermore, I will argue that, in spite of their motor *properties*, MNs do not possess a primarily motor *function*, because different cortical and subcortical mechanisms do exist to decouple MN output "from the motor." Finally, I will propose that by dissociating originally motor representations from the motor output, the extended MN network can make these representations available for the implementation of perceptual, cognitive, and even social functions. A direct demonstration of a possible causal link between these functions and MN activity is still lacking and should thus be a crucial priority for future studies.

Mirroring One's Own and Others' Actions

Most extant studies of mirroring mechanisms, in both humans and monkeys, have focused on the observation of others' actions (see Kilner and Lemon 2013). Nevertheless, in everyday life, we certainly have more frequent opportunities to observe our *own* actions than those of others. Indeed, from birth, the motion of our own hands constitutes an extremely engaging stimulus (White and others 1964) and a crucial source of information for driving sensorimotor development (Held and Bauer 1967; van der Meer and others 1995). This has led many authors to propose that infants' early experience with their own actions is crucial in order to endow originally motor neurons with mirror properties (Casile and others 2011; Del Giudice and others 2009; Press and others 2011; Tkach and others 2008). If this is the case, although technical and ethical problems prevent researchers from verifying this hypothesis by recording single-neuron activity in newborn primates, it is reasonable to expect that own-hand visual feedback is a stimulus that retains a particular relevance for MNs' discharge even in adulthood, and as a consequence, neurons in the MN network could be sensitive to the sight of one's own actions in addition to those of others.

Previous single-neuron studies on area AIP (Sakata and others 1995) have reported the existence of a particular class of neurons called "visual dominant non-object neurons," which exhibited the intriguing property of firing when the monkey grasped an object in the light, but not in the dark. Importantly, these neurons did not fire when the object was simply visually presented, suggesting that they specifically contribute to the visuomotor

processing of own-hand actions. More recent studies (Maeda and others 2015; Pani and others 2014) have revealed that inferior parietal neurons can also discharge when the monkey simply observes, from a subjective viewpoint, a hand grasping. In particular, Maeda and others (2015) demonstrated that a set of AIP neurons fitting with the original description of visual dominant non-object neurons, in addition to responding during the monkey's grasping act in the light but not in the dark, discharged when the monkey observed its own action presented on a screen from a subjective viewpoint, even when the target object was artificially removed with video-editing techniques. Thus, at least some AIP neurons can specifically process visual information related to own-hand actions.

We reached a similar conclusion in another recent study carried out on area F5 (Maranesi and others 2015). In this study, we recorded single-neuron activity during grasping executed by the monkey in the light and in the dark, as well as during observation of a similar grasping motor act performed by an experimenter and viewed by the monkey from a subjective perspective (Fig. 2A). We showed that F5 MNs, in addition to encoding others' observed action, discharged stronger during the execution of grasping in the light than in the dark, thus displaying a particular sensitivity to the sight of the monkey's own hand (Fig. 2B), even relative to grasping neurons devoid of mirror properties (Fig. 2C) simultaneously recorded in the same cortical sites. Furthermore, we found that the increased MN activity induced by monkey's hand visual feedback and that induced by the experimenter's observed action were positively correlated (Fig. 2D). These findings suggest that at least some of the ventral premotor MNs in the adult monkey can process similarly the visual information coming from both its own hand and that coming from another's hand, thus supporting previous models in which MNs are deemed to play a role in monitoring one's own actions (Bonaiuto and Arbib 2010) as well as in predicting those of others (Keysers and Gazzola 2014).

Although a small percentage (4.7%) of neurons specifically tuned to the observation of another's action (i.e., "mirror-like" neurons, devoid of any response during grasping execution) have also been described since the original report by Gallese and others (1996), similar cells are more frequently found in the pre-SMA (21.7%) and adjacent cingulate (9.5%) cortex (Yoshida and others 2011). Interestingly, a recent study demonstrated the existence of "other-predictive neurons" in the anterior cingulate cortex with the capacity to selectively encode an opponent's yet-unknown decision during a prisoner's dilemma: this set of neurons appears to be important for enacting cooperative interactions (Haroush and Williams 2015).

The findings so far reviewed support the idea that all the regions of the extended cortical MN network host neurons specifically involved in the processing of one's own or others' actions, besides those with mirror properties. On the one hand, the presence of neurons modulated by hand visual feedback could be the vestigial sign of their ontogenetic origin from individuals' visuomotor experience with their own actions. On the other, this property can retain an important role even in adulthood, constituting a developmentally preserved resource of neural plasticity for the fine-tuning of MNs' *visual* properties as a consequence of *sensorimotor* learning (Casile and Giese 2006; Engel and others 2012; Oztotop and others 2013; Wiggett and others 2012).

Neural Mechanisms for Decoupling Motor Representations from the Motor Output

By exploiting one's own motor neurons to map others' observed actions, the brain needs to solve a crucial problem: how can it prevent us from automatically enacting the observed action? Neurophysiological studies on the ventral motor and premotor region of the macaque have shown that the overall electrical stimulation thresholds and the proportion of nonexcitable sites are higher in area F5 than in the adjacent ventral premotor areas F4 and M1 (Maranesi and others 2012), suggesting that F5 plays a more indirect role in motor control. In addition, Maranesi and others (2012) showed that the specific penetrations in which they found MNs were, for the most part (65%), not electrically excitable (with 50 ms trains of pulses at 330 Hz, of up to 40 μ A of current intensity). The opposite trend was observed for penetrations carried out in the dorsal part of area F4 hosting peripersonal neurons (Fogassi and others 1996), the great majority of which (74%) were electrically excitable. The anatomical basis of these differences likely consists in the variable proportion of direct corticospinal projections of each of these premotor regions: the dorsal part of area F4, involved in the coding of peripersonal space for arm reaching and defensive reactions (Cooke and Graziano 2004; Fogassi and others 1996) and the portion of area F5 that lies in the bank of the arcuate sulcus (F5p) and hosts "canonical neurons" (Murata and others 1997), have a relatively robust projection to the spinal cord (Borra and others 2010). Instead, the convexity of area F5 (F5c) can influence the motor output only indirectly, by means of either corticotectal projections (He and others 1993) or via its connection with M1 (Kraskov and others 2011; Schmidlin and others 2008). These findings suggest that the cortical sector hosting MNs is on the whole less linked to the motor output than other functionally similar and adjacent sectors of the PMv.

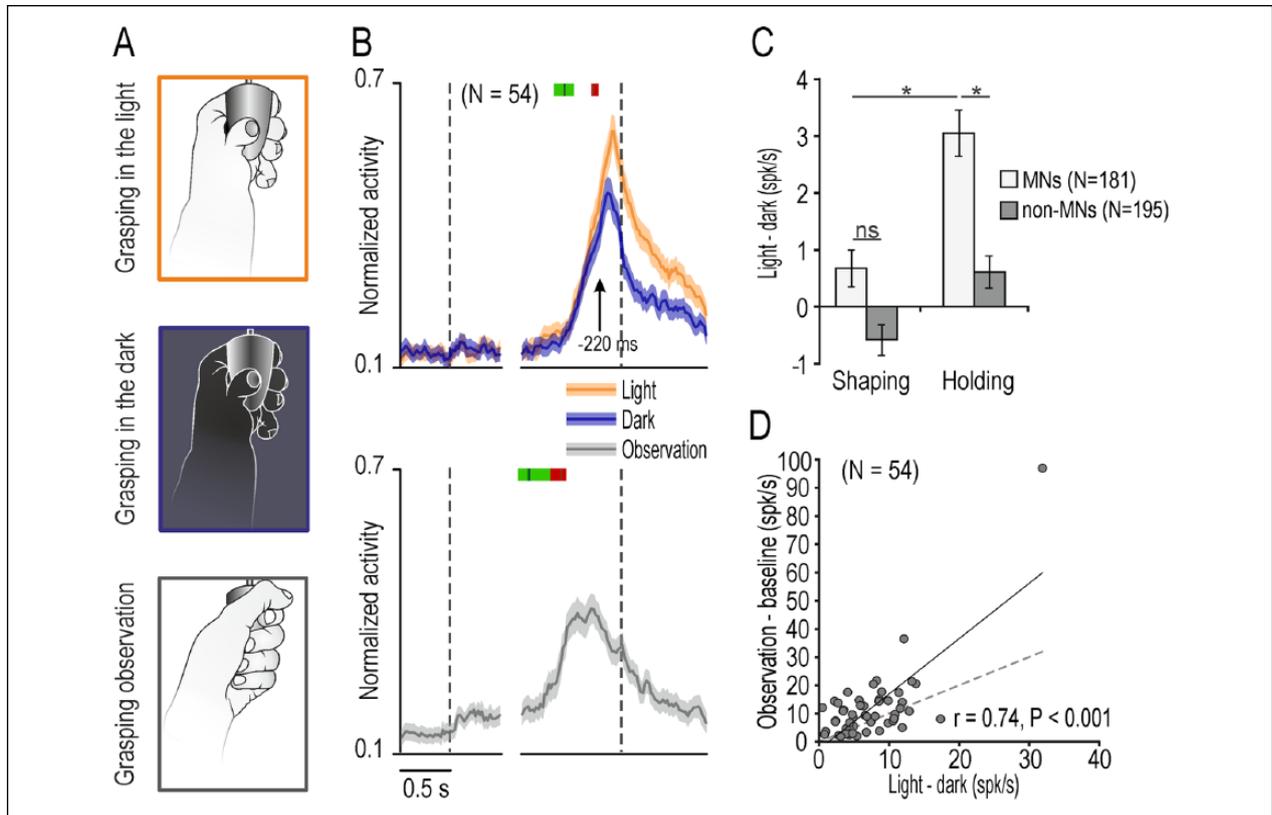


Figure 2. Impact of own hand visual feedback on mirror and non-mirror neurons discharge and its relationship with the magnitude of MNs visual response. (A) Schematic representation of the main conditions of the experiment by Maranesi and others (2015). The subject (monkey or experimenter) was first presented with a graspable object. Then, when a go-signal was provided, the object had to be grasped and pulled. (B) Population response of MNs influenced by own-hand visual feedback during the execution of grasping/pulling in the light (orange) and in the dark (blue), and during the observation of the experimenter's grasping seen from a subjective viewpoint. The activity is aligned relative to the presentation of the target object (first dashed line on the left), and then relative to the object pulling phase. Shaded regions represent 1 SEM. The median time of the go signal and reaching onset are indicated with the green and red markers, respectively; the shaded areas around each marker represent the 25th and 75th percentile times of other events of the same type. Black arrow indicates the time of the first of a series of at least 5 consecutive 100 ms bins in which population activity differed significantly between the two conditions (paired-samples t tests, $P < 0.05$). (C) Differential activity between grasping in the light and in the dark during shaping and holding epochs in all the recorded mirror and non-mirror neurons. $*P < 0.001$. (D) Correlation plot between the effect of own-hand visual feedback (obtained by subtracting the response during grasping in the dark from that during grasping in the light) and the net grasping observation activity of the same MN. The dashed line represents the function $x = y$.

The most direct support for this latter claim comes from reversible inactivation experiments. In these studies, muscimol (a GABA-agonist that suppresses neuronal activity) is injected locally into functionally characterized regions in order to assess the possible behavioral outcomes. The inactivation of area F4 reduces motor reactions aimed at avoiding stimuli invading the monkey's peripersonal space (Cooke and Graziano 2004). The inactivation of area F5p strongly impairs hand shaping during visually guided grasping (Fogassi and others 2001); in contrast, this latter study clearly showed that the inactivation of the MN sector, in the dorsal part of area F5c, has no relevant motor consequence.

It must be noted that MNs are clearly characterized by vigorous motor responses, often selective for a specific type of grip, as are the great majority of purely motor and canonical neurons simultaneously recorded in the same region (Bonini and others 2014b). However, based on the evidence so far reviewed, it is clear that a neuron endowed with a given *functional property* (e.g., discharging during grasping) does not necessarily play a relevant *functional role* in that specific function (e.g., controlling grasping execution). Indeed, the anatomical location and connections of neurons with similar functional properties enable them to play (or not to play) a role in a given function. For example, grasping neurons of area F5p do play a causal

role in the control of visually guided hand actions, whereas those of F5c (and hence MNs) do not (Fogassi and others 2001). What might be the mechanisms that enable the decoupling of functionally “motor” neurons from the motor output?

Cortical Mechanisms

Most published records of MNs have described patterns of increased firing rate during both execution and observation of grasping acts. Nevertheless, it has also been shown that among cortical neurons whose axons contribute to the pyramidal tract (pyramidal tract neurons [PTNs]), some exhibit the “classical” MN activation pattern, discharging during both action execution and observation (facilitation MNs), whereas others, in both areas F5 (Kraskov and others 2009) and M1 (Vigneswaran and others 2013), become active during action execution but exhibit suppressed discharge during action observation (suppression MNs). In Kraskov and coworkers’ data set, 11 F5 PTNs were facilitation MNs (23%) and 14 were suppression MNs (29%), whereas the remaining ($N = 23$, 48%) were considered “non-mirror PTNs.” Interestingly, the population activity of the non-mirror PTNs showed the same suppression pattern exhibited by suppression MNs during action observation (see Fig. 3 in Kraskov and others 2009). Although the authors did not formally analyze this phenomenon and simply described it as a “slight deviation from baseline throughout the whole observation period”, they noted that, during active grasp, non-mirror PTNs “were activated to a somewhat less marked degree than mirror PTNs.” Altogether, these findings strongly suggest an important conclusion: PTNs of area F5 seem to be subject to an overall suppression of their activity during action observation, regardless of whether they can be classified as “mirror,” thus reducing the overall corticospinal output during action observation.

Nevertheless, as discussed above, the corticospinal output is certainly the weakest way through which F5 can contribute to movement production, whereas its connections with M1 play a major role. A crucial issue was therefore to establish what happens in M1 during action observation. Vigneswaran and others (2013) demonstrated the existence of facilitation and suppression MNs also in this latter region, and concluded that a consistent “disfacilitation” of corticospinal output from M1 does occur during action observation. Indirect evidence supports this conclusion, showing that whereas grasping execution induces an increase of glucose consumption in the spinal forelimb representation ipsilateral to the limb used for acting, grasping observation induces a bilateral decrease of glucose utilization in the same spinal region (Stamos and others 2010). This is likely the result of reduced (corticospinal) facilitatory input (Nudo and Masterton 1986),

thus supporting the idea that the overall corticospinal output during action observation, although present, is too weak to cause overt movements to occur (see also Schieber 2011).

Subcortical Mechanisms

In addition to the above-described cortical mechanisms for decoupling motor neurons from the output, several alternative but nonmutually exclusive subcortical mechanisms can be hypothesized, and should be directly scrutinized in future experiments. For example, spinal interneurons with response properties comparable to those of cortical neurons (see Fetz and others 2002) might exist, and could exert a local inhibitory effect on spinal motor neurons during motor preparation, action observation, and imagery processes that deploy neuronal resources of the cortical motor system.

A number of studies support the idea that cortico-BG-thalamo-cortical loops also play a crucial role in the suppression of unwanted movement. Corticospinal and corticostriatal neurons of area M1 constitute relatively segregated populations in primates (Bauswein and others 1989; Turner and DeLong 2000). Corticostriatal neurons in layer 2/3 and upper layer 5 often project to other cortical regions (intra-telencephalic neurons [ITNs]; see Reiner and others 2010), whereas axons of some PTNs have been described as sparsely branching to the striatum, with no additional connections with other forebrain or midbrain regions (Parent and Parent 2006). Furthermore, alterations of the cortico-BG circuits impact more specifically on PTNs than on ITNs (Pasquereau and Turner 2011) suggesting that PTNs are particularly subject to the facilitation/disfacilitation effects exerted by the thalamocortical projections, in turn modulated by BG activity. Based on these considerations, an intriguing hypothesis to be explored in future studies is the following. Specific ITNs endowed with mirror properties, in both primary motor and premotor cortices, could be preferentially linked with striatal neurons belonging to the indirect (rather than direct) pathway, and hence characterized by the expression of type D2 dopamine receptors. If this is the case, the activity of neurons with mirror properties in the putamen should be more influenced by local injections of agonists of D2 receptors than that of motor neurons lacking mirror properties in the same region. The activation of this ITNs MNs during action observation would therefore result in a reduced thalamic facilitation of PTNs neurons. An alternative (though not mutually exclusive) possibility is that the same effect is promoted by direct projections of cortical MNs to the subthalamic nucleus (hyperdirect pathway) whose final effect would be, again, a reduced thalamocortical facilitation (Nambu and others 2002; Rektor and others 2015). In this view,

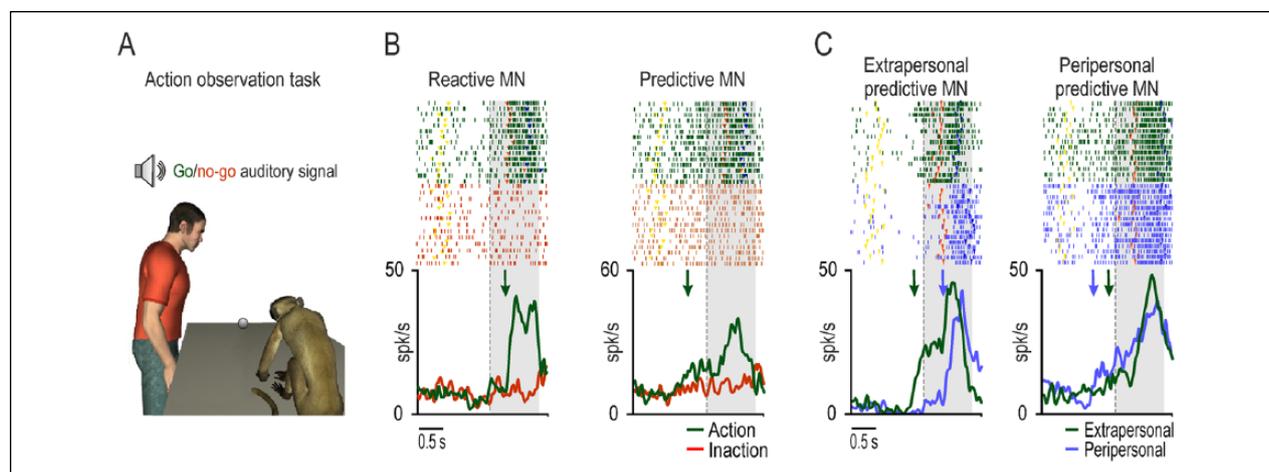


Figure 3. MN response during action observation in a predictable context. (A) Each action observation trial started in complete darkness. Both the monkey and the experimenter listened to an auditory signal constituted by a high (go) or low (no-go) continuous pure tone. While the sound was playing, the experimenter's target object was presented. At the end of the sound (which occurred from 0.8 to 1.2 seconds after target presentation), the experimenter reached, grasped, and pulled the object (Action) or remained still until the end of the trial (Inaction). (B) Examples of two different MNs aligned on the go/no-go signal (dashed line). Green and red rasters and histograms correspond to Action observation and Inaction trials, respectively. The grey-shaded regions correspond to the temporal window used for statistical analysis of the action observation response. Colored triangular markers: yellow, object presentation; orange, detachment of monkey's hand from the starting position (movement onset); blue, object pulling onset. The green arrows indicate the neurons response onset during Action condition (note that the predictive neuron discharges well in advance of the go signal). (C) Examples of the response of two different MNs tested during the observation of an action performed in the monkey's extrapersonal (green) or peripersonal (violet) space. All the conventions as in B, but green and violet arrows indicate each neuron response onset to the observation of the action in the extrapersonal and peripersonal space, respectively.

both the indirect and hyperdirect pathways driven by the activity of (facilitation) cortical MNs would provide a crucial contribution to reducing, or even suppressing, the activity of PTNs during action observation.

Of course, this model needs to be experimentally assessed and demonstrated, especially concerning possible mirror properties of corticostriatal neurons, as well as the presence of neurons with mirror properties in the BG, which is supported by the results of previous human studies (Alegre and others 2010; Kessler and others 2006). In any case, it is very likely that cortical and subcortical mechanisms work in concert to decouple cortical motor representations from the motor output in order to render them exploitable for high-order perceptual, cognitive, and even social functions.

From Motor Representations to Perception, Prediction, and Concepts

Why should motor neurons play a role in the representation of *observed* actions? As James Gibson wrote, "animals are by far the most complex objects of perception that the environment presents to an observer" (Gibson 1979), and the success of most of our social interactions relies on the rapid recognition, or even the anticipation, of

others' behaviors. The possibility of exploiting the neural machinery underlying the representation of one's own actions in familiar contexts may offer the opportunity to achieve highly complex and fast computations with limited neural resources (see Bonini and Ferrari 2011; Giese and Rizzolatti 2015). Recent neurophysiological data, reviewed from this point forward, support this idea as it applies to many domains, ranging from action perception and prediction to the formation of motor concepts.

Action Recognition and Perceptual Functions

The processing of observed actions in visual areas, such as STS, is mostly characterized by viewpoint, motion direction, and body-part specificity (Oram and Perrett 1994; Perrett and others 1989). However, we are able to *recognize* an action in spite of the multiplicity of viewpoints from which it might be observed. The MNs system can play a role in the emergence of perceptual-invariant recognition by linking viewpoint-selective neuronal representations of an action (such as object grasping) with their behavioral meaning, which is the goal of the action (i.e., taking possession of an object) encoded in a motor format. Indeed, Caggiano and others (2009) tested MN visual response by presenting monkeys with filmed grasping

actions as seen from different points of view, and demonstrated that about 30% of the recorded MNs were strictly selective for one point of view, 45% exhibited multiple view preference, and 25% were completely view invariant, supporting the idea of a possible role of MNs in the emergence of visual-invariant action representations (see also Fleischer and others 2013).

A certain degree of view invariance in the encoding of biological motion was already described in STS neurons (Oram and Perrett 1996), which are deemed to constitute the major source of visual information to area F5 (Nelissen and others 2011). Visual information can reach F5 both through direct and indirect pathways (Ferrari and others 2009): the classical direct pathway involves the inferior parietal areas AIP (Borra and others 2008) and PFG (Rozzi and others 2006), whereas the indirect pathways, which are still poorly investigated, may involve the VLPF and the MFC, which are anatomically linked with both inferior parietal and temporal cortices (Borra and others 2011; Gerbella and others 2013; Luppino and others 1990; Luppino and others 1993; see Fig. 1A). If this model is correct, an obvious prediction is that areas forming the intermediate steps between STS and F5 (i.e., AIP/PFG, VLPF, and MFC) should exhibit a variable degree of view invariance, depending on their hierarchical position in the stream that links visual information, on one hand, with invariant, conceptual-like representations of actions, on the other. Recent studies carried out on area AIP (Maeda and others 2015; Pani and others 2014) and MFC (Yoshida and others 2011) neurons have shown that these areas can play a role in the distinction between the visual representation of one's own and others' action, and support the idea that view-dependent and view-independent mirror-like neurons exist also in these regions. However, these studies were not specifically aimed at investigating neurons' viewpoint selectivity; they only tested neuronal responses to one or two visual perspectives, thus rendering it difficult to compare the findings with those previously reported for area F5 (Caggiano and others 2011).

Although these studies greatly contributed to clarifying the possible mechanisms underlying the recognition of others' observed actions, a crucial issue still remains unresolved: do MNs play a *causal* role in action recognition, or is their activation simply the by-product of a recognition process operated by other mechanisms and brain areas (see, e.g., Csibra 2007)? A recent human transcranial magnetic stimulation study (Michael and others 2014) and the results of a meta-analysis of lesion-symptom mapping studies in brain-injured patients (Urgesi and others 2014) favor the former hypothesis. However, single-neuron evidence of a direct causal role of MNs in action recognition is still lacking, thus constituting one of the main challenges for future neurophysiological studies.

Predictive Representation of Others' Actions

In addition to recognizing others' actions while they are occurring, a crucial skill in social contexts consists in the capacity to predict them before their actual onset. However, since the earliest reports (di Pellegrino and others 1992; Gallese and others 1996), it has been claimed that the visual response of MNs is triggered by the direct observation of others' motor acts. Several subsequent neurophysiological studies supported this view, suggesting that some kind of visual (Fogassi and others 2005; Maranesi and others 2013; Umiltà and others 2001) or auditory (Kohler and others 2002) sensory information regarding the ongoing action was always necessary to trigger MN response. More recently, Maranesi and others (2013) demonstrated that, at the population level, MN response to an observed agent's reaching-grasping action starts about 60 ms after the beginning of the reaching movement, supporting the idea that MNs generate a reactive, sensory-driven representation of observed actions. However, all these studies investigated MN response during completely unpredictable actions, whereas in many familiar daily situations contextual cues allow one to predict the upcoming behavior of observed agents.

Previous human studies have shown that cortical motor areas can activate prior to the observation of another's action when sufficient contextual cues are available (Kilner and others 2004). Nevertheless, no single-neuron evidence was available to support this claim. In a recent study (Maranesi and others 2014), we tested the activity of ventral premotor area F5 MNs while monkeys observed an experimenter performing or withholding a grasping action (Fig. 3A). Crucially, a previously presented auditory signal allowed the monkey to predict whether and when the experimenter's action was about to start. Although some MNs discharged in tight relationship with the observed movement onset (reactive MNs), many of them exhibited a largely predictive activation pattern (predictive MNs) relative not only to the observed action onset but even to the go signal (see examples in Fig. 3B). Preliminary evidence (Papadourakis and Raos 2013) showed that the same MNs can shift from a predictive to a reactive activation pattern depending on the presence or absence, respectively, of a visual contextual cue enabling the prediction. Thus, the MN system can play a role both in sensory-driven recognition of others' actions, through the temporo-parieto-frontal sensorimotor pathways (Nelissen and others 2011), and in context-based action prediction, likely through indirect prefronto-premotor routes (Borra and others 2011; Gerbella and others 2011; Gerbella and others 2013; see also Ferrari and others 2009).

The capacity to predict others' actions may be particularly relevant to the preparation of appropriate behavioral reactions during social interactions. Single-neuron studies have shown that actions performed by others may

have different relevance for the observer, and induce different MN visual responses, depending on the location in space (peri- or extrapersonal) of the observed action relative to the monkey (Bonini and others 2014b; Caggiano and others 2009). These findings make it necessary to extend the function of MNs beyond action recognition, suggesting that these cells might play a role in the selection of appropriate behavioral responses to observed actions. In line with this view, we showed that MNs tended to become active earlier when the observed action was performed in the monkey's extrapersonal space. However, some MNs even switched their firing pattern from predictive to reactive (or vice versa) depending on the space in which the observed action occurred (Fig. 3C), suggesting that motor prediction may play different roles in order to enable the preparation of specific behavioral reactions, such as approaching or avoidance, depending on the social context. These fascinating hypotheses should be directly investigated in future studies by recording monkey MN activity during free social interactions, which is now possible thanks to the recent advances in wireless recording techniques (Gilja and others 2010; Yin and others 2014).

From Multimodal Representation of Actions to Concepts

Several daily actions can be recognized by means of multiple sources of information. For example, many actions (such as breaking, ripping, etc.) can produce typical acoustic consequences, and MNs have been shown to be capable of generating an internal representation of a motor action not only when the subject performs it but also when he/she sees or listens to its acoustic consequences (Kohler and others 2002). A number of studies have replicated and extended this finding in humans, showing that multimodal access to motor representations of actions based on the subject's sensorimotor experience is a hallmark of the premotor cortex (Aziz-Zadeh and others 2004; Caetano and others 2007; Gazzola and others 2006; Hauk and others 2006; Pineda and others 2013; Ricciardi and others 2009). In addition, it has been shown that neutral sounds arbitrarily associated with specific voluntary actions can generate novel cross-modal representations of the action goal in the human motor system (Ticini and others 2012).

In a recent study, we found compelling evidence of such flexibility in the recruitment of motor representations of actions at the single-neuron level (Bonini and others 2014a). Indeed, we showed that although the majority of grasping neurons in area F5 remained silent when the monkey refrained from grasping an object, others, recorded simultaneously with the former, discharged both when the monkey grasped the object ("action") and

when it intentionally refrained from doing so ("inaction") based on a specific acoustic signal. Interestingly, some neurons with mirror properties (i.e., responding during both execution and observation of actions) became active in a similar manner when an experimenter refrained from grasping an object during the inaction condition of an observation task (Fig. 4). Notably, neurons discharging during inaction specifically encoded either the monkey's own (during the execution task) or other's (during the observation task) inaction, but not both. Thus, single-neuron representations of one's own and others' action in area F5 can be encoded at a highly abstract, conceptual level. "Action concepts" might therefore be crucial to understanding not only what we, or others, are doing, but also what we, or others, are refraining from doing. In other words, negative polarity action-related information (i.e., "don't grasp") deploys a part (though a small one) of the same neuronal substrates activated for representing the positive polarity of that content (i.e., "grasping").

Human studies allow researchers to extend the motor system's capacity to generate conceptual-like representations of actions to even higher and uniquely human levels of abstraction. Indeed, motor areas of the human brain play specific roles in the processing of motor concepts in a multimodal way, regardless of the sensorial or linguistic format of the information to be processed (Pulvermuller 2013; Pulvermuller and Fadiga 2010; Tettamanti and others 2008), thus grounding at least some aspects of semantic processes in the sensorimotor system.

Conclusions

Although the existence of neurons with mirror properties has by now been clearly established by several independent laboratories, ever since their discovery students continue to pursue heated debates on the ontogenetic origin and functional roles of MNs as well as the mechanisms that underlie their functioning (see Cook and others 2014; D'Ausilio and others 2015; Ferrari and others 2013; Hickok 2009; Rizzolatti and Sinigaglia 2010). The aim of this review was to scrutinize the most recent neuroanatomical and neurophysiological evidence of an extended network of cortical and subcortical areas that host, or may host, MNs in the primate brain. The emerging picture highlights several novel issues concerning both the functional role and cellular mechanisms underlying the extended MN network, but it also raises some crucial unanswered questions that should constitute the targets of future experimental investigations.

1. *Anatomical network.* Are there MNs in the BG? What are the cellular mechanisms that enable the exploitation of the same cortical neurons for action execution and observation as well as for

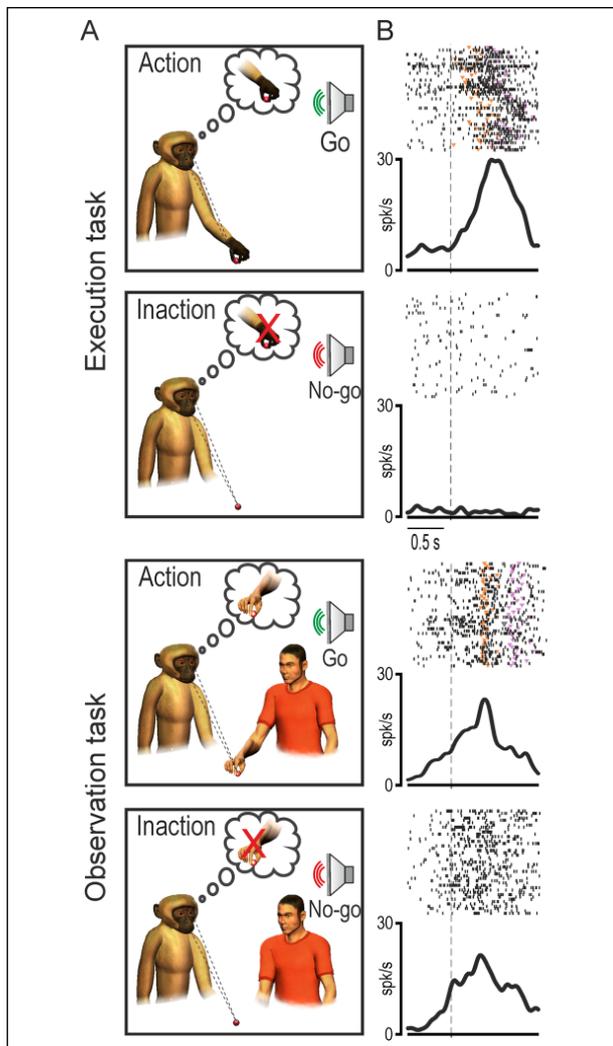


Figure 4. Inaction MNs. (A) The monkey performed an Execution task and, in a separate block of trials, observed an experimenter performing the same task (see Bonini and others 2014a). The end of two different cue sounds instructed the monkey (or the experimenter) regarding whether to grasp a target object (go trials—Action) or to refrain from grasping it (no-go—Inaction). Note that the Inaction conditions were behaviorally exactly the same for the monkey, regardless of the Execution or Observation context in which they occurred, since the animal was only required to fixate the target and to remain still until the end of the trial to get the reward. (B) Example of an Inaction MN discharge. The neuron’s activity is aligned on the go/no-go signal (dashed line), depending on the experimental condition. Orange and violet triangular markers indicate the moment when the (monkey’s or experimenter’s) hand detached from the starting position and the beginning of object pulling onset, respectively. It is clear that the neuron fired vigorously when the monkey performed a grasping act, but not at all during the inaction condition of the execution task. As a MN, it also fired when the monkey observed an experimenter grasping during the Action condition of the observation task but, surprisingly, it also became active in a very similar way when the monkey observed the experimenter refraining from grasping during the Inaction condition.

higher-order motor-based cognitive functions? Are there neurons with mirror properties in VLPF as well, or does this region exert some top-down modulation of MN activity in more posterior brain regions?

2. *Development.* To what extent is MN activity subject to plastic changes during development? Can sensorimotor learning of new skills (such as tool use) shape and change the response properties of single neurons chronically recorded before, during, and after the learning period? Can “new” MNs in MN brain areas originate as a result of sensorimotor learning processes even in the adulthood?
3. *Functions.* Is there any causal contribution of MN activity to behavioral recognition of observed actions (see Orban and Platonov 2015), as previously shown for face-selective (Afranz and others 2006) and direction-selective (Newsome and others 1989) cells in visual brain areas? A likely prediction might be that the manipulation of MN activity (i.e., stimulation or inhibition) can differently affect the monkey’s behavioral recognition of observed actions versus non-action stimuli.
4. *Ecological validity.* What is the link between MN activity recorded wirelessly during free interactions of a monkey with a partner and its overt social behavior? If MNs do play a crucial role in social processes, as proposed in many recent studies reviewed here, their activity and functional properties might strongly vary when tested during unconstrained social situations relative to constrained laboratory settings, shedding new light on the ethological relevance of the mirror mechanisms.

Whatever they might be, the answers to these extremely challenging questions will contribute substantially to our understanding of the neural mechanisms underlying the functioning of our “social brain in action.”

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