Title: Grasping Synergies: A motor-control approach to the mirror neuron mechanism

Short Title: Mirror resonance and motor synergies

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Abstract

The discovery of mirror neurons revived interest in motor theories of perception, fostering a number of new studies as well as controversies. In particular, the degree of motor specificity with which others' actions are simulated is highly debated. Human corticospinal excitability studies support the conjecture that a mirror mechanism encodes object-directed goals either or low-level kinematic features of others' reaching and grasping actions. These interpretations lead to different experimental predictions and implications for the functional role of the simulation of others' actions. We propose that the representational granularity of the mirror mechanism cannot be any different from that of the motor system during action execution. Hence, drawing from motor control models, we propose that the building blocks of the mirror mechanism are the relatively few motor synergies explaining the variety of hand functions. The recognition of these synergies, from action observation, can be potentially very robust to visual noise and thus demonstrate a clear advantage of using motor knowledge for classifying others' action.

Introduction

The discovery of mirror neurons in monkey premotor cortex in the early nineties (Di Pellegrino et al., 1992) motivated a number of human studies on the topic (Rizzolatti, Craighero, 2004). The critical finding was that some ventral premotor neurons are engaged during visual presentation of actions performed by conspecifics. More importantly, those neurons were shown to encode also the actual execution of similar actions, suggesting that they encode actions irrespective of who the acting individual is. In fact, this led to a resurgence of interest in motor theories of perception (Fowler et al., 2003), including theories such as the motor theory of speech perception (Liberman et al., 1967) and the theory of direct perception (Gibson, 1979).

Although different flavors of motor theories can be traced back to the XIX century (Young, 1970), the first modern proposal was that of the analysis by synthesis (Stevens, Halle, 1967). This model proposed that perception is derived from the computational re-creation of the input (Bever, Poeppel, 2010). Visuomotor neurons, like mirror neurons, were thus considered a possible biological substrate to prove the theoretical existence of a common code or parity between the visual and the motor representations of the same action (Fowler et al., 2003). More recently it has been proposed that the recruitment of motor programs, during action perception, may also have an important anticipatory function. In fact, it may also allow the active selection of specific input features that maximize the discrimination between two perceptual hypotheses (Friston et al., 2011). Along this line, the level of motor detail implemented in mirror neuron activity, or its motor representational granularity, is of critical importance to understand its potential contribution to perception and its functional role in general. In fact, the intrinsic properties of such an anticipatory and dynamical sensory gain, applied to incoming information, must be consistent with the sensorimotor resolution allowed by the mirror neuron mechanism (or its representational granularity).

However, the granularity of the human mirror mechanism is currently debated. At present, the discussion mainly revolves around two alternative possibilities. In fact, the mirror activities could map low-level movement implementation details such as the pattern of muscle activity that is tightly associated to visible kinematic changes in joint angles. Alternatively, these activities could

be preferentially engaged by the movement goals such as the attainment of a distal object-directed grasp (i.e. grasping and releasing objects). It is worth noting that movement goals can potentially be dissociated with respect to the electromyographic pattern and thus the visual appearance of others' action.

In this review we will focus on human neurophysiological research regarding the motor representational granularity of the mirror mechanism. In doing so, we will first have to set the context by briefly reviewing monkey neurophysiological studies (section 1). Subsequently, we will move to the core of the review and discuss human motor neurophysiological research. Specifically, we will highlight recent controversies emerging from the investigation of the modulation in corticospinal excitability during action observation (section 2). In section 3, we will move to the motor control literature to ground our new proposal regarding the human mirror representational granularity. In fact, we advocate the view that motor principles, such as the synergistic control of movement, should be applied to human mirror research. Along these lines, in section 4, we will suggest that the application of the synergy principle to human mirror research may solve previous controversies and offer further testable hypothesis at the same time.

1 - Monkey single unit research on the mirror mechanism granularity

In recent years, single-unit studies on the ventral premotor (vPM) and primary motor cortex (M1) of the monkey have been carried out in order to better characterize the mirror-like properties of neurons in these regions (For a review see: Rizzolatti, Sinigaglia, 2010, Casile et al., 2011: Kilner, Lemon, 2013). The first attempt to obtain a description of the visuomotor coding properties of mirror neurons in vPM was the work of Gallese and coworkers (Gallese et al., 1996). In this study, several of these mirror neurons showed their visual response for the observation of actions executed with both hands, thus suggesting that specific movement features were not encoded by these neurons. Along this line of research, Umiltà et al. (2001) showed that the presence of an object to act upon (or the knowledge that the object was present behind a screen) was necessary for mirror neurons to discharge. These studies supported the claim that mirror neuron coding was centered on a rather abstract description of object-directed grasping.

Furthermore, Umiltà et al. (2008) reported the presence of mirror-like responses in the monkey vPM cortex during the observation of actions performed with tools (pliers). Interestingly, classic and reversed pliers enabled the dissociation between object grasping and muscle-level implementation. Training monkeys to use normal and reversed pliers showed that mirror neurons coded for the goal (grasping the object) and not for the actual muscle-level implementation of actions (finger flexion or extension). This result is in agreement with the original proposal (Gallese et al., 1996), suggesting that mirror neurons may be sensitive to a family of action-related visual stimuli sharing the same object-grasping goal. In fact, it was shown that mirror neurons do not code for the fine-grained parameters of muscle or joint angle implementation.

Some more recent studies, however, are in conflict with such data. Recent studies investigated the mirror properties of pyramidal tract neurons within vPM of the monkey (Kraskov et al. 2009; 2014). They found a quite significant percentage of mirror neurons (29%) responding to intransitive actions. Thus no hand-object interaction or apparent object-directed goal was needed to elicit a response during passive action observation.

Furthermore, other studies revealed mirror-like properties also in M1 (Tkach et al., 2007; Dushanova, Donoghue, 2010; Vigneswaran et al., 2013). For example in one study, the monkeys were engaged in a classic tracking task with a robotic manipulandum, as well as in the passive observation of the replay of their cursor trajectories. Typical activity modulation following the preferred directional tuning during actual movement was present also for the observation of cursor trajectory (Tkach et al., 2007). Mirror-like properties in M1 neurons were also reported in a study by Dushanova and Donoghue (2010). Almost half of the neurons that were modulated during movement execution and that showed directional tuning were modulated and tuned to the direction of movement performed by another individual in the same motor task. In these studies, activity in M1 mirror neurons seems to be associated with the mapping of others' movement low-level implementation rather than object-directed goals.

To conclude this brief section on monkey neurophysiological investigations, we understand that mirror neurons may belong to a heterogeneous class of

cells responding to different levels of movement features. It is possible that such a difference is partially based upon whether they are located in M1 or vPM areas. However, only future research will clarify whether there is a gradient of responses across M1 and vPM or whether there are segregated populations of neurons coding for different movement features.

2 - Human research on the mirror mechanism granularity

Similar research questions regarding the representational granularity of the human mirror mechanism have emerged in parallel. In this sense, the measurement of corticospinal excitability modulation during action observation, via Transcranial Magnetic Stimulation (TMS), has become a fundamental tool for studying these mechanisms in humans (Fadiga et al., 1995; Fadiga et al., 2005; Naish et al., 2014).

This is mostly because recording motor evoked potentials (MEPs) is a fairly direct and temporally specific method to study the recruitment of the motor system during passive action observation. As far as spatial specificity, TMS can selectively target specific effectors in the motor strip (arm, leg, face) as well as specific muscles in some effectors (i.e. First Dorsal Interosseous or Abductor Digiti Minimi). However, a supra-threshold magnetic stimulation measures both local and distant cortical effects. In fact, TMS mostly activates intracortical horizontal fibers (Rothwell, 1997), connecting extended cortical networks that are presynaptic to the corticospinal neurons (Huntley, Jones, 1991). Therefore, the stimulation of one muscle group in M1 (i.e. intrinsic hand muscles) probes the whole afferent connections to that specific population of neurons. These afferents include inputs from the parietal cortex (somatosensory areas and the posterior parietal cortex), somatotopic projections from lateral premotor areas, supplementary motor area and the cingulate motor areas as well as thalamic inputs, mainly from the ventrolateral (VL) and ventral anterior (VA) nuclei. These latter connections indirectly provide information from the basal ganglia via VA and the cerebellum via VL.

Other popular methods, such as fMRI, EEG and MEG, cannot grant the same level of spatial and temporal specificity when probing the activity of the motor system (please also refer to Turella et al., 2009 on the perils of neuroimaging inferences about human mirror activity and to Kilner and Lemon 2013 about

the risks of comparing neuroimaging data and single unit studies) and, for this reason, we will now focus on studies probing the corticospinal excitability modulations induced by action observation.

Does the human mirror mechanism map low-level movement features?

The mirror mechanism, as measured via corticospinal excitability indexes (Fadiga et al., 1995), was shown early on to be sensitive to rather low-level features of the observed movement, such as kinematics (Gangitano et al., 2001; Borroni et al., 2005), muscle activity (Alaerts, et al., 2009) and forces (Alaerts, et al., 2010a; Senot et al., 2011). This was true for both transitive and intransitive action. Hence, human data, when compared with early monkey studies (Gallese et al., 1996; Umiltà et al., 2001), initially suggested that motor resonance for action observation may be based on quite different principles. Bearing in mind the obvious difference between measuring the corticospinal excitability and the pattern of single neuron firing, it was nevertheless surprising that the human and monkey mirror mechanisms differed so much. The first was sensitive to low-level movement features, whereas the second responded to object-directed grasping, independently of the kinematic or muscular pattern.

However, as shown in the previous section, recent single cell studies are starting to suggest a different and more articulated picture including the coding of low-level movement features. Therefore, it is now important to understand to what extent the human mirror mechanism, as investigated via TMS, can also show tuning for higher-level object-directed goal features during transitive action observation.

Does the human mirror mechanism map object-directed goal features?

Recent TMS research has indeed opened a controversy as to whether "mirror-resonance" reflects the low-level parameters of observed movements or, rather, the object-directed goal of actions (Borroni et al., 2011; Sartori et al., 2013). In fact, it has been shown that the observation of a one-hand intransitive movement evokes a bimanual resonant response (Borroni et al., 2008), in partial analogy with early monkey neurophysiology results (Gallese et al., 1996). Furthermore, corticospinal excitability can be modulated by

object-grasping regardless of the muscular pattern implicated in attaining the object (Cattaneo et al., 2009), as was also shown at the single-cell level (Umiltà et al., 2008).

In fact, Cattaneo and colleagues (2009) used the same tools (normal and reversed pliers) employed by Umiltà and coworkers (2008). They showed that during the observation of intransitive actions (no object was present) the corticospinal excitability reflected the muscular pattern involved in action execution. In contrast, if the object was present, the corticospinal modulation shifted to an object-directed coding, evidently independent of the visual presentation of a finger flexion or extension action. However, a subsequent study questioned this result by using the same two pliers together with a new magnetic plier (Cavallo et al., 2012). In fact, these tools could dissociate between hand movement, object-directed goal and tool movement, finding corticospinal modulation for hand movement only (but see also Cattaneo et al., 2013 in this respect).

Generally speaking, there is some evidence that corticospinal excitability can show some degree of action abstraction and generalization. In fact, resonance for low-level motor control parameters is not limited to the contralateral motor cortex but, rather, is bilateral also for intransitive action observation. Moreover, motor activities seem to map also higher-level object-directed features, during transitive action observation. However, comparing these findings with those of the previous section, how is it possible to reconcile the findings showing that, depending on the study, different levels of action representation similarly modulate corticospinal excitability?

How to reconcile the (potential) existence of both coding levels?
A solution was suggested in a review proposing that parallel but interacting processes run computations at different levels of complexity in response to the same observed actions (Rizzolatti, Sinigaglia, 2010). Although the results just reviewed seem to partially support this claim, a specific investigation of the mutual interactions between these processes is still sketchy. In support of a parallel mechanism, it was proposed that task constraint might modulate the relative contributions of the two. In fact, it has been shown that the relative influence of object-directed goal coding and low-level motor coding depend on

the information available to the observer and thus on the task requirements (Mc Cabe et al., 2014).

Otherwise, some other data suggest it might be a serial mechanism, rather than a parallel one. A first object-directed goal extraction might be followed, when approaching the object to be grasped, by a later sensitivity to lower level movement information (Lago, Fernandez-del-Olmo, 2011; Cavallo et al., 2013a). However, a strict temporal gradient of object-directed versus low-level feature extraction seems to be at odds with other empirical data. In fact, in a reach-to-grasp action observation study, corticospinal excitability was significantly more modulated by transitive actions as opposed to intransitive ones (Enticott et al., 2010). In this case, TMS pulses were delivered just before object contact, at which point other studies predicted that no such object-related modulation should be present (Lago, Fernandez-del-Olmo, 2011; Cavallo et al., 2013a).

Summing up, there has been an active debate about the level of granularity that is specifically extracted by the human mirror mechanism during action observation. As a consequence, few recent studies have approached this problem by investigating how both coding schemas could fit into the same theoretical picture by examining their interaction. However, it is yet not clear whether i) different levels act in parallel or in series, ii) whether they are mutually exclusive or interact (and if so, how), ii) whether and how they can be modulated by the task, and iv) whether transitive and intransitive action observation are different in this regard. In the following section we will instead pursue a different path. We will highlight the reasons why the separation between these two proposed coding schemas might be arbitrary and misleading in most cases.

Stability and separability of the two coding levels

As discussed in the previous sections, a considerable body of literature has reported contrasting results regarding the representational granularity of the human mirror mechanism. As a consequence, more recent studies have tried to reconcile these contrasting results by investigating the temporal (parallel or serial mechanisms) and functional (task dependency) relation between the different levels of action feature extraction.

However, a first critical point is that the coding scheme for others' actions may be unstable across tasks and time (Catmur et al., 2007; but see also Barchiesi et al., 2013; Cavallo et al., 2013b; Ubaldi et al., 2013). In fact, training may heavily impact such a coding scheme. The clearest example is given by motor experts. A motor expert, be it a musician or an athlete, is in the first instance an individual with a domain-specific increase in sensory acuity and motor control capability. Such specific sensorimotor augmentation has often been associated with a refined mirror-like sensitivity to low-level features of others' actions (Aglioti et al., 2008).

However, even if we set aside training-induced plasticity, there are other issues that make the distinction between the two proposed granularity levels at least fuzzy. Among these issues is a finding reported by Gangitano et al. (2001), who showed that the largest corticospinal modulation during the observation of a reach-to-grasp action corresponded to maximal finger aperture during reaching. Although this result seems to directly associate mirror responses with low-level motor analysis, it hides a possible confounding factor. Indeed, maximal grip aperture scales for object-intrinsic features (like size and shape), thus presenting a critical cue for the recognition of the object-directed action goal (Jeannerod, 1984; Figure 1). This ambiguity stems in part from the fact that movements are co-articulated in a way that the two levels are co-expressed, in object-directed action. As previously suggested, maximal grip aperture is at the same time a powerful low-level motor cue and an object-goal cue, suggesting that the experimental prevalence of either of the two coding schemes could be misleading.
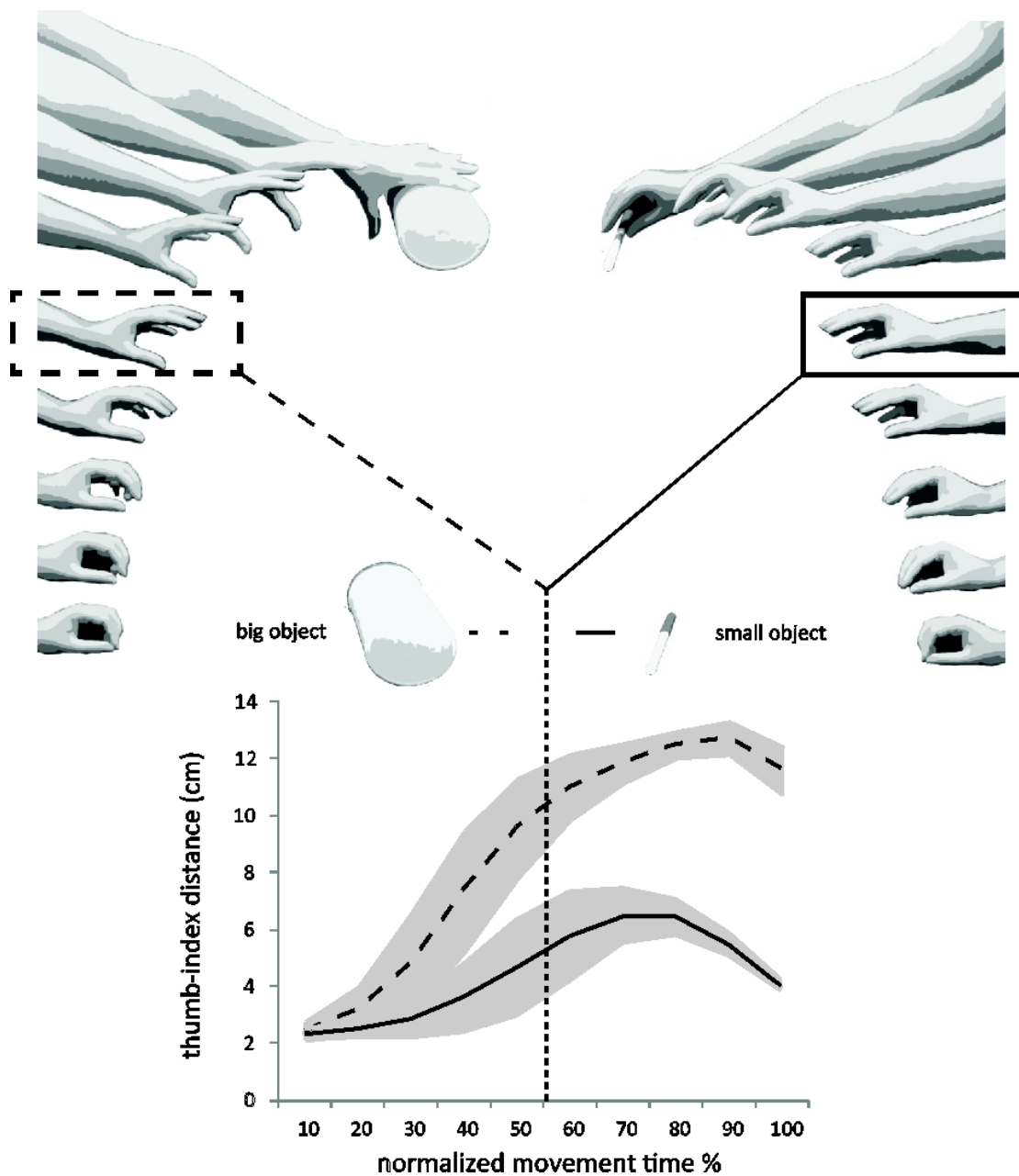
Figure 1. Movement and object-directed goal features overlap

The upper part of the figure shows the reach to grasp movement directed at two objects with different size. Notice how differences between hand configurations start quite early. The lower part of the figure shows grip aperture over time. Grip aperture (thumb and the index distance) is a classical low-level feature used to discriminate between these two object-directed actions and in fact, the dissociation emerges already at 40-60% of the movement time. Since grip aperture is at the same time a low-level motor cue

and an object-goal cue, the dissociation between the two representational granularity levels appear quite arbitrary sometime.

In addition, studies investigating the timing of anticipatory gaze during goal-directed action observation demonstrate that subjects' gaze follows the hand trajectory until it jumps to the anticipated goal (Flanagan, Johnasson, 2003). Such anticipatory eye shifts are triggered by the subtle hand-kinematic features (i.e. trajectory) that disambiguate the final target object location (Rotman et al., 2006) and are driven by an effector-specific motor activation (Elsner et al., 2013). These two arguments suggest that prediction of target object location and object-related characteristics may coincide with the successful extraction of low-level kinematic features (i.e. trajectory or hand opening) during the early phases of object reaching.

Actually, according to a direct realistic view, graspable objects themselves specify the appropriate grip characteristics or affordances (Gibson, 1979). Therefore, a particular object permits a limited set of grasping interactions (and thus hand configurations). These hand configurations, already detectable during reaching, are very informative about the specific object-directed action goal. In support of this claim, object observation has indeed been shown to modulate corticospinal excitability (Cardellicchio et al., 2011; Franca et al., 2012), and to do so in a manner that matches with the specific grasping action that could potentially be directed towards the object (Bartoli et al., 2014).

Following this line of reasoning, we suggest that, at least in object-directed action, low-level features by definition specify higher-order object-directed goal features, and both are constrained by object characteristics. Hence, the two levels of representation discussed so far are, at best, highly correlated and overlapping in time, making the distinction between them somewhat arbitrary. Nevertheless, we firmly believe that an understanding of the representational granularity of the mirror mechanism is of critical importance for ascertaining its potential role in action perception.

Understanding the representational granularity of mirror mechanism coding
The question as to whether the mirror mechanism preferentially represents others' actions at the muscle level, at the level of joint configurations, or at the

goal level is of the utmost importance, as it would define the mechanism's motoric frame of reference. Such a frame of reference is certainly based on our motor planning-execution hierarchy, but each complexity level has different properties and allows different inferential power about the future course of others' actions (Friston et al., 2011). In fact, while a low-level motor code (i.e. muscle- or posture-based) would refer to an intrinsic motoric reference frame, an object-directed goal representation also has to integrate an extrinsic reference frame. It is likely that the predictive power (and as a consequence the behavioral relevance) of the two alternative coding types would be very different.

In particular, a coding type based on object-directed goals may have a deeper temporal horizon, and could therefore underpin a predictive system with the potential to project much further into the future of observed actions. Furthermore, such a coding type may integrate intrinsic and extrinsic coordinate systems, thus encompassing the relation between body-schema and object-centered coordinates. Such a mixed body-object space system could sustain a more effective generalization and abstraction across actions viewed from different perspectives and across more variations of the same action.

A low-level motor control coding system, in contrast, may support short-term local prediction, but with a higher degree of resolution. For instance, a low-level coding system could perhaps anticipate the intensity and direction of forces applied during the grasping of an object. Such a system could model this information by visual examination of object geometry, and could include estimates of surface friction and object weight, as well as the complete pattern of muscle activities. Such a fine-grained and short-lived anticipation of low-level motor control parameters could hardly support generalization and abstraction as suggested for the other coding schema.

In conclusion, it is evident that the determination of the exact motor granularity is of critical importance in understanding the behavioral relevance that the mirror mechanism may have in supporting the processing of others' actions. To summarize this section, we first reviewed empirical research suggesting that action observation triggers low-level motor simulation in the observer. We continued by reporting studies showing that the mirror mechanism could

instead be tuned to higher-level object-directed action goals. Then we moved on to discuss investigations trying to reconcile this obvious contradiction by suggesting that both coding schemas exist and interact in a way that might be driven by task constraint. In contrast with such proposals, we offered arguments, based on empirical data, suggesting that the distinction between these two specific coding schemas might be an arbitrary one. Finally, we defended the need to define the exact representational granularity implemented by the mirror mechanism. The next section will propose a new single coding schema based on how neural control of movement is implemented and on knowledge about the functional properties of object-directed motor control for the hand

3 - A functional perspective derived from motor control

In the following sections, we will propose that the dilemma between low-level motoric coding and object-directed goal coding might arise from an ill-defined question. In fact, we will propose that the difficulties in understanding the complexity of mirror coding stem directly from basic properties of the motor system. From this perspective, knowledge about the neural encoding of movement could be central in the attempt to better define the properties of the human mirror mechanism.

Coding of intrisic vs extrinsic movement features in the motor system
Starting in the sixties, neuroscientific research has focused on neural coding within M1. At first, investigations focused on individuating the parameters controlled by the motor cortex in order to produce overt behavior (Evarts, 1968). The first attempts were devoted to distinguishing between muscle-level control and movement control by neurons in M1. Later, in the eighties, the pioneering work of Georgopoulos and co-workers (Georgopoulos et al., 1982) shifted attention to the level of neural populations, namely by examining the directional tuning of motor neurons to extrinsic parameters such as the direction of arm movement.

Tuning curves appeared to differ between different neurons, and overlapped partially, suggesting that a movement trajectory in a desired direction could be given by the weighted summation of the contribution of single cells, thus

leading to the concept of a population code. The population code hypothesis claimed that the role of motor cortex is to control direction of movement in an extrinsic reference frame, thus coordinating the activity of different muscles rather than a single muscle (Georgopoulus, 1995).

Motor coding may be mixed, task dependent and unstable

Later, in the nineties, it was demonstrated that the directional tuning shifted as the monkey changed its arm posture, thus suggesting that the neural coding could not refer solely to an extrinsic reference frame (Scott, Kalaska, 1995). These and many other studies suggested that the role of M1 and PMv cannot be captured by appealing to an extrinsic reference framework alone (Scott et al., 2001; Strick et al., 1999; 2001). Furthermore, it was also shown that neurons could switch their representational frame of reference across different motor behavior (Kurtzer et al., 2005), that motor training can induce a sharpening of neural tuning (Paz, Vaadia, 2004), and that such tuning is also subject to slow drifts, even in the absence of any learning (Rokni et al., 2007). These results have a critical impact on very important debates, such as the nature of the motor engram (Lukashin et al., 1994) and more generally on the stability-plasticity dilemma in the motor system (Ajemian et al., 2013). At present, in fact, research on the neural control of movement has in part changed. Increasingly, the focus of interest is shifting from the project of identifying what is encoded by neural discharge patterns to the problem of understanding actual movement control, thus giving rise to a functional perspective.

A functional perspective based on motor synergies

The adoption of a functionally oriented perspective suggests a focus on behavioral complexity and on the associated problems of controlling many degrees of freedom at once (Bernstein, 1967). These issues cannot be solved by either the independent control of muscle activity or the control of few extrinsic parameters (i.e. movement direction), especially when dealing with the complexity of a reaching-grasping action.

Complex intentional and automatic movement control is often modeled as the summation of simple motor primitives (Flash, Hochner, 2005; Poggio, Bizzi,

2004). Typically, primitives have been defined in terms of overt movement kinematics or basic hand movement postural synergies (Santello et al., 1998; Mason et al., 2001). But in some contexts motor primitives have also been defined as synergistic muscular activities (Brochier et al., 2004). In general, the problem of controlling the large number of degrees of freedom for the hand could be simplified by controlling muscle synergies (Overduin et al., 2012).

Synergies are invariant, hard-wired patterns of activation across muscles that could be linearly summed, with specific amplitude and timing co-efficients, to generate the large variety of hand functions (Overduin et al., 2008). Hand synergies amount to coordinated patterns of muscular activity during natural movements. Few time-varying synergies usually explain a very large portion of the electromyographic and kinematic variance during a variety of tasks (Santello et al., 2013). Each synergy, through its scaling and modulation in time, adapts to grasping objects of different sizes and/or shapes. More interestingly, hand synergies are very similar across individuals, despite evident differences between grasp postures.

Therefore, the natural variability in reaching-grasping behaviors might be handled via the control of a small set of motor synergies. From a functional perspective, synergies offer a quite compact representation that still manages to achieve a huge variability in behavior in the face of a large motor control redundancy. In the next section we will discuss how this stereotyped and modular control strategy allows for the learning of new skills, which is the hallmark of human capabilities.

Stability of synergy coding

Overlearned behaviors might be controlled via the mixing of few stable motor synergies. However, humans exhibit massive behavioral flexibility, which might not be explained by the combination of a fixed number of synergies (Gentner et al., 2010). In fact, it has been shown that short-term (Classen et al., 1998) and long-term motor training (Gentner et al., 2010) can modulate the expression of hand synergies.

In this sense, a great deal of adaptive potential can be obtained by the direct and relatively independent control of finger movements. In fact, it is possible

to glean important insights from comparative analyses of the corticospinal tract. The human corticospinal tract is a recently evolved system that should subserve an evolutionarily new feature of motor behavior, such as the performance of relatively independent finger movements (Porter, Lemon, 1993). The monosynaptic connections of the corticospinal tract may facilitate the dexterous control of such finger movements. Interestingly, many of the species with well-developed monosynaptic connections are also those capable of acquiring new complex hand motor skills (Lemon, Griffiths, 2005). However, the notion of relatively independent finger movements is essentially an anatomical one, and does not really explain behavior, which may be better represented by the synergy model. Therefore, voluntary and independent finger control may constitute the pathway to adapting otherwise stable synergies to new contexts or tasks, thus enabling the necessary behavioral plasticity.

In the next section we will suggest specific methodological caveats to observe in applying the synergy idea to the investigation of the mirror mechanism. Furthermore, we will also stress the advantages that such synergy coding would grant to the classification of others' actions.

4 - A motor-derived functional approach to the mirror mechanism

The concept of synergy might potentially apply to human research on the properties of the mirror mechanism. However, current studies do not permit an evaluation of any synergies that may be evoked during action observation. In the following section we will first suggest a few methodological changes that are necessary in order to exploit the full potential of the synergy idea in mirror research.

A synergy-based investigation of the human mirror mechanism

The adoption of a synergy-oriented perspective in the study of the mirror mechanism in humans may require some methodological adaptations. In fact, one aspect of the granularity controversy may originate in part from a methodological issue. MEP size presents only a noisy and partial picture of what is actually happening in the motor system during action observation. In fact, the effect of a single supra-threshold TMS pulse over the motor cortex is

conventionally measured via the recording of only a few (usually up to two or three) muscles by using surface electromyography (EMG). However, a supra-threshold magnetic stimulation evokes EMG activity in several adjacent (un- measured) muscles (Rothwell, 1997).

Importantly, according to the definition of hand synergies, a very similar amount of EMG activity (in a specific time window) in one muscle can be observed across very different hand postures and behaviors, making it a rather unreliable measure of the functional state of the motor system. Thus, recording MEPs from a limited number of muscles, with small functional specificity, represents a dramatic reduction of the inferential power allowed by this technique.

All the system-level changes that are potentially evoked by action observation cannot be represented in the amplitude modulation of MEPs recorded from a few selected muscles. Indeed, we know that both the electrical stimulation of the monkey motor cortex (Overduin et al., 2012) and the magnetic stimulation of human motor areas (Gentner, Classen, 2006) evoke synergistic whole-hand postural configurations rather than single isolated muscle contractions.

Therefore, we propose that research on the mirror mechanism should draw from methods and models developed to study motor control, and should be informed by the functional aspects of hand motor control. In this sense, a more reliable measure of the activation of the motor system can be obtained by the recording of TMS-evoked motion kinematics (Classen et al., 1998; Stefan et al., 2005; 2008; Bartoli et al., 2014; D'ausilio et al., 2014) or TMS-evoked activities in a large number of muscles (Lemon et al., 1995).

Recently, an investigation from our group (D'Ausilio et al., 2014) combined TMS of the motor cortex and Ultrasound Tissue Doppler Imaging (UTDI) to gain deeper understanding of speech-induced motor mirroring. With this approach, we differentiated the sub-threshold tongue movement synergies evoked by passive listening to specific speech sounds. Importantly these movement synergies were in detailed agreement with known articulatory descriptions of speech production. Such a level of fine-grained detail was made possible only by using new methods to extract motor synergies from tongue kinematics. In fact, the classic TMS recording of corticobulbar

excitability can only show a rather coarse picture of the tongue motor activation during passive speech listening (Fadiga et al., 2002; D'Ausilio et al., 2011). Importantly, both corticospinal and corticobulbar excitability measures cannot offer any hints about the functional goal-directed postural configuration evoked in the effector of interest.

The novel approach presented in D'Ausilio et al. (2014) shows a clear theoretical potential, with respect to previous studies, that we hope can be extended to hand action observation too. In fact, movement (or the full pattern of muscle activity) is the final functional output of the motor system, and thus the only realistic window through which to study the motor representational granularity evoked by action observation (Figure 2).

PASSIVE OBSERVATION OF HAND MOVEMENTS

TMS-EVOKED WHOLE-HAND SYNERGIES
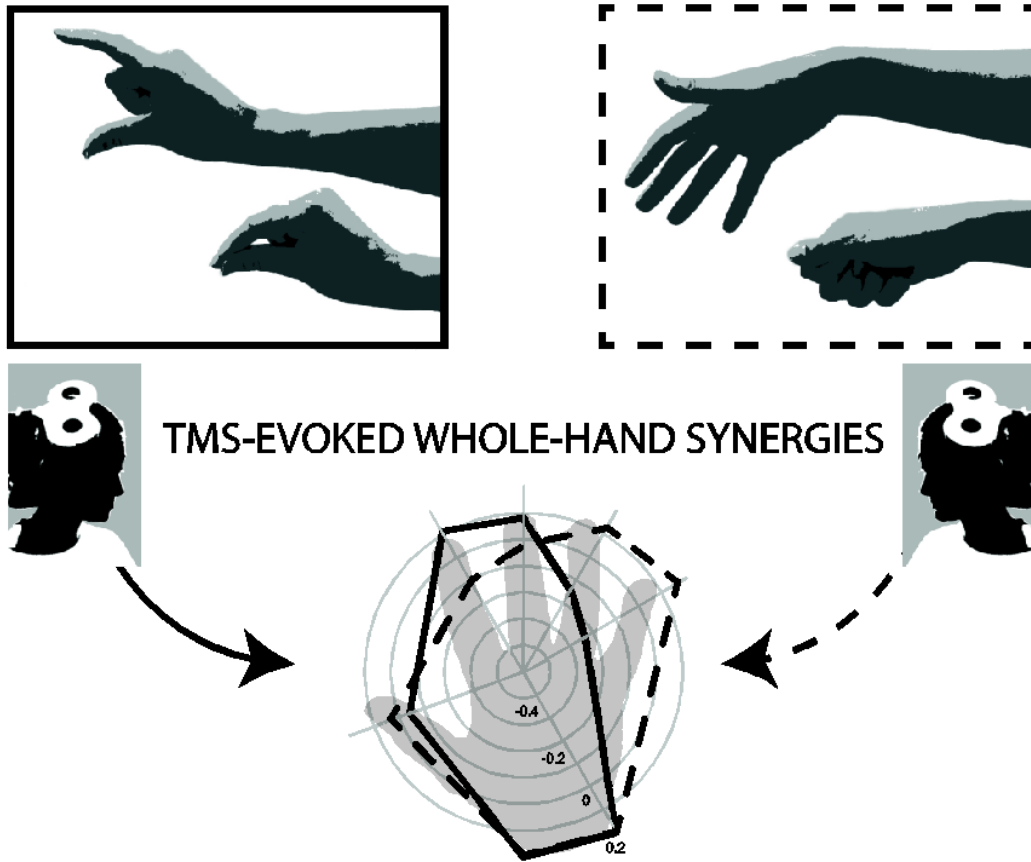
EXAMPLES OF RECORDING TECHNIQUES

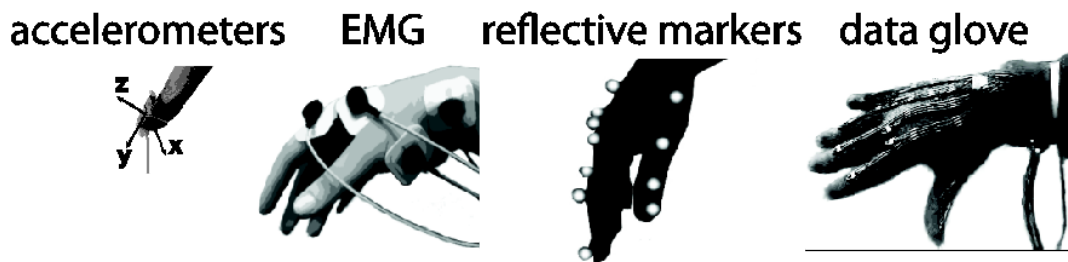accelerometers   EMG   reflective markers   data glove

Figure 2. Testing the mirror synergy hypothesis

The upper panel shows an example of two different movements to be used in classical action observation studies. The two movements depict a two-finger (left) and a whole-hand grasp (right). The magnetic stimulation of the motor cortex may be used to test the specificity of the complex hand synergies

evoked by passive action observation. The figure in the middle shows the specific whole-hand postural synergies evoked during passive observation of the two grasp types (adapted from Bartoli et al., 2014). The lower panel shows some of the recording techniques that can be used to describe fine-grained TMS-evoked synergies. These techniques include multiple EMG channels (Lemon et al., 1995), small accelerometers (Classen et al., 1998), data gloves measuring joint angles (Gentner, Classen, 2006), or motion capture systems measuring whole hand movements and postural configurations (Bartoli et al., 2014).

Approaching the problem from such a radically different perspective, we suggest that asking if the mirror mechanism extracts low-level movement features or higher-level, object-related ones, may just be an ill-posed question.

Nevertheless, virtually all studies investigating the human mirror system via TMS have used the rather unspecific MEPs measurement from just a few muscles during action observation (Fadiga et al., 1995; Strafella, Paus, 2000; Gangitano et al., 2001; Borroni et al., 2005; Romani et al., 2005; Borroni et al., 2005; Avenanti et al., 2007; Alaerts, et al., 2009, Alaerts, et al., 2010a; 2010b; Senot et al., 2011; Lago, Fernandez-del-Olmo, 2011; Cavallo et al., 2013a; 2013b; Barchiesi et al., 2013; Ubaldi et al., 2013; Aglioti et al., 2008; Urgesi et al., 2006a; 2006b; 2010). Although some of them were directly trying to describe the granularity of the mirror mechanism, very few used TMS-evoked features that enable the effective description of motor granularity (Bartoli et al., 2014).

In contrast, if we adopt a synergy-based approach, we are led to believe that the appropriate level of granularity of the mirror mechanism is neither that of low-level movement features nor that of object-directed goal representation. In fact, we suggest that its granularity cannot be any different from the granularity of the motor system, which is instantiating the mirror mechanism.

Along these lines, we speculate that the mirror system might replicate the same computational mechanisms shown for motor control and allowed by the properties of the motor system. More precisely, the observation of prototypical

and overlearned actions may elicit the activation of a few hand synergies able to explain most of the functional variability of human hand behaviors – regardless of the presence of any object-directed action. In the next section we will discuss the computational advantages of a synergy-based encoding of others' actions.

Advantages of a synergy-based approach to the mirror mechanism

Motor synergy extraction from action observation might also have several advantages. The first one is related to computational costs and to the robustness of an action recognition system based on synergies. From an action observation point of view, synergies are indeed a limited set of non-overlapping hand configurations (Santello, Soechting, 1998; Gentner, Classen, 2006), which are shaped around biomechanical constraints and extensive hand use (Santello et al., 2013). Such configurations are postural prototypes that are not effected by small local variations, and are thus robust to quite moderate amounts of noise (Santello et al., 1998).

This might be a critical property for a neural system converting the visual appearance of actions into their motor representation. In fact, occlusions, distractors and noise of all kinds often affect action observation. Thus, computationally speaking, the recognition of a few non-overlapping prototypical hand configurations, by using partial and noisy data, could still be achieved with relatively acceptable error rates.

Comparatively, a low-level motor coding system could not achieve such robustness. In fact, visual occlusions obliterate the detection of critical kinematic features. On the other hand, object-directed goal coding critically depends on the task and on the specific object characteristics, and would therefore require a capability to recognize a large number of action-classes, some of which might even be new to the observer. More importantly, from a postural (synergistic) point of view, these action-classes may largely overlap, and thus be visually identical to the observer. In sum, recognition based on object-directed goal coding seems rather unreliable due to the large number of action-classes, their overlap as well as the likelihood of encountering novel un-trained ones.

From a functional perspective, in contrast, the recognition of a given hand postural synergy could already be very informative about the goal of the action. In fact, hand shaping, according to a given synergy, imposes important constraints on hand-object interaction potentialities. These constraints reduce the range of possible action outcomes and are thus extremely informative in anticipating the object to be grasped by the actor. Furthermore, hand synergies can specify particular uses of a given tool, thus providing information about the hierarchically superordinate goal the actor is attempting to bring about with the object.

A further, but still related, point concerns the fact that the temporal deployment of postural synergies could be extremely informative by itself. In fact, as soon as a certain postural synergy emerges during action execution, the observer can exploit this information to support and refine her anticipatory computations (Santello, Soechting, 1998). In fact, the pre-selection of a specific synergy, in conjunction with knowledge about hand biomechanics, may be very powerful in extracting additional lower-level features. Indeed, refining the anticipatory mechanisms might consist also in searching for a specific set of movement features to confirm the observer's hypothesis.

According to this view, the concept of postural synergies also entails the possibility of extracting movement-level and/or muscle-level information with relatively little effort. In fact, these few hand synergies correspond to a few highly recognizable visual hand postures during action observation. At the same time, the reactivation within the motor system of a given hand synergy entails the recall of its complex pattern of muscular activities over time. Therefore, the pre-emptive synergy recognition would critically reduce the feature search-space when back-reconstructing the movement-level and/or muscle-level implementation details associated with a given action. According to this view, when under pressure from task constraints, or when learning is required, the recognition of synergies may still support the simulation of finer kinematic sub-components of the observed action.

5 - Conclusion

In this work we first reviewed the inconsistencies regarding the representational granularity of the human and the monkey mirror

mechanisms. Focusing on TMS research on the human mirror mechanism, however, we have suggested that the popular use of MEP data, obtained from few muscles, opens up only a partial and possibly biased window onto these mirroring processes. The very essence of this bias is explained by the knowledge that research in motor neurophysiology has accrued about how movement is organized. According to this literature, movement might be organized around the synergistic composition of muscle activities towards the expression of prototypical postural configurations over time. One consequence of using a distorted lens to investigate the properties of the mirror mechanism is that whole-hand synergistic motor resonance might be mistakenly regarded as the processing of object-directed goal information. In fact, all object- related goals map to few hand synergies. Similarly, and more importantly, resonance for low-level movement details could be mistakenly regarded as forming the basic building block of mirror system processing. In contrast, our appeal to basic motor control knowledge, suggests a different picture. On the present proposal, the basic building block of the motor system and thus of the mirroring mechanism is based on movement synergies. We suggest that the mirror mechanism may extract whole-hand movement synergies from the visual appearance of others' grasping actions. Such a mechanism is potentially very robust to noise and permits a high degree of predictive power about action outcomes. Furthermore, such a mechanism also has the potential to extract, via higher-order inferential processes, lower-level features when this is called for by the task.

References

Aglioti, S.M., Cesari, P., Romani, M., Urgesi, C., 2008. Action anticipation and motor resonance in elite basketball players. Nat. Neurosci. 11:1109–1116.

Ajemian, R., D'Ausilio, A., Moorman, H., Bizzi, E., 2013. A theory for how sensorimotor skills are learned and retained in noisy and nonstationary neural circuits. Proc. Natl. Acad. Sci. U S A. 110:E5078–5087.

Alaerts, K., Swinnen, S.P., Wenderoth, N., 2009. Is the human primary motor cortex activated by muscular or direction-dependent features of observed movements? Cortex. 45:1148–1155.

Alaerts, K., Senot, P., Swinnen, S.P., Craighero, L., Wenderoth, N., Fadiga, L., 2010a. Force requirements of observed object lifting are encoded by the observer's motor system: a TMS study. Eur. J. Neurosci. 31:1144–1153.

Alaerts, K., Swinnen, S.P., Wenderoth, N., 2010b. Observing how others lift light or heavy objects: which visual cues mediate the encoding of muscular force in the primary motor cortex? Neuropsychologia. 48:2082–2090.

Avenanti, A., Bolognini, N., Maravita, A., Aglioti, S.M., 2007. Somatic and motor components of action simulation. Curr. Biol. 17:2129–2135.

Barchiesi, G., Cattaneo, L., 2013. Early and late motor responses to action observation. Soc. Cogn. Affect. Neurosci. 8, 711–719.

Bartoli, E., Maffongelli, L., Jacono, M., D'Ausilio, A. 2014. Affordance encoding in primary motor cortex: a state-dependent effect. Neuropsychologia. 61:335-344.

Bever, T.G., Poeppel, D. 2010. Analysis by synthesis: a (re-)emerging program of research for language and vision. Biolinguistics. 4(2–3):174–200.

Bernstein, N.A. 1967. The co-ordination and regulation of movements. Pergamon Press, Oxford.

Borroni, P., Gorini, A., Riva, G., Bouchard, S., Cerri, G., 2011. Mirroring avatars: dissociation of action and intention in human motor resonance. Eur. J. Neurosci. 34:662–669.

Borroni, P., Montagna, M., Cerri, G., Baldissera, F., 2005. Cyclic time course of motor excitability modulation during the observation of a cyclic hand movement. Brain. Res. 1065:115–124.

Borroni, P., Montagna, M., Cerri, G., Baldissera, F., 2008. Bilateral motor resonance evoked by observation of a one-hand movement: role of the primary motor cortex. Eur. J. Neurosci. 28:1427–1435.

Brochier, T., Spinks, R.L., Umilta, M.A., Lemon, R.N., 2004. Patterns of muscle activity underlying object-specific grasp by the macaque monkey. J. Neurophysiol. 92:1770–1782.

Cardellicchio, P., Sinigaglia, C., Costantini, M., 2011. The space of affordances: a TMS study. Neuropsychologia. 49:1369–1372.

Casile, A., Caggiano, V., Ferrari, P.F., 2011. The mirror neuron system: a fresh view. Neuroscientist 17, 524–538.

Catmur, C., Walsh, V., Heyes, C., 2007. Sensorimotor learning configures the human mirror system. Curr. Biol. 17:1527–1531.

Cattaneo, L., Caruana, F., Jezzini, A., Rizzolatti, G., 2009. Representation of goal and movements without overt motor behavior in the human motor cortex: a transcranial magnetic stimulation study. J. Neurosci. 29:11134–11138.

Cattaneo, L., Maule, F., Barchiesi, G., Rizzolatti, G., 2013. The motor system resonates to the distal goal of observed actions: testing the inverse pliers paradigm in an ecological setting. Exp. Brain Res. 231:37-49.

Cavallo, A., Becchio, C., Sartori, L., Bucchioni, G., Castiello, U., 2012. Grasping with tools: corticospinal excitability reflects observed hand movements. Cereb. Cortex. 22:710–716.

Cavallo, A., Bucchioni, G., Castiello, U., Becchio, C., 2013a. Goal or movement? Action representation within the primary motor cortex. Eur. J. Neurosci. 38:3507–3512.

Cavallo, A., Heyes, C., Becchio, C., Bird, G., Catmur, C., 2013b. Timecourse of mirror and counter-mirror effects measured with transcranial magnetic stimulation. Soc. Cogn. Affect. Neurosci. In press.

Classen, J., Liepert, J., Wise, S.P., Hallett, M., Cohen, L.G., 1998. Rapid plasticity of human cortical movement representation induced by practice. J. Neurophysiol. 79:1117–1123.

D'Ausilio, A., Maffongelli, L., Bartoli, E., Campanella, M., Ferrari, E., Berry, J., Fadiga, L., 2014. Listening to speech recruits specific tongue motor synergies as revealed by transcranial magnetic stimulation and tissue-Doppler ultrasound imaging. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369(1644):20130418.

D'Ausilio, A., Jarmolowska, J., Busan, P., Bufalari, I., Craighero, L., 2011. Tongue corticospinal modulation during attended verbal stimuli: priming and coarticulation effects. Neuropsychologia. 49(13):3670-6.

Di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., Rizzolatti, G., 1992. Understanding motor events: a neurophysiological study. Exp. Brain Res. 91:176–180.

Dushanova, J., Donoghue, J., 2010. Neurons in primary motor cortex engaged during action observation. Eur. J. Neurosci. 31:386–398.

Elsner, C., D'Ausilio, A., Gredeback, G., Falck-Ytter, T., Fadiga, L., 2013. The motor cortex is causally related to predictive eye movements during action observation. Neuropsychologia 51:488–492.

Enticott, P.G., Kennedy, H.A., Bradshaw, J.L., Rinehart, N.J., Fitzgerald, P.B., 2010. Understanding mirror neurons: evidence for enhanced corticospinal excitability during the observation of transitive but not intransitive hand gestures. Neuropsychologia 48:2675–2680.

Evarts, E.V., 1968. Relation of pyramidal tract activity to force exerted during voluntary movement. J. Neurophysiol. 31:14–27.

Fadiga, L., Craighero, L., Olivier, E., 2005. Human motor cortex excitability during the perception of others' action. Curr. Opin. Neurobiol. 15:213:218.

Fadiga, L., Fogassi, L., Pavesi, G., Rizzolatti, G., 1995. Motor facilitation during action observation: a magnetic stimulation study. J. Neurophysiol. 73:2608–2611.

Fadiga, L., Craighero, L., Buccino, G., Rizzolatti. G., 2002. Speech listening specifically modulates the excitability of tongue muscles: a TMS study. Eur J Neurosci. 15(2):399-402.

Ferrari, P.F., Gallese, V., Rizzolatti, G., Fogassi, L., 2003. Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. Eur. J. Neurosci. 17:1703–1714.

Flanagan, J.R., Johansson, R.S., 2003. Action plans used in action observation. Nature. 424:769–771.

Flash, T., Hochner, B., 2005. Motor primitives in vertebrates and invertebrates. Curr. Opin. Neurobiol. 15:660–666.

Fowler, C. A., Galantucci, B. and Saltzman, E. (2003). Motor theories of perception. In: Arbib, M. (Ed.), The handbook of brain theory and neural networks. MIT Press, Cambridge MA, pp. 705–707.

Franca, M., Turella, L., Canto, R., Brunelli, N., Allione, L., Andreasi, N.G., Desantis, M., Marzoli, D., Fadiga, L., 2012. Corticospinal facilitation during observation of graspable objects: a transcranial magnetic stimulation study. PLoS One. 7: e49025.

Friston, K., Mattout, J., Kilner, J., 2011. Action understanding and active inference. Biol. Cybern. 104:137–160.

Galantucci, B., Fowler, C.A., Turvey, M.T., 2006. The motor theory of speech perception reviewed. Psychon. Bull. Rev. 13:361–377.

Gallese, V., Fadiga, L., Fogassi, L., Rizzolatti, G., 1996. Action recognition in the premotor cortex. Brain. 119:593-609.

Gangitano, M., Mottaghy, F.M., Pascual-Leone, A., 2001. Phase-specific modulation of cortical motor output during movement observation. Neuroreport. 12:1489–1492.

Gentner, R., Classen, J., 2006. Modular organization of finger movements by the human central nervous system. Neuron. 52:731–742.

Gentner, R., Gorges, S., Weise, D., aufm Kampe, K., Buttmann, M., Classen, J., 2010. Encoding of motor skill in the corticomuscular system of musicians. Curr. Biol. 20:1869–1874.

Georgopoulos, A.P., 1995. Current issues in directional motor control. Trends Neurosci. 18:506–510.

Georgopoulos, A.P., Kalaska, J.F., Caminiti, R., Massey, J.T., 1982. On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. J. Neurosci. 2:1527–1537.

Gibson, J.J. 1977. The theory of affordances. In: Shaw, R., Bransford, J. (Eds), Perceiving, Acting and Knowing. Wiley, New York, pp. 67-82.

Graziano, M.S.A., Aflalo, T.N.S., Cooke, D.F., 2005. Arm movements evoked by electrical stimulation in the motor cortex of monkeys. J. Neurophysiol. 94:4209–4223.

Graziano, M.S.A., Taylor, C.S.R., Moore, T., 2002. Complex movements evoked by microstimulation of precentral cortex. Neuron 34, 841–851.

Huntley, G.W., Jones, E.G., 1991. Relationship of intrinsic connections to forelimb movement representations in monkey motor cortex: a correlative anatomic and physiological study. J. Neurophysiol. 66(2):390-413.

Jeannerod, M., 1984. The timing of natural prehension movements. J. Mot. Behav. 16:235–254.

Kakei, S., Hoffman, D.S., Strick, P.L., 1999. Muscle and movement representations in the primary motor cortex. Science. 285:2136–2139.

Kakei, S., Hoffman, D.S., Strick, P.L., 2001. Direction of action is represented in the ventral premotor cortex. Nat. Neurosci. 4:1020–1025.

Kilner, J.M., Lemon, R.N., 2013. What we know currently about mirror neurons. Curr. Biol. 23:R1057-1062.

Kohler, E., Keysers, C., Umilta, M.A., Fogassi, L., Gallese, V., Rizzolatti, G., 2002. Hearing sounds, understanding actions: action representation in mirror neurons. Science. 297:846–848.

Kraskov, A., Dancause, N., Quallo, M.M., Shepherd, S., Lemon, R.N., 2009. Corticospinal neurons in macaque ventral premotor cortex with mirror properties: a potential mechanism for action suppression? Neuron. 64:922–930.

Kraskov, A., Philipp, R., Waldert, S., Vigneswaran, G., Quallo, M.M., Lemon, R.N., 2014. Corticospinal mirror neurons. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369(1644):20130174.

Kurtzer, I., Herter, T.M., Scott, S.H., 2005. Random change in cortical load representation suggests distinct control of posture and movement. Nat. Neurosci. 8:498-504.

Lago, A., Fernandez-del-Olmo, M., 2011. Movement observation specifies motor programs activated by the action observed objective. Neurosci. Lett. 493:102–106.

Lang, C.E., Schieber, M.H., 2004. Human finger independence: limitations due to passive mechanical coupling versus active neuromuscular control. J. Neurophysiol. 92:2802–2810.

Lawrence, D.G., Kuypers, H.G., 1968. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. Brain. 91(1):1-14.

Lemon, R.N., Johansson, R.S., Westling, G., 1995. Corticospinal control during reach, grasp, and precision lift in man. J. Neurosci. 15(9):6145-56.

Lemon, R.N., Griffiths, J., 2005. Comparing the function of the corticospinal system in different species: organizational differences for motor specialization? Muscle Nerve. 32:261–279.

Liberman, A.M., Cooper, F.S., Shankweiler, D.P., Studdert-Kennedy, M., 1967. Perception of the speech code. Psychol. Rev. 74:431–461.

Lukashin, A.V., Wilcox, G.L., Georgopoulos, A.P., 1994. Overlapping neural networks for multiple motor engrams. Proc. Natl. Acad. Sci. U S A. 91:8651–8654.

Mason, C.R., Gomez, J.E., Ebner, T.J., 2001. Hand synergies during reach-to-grasp. J. Neurophysiol. 86:2896–2910.

Mc Cabe, S.I., Villalta, J.I., Saunier, G., Grafton, S.T., Della-Maggiore, V., 2014. The Relative Influence of Goal and Kinematics on Corticospinal Excitability Depends on the Information Provided to the Observer. Cereb. Cortex. In Press

Naish, K.R., Houston-Price, C., Bremner, A.J., Holmes, N.P. 2014. Effects of action observation on corticospinal excitability: Muscle specificity, direction, and timing of the mirror response. Neuropsychologia. In Press.

Overduin, S.A., d' Avella, A., Carmena, J.M., Bizzi, E., 2012. Microstimulation activates a handful of muscle synergies. Neuron. 76:1071–1077.

Overduin, S.A., d' Avella, A., Roh, J., Bizzi, E., 2008. Modulation of muscle synergy recruitment in primate grasping. J. Neurosci. 28:880–892.

Paz, R., Vaadia, E., 2004. Learning-induced improvement in encoding and decoding of specific movement directions by neurons in the primary motor cortex. PLoS Biol. 2:e45.

Poggio, T., Bizzi, E., 2004. Generalization in vision and motor control. Nature 431:768–774.

Porter, R., Lemon, R.. 1993. Corticospinal function and voluntary movement. Oxford Science, Oxford.

Rizzolatti, G., Craighero, L., 2004. The mirror-neuron system. Annu. Rev. Neurosci. 27:169–192.

Rizzolatti, G., Sinigaglia, C., 2010. The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. Nat. Rev. Neurosci. 11:264–274.

Rokni, U., Richardson, A.G., Bizzi, E., Seung, H.S., 2007. Motor learning with unstable neural representations. Neuron. 54:653–666.

Romani, M., Cesari, P., Urgesi, C., Facchini, S., Aglioti, S.M., 2005. Motor facilitation of the human cortico-spinal system during observation of bio-mechanically impossible movements. Neuroimage. 26:755–763.

Rothwell, J.C., 1997. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. J. Neurosci. Methods 74, 113–122.

Rotman, G., Troje, N.F., Johansson, R.S., Flanagan, J.R., 2006. Eye movements when observing predictable and unpredictable actions. J. Neurophysiol. 96:1358–1369.

Santello, M., Flanders, M., Soechting, J.F., 1998. Postural hand synergies for tool use. J. Neurosci. 18:10105–10115.

Santello, M., Soechting, J.F. 1998. Gradual molding of the hand to object contours. J. Neurophysiol. 79(3):1307-20.

Santello, M., Baud-Bovy, G., Jörntell, H. 2013. Neural bases of hand synergies. Front Comput Neurosci. 7:23.

Sartori, L., Begliomini, C., Castiello, U., 2013. Motor resonance in left- and right-handers: evidence for effector-independent motor representations. Front. Hum. Neurosci. 7:33.

Scott, S.H., 2008. Inconvenient truths about neural processing in primary motor cortex. J. Physiol. 586:1217–1224.

Scott, S.H., Gribble, P.L., Graham, K.M., Cabel, D.W., 2001. Dissociation between hand motion and population vectors from neural activity in motor cortex. Nature. 413:161–165.

Scott, S.H., Kalaska, J.F., 1995. Changes in motor cortex activity during reaching movements with similar hand paths but different arm postures. J. Neurophysiol. 73:2563–2567.

Senot, P., D'Ausilio, A., Franca, M., Caselli, L., Craighero, L., Fadiga, L., 2011. Effect of weight-related labels on corticospinal excitability during observation of grasping: a TMS study. Exp. Brain Res. 211:161–167.

Stefan, K., Classen, J., Celnik, P., Cohen, L.G., 2008. Concurrent action observation modulates practice-induced motor memory formation. Eur. J. Neurosci. 27:730–738.

Stefan, K., Cohen, L.G., Duque, J., Mazzocchio, R., Celnik, P., Sawaki, L., Ungerleider, L., Classen, J., 2005. Formation of a motor memory by action observation. J. Neurosci. 25:9339–9346.

Stevens, K.N., Halle, M., 1967. Remarks on analysis-by-synthesis and distinctive features. In: Wathen-Dunn, W. (Ed.), Models for the Perception of Speech and Visual Form, MIT Press, Cambridge MA, pp. 88-102.

Strafella, A.P., Paus, T., 2000. Modulation of cortical excitability during action observation: a transcranial magnetic stimulation study. Neuroreport 11:2289–2292.

Strick, P.L., 2002. Stimulating research on motor cortex. Nat. Neurosci. 5:714–715.

Tkach, D., Reimer, J., Hatsopoulos, N.G., 2007. Congruent activity during action and action observation in motor cortex. J. Neurosci. 27:13241–13250.

Turella, L., Pierno, A.C., Tubaldi, F., Castiello, U., 2009. Mirror neurons in humans: consisting or confounding evidence? Brain Lang. 108:10-21.

Ubaldi, S., Barchiesi, G., Cattaneo, L., 2013. Bottom-Up and Top-Down Visuomotor Responses to Action Observation. Cereb. Cortex. In Press.

Umilta, M.A., Escola, L., Intskirveli, I., Grammont, F., Rochat, M., Caruana, F., Jezzini, A., Gallese, V., Rizzolatti, G., 2008. When pliers become fingers in the monkey motor system. Proc. Natl. Acad. Sci. U S A. 105:2209–2213.

Umilta, M.A., Kohler, E., Gallese, V., Fogassi, L., Fadiga, L., Keysers, C., Rizzolatti, G., 2001. I know what you are doing. a neurophysiological study. Neuron. 31:155–165.

Urgesi, C., Candidi, M., Fabbro, F., Romani, M., Aglioti, S.M., 2006a. Motor facilitation during action observation: topographic mapping of the target

muscle and influence of the onlooker's posture. Eur. J. Neurosci. 23:2522–2530.

Urgesi, C., Maieron, M., Avenanti, A., Tidoni, E., Fabbro, F., Aglioti, S.M., 2010. Simulating the future of actions in the human corticospinal system. Cereb. Cortex. 20:2511–2521.

Urgesi, C., Moro, V., Candidi, M., Aglioti, S.M., 2006b. Mapping implied body actions in the human motor system. J. Neurosci. 26:7942–7949.

Vigneswaran, G., Philipp, R., Lemon, R.N., Kraskov, A., 2013. M1 corticospinal mirror neurons and their role in movement suppression during action observation. Curr. Biol. 23:236–243.

Young, R.M. 1970. Mind, brain and adaptation in the nineteenth century. Cerebral localization and its biological context from Gall to Ferrier. Clarendon Press, Oxford.