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Reply to comment

Motor control may support mirror neuron research with new hypotheses and methods

Reply to comments on "Grasping synergies: A motor-control approach to the mirror neuron mechanism"

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We are grateful to all commentators for their insightful commentaries and observations that enrich our proposal. One of our aims was indeed to bridge the gap between fields of research that, progressing independently, are facing similar issues regarding the neural representation of motor knowledge. In this respect, we were pleased to receive feedback from eminent researchers on both the mirror neuron as well as the motor control fields. Their expertise covers animal and human neurophysiology, as well as the computational modeling of neural and behavioral processes. Given their heterogeneous cultural perspectives and research approaches, a number of important open questions were raised. For simplicity we separated these issues into four sections. In the first section we present methodological aspects regarding how synergies can be measured in paradigms investigating the human mirror system. The second section regards the fundamental definition of what exactly synergies might be. The third concerns how synergies can generate testable predictions in mirror neuron research. Finally, the fourth section deals with the ultimate question regarding the function of the mirror neuron system.

Before discussing the important observations risen by commentators (Enticott [1], Frey and Chen [2], Naish and Holmes [3], Casile [4], Pezzulo, Donnarumma, Iodice, Prevete and Dindo [5], Santello [6], Swinnen and Alaerts [7], Cattaneo [8], Candidi, Sacheli and Aglioti [9], Cavallo, Ansuini and Becchio [10], de C. Hamilton [11]) we wish to stress the almost unanimous awareness that we indeed have a problem. Human mirror neuron research has almost ended up in a theoretical *cul de sac*, and we are in need for new falsifiable models on the function of this system [12]. We are very pleased to observe that our aim to infuse some fresh blood, coming from more mature fields of research, was appreciated by almost all commentators, giving raise to intriguing new suggestions.

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1. Measuring synergies during action observation

First of all we agree that no strong parallel could be drawn between monkey and human research [1,2]. In fact, these research streams often use incommensurable methods. We had exactly this in mind when we focused on Transcranial Magnetic Stimulation (TMS) research, which represent the best tool to study the human mirror mechanism [3]. In fact, TMS is first of all a very effective tool to study the motor system and this matches our proposition that methods and models used in motor neuroscience could inform future research on the mirror mechanism – a proposition shared by many commentaries [4–6].

However, we agree that any novel approach needs clear definitions and clear methods to measure and/or interfere with motor synergies during action observation [1,3]. If on one hand TMS-evoked electromyographic (EMG) activities during action observation are well characterized, these might be suboptimal to investigate complex TMS-evoked hand synergies [3,7,8]. On the other hand, TMS-evoked kinematics might be a promising tool [3,8], although it was correctly suggested that particular care is given to the different electromechanical delays that could characterize different body parts ([8]; see [13] for forearm muscles and [14] for some preliminary data on the tongue). The electromechanical delay, which is the delay between the onset of muscle activation and the onset of force or motion, should be carefully investigated. In fact, early studies observed quite long delays during voluntary muscle contraction [15], which were later recognized to be critically affected by instrument driven artifacts [16]. In line with this issue, we agree that we are still missing standard methods and normative data to guide the use of TMS-evoked movements as a reliable dependent variable [8].

An additional source of noise consists in the absence of experimental and data handling standards. For instance, the lack of homogeneity on the choice of control conditions and/or baseline is one of the main issues in this field [1]. The need for a methodological consensus becomes even more acute when applying the concept of synergies. In fact, synergies have been defined in different ways and linked to coordination patterns at different levels, including the kinematic, kinetic and neural ones [5,6]. In fact, when coping with the inherent complexity of synergies definition and measurement, we may even need to use new experimental paradigms including the active movement of the observer [3,9–11].

2. The use and definition of synergies

Importantly, we have to concur with Casile about the fact that synergies are only one of the possible models we can import from motor control literature [4]. The reasons why we proposed the synergy idea are several. First of all, it matches a Gibsonian perspective of how graspable objects directly specify affordances in a whole-hand grasping frame of reference. Furthermore, synergies intuitively avoid any artificial separation between goal and kinematics, embracing a functional and ecological perspective on behavior [3,6,10].

However, a critical point regards the level of the CNS at which synergies emerge, which may not match that of the mirror system. Indeed, as correctly stated by Cattaneo, synergies are not necessarily cortical in origin [8], rather they are classically considered as being expressed at the spinal level [17]. Nevertheless, there are different sources of evidence suggesting at least an important cortical contribution. Beside the fact that cortical stimulation elicits synergistic pattern of activities [18,19], it was shown that sensorimotor brain lesion affect the expression of synergies [20] and that neurons in the primary motor cortex (M1) seem to encode the activity of a relatively small number of functionally related groups of muscles [21]. In this vein, a recent integrative proposal suggests that recurrent activity propagating between M1, muscles, and back to M1 could maintain accurate and discrete representations of muscle synergies in M1 [22]. Nevertheless, if and how synergies map into neuronal “domains” is still an outstanding question [5,6].

In this respect, we need to be careful as the whole issue of synergy localization could be an ill-posed problem by itself. Indeed, synergies are derived from behavior and consist in a statistical description of movement, which do not necessarily have to match a localized neural representation [6]. This latter point also relates to another interesting comment. In fact, synergies offer an efficient description of voluntary movements but they do not necessarily explain the same motor variance generated by mirror neurons [8], which are fast and automatic [13]. However, we have to report that grasp synergies in the kinematic domain are usually considered to emerge from the interaction between biomechanical and neural constraints [6], which affect voluntary and involuntary movements in a similar manner [18,23].

3. Theoretical advantage of synergies in mirror neuron research

Some commentators generally recognized that our proposal represents a derivation from the original one [24]. In fact, the original view was that mirror neurons might constitute the "translation mechanism" between motor and visual representations of actions [4,8]. However, the original proposal was also based on the rough matching of neuronal firing rate between action execution and action observation features. A more quantitative description of both actor and observer behaviors, together with a motor theoretically grounded set of hypothesis may potentially remove some of the remaining skepticisms and controversies around mirror neuron research.

Thus, a key point regards the use of motor control models to guide the understanding of the mechanisms leading to the intriguing neural phenomenon we observe in mirror neurons activity (as well as in the human mirror-like properties). We gave only an initial bird-eye view on the potential mechanisms, and the diverse comments we elicited, all agree on the need to obtain new methods to understand the properties of the motor system in a unified model. The computational mechanism we only briefly sketched was derived from literature on internal models and active inference, which are also perfectly clarified by Pezzulo and colleagues [5].

The novelty is that synergies yield the useful advantage of being spatially and temporally abstract [5]. This would in turn simplify both high-level tasks (i.e. the goal recognition) and low-level tasks (i.e. action prediction). As a matter of fact, these exclusive properties of synergy do not prevent from making inferences at other hierarchical levels, which was also an important point raised by other commentators [7,9,11]. The elegance of these generative models is that they avoid any aprioristic definition of how many levels are present in this hierarchy, their characteristics and when they are predominantly activated [8]. In fact, in this framework, synergies emerge by the combination of multiple sources of bottom-up and top-down evidence, at multiple levels of complexity, and weighted according to their reliability, precision or contextual requirements [5].

4. Implications for the function of the mirror system

Even if we were able to describe the exact details of how neural activities for action execution and action observation match, we still have to answer the real question regarding the function of this system. The same question was also shared by several commentators [1,3,5,8–11]. First and foremost we cannot agree more on the fact that action perception and action production absolves two very different functions [10]. Goals and intentions drive action execution whereas these have to be inferred during action observation. This suggestion is also strengthened by the existence of a fair amount of pyramidal tract neurons (PTNs) that suppress their activity during action observation, instead of increasing it. According to these results, neurons in both F5 and M1 exhibit classical mirror responses, mirror suppression properties (decrease below baseline during observation, increase during execution) along with classical motor neurons [25]. It was speculated about the existence of a signal that allows the switching between observation and execution behaviors in these neurons [25]. The possibility to store action representations and to use suppression signals to switch on and off the output from the motor cortex could open intriguing connections with the fields of research on action competition and inhibition [26]. However, we believe that current knowledge about action-suppression mirror neurons is too limited, especially about their physiology and anatomical characteristics, to grant any real speculation regarding their functional role.

Furthermore, and similarly advocating for a clear definition of the differences between action perception and execution, it was also suggested that action production affects action perception, but this does not mean that mirror neurons serve action perception [8]. Although we know that interference of motor centers has an impact on our ability to understand or at least discriminate among action variations (for a review see [27]), this cannot be taken as a conclusive proof that the function of mirror neurons is action perception. Indeed, our main motivation was to anchor mirror research to action execution research. In fact, even the mere definition of what action perception is, forces us to sign up for risky or controversial definitions. In our view, it would be a wise move to remain at least agnostic about "action perception" as it could include multiple and intertwined inferential processes, at levels that may not be necessarily motoric [8,11].

Instead, by embracing a functional/ethological perspective, the mere fact that behavior has some reliable statistical properties should offer a great advantage for any system that tries to optimize behavioral interaction [9]. In fact, if the mirror neuron network is preferentially activated by the observation of behaviorally relevant action and other's action execution has a stable statistical organization it would be extremely ineffective not to use our motor knowledge about synergies. In this sense, synergies are not intended as a coding schema but rather as generative engine for different levels of features. Moving from representations to processes means also that the levels characterizing the mirror neuron mechanism are way less interesting than investigating the neural control scheme of mirror neurons [5]. In such a view synergies constitute "solely" the most compact statistical description of behavior, for which we happen to have the "neural machinery" to exploit their generative power.

5. Conclusions and open issues

Synergies are both the final output of intentions and the potential input from which the observer builds inferences about others' intentions [10]. If this could be true for any other set of motor features [5], synergies might have the important advantage of being the simplest and most compact description of behavior [6]. In fact, the specific characteristics of synergies, may grant enough generative capabilities to derive other kind of features that, depending on the context, may be discriminative of other's intentions [5]. Finally, the elegance of using the synergy concept in mirror-like research is that it can readily be falsified. If we have subjects observing actions and we measure TMS-evoked movements not complying with the synergistic organization of the observed action, we can lightheartedly falsify such proposal. In fact, commentators already sketched a number of intriguing avenues of research. All of them could be excellent starting points to exploit the synergy hypothesis.

Among them we would like to mention i) the need to perform experiments separating low level, high level and synergy level [11]; ii) the need to understand the complexity of the motor system considering also bimanual actions synergies [7]; iii) the need to combine different techniques to exploit their complementary strengths (i.e. TMS and electroencephalography) [1]; iv) the need to investigate the negative part of motor control, which is motor inhibition [10] as well as v) the extent to which observers can extract information about the action's goals from grasp synergies observation [6], or their role in facilitating activity-dependent plasticity in patients with limited motor capacity, via action observation [2]. In conclusion, as we hoped, our provocative manuscript has encouraged researchers to brainstorm around an idea that may potentially push forward the understanding in the field, by offering few key practical and testable predictions.

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