

Review

“Mirror neurons: the enigma of the past three decades”

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Abstract

Mirror neurons, first discovered in the early nineties by Rizzolatti et al. in the ventral premotor area F5 of the monkey brain, are a class of neurons that respond during the execution as well as the observation of goal-directed motor acts. They were classified as "mirror" neurons because their activity in the observer's brain seems to reflect the activity of neurons in the performer's brain. Since then, a lot of research was conducted on mirror neurons and the discovery of their intriguing response properties was considered a breakthrough not only on neuroscience but also on psychology and psychiatry. There has been much speculation and controversy about their possible functional role with a particular focus in social cognition. This class of neurons has been proposed to be the neural substrate of many different functions ranging from basic cognitive functions such as the understanding of the goal of the action performed by another person, to more advanced functions like empathy, which is the ability to sense other people's feelings. The aim of this review is to present what is currently known about mirror neurons, their basic properties, and the cortical areas where they have been found and to summarize the basic theories concerning their functional role. For this purpose, this review is based primarily on studies that employed the single cell recording method that provides information of high temporal resolution about the signals carried by neurons and is the most suitable technique to yield direct information about the high-level functions of the primate brain.

Key words: Mirror neurons

Introduction

In 1996 two papers fascinated the neuroscientific community and at the same time triggered a debate that is lasting still nowadays [1], [2]. Mirror neurons were first reported in the monkey ventral premotor area F5 and were originally defined as neurons which discharge both during monkey's active movements and when the monkey observes meaningful hand movements made by the experimenter. These first two papers gave a detailed description of the basic properties of mirror neurons. First, the interaction between the agent of the action (hand or mouth) and the object was found to be a fundamental requisite for mirror neurons' activation. The presentation of 3D objects or of an agent alone did not trigger mirror neurons' response. Similarly, no response was observed when the action was made using a tool or when the action was mimicked (that is making the movement without the object). Gallese et al. [2] investigated the responses of 536 neurons from area F5. 96 neurons (about 18%) exhibited responses both during active goal-directed motor acts of the monkey and observation of similar movements performed by the experimenter and therefore, were classified as mirror neurons. These 96 mirror neurons were further categorized into three classes based on the correspondence between their motor and visual responses; in other words the relative selectivity of their discharge during action execution and observation. In strictly congruent mirror neurons (31.5%), the effective observed and executed action corresponded both in terms of general action, for instance grasping, and in terms of the hand configuration used to grasp. The majority of neurons (60.9%) was represented by broadly congruent mirror neurons in which there was a link, but not identity, between the effective observed and executed action. The remaining 7 neurons were characterized as non-congruent. No mirror activity was found in the primary motor cortex.

Rizzolatti et al., considering the above results and especially based on the visuomotor congruence (congruence between the effective observed and the effective executed action) suggested that a possible function of mirror neurons is “understanding motor events”, that is the capacity to recognize the presence of another individual performing an action, to distinguish this action among other actions and to use this knowledge in order to react [1],[2]. Understanding motor events is thought to be based on an observation/execution matching system, which can extract the essential elements describing the agent of action and in the same time, code them on F5 motor vocabulary [2].

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Mirror neurons in premotor area F5

The first seminal papers [1], [2] described the basic properties of mirror neurons. The subsequent papers, in general, investigated modulations of mirror neurons response with some form of task manipulation.

Most studies have been based on a naturalistic testing of the visual responses of mirror neurons; that is, the motor acts were executed in front of the monkey by an experimenter. Two studies [3], [4] showed that mirror neurons also responded visually to filmed actions. The neuronal responses to naturalistic and movie stimuli were very similar not only in terms of average and peak response but also with respect to their temporal evolution [3].

Ferrari et al. [5] demonstrated that the observation of actions made by tools could elicit mirror neuron responses. This finding contradicted the first two seminal papers. This category of mirror neurons had higher responses to observation of actions made with a tool when compared with actions made with a biological effector, either the hand or the mouth. Also, these mirror neurons did not respond to observation of actions mimed with the tool or with a biological effector. Similarly, they did not respond to simple presentation of an object when this was presented on the tip of the tool. The tool-responding mirror neurons were found mainly in the lateral sector of F5. Furthermore, visual responses to actions made with tools were found after a long period of experiments and of repeated visual exposure to the observation of the experimenter using tools. This latter remark raises the question whether the mirror neuron system possesses any degree of plasticity [5].

Umiltà et al. [6] recorded the visual responses of mirror neurons under four different conditions. In the full vision condition the whole observed action was visible. It could be performed either on an object (grasping) or just mimicked (making the same action without an object). In the hidden condition the monkey was first shown that an object was present (or was not present in the mimicking condition) and then an opaque screen hid the final part of the action performed by the experimenter. As it was expected, the mirror neurons responded in the full vision condition but not in the full vision-mimicking condition. The intriguing fact is that even if what the monkey saw in both hidden and hidden mimicking condition was identical, the mirror neurons responded only in the former one. The difference was the knowledge of the presence of the object. A population of mirror neurons is, therefore, able to represent actions also when crucial parts of these actions (such as the interaction between the agent and the object which was considered a fundamental requisite for the activation of mirror neurons) are hidden and can only be inferred [6].

A notable type of modulation of mirror neurons was reported in another study published in 2009 [7]. Caggiano et al. tested the visual responses mirror neurons when the experimenter performed different types of motor acts at two different distances from the monkey's body: within and outside the peri-

personal space of the monkey. Some mirror neurons responded more strongly when the action was executed inside the monkey's peri-personal space, while others responded more strongly when the action was executed in the extra-personal space of the monkey. When the frontal panel of the primate chair was closed, thus preventing the monkey from reaching objects close to his body, space-selective mirror neurons changed their tuning; neurons selective for the extrapersonal space started to respond also in the peripersonal space, while neurons selective for the peripersonal space ceased to respond. It was thus suggested that space-selective neurons do not encode the peri- and extrapersonal spaces on a metric format (the boundary between the peri and extra-personal spaces is fixed and depends only on the distance of the monkey's body) but most probably in an operational format (the boundary is dynamic and depends on the workspace of the monkey, so it can be changed according to the possibility that the monkey will act.). This "knowledge" is considered crucial by the authors for selecting the most appropriate reaction [7].

A more recent study published in 2012 [8] indicated that mirror neurons response is modulated by the value that the monkey associates with the grasped object. The visual responses of most mirror neurons were stronger if the observed motor act was associated with the most relished reward. Based on these findings, the authors speculated that the differential discharge of mirror neurons would allow the observer to understand the motor intention of the observed agent.

Kraskov et al. [9] discovered a special class of F5 mirror neurons with a steady resting discharge which was suppressed during action observation, whereas their discharge was increased during action execution. The authors proposed that these neurons might be part of a system that inhibits self-movements during action observation, even if the premotor cortex is activated [9],[17].

Finally, a question was whether there are mirror neurons in area F5 that respond not only to visual stimuli but also to sound stimuli, as many object-related actions can be recognized by their sound. Indeed, Kohler et al. [11] discovered F5 mirror neurons that discharged both when the monkey performed a hand action and when it heard the related sound. These mirror neurons discharged in a stronger manner during presentation of one of the tested sounds in comparison with the others, so they were called selective auditory mirror neurons. In this way, the monkey could discriminate between the sounds of different actions.

To sum up, mirror neurons in area F5, have been found to respond visually to filmed actions [3], [4] and to the observation of actions made with a tool [5]. It has been reported that mirror neurons response is modulated by different factors: occlusion [6], the relative distance of the observed action [7], the view point of the observed action [3] and the reward value associated with the target object of the motor act [9]. One study described a class of mirror neurons with a steady resting discharge which was suppressed during action observation, the so-called "suppression mirror neurons"

[8]. Furthermore, there have been found F5 mirror neurons that respond to the sound of an action. [10]. Finally, one third of F5 mouth motor neurons show also mirror responses, that is they discharge during the observation of another individual performing mouth actions [11].

Mirror neurons in the inferior parietal lobule

One of the first studies, which showed that there are neurons in the inferior parietal lobule (IPL) with mirror responses, was published in 2005 by Fogassi et al. [12], almost ten years later after the publication of the first seminal papers [1], [2]. IPL neurons code motor acts chained together into complex actions, for instance grasping to eat or grasping to place. IPL mirror neurons respond during the execution as well as the observation of such complex motor actions. The most notable result of this study was that the neuronal discharges during the observation of grasping were influenced by the subsequent motor act.. Based on the above results, Fogassi et al. suggested that most of the mirror neurons of the IPL code the same act (grasping) in a different way according to the final goal of the action in which the act is embedded.

Three years later, Rozzi et al. [13] explored in detail the basic properties of IPL mirror neurons. Based on the correspondence between the motor and visual responses, they were further classified as: broadly congruent (54%), strictly congruent (29%), logically related (6%) and non- congruent (11%). The new category imported is the logically related neurons. According to the authors, in this category of congruence, “the effective executed motor act could be interpreted as a logical consequence of the effective observed one”, for instance visual grasping and motor placing.

In a more recent study the neuronal responses in area F5 and IPL were compared [14]. The new finding was that the one third of the tested F5 motor neurons were also action goal related.

Mirror responses in primary motor cortex (M1)

The first papers [1], [2] which described the basic properties of mirror neurons reported no mirror activity in primary motor cortex. However, a subsequent study published in 2007 [15] proved that the motor system of M1 is activated during action observation. The experimental task required the monkeys to move the cursor to a target that appeared at a random location within the workspace and in a second phase to observe the experimenter executing the same action. The intriguing finding of this study was that the discharge of M1 neurons was modulated during the observation phase and when the cursor and the target interacted, the modulation of the neuronal responses was very similar to that during the execution condition. The congruent activity during action observation and execution is a major characteristic of mirror neurons. However, it is unknown whether the recorded neurons of this

experiment would also respond to an interaction between a biological effector and an object, which is also fundamental for their characterization as mirror neurons [1],[2].

The latter question was addressed by Dushanova and Donoghue [14], three years later. They demonstrated that there are neurons in the primary motor cortex, which discharge both during the execution of an action and during the observation of the same action, for which the interaction of a biological effector and an object is crucial. The motor neurons of M1 are directionally tuned during the execution of the task and those which had mirror properties were also directionally tuned when the monkey was observing the experimenter.

A challenging question is how activity in M1 during observation does not lead to movement. It was proved that there are neurons in the primary motor cortex that decrease their baseline activity during action observation [17], like the neurons found in F5 [9]. Indeed, the neurons in the primary motor cortex that discharge during action observation are half as active compared to those that decrease their baseline activity [17].

Other “mirror” responses

Mirror-like responses have been described in two further areas of the monkey brain, the lateral intraparietal area (LIP) and the ventral intraparietal area (VIP).

In particular, a subpopulation of LIP neurons modulated its response not only when the monkey performed a saccade (that is oriented its attention) towards their RFs, but also during the observation of others orienting their attention in the same RFs [18].

One interesting phenomenon was discovered in VIP [15]. It has been known since 1998 [16] that a considerable amount of neurons in VIP area are bimodal; they respond to both tactile stimulation (a light touch on the monkey head or body) and visual stimulation (when an object moves relatively close to the monkey). The tactile and visual RFs are aligned in a congruent manner. The new finding was that visuotactile neurons in area VIP had visual receptive fields close to the experimenter’s body; that is, they responded when an object was moved toward or away the experimenter’s body[19].

Discussion

The discovery of mirror neurons is one of the most exciting achievements of modern cognitive neuroscience. Despite almost three decades of intense studies, one important question remains still largely unanswered: what their possible functional and cognitive role is.

Mirror neurons were originally defined as “neurons which discharged both during monkey’s active movements and when the monkey observed meaningful hand movements made by

the experimenter". Two basic properties of mirror neurons were found to be: a) the interaction between a biological effector and an object as a requisite for their activation, b) the congruence between the visual and motor responses [1],[2]. However, in subsequent studies mirror neurons found to be activated by movie stimuli [3], [4] and during the observation of an act made with a tool [5]. Consequently, the interaction between a human hand and the object is not the single case of mirror neuron activation.

The original discoverers of mirror neurons introduced the "action understanding" theory. The first seminal papers [1], [2] suggested that the mechanism for achieving action understanding is based on the direct-matching hypothesis. According to this hypothesis, "an observation/execution matching mechanism extract the essential elements describing the agent of the action and code them directly on specific sets of neurons with motor properties like those of F5 motor vocabulary" [2]. Based on this theory, one could suppose that a tight linkage between the kinematics of the observed and the executed action would be essential: the more accurate the visuo-motor similarity, the better the translation and therefore the understanding of the observed action. However, it was demonstrated that kinematic differences (for example different starting position of the hand) produced identical neural responses, while on the contrary, identical kinematics produced different neural responses [6]. Without doubt, the strictly-congruent mirror neurons are compatible with the "direct-matching hypothesis". However, this class of neurons represented approximately the one third of mirror neurons [2]. The majority of mirror neurons were classified as broadly-congruent mirror neurons. The previously mentioned arguments led Rizzolatti et al. [21] to propose that mirror neurons have the property to generalize the meaning of an observed action independently of its specific visual features. This suggestion is rather controversial to the previous "direct-matching hypothesis". Mirror neurons either "unify" the observed motor act with the executed one in order to understand its meaning or generalize already understood actions into abstract action-concepts such as action-goal.

The issue gradually became more perplexing. Several "classes" of mirror neurons were reported, each of which was influenced by different aspects of an observed action, e.g., the distance of the observer from the observed action [7] and the subjective value associated with the target-object of the movement [8]. These two findings led to the suggestion that mirror neurons during action observation have access to information which will influence the behavioral response of the observer [7],[8].

After the discovery of mirror neurons in the inferior parietal lobule, Rizzolatti et al. [22] argued that the mirror mechanism consists of two main regions in monkey brain: the ventral premotor cortex (area F5) in the frontal lobe and the inferior parietal lobule. Mirror neurons in IPL code the same act in a different way according to the final goal of the action in which the act is embedded [12], [13], [14].

This explanation seemed persuading until mirror-like re-

sponses were reported in LIP [18] and VIP [19]. The finding that the primary motor cortex is activated during observation was considered extraordinary [15], [16].

At this point, it must be said that there are many inconsistencies concerning what the scientists conceive as "mirror neuron" or "mirror property" or "mirror response". The first seminal papers gave us a strict definition of mirror neurons, which gradually expanded. For example, the interaction of a biological effector with an object and the direct vision of the last part of the action, were not necessary to elicit mirror neuron discharge as referred above [6]. The most extraordinary paradigm is that of the auditory-only mirror neurons, neurons that respond both to the sound related with the action and the execution of the action but not at the sight of the action [11]. One considers whether an enrichment of the definition of mirror neurons is essential, for example mirror neurons should be classified as those neurons that respond both to the execution of movement and a sensory modality (visual, sound, touch or smell stimuli) related to this movement. Are mirror neurons also activated when we observe an action that we cannot execute because of disability?[26] So, we come to the question whether mirror neurons are a specific class of neurons in specific areas with specific properties, that play an auxiliary role in action understanding or the answer lies in a more complex brain circuitry, a so called mirror mechanism, which is the neural substrate of more complex cognitive functions.

Savaki [23] suggested that understanding the actions of other subjects encompasses the entire brain circuitry that supports action execution, rather than just the part of cortex containing 'mirror neurons'. In other words, "we decode others' actions by activating our own action system, i.e. by mentally simulating the observed acts". In two prior studies, which used the quantitative ¹⁴C-deoxyglucose method, Raos et al [24], [25] demonstrated that the forelimb regions of the primary motor cortex and the somatosensory cortex are activated both during the observation of the experimenter grasping a three-dimensional object and during the execution of the movement. The authors proposed that movements and their proprioceptive components are stored as motor and somatosensory representations in motor and somatosensory cortices. The so-called "mirror-like" responses in several brain areas might be compatible with this hypothesis of mental simulation. One considers if this mechanism is the explanation of empathy.

Empathy is supposed to be a human function. Neuroimaging studies (especially fMRI) give evidence but not proof of the existence of mirror neurons in human brain [27], [28], as they do not monitor the activity of individual neurons like the single cell recording technique applied in monkeys. In other words, fMRI studies show that that one brain region for example Broca area of human brain is activated both during action observation and action execution [28], but we cannot be sure if the same neurons are activated in both conditions. Indeed, there are studies, that doubt the existence of mirror neurons in human brain [29]. One fMRI study showed that individuals with ASD (autism spectrum disorder) have abnormalities in mirror neuron networks, so they cannot experience empathy

[30]. However, these results failed to replicate multiple times [31].

To sum up, mirror neurons and their functional role is one of the most interesting fields of cognitive neuroscience. However, it is best to be conservative in our interpretations especially when we expand the findings concerning the monkey brain to the human brain. Before attributing to mirror neurons a number of cognitive roles, it is of crucial importance to investigate further their anatomical organization and their basic properties in primates and human brain. Understanding the goals of our own brains will lead us to the understanding of the others.

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