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Review

Mirror neurons 30 years later: implications and applications

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Mirror neurons (MNs) were first described in a seminal paper in 1992 as a class of monkey premotor cells discharging during both action execution and observation. Despite their debated origin and function, recent studies in several species, from birds to humans, revealed that beyond MNs properly so called, a variety of cell types distributed among multiple motor, sensory, and emotional brain areas form a 'mirror mechanism' more complex and flexible than originally thought, which has an evolutionarily conserved role in social interaction. Here, we trace the current limits and envisage the future trends of this discovery, showing that it inspired translational research and the development of new neurorehabilitation approaches, and constitutes a point of no return in social and affective neuroscience.

The mirror neuron legacy

October 1992 witnessed the first published description of a class of cells in the monkey premotor area F5 that exhibited the fascinating property of discharging both when the animal performed a goal-directed action (e.g., grasping a food morsel) and when the animal observed an experimenter [1] or another monkey [2] performing the same or similar action. A few years later, these cells were named 'MNs' [3] to emphasize the motor system's capacity to 'reflect' observed actions of others by recruiting the same neuronal substrates involved in action planning and execution. Its apparent simplicity and distribution across brain areas, functional domains, and animal species [4] led researchers to view the mirror mechanism as a basic principle of brain function [5].

Within a few years after their discovery, MNs had attracted lively interest in the scientific community; some scholars claimed that MNs 'will do for psychology what DNA did for biology' [6], whereas others defined them as 'the most hyped concept in neuroscience' [7]. An analysis of the PubMed articles citing the five most-cited papers on MNs in monkeys [1–3,8,9] offers a very conservative, empirical estimate of the MN legacy, indicating that the emerging topics encompass social and nonsocial cognition, language, perception, motor action, and emotion (Figure 1A). Only a small part of the research derived from the discovery of monkey MNs involved non-human animals (8%); it largely fueled human-based research (60%) in either healthy or clinical subjects and theoretical studies (32%) (Figure 1B). Human studies leveraged mostly indirect, non-invasive techniques (Figure 1C) to validate predictions derived from animal experiments or to explore uniquely human domains, such as imitation, speech, sport, and aesthetics. Furthermore, human studies explored the translational relevance of the MN discovery in a variety of clinical conditions (Figure 1D).

Following years of debate (Box 1), it was recently suggested that the impact of the discovery of MNs reached its zenith over the past decade and we are now witnessing its sunset [10]. However, we believe that the most recent discoveries in basic and clinical research indicate that the propulsive drive of MNs is not extinguishing but evolving.

Highlights

The discovery of mirror neurons (MNs) in several animal species showed that multimodal information about others' actions, emotions, sensations, and communicative messages are mapped onto the beholder's neural substrates devoted to those first-person processes.

The mirror mechanism allows a basic and evolutionary widespread remapping of other-related information onto primarily self-related brain structures, in a large variety of domains, with a major role in social cognition and in guiding social interactions.

Other-selective neurons may control one's own behavior and intersubject coordination during social interactions, supporting a 'social affordance' hypothesis: hyperscanning studies show similar neural dynamics at the network level in humans.

The recruitment of an emotional brain network when observing others' emotional displays subserves autonomic and affective alignment or misalignment with others during social exchanges.

Basic research findings inform translational and clinical applications of mirroring mechanisms in a variety of neurorehabilitation approaches and foster biocultural bridges between neuroscience and the humanities.

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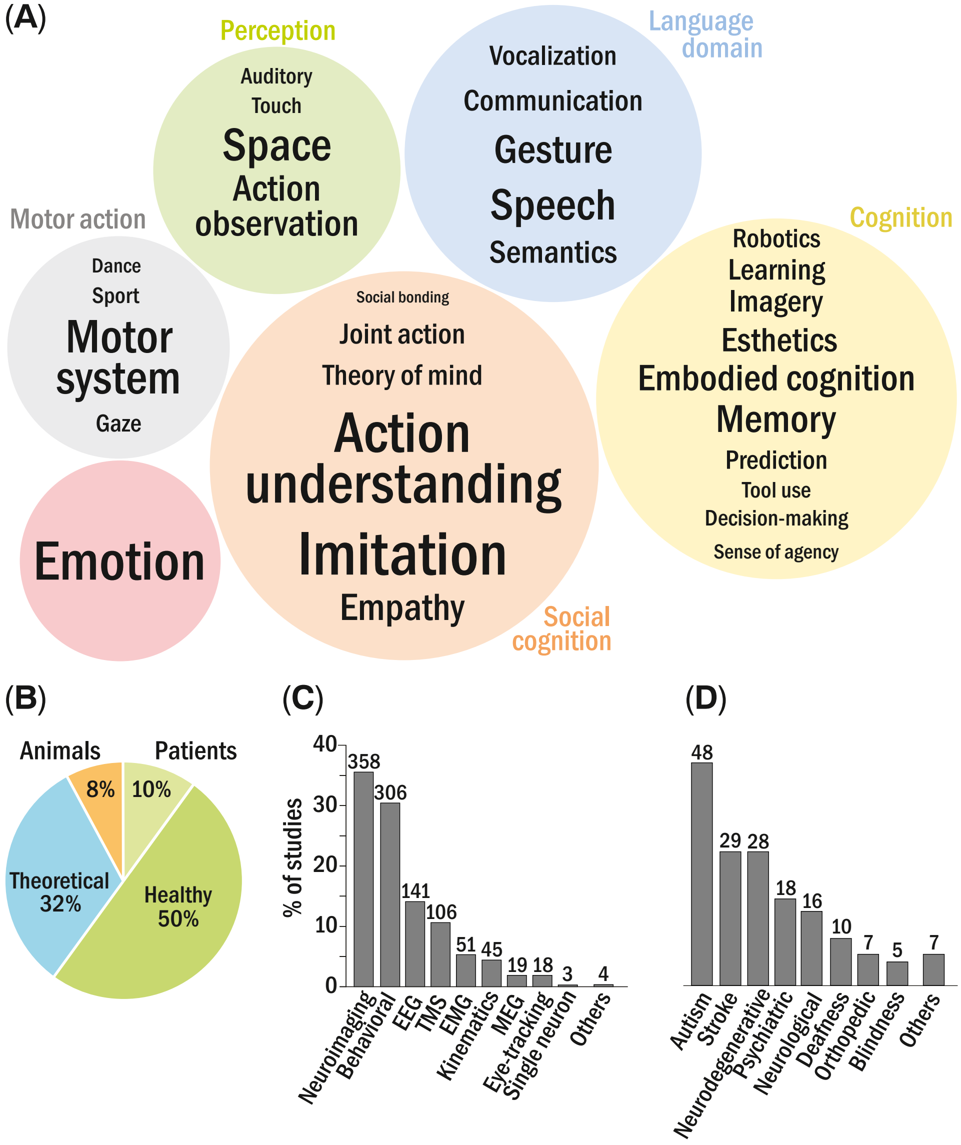

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Figure 1. Quantitative estimate of the mirror neuron (MN) legacy. (A) Main topics covered by the 1678 articles constituting the PubMed cited-by database (updated 30 September 2021) of the five most-cited MN research articles [1–3,8,9]. Circle size is a function of the number of articles on a topic. The number of articles per topic resulted from a sorting procedure from PubMed keywords using T-LAB text-mining software; the provisional list was further processed manually by merging the occurrences of multiple related keywords into a single one (e.g., the merging of 'embodied cognition', 'embodiment', and 'embodied simulation' into 'embodied cognition'). The same paper can contribute to multiple keywords and topics. The size of each keyword is a function of the number of related articles, from *N* = 20 (social bonding) to *N* = 245 (imitation). (B) Types of study in the database. 'Theoretical' includes review articles/meta-analysis, computational models, and opinion articles; 'Animals' includes neurophysiological and behavioral experiments; 'Patients' and 'healthy humans' includes experiments on humans. (C) Frequency distribution of human studies based on different techniques. Each label can include multiple techniques [e.g., 'Neuroimaging' includes MRI, positron emission tomography (PET), and near-IR spectroscopy (NIRS)]. (D) Frequency distribution of the pathologies investigated in the group of patient studies. Abbreviations: EEG, electroencephalogram; EMG, electromyography; MEG, magnetoencephalography; TMS, transcranial magnetic stimulation.

Box 1. Past and future in the MN debate

Following years of debate over the origin and functions of MNs [111], researchers have finally reached a basic agreement regarding the involvement of MN brain regions in the perception of motor actions, human speech discrimination, and imitative responses [10].

Current research directions aim mainly to determine which features of observed actions are primarily (or specifically) processed by the observer's motor system and why [97]. Nonetheless, the deep impact of prior experience on the contextual flexibility of activation of MN brain areas still fuels the idea that MNs might be a simple byproduct of other basic neurophysiological mechanisms, such as Pavlovian sensorimotor associative learning. Indeed, one of the central remaining controversies concerns the ontogenetic origin of MNs, that is, whether they are innate or forged by learning processes.

Until single neuron evidence in early developmental stages is available, the ontogeny of MNs will remain an open issue. Neonatal imitation, that is, the newborn's capacity to reproduce observed facial gestures, has been hotly debated as potential evidence of an innate MN mechanism [112]. Nonetheless, it is undeniable that early sensorimotor experience has an instrumental role in tuning self-related brain structures on other's behavior [113,114], possibly even before birth [115], making it unlikely that any direct experimental evidence will ever solve this issue conclusively. Accepting the hypothesized homology between audiovocal MNs in birds and MNs in mammals (see Figure 2A in main text) may commit one to the conclusion that the capacity to remap other-related information onto neural substrates devoted primarily to self-related processes is a shared, genetically canalized acquisition during ontogeny. In line with this hypothesis, a monkey genetic variant linked to human neuropsychiatric disorders is also associated with the lack of medial frontal cortex neurons responding to others' actions [116], which are, instead, abundant in control animals; importantly, this variant does not imply any associative learning impairment, supporting the view that sensorimotor plasticity can shape a genetically driven anatomofunctional architecture.

The discovery of MNs has shown that other-related information mapped onto self-related brain structures can modulate the ways in which humans and other animals respond to others. Future studies should investigate how this mapping occurs and develops in ontogeny, across animal species, from local assemblies of cells that do not necessarily correspond to MNs to brain circuits, and in multiple domains. This approach may pave the way for discoveries regarding social remapping mechanisms, beyond the MN debate.

The mirror mechanism in animals: a comparative perspective

Initially, the surprising property of some premotor neurons to respond not only during action execution, but also during the observation of actions performed by others prompted the discoverers of this phenomenon to establish very restrictive response criteria for defining a neuron as a MN [3]. This was vital to rule out alternative explanations and to demonstrate the robustness of the phenomenon. Subsequently, the main finding has been replicated in many studies from several independent laboratories and with increasingly sophisticated techniques; this research produced a progressive broadening of the original criteria defining MNs. Indeed, unbiased, large-scale recordings of multiple individual neurons with chronic multielectrode arrays during the execution and observation of actions [11–14] would have yielded much fewer MNs if the original criteria were rigidly applied (Box 2). Instead, these findings robustly confirmed the essence of the mirror mechanism: other-related information is mapped onto the neural substrates primarily involved in the encoding of self-related processes in an extended network of brain areas [15–17] that encompass multiple domains, from motor actions, sensations, and emotions to decisions and spatial representations (Figure 2A), and multiple animal species (Figure 2B).

Instead of a rigid and stereotyped 'grandmother-cell' concept of individual neurons faithfully reflecting otherness onto self, recent studies stemming from the MN discovery emphasize agent-based, rather than agent-shared, coding [13], in particular, the neural selectivity for information related to others. Since the publication of the seminal paper describing MNs, it has become clear that a sizable fraction (≈20%) of F5 (non-mirror) neurons responding during the observation of others' actions lack a truly motor response during action execution: thus, these cells were termed 'mirror-like' neurons [3]. Although initially neglected for several years, neurons with this property were re-evaluated after their discovery in the mesial frontal cortex [18], which attracted serious interest because, despite their location in a frontal motor area, they could code the action of others, even exclusively. To date, other-related neurons have been found in a variety of brain areas

Box 2. MNs in the monkey

What is a MN?

According to the pioneering studies [1–3], a MN: (i) responds selectively to the actions of others and not to visually presented objects, tool actions, or nonbiological movements, regardless of the distance of the observed action from the observer or its subjective value; (ii) becomes active during action execution in the dark; (iii) displays a clear relationship between its visual and motor responses, with ~30% of the MNs (termed 'strictly congruent') exhibiting strict correspondence between both the type of visually and motorically coded action (e.g., grasping) and how the action is performed (e.g., with precision grip).

Subsequent studies broadened these restrictive criteria. In fact, area F5 MNs can respond to both observed actions and visually presented objects [11], to actions performed with a tool [117,118], and to nonbiological moving objects [119]. Often, MNs exhibit a remarkable specificity for the space sector in which the observed actions occur [120,121]. In highly familiar contexts, MNs can code others' withheld actions, becoming active even if no observed movement occurred [122], and exhibit the capacity to predict others' impending actions [41,42]. In addition, the MN visual response can reflect the subjective value of observed actions [123].

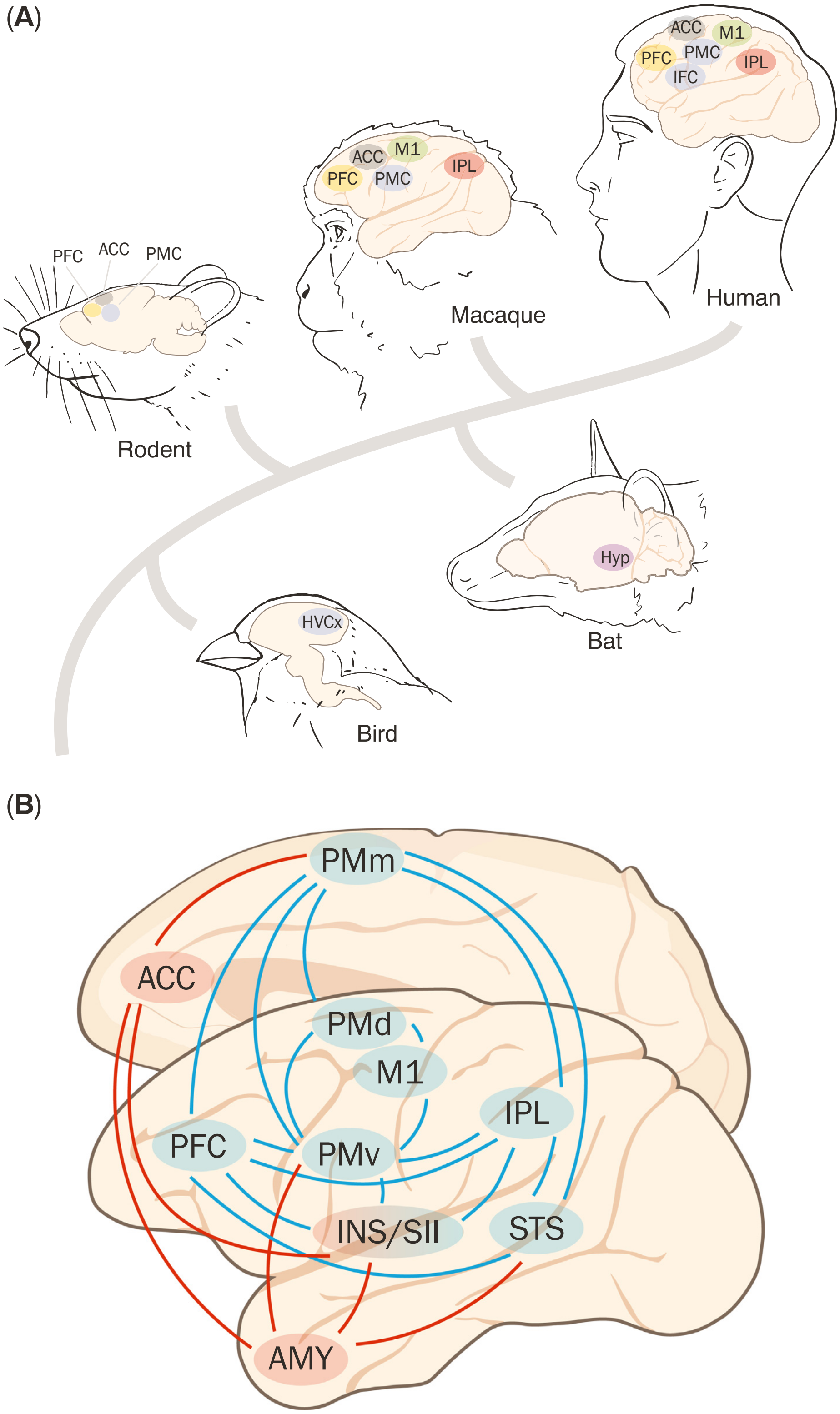
A sizable fraction (≈20%) of F5 neurons responding to observed manual actions do not discharge during action execution in the dark. Initially classified as 'mirror-like' neurons [3], these cells did not receive much attention. Furthermore, subsequent studies showed that, relative to the motor response of simultaneously recorded non-MNs, the motor response of MNs is generally sensitive to the sight of the monkey's own hand during object grasping [124], suggesting their role in self-action monitoring.

Finally, recent studies have shown that the congruence between the visual and motor selectivity of MN discharge is a property emerging mostly from neuronal populations rather than from the activity of individual neurons [12,125].

Over the past two decades, anatomofunctional studies have indicated that MNs form partially distinct brain networks for bodily and visceromotor actions, producing a multifaceted and highly plastic neural representation of others' actions and emotions.

and animal species, encoding not only observed actions [13,18–20], but also emotions [21,22], spatial locations [23], decisions or choices [24–26], rewards [27], the direction of attention [28], and beliefs [29]. A general feature of other-selective neurons is that they are hosted in brain structures primarily devoted to self-related information processing, and are usually found intermingled with neurons selective for the self or exhibiting mirror properties. What, then, is the advantage of neural selectivity for other-related information in brain regions devoted to self-related processes?

Recent animal studies have provided compelling causal evidence related to this fundamental question. Single neurons of the rat anterior cingulate cortex (ACC) encode the pain inflicted to others in a rather specific manner and do not respond to a fear-conditioned sound [21]. If the GABA agonist muscimol is injected into the rat ACC, thus inhibiting its activity, freezing behaviors naturally elicited when seeing another receiving a foot shock are reduced in the observer as well as in the observed animal, suggesting that neurons encoding others' behavior influence the behavior of both partners in dyadic interactions [30]. In the monkey, single ACC neurons selectively encode reward delivery to the self, a partner, or both monkeys in a vicarious reinforcement task, but, after ACC lesion, prosocial preference is reduced and the acquisition of new prosocial preferences is impaired [31]. Another example concerns neurons in the monkey lateral hypothalamus, which encode the availability of reward to others [27]: reversible inactivation of this region impacts the observer's behavior by eliminating the motivational impact of rewards given to others. As a whole, these findings indicate that other-selective neurons support social learning and the planning of behavioral responses to others in a variety of domains and social contexts. However, what is the specific neural mechanism that enables observers to turn the observed displays of others into their own behavioral reactions?



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First, seeing another acting or displaying internal states does not necessarily mean that the observer will react overtly and automatically. In fact, premotor neurons, especially the corticospinal cells that control spinal motor circuits, are often suppressed during action observation [32,33], and neural dynamics in the primary motor cortex during action observation more closely resemble those that occur during No-Go trials rather than those associated with execution trials, suggesting that they contribute to withholding unwanted replay of self-movement while observing others [34]. Thus, some other-related neurons can play a role in preventing unwanted movement. Second, neurophysiological studies in songbirds revealed another set of neurons (anatomofunctionally homologous to primates' corticostriatal cells) that do not directly influence the motor output but exhibit audiovocal mirror properties by receiving auditory information and a corollary discharge of the motor-related activity, with high audiomotor specificity for the vocal sequence [35]; this mechanism subserves song learning by imitation and may represent an evolutionarily conserved solution for social learning in other vertebrate species. Third, recent evidence from monkey studies in different parietal and frontal areas indicates that the most classical MNs, which exhibit a shared coding of both one's own and others' actions, have spike-shape features considered distinctive of inhibitory interneurons [36], suggesting the existence of 'mirror interneurons'. Therefore, a rich variety of cell classes appears to be involved in the encoding of other-related information within brain regions primarily devoted to self-related processes; in turn, each region makes a different contribution to distributing incoming information to other anatomically connected areas in the network (Figure 3, Key figure).

Although with little or no mention of the MN literature, recent studies have demonstrated that distinct self- and other-related neuronal populations in the mouse prefrontal cortex drive interbrain correlations in pairs of socially interacting animals [37]; in turn, interbrain correlation driven by the coupling of self- and other-related neurons plays a role in coordinating and sustaining social interaction in multi-individual systems [37]. Thus, it may not be exclusively or even primarily the individual (mirror) neuron that mirrors others' behavior, but a more complex neural machinery constituted by a variety of cell types that are distributed among multiple brain areas and play an evolutionarily conserved and fundamental role in social learning and behavioral coordination. According to this hypothesis, other-selective neurons drive the activity of more executive, self-related cells, which can select and plan behavioral responses depending on the behavior of others, thus making the mirror mechanism more flexible and extensively articulated than previously thought.

In line with this view, the mirror mechanism does not appear to be reducible to a one-to-one sensory-driven matching of another's action with the observer's own motor plan of that action, as initially hypothesized. In fact, the parietal and frontal nodes of the MN network are reciprocally connected but almost completely lack direct connections with visual areas of the superior temporal sulcus (STS) [16], except for area AIP, which has been shown to have a leading

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Figure 2. Species and brain areas with evidence of mirror neurons (MNs), and the mirror networks in the primate brain. (A) MN regions across species and brain areas. The same color code for different areas suggests possible homologies across species. (B) Organization of primate sensorimotor (light-blue) and emotional (red) MN networks based on macaque neuroanatomical studies on areas in which neurons with mirror properties have been found. The sensorimotor network [14,16,17] includes, in addition to the ventral premotor cortex (PMv) [36], primary motor cortex (M1) [33], inferior parietal lobule (IPL) [42] and anterior intraparietal area (AIP) [14,133], the dorsal premotor (PMd) [119,125] and mesial premotor (PMm) [13,18,26] cortex, prefrontal cortex (PFC) [134], and secondary somatosensory cortex (SII) [135]. The emotional network includes the anterior cingulate cortex (ACC), amygdala [22], and insula [136,137]. According to additional evidence in humans, the basal ganglia and the cerebellum (not shown) might have a role in these networks [138]. Abbreviations: HVCx, caudal nucleus of the ventral hyperstriatum projecting to area X; Hyp, hippocampus; IFC, inferior frontal cortex; PMC, premotor cortex.

Key figure

Schematic of the established and hypothesized anatomofunctional classes of cell and local circuitries of the mirror mechanism

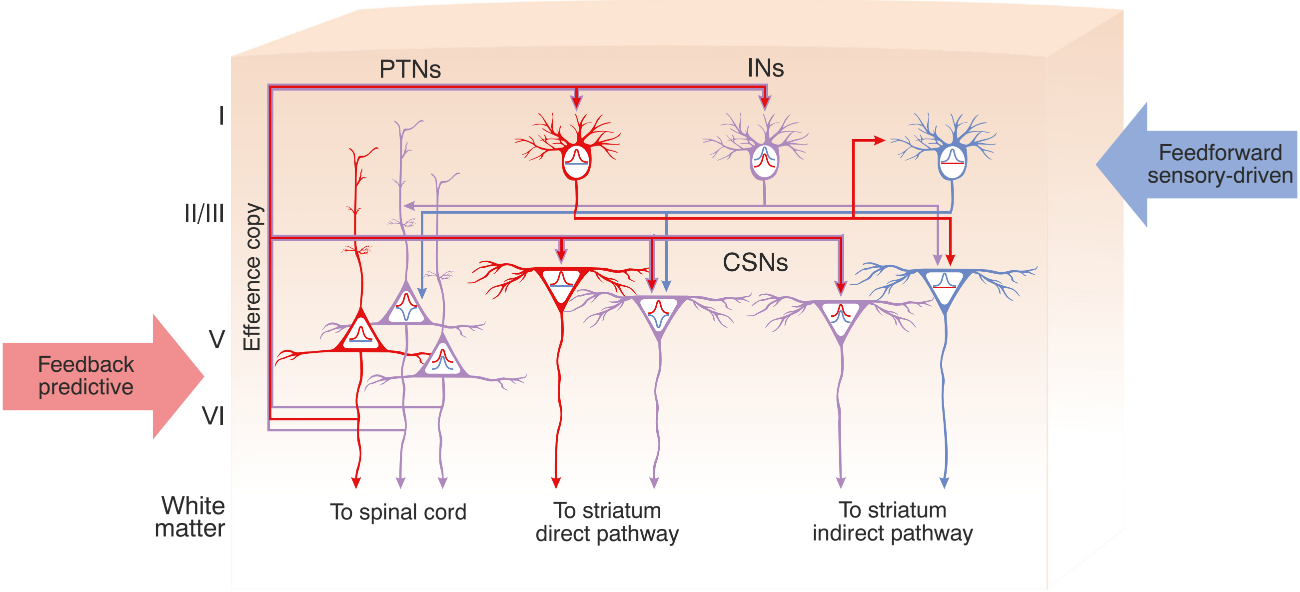

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Figure 3. Predictive feedback signals from prefrontal and mesial frontal regions (red arrow) contribute to the selection and activation of pyramidal tract neurons (PTNs; upward-pointing triangles) and corticostriatal neurons (CSNs; downward-pointing triangles) for action execution. The curves inside each neuron illustrate the discharge modulation during action execution (red) and observation (light-blue). PTNs can display purely motor (red) or mirror (purple) properties, and the latter exhibit either a facilitated or suppressed response during action observation [32,34]. Efference copies of PTNs' output may be fed to interneurons (INs) with mirror properties [36] and CSNs, according to evidence from studies of songbirds' audiovocal mirror neurons (MNs) [35]. INs may contribute to inhibitory sculpting of the response of PTNs and CSNs endowed with mirror properties, as a result of the contribution of additional sensory-driven feed-forward signals (light-blue arrow), which may explain the overall reduced (or even suppressed) premotor activity typically recorded during action observation [11]. In addition, CSNs MNs may contribute to the selectively suppression of PTN output during action observation by recruiting D2-expressing striatal neurons of the indirect pathway, thereby functionally decoupling mirror activity from the descending motor output and contributing to the selection of potential motor responses afforded by the observation of actions performed by others [39]. Note that a considerable proportion of neurons with mirror properties (not shown) should also contribute corticocortical projections.

role in routing feed-forward visual information regarding both observed objects and others' actions [11,14], thereby overcoming the classical anatomofunctional segregation between the processing of observed objects and actions. This pathway may contribute to the selection of behavioral responses: just as observed objects afford specific manual actions [38], the observation of others' actions can afford specific behavioral reactions during social exchanges [39]. Furthermore, ample evidence supports the capacity of the mirror mechanism to function independently from incoming sensory input, according to a predictive architecture [40] when sufficient contextual information is available [12,41–43]. Consistent with neuroanatomical and functional evidence from monkey studies [16,41], feedback projections from prefrontal to premotor brain regions and finally back to parietal and visual areas appear to drive the predictive coding of others' actions [44]. In turn, the monkey middle STS hosts other-selective neurons that respond proactively during a live turn-taking task when predictions about the partner's action were violated, thereby providing a feed-forward prediction error specific to the action domain [45]. This anatomofunctional architecture appears to be an ancient evolutionary feature of primates' mirror mechanism, adding flexibility and allowing subjects to efficiently anticipate, rather than merely react to, others' observed actions, exploiting feed-forward sensory input to update one's own motor plans during interactions with others.

In a large part, mechanistic characterization of the link between other- and self-related information at both the local and system levels (see Outstanding questions) still requires elucidation. However, the findings reviewed here suggest that the most evolutionarily shared and original function of these circuits is an active one, because they evolved primarily to enable the readout of social interactions, promote vicarious learning, and facilitate the planning of behavioral responses to others.

The human mirror mechanism

Most studies stemming from the MN discovery have been carried out in humans, but only one recorded single-neuron activity while patients executed or observed hand-grasping actions and facial emotional expressions, providing direct evidence of the mirror mechanism in several very different human brain regions [19]. fMRI studies in both humans [46] and monkeys [47] have shown that the same network of sensorimotor cortical areas becomes active during action execution and action observation in both species (light-blue nodes in Figure 2B).

Interestingly, emotional displays of others, which can be considered a form of bodily action [48], appear to be processed according to a similar mechanism. Indeed, similar to bodily actions, emotional displays are observable, can be triggered by animate and inanimate objects, can show contextual specificity, and are characterized by a visceromotor component associated with subjective arousal and emotional feeling. A set of deep brain regions (red nodes in Figure 2B) that partially interact with the somatomotor cortical circuit has been shown to subserve both the expression and perception of emotions in several animal species and to have a role in allowing humans to coordinate emotional reactions and social behaviors with those of others.

In the next two sections, we propose a unitary framework for interpreting the basic somatomotor and emotional MN mechanisms in humans as well as other animals. Our framework emphasizes a broad other-to-self mapping that links the perception of bodily actions and emotional displays of others to the observer's motor and visceromotor structures subserving a variety of adaptive, but not necessarily matched, behavioral responses to them.

Perception of bodily actions and action planning during social interactions

A growing body of evidence shows that the human brain areas subserving action planning and execution also have a role in others' action perception and prediction. Lesion-symptom mapping studies in human patients showed that impairments in the perceptual judgments regarding others' observed actions typically occur in association with lesions involving the left inferior frontal, inferior parietal, and middle-superior temporal cortex [49]. Moreover, patients with apraxia, whose ability to perform gestures is impaired, also exhibit more marked impairments in the recognition of familiar gestures compared with nonapraxic patients, and the greater recognition deficits are associated with the involvement of the opercular and triangularis portions of the left inferior frontal gyrus [50]. Additional causal evidence of the involvement of the motor system in recognizing others' actions comes from continuous theta-burst stimulation (cTBS) experiments: when applied over the hand and lip areas of healthy humans' left premotor cortex, cTBS produced a double dissociation reducing the participants' accuracy in recognizing pantomimed hand or mouth actions, respectively [51]. When cTBS was applied over inferior parietal lobule (IPL) regions the fMRI activity of which could predict the intention behind reach-to-grasp actions, subjects were impaired in their capacity to exploit the readout of hand kinematics to attribute intentions to others' observed actions [52].

These perceptual and predictive functions of the human motor system may be primarily linked with its evolutionarily conserved role in the planning and coordination of behavioral responses to others' actions; not surprisingly, one of the most widely accepted roles of the human MN mechanism is its mediation of imitative phenomena [10]. However, when subjects witness another's action, they have a variety of options that are known to recruit the main nodes of the human MN network: (i) faithfully imitating or emulating the observed action [53], (ii) avoiding doing so [54], or (iii) executing a complementary [55] or alternative [56] action. The environmental context and the internal state of the observers (i.e., knowledge, motivation, emotion, etc.) profoundly shape the way in which an observed action is mapped onto their own motor system. In fact, transcranial magnetic stimulation (TMS) perturbation of neural dynamics during action observation revealed that an early, sensory-driven, and rather unspecific motor response occurs within ~150 ms after the observed action onset, whereas a later motor response is evoked later, ~300 ms after the stimulus onset [57], exhibiting flexibility and potentially reflecting the capacity of prior training to enable a different, voluntary response to the observed action. Interestingly, the fastest activation of the motor system appears to depend on a bottom-up information flow, which is modulated by TMS-induced perturbation of the left posterior parietal cortex, whereas the slower, top-down modulated motor responses are altered by TMS-induced perturbation of the left dorsolateral prefrontal cortex [57]. Moreover, a very recent ultra-high-field fMRI study demonstrated that the observation of complex everyday action sequences in their natural order triggers increased information flow from frontal premotor output layers to parietal input layers; this did not occur when the very same actions were randomly arranged in a sequence that hindered predictions [44]. This finding provides anatomofunctional support for the hypothesis that frontal areas feed expected perceptual outcomes of others' actions back to parietal areas, which in turn integrate incoming sensory signals about the ongoing observed action in the form of a prediction error [58].

Although non-invasive human studies have convincingly demonstrated that the mirror mechanism plays a role in action perception, prediction, and social coordination, they generally do not enable researchers to directly investigate the neural dynamics between the agent-based and agent-shared codes underlying adaptive social behavior. However, recent hyperscanning techniques are making it possible to go beyond the traditional 'one-brain' approach, in which a single subject's brain is studied in situations of social observation. These techniques will enable a truly social 'two-brain' paradigm [59] in which the real-time reciprocal interactions of a pair or even a group of subjects can be investigated as a single system [37]. From this perspective, it may be that interbrain synchronies guide social interaction by means of underlying neural machinery in which self-related neurons in the brain of Subject 1 control behavior and thereby cause the activity of other-selective neurons in the brain of Subject 2, which finally lead to an adaptive behavioral response of Subject 2 by activating self-related neurons. This is supported by the observation that interbrain synchrony among individuals' motor systems grows as a function of their direct involvement in social interaction. Indeed, fMRI patterns in the right IPL synchronize during simultaneous imitation of facial expressions but not when subjects imitated each other after a cue [60]. Although much work remains to be done, recent studies have elucidated the crucial role of agent-based representations in driving bidirectional interbrain correlations, even for highly complex, social behaviors, such as spontaneous communicative interactions [61]. Mutual synchronization of frontal and temporoparietal speech-related neural activity across the speaker's and listener's brains may further suggest that this approach could be extended to the investigation of the shared neural basis of human language [62], in which it has been shown that the MN mechanism has an important role [63]. Existing evidence shows that frontal motor areas are recruited together with auditory regions during both the production and reception of speech [64] and that perturbing this activity alters discrimination of speech by the listener [65], indicating that motor recruitment is likely a naturally occurring phenomenon during speech processing in daily-life environments. By introducing causal evidence provided by dual-brain invasive or non-invasive stimulation [66], these approaches will pave the way to a broader, more ecologically relevant, embodied perspective in social neuroscience.

Perception of emotional displays and emotional reactions

A large body of evidence indicates that human brain regions involved in the control and regulation of emotions also become active when witnessing emotional displays of others. Studies using a variety of approaches have provided robust evidence that a network (Figure 2B) including the amygdala [67], the insula [68], and the cingulate cortex [69] has a role in the expression, experience, and perception of facial and bodily emotional displays [70]. However, the existence of neuronal populations in these regions that selectively encode emotions of self, others, or both remains unknown, likely because the genuine physiological fingerprint of emotions, especially of those that emerge in social contexts, is generally difficult to reproduce in constrained laboratory settings.

Yet, evidence of a shared coding of the emotions of self and others can be obtained from studies of various clinical populations. Children with Moebius syndrome, a congenital inability to produce facial displays, exhibit alterations in the processing of observed facial expressions of others [71]. Patients with Parkinson's disease, which is characterized by reduced facial mimicry, exhibit impairments in the recognition of both facial [72] and bodily [73] emotional expressions relative to control subjects. Similarly, patients with schizophrenia exhibit a reduced ability to produce and recognize facial emotions [74], but notably, they can improve their recognition performance by undergoing specific training to mobilize their facial muscles for executing transitive actions [75]; conversely, blocking facial mimicry in healthy humans selectively impairs the recognition of emotion in not only facial, but also bodily expressions [76]. Together, these findings indicate that mimicry reflects a global sensorimotor simulation of others' emotions rather than a mere muscle-specific resonance, bolstering the idea that affective empathy [77] hinges on the capacity of social stimuli to trigger visceromotor, not simply somatomotor, actions in the observer [78].

In this regard, it is important to stress the relevance of the context in which others' emotional displays are observed because it can afford very different visceromotor and neurobehavioral reactions. For example, seeing a person injured on the ground may induce empathic alignment or even rage and hostility, depending on whether the person is a passerby injured by a criminal or a criminal injured by a police officer after having killed a man. The alignment of autonomic parameters and motor responses has been observed in settings in which people share positive emotional experiences and exhibit smiles [79] or laughter [69], and evidence suggests that anatomically distinct but interacting networks of brain areas underlie laughter in emotional and non-emotional contexts [80]. Other contexts can induce affective misalignment: during parent–infant interactions, despite an overall alignment in a dyad's affective state, when the overall arousal level of the dyad was high, parents responded to elevated arousal in the child by decreasing their own arousal, thereby helping to regulate the infant's affective state [81]. Another example comes from a setting in which people obeyed orders to inflict various levels of painful electrical stimulation in a laboratory context; they rated the shocks as less painful and exhibited reduced activation in empathy-related brain regions than when they were free to decide [82].

The active role of the mirror mechanism is evident even in the most apparently sensory, feed-forward domain, such as the involvement of somatosensory brain regions in the processing of others' observed touch (Box 3). Indeed, a recent study indicated that vicarious activation of the human somatosensory cortex can causally contribute to prosocial decision-making [83], assigning the sense of touch a critical role in modulating primates' social and relational life.

Box 3. The sense of social touch

Traditionally, researchers have advocated a clear distinction between unimodal structures for action and perception and supramodal associative areas devoted to multimodal integration. By contrast, accumulating evidence suggests that sensory and motor systems are inherently multimodal, likewise our bodies' interactions with the external physical and social world. Thus, even at the neural level, multimodality constitutes a necessary condition for the sensory systems (e.g., of sight and touch) and the motor system to work together. Grounding multimodality on motor and sensory neurons emphasizes the relevance of our bodily experience of the world over abstract and formal computational logic.

In this view, touch has a special role in our interactions with the outside world. Indeed, it is the first sense to develop during ontogeny [126], thereby fostering initial learning from both the physical and social outside world. It plays an early and pivotal role in social interactions, which, in the case of twin pregnancies, emerges during prenatal life [127], thereby making possible a first form of nonverbal communication.

The discovery of MNs for bodily actions triggered the hypothesis that a similar mechanism could apply to the observation of touch. Goldman and Gallese first hypothesized the existence of a somatosensory mirror mechanism that enables observers to map other individuals' tactile stimulations onto their own somatosensory system [128]. Subsequently, fMRI studies showed that observing another person being touched activates brain areas, such as the somatosensory areas SI, SII, and premotor cortex, that are normally activated when an individual's body is being touched [129]. The function of the somatosensory cortex has also been linked to empathic ability [78], the recognition of emotional expressions [130], and the affective valence and intensity of the observed social touch, such as caressing and slapping someone else's hand, which activate area SI and SII more strongly than during the observation of a simple contact without affective connotation [131]. A recent study [132] revealed affective touch in rodents, showing that neurons in the medial amygdala respond differentially to naive and distressed conspecifics and encode allogrooming behavior, demonstrating that prosocial affiliative touch is an evolutionarily ancient mechanism in mammals with critical importance in orchestrating social interactions.

Although more research is necessary to understand the flexible mapping of others' affective states on the subject's emotional brain regions, as previously proposed for bodily actions, a social affordance framework may be useful for future studies: others' emotional displays afford visceromotor reactions in the observer's brain, ranging from aligned, visceromotor mimicry to misaligned, complementary responses that promote social regulation or adaptive mutual behaviors.

Translational applications of the mirror mechanism

The discovery of MNs paved the way for a variety of clinical and translational applications. On the one hand, studies of the mirror mechanism led to new research avenues in neuropsychiatric conditions, such as autism and developmental disorders [84,85], as well as psychiatric [86] and neurological [87] diseases. Although no conclusive evidence for a 'broken mirror theory' [88] has been provided, this research has attracted attention to the previously neglected involvement of the motor system and motor coordination deficits in these diseases [84,89]. On the other hand, the robust and converging evidence that areas of the mirror network play a role in imitative skills fostered the development of new neurorehabilitation approaches based on the enhanced recruitment of corticospinal output during action observation, such as action observation treatment (AOT).

The clinical relevance of AOT has been scrutinized especially for its capacity to significantly improve and accelerate functional recovery in patients with motor impairments due to a variety of neurological diseases, including stroke, Parkinson's disease, or cerebral palsy, or to orthopedic surgery of the hip or knee [90]. In a typical AOT rehabilitation session, patients are asked to observe a specific object-directed action, most often with the upper limb, in a video clip or a live condition, and then to replicate it, practicing only one action during each rehabilitation session. The rationale underlying this approach, grounded on the evidence that AOT increases the cortical excitability of motor brain areas [91], is that plastic processes can occur during action observation, thereby facilitating the subsequent execution of relevant daily actions [87] or even preventing the decline of motor performance induced by limb non-use [92]. In fact, fMRI studies have shown that AOT promotes stronger activations of areas in the mirror network than when the same actions are simply observed with no prior request to imitate the observed gesture, suggesting that observational learning techniques may boost plastic changes [93]. From a technological point of view, leveraging virtual reality can make it possible to personalize the best stimuli for promoting the desired plastic changes following the intervention, and is suitable for use even in telerehabilitation protocols [94]. Although still limited in this respect, the existing literature has shown that another potentially relevant approach consists in the use of stimuli for AOT protocols that depict actions performed by models with levels of motor skill comparable to those of the observer [95]. Indeed, in children with unilateral cerebral palsy, the observation of grasping actions performed by a pathological model drove increased parietofrontal activations in MN regions relative to the observation of a healthy hand action [96].

Future studies should more extensively leverage the manifold findings of basic neurophysiological research on the mirror mechanism and the extensive knowledge about the factors that influence its functioning [97]. For example, a recent TMS study identified intracortical inhibition driven by AOT as a major predictor of the subjects' improvement in a motor task following action observation [98], suggesting that the recently identified putative inhibitory interneurons with mirror properties [36] may play a role in improving executive control over actions copied from others. Taken together, these findings call for a tight synergy between basic and translational research and for the identification of the neurophysiological signatures that can predict and explain AOT efficacy at the single-subject level, which will, in turn, inform the design of more refined and personalized clinical approaches.

Concluding remarks

Thirty years after their discovery, MNs have played a transformational role in several disciplines by stimulating the creation of new research directions and influencing the trends in previously existing ones, from basic animal research to human cognitive and social neuroscience. Indeed, a large body of evidence confirms the involvement of frontal motor regions in the processing of a wide range of other-related bodily displays [99,100], facial expressions [101], voices [102], and social [103] and communicative [104] interactions, indicating that the impact of the original MN discovery may have fostered unprecedented interest in the neural substrates of social perception, even outside the mainstream MN literature.

The discovery of MNs in different somatomotor and emotional areas of the rodent brain is a crucial prelude to new research avenues, from the cellular to the network level, concerning the highly debated topic of the ontogenetic development of sensorimotor mapping of otherness onto self, which is almost impossible to tackle in human and non-human primates. Furthermore, the growing attention to the brain processes that support the preparation of adaptive behavioral responses to others in social settings [39,100,105] strongly indicates the need to conduct basic animal and human studies based on more ethologically relevant paradigms and approaches, that is, to investigate pairs or groups of simultaneously recorded brains as a unique system during unconstrained social exchanges and interactions. Gradually abandoning the one-brain paradigm in favor of a multi-brain paradigm is of crucial importance to understanding the brain–behavior relationship in ecologically relevant conditions. This paradigm shift will enable researchers to shed light on emotional social processes, which, despite strong causal evidence in patients and animal models, still lack a detailed, single-neuron mechanistic explanation.

The expected progress in the understanding of the neural mechanisms underlying the mapping of others onto self in multiple domains will ultimately promote the refinement and personalization of neurorehabilitative interventions in various clinical populations and may even enable the identification of the actual contribution of an altered mirroring mechanism, so far only hypothesized, to a variety of human diseases.

Outstanding questions

What is the relative distribution of neuronal tuning for self- and other-related information among neuronal classes (e.g., pyramidal neurons vs. inhibitory interneurons) in different brain areas, and what are the functional interactions and causal relationships among them?

What are the neural mechanisms driving interbrain neural synchronies in somatomotor and visceromotor areas, and their impact on social coordination and interactive behaviors during hyperscanning recording sessions?

How can the explanatory gap between levels of description of the mirror mechanism, from microscopic characterizations in animal models to macroscopic functional networks in the human brain, be overcome and a unitary framework achieved?

What could be the contributions of embodied cognition perspectives to the understanding of linguistic functions and their possible translational applications (e.g., in neural decoding/encoding approaches)?

Can clinical approaches based on action observation protocols enable the development of future therapeutic interventions tailored on the individual patient?

Finally, over the past 15 years, research triggered by the discovery of MNs and the model of embodied simulation has fostered a fruitful dialog between neuroscience and the humanities [106,107]. Several lines of research in the domain of visual arts [108], film [109], and narrative fiction [110] have begun to show that even esthetic experience includes vicarious physiological mechanisms such as those mediating social cognition in real life, revealing a corporeal dimension of our engagement with cultural artifacts that can now be studied experimentally.

In conclusion, we believe that, enthusiasm and due caution notwithstanding, 30 years after their discovery, MNs represent a milestone in social and cognitive neuroscience, with an impressive capacity to open new research avenues, promote translational applications, and build bridges between neuroscience and the humanities.

Acknowledgments

The authors are grateful to F. Caruana for comments on an earlier draft of the manuscript. This work was supported by ERC Stg-2015 678307 (WIRELESS) and ERC CoG-2020 101002704 (EMACTIVE), and by the Italian MIUR grant GANGLIA (n. R16PWSFBPL) to L.B.

Declaration of interests

No interests are declared.

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