The mirror neuron system and the consequences of its dysfunction

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Abstract | The discovery of premotor and parietal cells known as mirror neurons in the macaque brain that fire not only when the animal is in action, but also when it observes others carrying out the same actions provides a plausible neurophysiological mechanism for a variety of important social behaviours, from imitation to empathy. Recent data also show that dysfunction of the mirror neuron system in humans might be a core deficit in autism, a socially isolating condition. Here, we review the neurophysiology of the mirror neuron system and its role in social cognition and discuss the clinical implications of mirror neuron dysfunction.

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Imitation is the most widely used form of learning during development, offering the acquisition of many skills without the time-consuming process of trial-and-error learning. Imitation is also central to the development of fundamental social skills such as reading facial and other body gestures and for understanding the goals, intentions and desires of other people[1,2]. Despite its central role in both learning and social cognition, until recently imitation had been studied almost exclusively by social scientists (BOX 1), and our knowledge of the neural mechanisms of imitation was limited. The recent discovery of mirror neurons[3] — premotor and parietal cells in the macaque brain that fire when the animal performs a goal-directed action and when it sees others performing the same action — has inspired a series of studies on the neural correlates of imitation. Moreover, given the already known behavioural links between imitation and other aspects of social cognition[4], there is now active research into the relations between mirror neuron areas and social cognitive processes such as understanding the intentions and emotions of other people. Furthermore, the hypothesis that dysfunction of mirror neurons might be one of the core deficits of socially isolating disorders such as autism[5] is now under active scrutiny. This article offers, for the first time, a review of recent studies investigating the development of the mirror neuron system (MNS) and its dysfunction in autism, vis-à-vis what we know about the neurophysiology and the connectivity of the MNS in primates and humans (FIG. 1) and in relation to imitation and social cognition.

The primate MNS

Frontoparietal circuits for sensorimotor integration. So far, mirror neurons have been identified in two cortical areas — the posterior part of the inferior frontal cortex and the anterior part of the inferior parietal lobule[3]. These two areas are anatomically connected[6] and so form an integrated frontoparietal MNS. This system is only one of the many parallel neural systems connecting frontal and parietal areas[7]. Cells in these frontoparietal neural systems have physiological properties that are highly relevant to sensorimotor integration. The MNS must be considered within the larger context of this massive and parallel frontoparietal network for sensorimotor integration to be properly understood.

The posterior sector of the frontal lobe (agranular frontal cortex) is concerned with movement and comprises various cortical areas[8]. Multiple representations of body parts are present in these motor areas[3,6]. This suggests that these motor areas are actively involved in transforming sensory inputs into appropriate actions. In fact, most of the frontal motor areas receive a robust sensory input (visual and somatosensory) from the parietal lobe[3,6]. Even though each frontal and parietal area is connected with several other areas, a clear pattern emerges. Typically, the examination of only the most robust connections shows that one frontal motor area is connected with one parietal area[6]. This pattern of connectivity supports relatively specialized frontoparietal systems. For example, the frontal area F4 in the ventral premotor cortex and the ventral intraparietal area (VIP) in the intraparietal sulcus form a system for axial and proximal movements including head-orienting

Theory of mind
Awareness that other people have beliefs and desires as we do, but different from our own, and that these beliefs and desires can explain the behaviour of others.

and reaching[9], for peri-personal space coding[10] and for defensive movements[11]. Cells in this system fire during neck, arm and mouth movements but also respond to tactile stimuli and to visual stimuli that are close to the body[12,13]. When stimulated, these areas elicit highly coordinated defensive movements[14].

A second example of a frontoparietal system for sensorimotor integration is provided by a system that controls grasping. This network is composed of frontal area F5 and the parietal area in the anterior part of the intraparietal sulcus (AIP). Cells in this system can be divided into three categories: visual dominant neurons, which fire while the monkey observes a graspable object and during grasping in light conditions, but do not fire during grasping in the dark; visuomotor neurons, which fire more vigorously during grasping in light conditions than grasping in the dark, but also fire at the simple sight of a graspable object; and motor dominant neurons that fire equivalently for grasping in light and dark conditions and do not fire at the sight of a graspable object[15,16]. Visual dominant neurons are found only in the AIP, whereas area F5 contains more motor dominant neurons and fewer visuomotor neurons than AIP[17]. Taken together, these physiological properties suggest that the AIP provides multiple object affordance descriptions to F5, where the selection of the grasping action necessary to achieve the intention of the agent ultimately occurs[6].

Interestingly, the F5-AIP grasping circuit is anatomically adjacent to the frontoparietal MNS. Whereas the F5-AIP circuit for grasping is located deep in the sulci — with F5 neurons grouped in the sector of F5 located in the bank of the arcuate sulcus (area F5ab) and AIP neurons obviously located deep in the intraparietal sulcus — mirror neurons are found in the adjacent convexity in both the inferior frontal and inferior parietal cortex[3]. Frontal mirror neurons are located in the sector of F5 on the convexity behind the arcuate sulcus (area F5c), whereas parietal mirror neurons are located in the rostral sector of the convexity of the inferior parietal cortex (presumably in areas PF and PFG)[18]. The motor properties of mirror neurons are indistinguishable from the motor properties of grasping-related neurons in F5-AIP[19]. The sensory properties, however, are very different. Mirror neurons do not fire at the sight of graspable objects, but do fire at the sight of object-oriented actions performed by other individuals[19] (see below).

It is important to consider the anatomical location of the MNS to understand the nature of its functions. Its proximity to frontoparietal systems that support various forms of sensorimotor integration (reaching and orienting in peri-personal space and body defence for the VIP-F4 system, grasping and manipulating for the F5ab-AIP system) suggests that the nature of action coding implemented by the MNS is also linked with some form of sensorimotor integration. Imitation is definitely one of the main forms of sensorimotor integration, with regard to the actions of other individuals. Indeed, there are

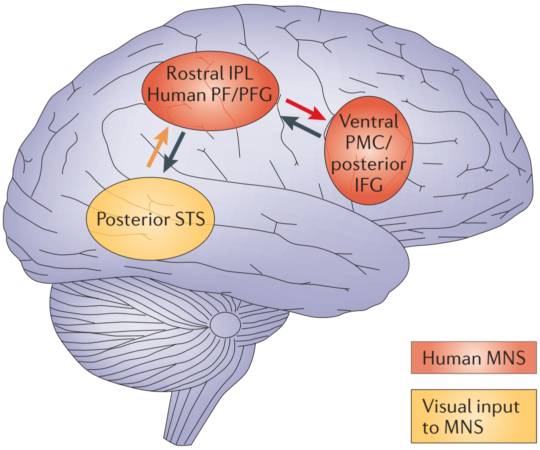

Figure 1 | **Neural circuitry for imitation.** Schematic overview of the frontoparietal mirror neuron system (MNS) (red) and its main visual input (yellow) in the human brain. An anterior area with mirror neuron properties is located in the inferior frontal cortex, encompassing the posterior inferior frontal gyrus (IFG) and adjacent ventral premotor cortex (PMC)[33,36,38,45,46,48,53,62]. A posterior area with mirror neuron properties is located in the rostral part of the inferior parietal lobule (IPL), and can be considered the human homologue of area PF/PFG in the macaque[55,109]. The main visual input to the MNS originates from the posterior sector of the superior temporal sulcus (STS)[113]. Together, these three areas form a 'core circuit' for imitation[41]. The visual input from the STS to the MNS is represented by an orange arrow. The red arrow represents the information flow from the parietal MNS, which is mostly concerned with the motoric description of the action[33,40], to the frontal MNS, which is more concerned with the goal of the action[33,38]. The black arrows represent efference copies of motor imitative commands that are sent back to the STS to allow matching between the sensory predictions of imitative motor plans and the visual description of the observed action[42]. Anatomical image adapted, with permission, from REF. 114 © (1996) Appleton & Lange.

Box 1 | Imitation in the social and psychological sciences

Imitation has been studied extensively using a wide variety of approaches in diverse disciplines, including anthropology, economics, sociology, ethology, philosophy, robotics and social, developmental and experimental psychology. A recent collection of essays captures the wide range of disciplines concerned with imitation[1]. Among the large numbers of highly interesting themes that emerge from this rich literature, there are some that seem particularly relevant to neuroscientists. For example, the literature on imitative behaviours in animals highlights that a key issue in this area is the differentiation between various forms of mimicry and contagion and true imitation — that is, adding something new to one's own motor repertoire after observing others carrying out that action[89,90]. This differentiation maps well in neural terms with the interactions between the mirror neuron system (MNS) and prefrontal and motor preparation structures during imitative learning and the interactions between the MNS and the limbic system during social mirroring[41].

In developmental psychology, the seminal work of Meltzoff in the 1970s showed that babies have some rudimentary forms of imitative behaviour early in their development[64], suggesting that a key form of learning early in life is through imitation. Another important theme that emerges from the developmental psychology literature is the functional link between imitation and social cognition, in particular the ability to develop a theory of mind[91].

Whereas the social psychology literature reminds us how pervasive and automatic mimicry is in social interactions[49], the experimental psychology literature has often looked at the functional aspects of imitation to better understand the sharing of common codes between perception and action[92]. The neuroscience of the MNS obviously also maps well onto these themes.

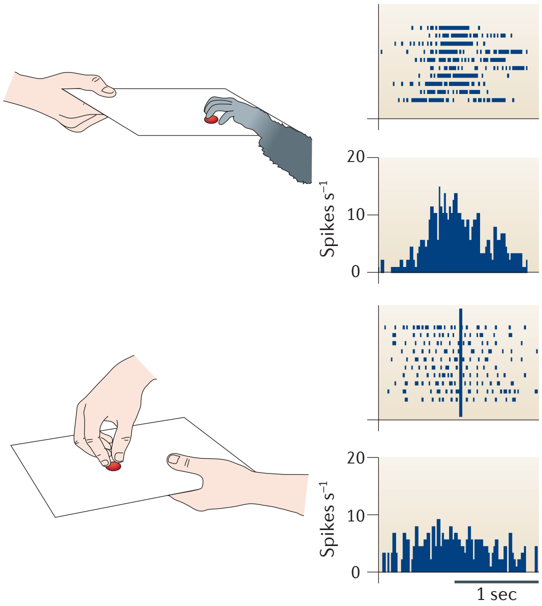

Figure 2 | **Mirror neurons in area F5.** The recordings show neural discharges of a mirror neuron in area F5 of the macaque inferior frontal cortex when the monkey grasps food (top) and when the monkey observes the experimenter grasping the food (bottom)[19]. Note that both tasks elicit strong neural responses in area F5. Modified, with permission, from REF. 115 © (2001) Macmillan Publishers Ltd.

strong links between imitation and the MNS in humans (see below). In monkeys, imitative responses[20] and the recognition of being imitated[21] are probably supported by mirror neurons, although no direct data are available yet to correlate mirror neuron spiking with imitation in monkeys.

Single-unit properties of mirror neurons. In the macaque brain, mirror neurons have been located in area F5c of the inferior frontal cortex[3] and in the rostral inferior parietal cortex (probably area PFG and PF)[18]. These cells fire during goal-directed actions such as grasping, holding and manipulating objects. They also fire (FIG. 2) when the monkey is not moving and simply observing the same actions performed by others, either monkeys or humans[3,19].

There are two main levels of congruence between the observed action and the executed action in mirror neurons. 'Strictly congruent' mirror neurons fire for observed and executed actions that are substantially identical, whereas 'broadly congruent' mirror neurons fire in response to the observation of an action that is not necessarily identical to the executed action, but achieves the same goal[3] (for example, grasping food with the whole left hand or with only the index and thumb of the right hand). The discharge of mirror neurons during action observation is neither modulated by the object to be grasped nor by the distance of the observed action from the monkey. The firing rates of mirror neurons are equivalent for observed grasping actions made by humans and monkeys, and their discharge is also similar if the experimenter grasping a piece of food gives it to the monkey being recorded or to a second monkey[3]. An interesting class of mirror neurons is the one that codes observed actions which are preparatory or logically related to the executed actions — for example, the observed action is to place food on the table and the executed action is to grasp the piece of food and bring it to the mouth[22].

From this initial survey of the properties of mirror neurons, it seems clear that these cells code relatively abstract aspects of observed actions. But how abstract is this coding? One of the first observations of these cells was that they do not fire at the sight of a pantomimed grasping action in the absence of a graspable object[19]. This initially suggested that the whole action had to be seen. However, a later study demonstrated that mirror neurons also discharge when actions are partly hidden[23]. Here, monkeys first observed an object on a table that was later occluded by a screen. Subsequently an experimenter reached for the object behind the screen and some mirror neurons (approximately 50% of the units tested) discharged even though the grasping action was not visible. In a control condition, monkeys could see that no object was present before the screen occluded the sight of the table. When the experimenter reached behind the screen, mirror neurons did not discharge. Although the visual input between the hidden action condition and the control condition (practically a hidden pantomime of grasping) were identical, the prior knowledge of the presence or absence of the object behind the screen allowed mirror neurons to discriminate between the two conditions, therefore indicating that these cells can code highly abstract aspects of the actions of others.

This concept of abstract coding was reinforced by a later study. Some actions are consistently associated with sounds. For example, breaking a peanut produces a characteristic sound. Some mirror neurons in monkeys fire not only in response to the sight of a peanut being broken, but they also fire to the sound of breaking a peanut (and other action sounds, of course), even in the absence of the visual presentation of the action[24,25]. The fact that mirror neurons discharge specifically to action sounds demonstrates the remarkably abstract type of action coding that these cells can implement. This is also an important empirical observation because it demonstrates an auditory input to the MNS. Such auditory input is necessary to support the hypothesis that the MNS could be a precursor of neural systems for language, given that language is mostly spoken (BOX 2).

A more recent study in monkeys reveals some even more remarkable properties of mirror neurons. In the inferior parietal lobule there is differential discharge from the same cell during grasping actions associated with different intentions[26]. Using food as the object, approximately one-third of the units tested discharged equivalently during grasping with the intention to eat the food and grasping for placing it in a container. Of the remaining two-thirds, roughly 75% of the cells discharged more while the monkey was grasping the food before

Box 2 | **Mirror neurons and language**

There are several themes that link mirror neurons with language. An evolutionary argument has been made suggesting that mirror neurons might be precursors of neural systems concerned with language in the human brain[93,94]. This argument is mostly based on the anatomical homology between area F5 of the macaque brain and Brodmann area 44 in the posterior inferior frontal gyrus in the human brain[93], an area that has been strongly linked with language. This argument is also generally taken to support the evolutionary theory of a gestural origin of language[95].

However, another argument concerns the functional role of mirror neurons in creating a common code, a parity, between observer and actor[93] that is reminiscent of the parity between the sender and the receiver of a message posited by some speech perception theories. Specifically, the involvement of motor structures in perception as demonstrated by mirror neurons was first suggested in the motor theory of speech perception[96], which proposed that the objects of speech perception are the intended phonetic gestures of the speaker, rather than the acoustic cues of speech sounds. A series of recent transcranial magnetic stimulation (TMS)[97–99] and functional MRI studies[100,101] has provided evidence for the activation of motor speech areas during speech perception. Whether this activation is necessary for comprehension is still unclear.

Several TMS and imaging studies have investigated shared neural systems between language and motor structures in general, or the mirror neuron system in particular. Here, the main functional framework inspiring this work is the embodied semantics framework, according to which linguistic concepts are built bottom up, using the sensorimotor representations necessary to enact those concepts[102–104]. In support of this theory, there is evidence that the processing of linguistic material activates motor areas[105], and that linguistic material relative to body parts and action evokes activity in motor areas representing those specific body parts[106,107]. A recent study showing shared premotor body maps for action observation and for action sentences specifically supports a key role for mirror neurons in embodied semantics[108].

Transcranial magnetic stimulation
(TMS). TMS involves creating a strong localized transient magnetic field that induces current flow in underlying neural tissue, causing a temporary disruption of activity in small regions of the brain.

Positron emission tomography
(PET). *In vivo* imaging technique used for diagnostic examination that involves the acquisition of physiological images based on the detection of positrons, which are emitted from a radioactive substance previously administered to the patient.

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eating it, compared with grasping the food before placing it in a container. Approximately 25% of the remaining cells showed the opposite pattern, with increased firing rate during grasping for placing compared with grasping for eating. A very similar pattern was recorded during action observation, for which the presence or absence of a container signalled the intention to place the food in the container or to eat it. Importantly, units that discharged more during grasping to eat also discharged more while the monkey was observing the experimenter grasping with the intention to eat. The same mirror pattern was observed for units that preferred grasping with the intention to place[26]. These data indicate that the MNS does not simply provide a relatively abstract representation of the actions of others, but also that it codes the intention associated with the observed action. This neural mechanism for intention understanding seems to be a basic form of understanding the mental states of others.

Another study has shown that some F5 units discharge during the execution and observation of ingestive and communicative mouth actions[27]. The existence of mirror neurons for mouth actions, especially for communicative mouth actions, is important with regards to the hypothesis — actively studied in humans (see below) — that mirror neurons might be vital for understanding the emotional states of other people, which tend to be transmitted through facial expressions.

Finally, a recent study has reported the existence of mirror neurons responding to tool use actions, in the lateral sector of area F5 (REF. 28). One of the initial observations on mirror neurons was that they fire when the monkey sees the experimenter grasping a piece of food with the hand but not when the same piece of food is grasped by the experimenter with a tool, such as a stick or a pair of pliers[19]. This observation made sense in light of the fact that monkeys are not expert tool users. However, a population of mirror neurons has been recently identified that respond more to the sight of the experimenter performing an action with a tool, compared with performing the same action with the hand[28]. Given that the monkeys being recorded had not learned to use tools, it is reasonable to assume that these mirror neuron responses are acquired through visual experience. The repeated sight of humans in the laboratory carrying out a goal-directed action using tools reinforces the association between the visual aspect of these types of action and the cells that code — in motor terms — those actions of the monkeys' motor repertoire that have the same goal as the observed action when using tools. This is evidence that the MNS can be shaped by experience and might support observational learning. In humans, one of the most widely used forms of learning depends on imitation. Given the physiological properties of mirror neurons, the next logical step was to use brain imaging to investigate the links between the human MNS and imitation.

The MNS in humans

The human MNS and imitation. Early action observation studies in the mid-1990s, using both transcranial magnetic stimulation (TMS)[29] and positron emission tomography (PET)[30], provided some evidence for the existence of a human MNS. However, those studies did not examine imitation. In the late 1990s, when investigators tackled the issue of the links between mirror neurons and imitation in humans using functional MRI (fMRI), a basic problem had to be addressed: how does one go from the pattern of activity observed in single-unit recordings in non-imitative tasks to the pattern of activity observable using fMRI during imitative tasks? Assuming some level of correlation between neuronal firing and fMRI signal in the cortex — an assumption subsequently supported by empirical data[31,32] — a relatively simple model was proposed. Given that mirror neurons discharge more during the execution than the observation of an action, and given that during imitation one simultaneously observes and performs an action, it could be predicted that human mirror neuron areas would show higher activity during execution compared with observation of action, and highest activity during imitation, which should reflect the sum of the activity attributable to action observation and execution. An fMRI study on the imitation of finger movements demonstrated that two human cortical areas had this predicted pattern of activity (FIG. 3). One was located in the pars opercularis of the inferior frontal gyrus (within Broca's area, an important language area) and the other was located in the rostral posterior parietal cortex[33]. The anatomical location of these areas corresponds well with the anatomical location of monkey mirror neuron areas. Moreover, fMRI signal that is compatible with mirror neuron activity in Broca's area supports the hypothesis that mirror neurons might have been evolutionary precursors of neural mechanisms for language (BOX 2).

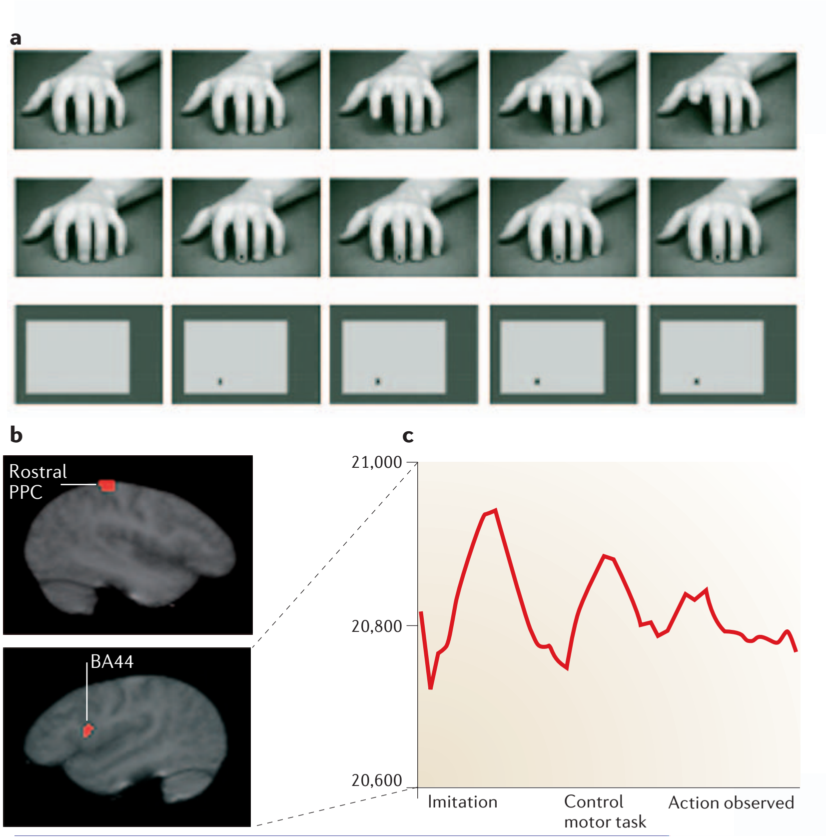

Figure 3 | **The human mirror neuron system and imitation.** Functional MRI (fMRI) study of imitation of finger movements showing two human cortical areas with the predicted pattern of activity for mirror neuron areas[33]. **a** | Participants observed or imitated the lifting of the index or the middle finger (top). In visual control conditions they observed a cross appearing on the index or middle finger of a static hand (middle), or appearing on the left or right side of a grey rectangle (bottom). In motor control conditions, partipants lifted the index or middle finger in response to the appearance of the cross. **b** | The two areas showing the predicted pattern of higher activity for the control motor task compared with action observation, and highest activity during imitation, were located in the inferior frontal cortex (Brodmann's area 44; BA44) and in the rostral part of the posterior parietal cortex (PPC)[33]. **c** | Blood-oxygen-level-dependent (BOLD) fMRI activity in signal intensity rescaled by smoothing measured in BA44 shows the predicted pattern of activity for mirror neuron areas. Panels **a** and **b** reproduced, with permission, from REF. 33 © (1999) American Association for the Advancement of Science.

Diffusion tensor imaging
A technique developed in the mid-1990s, based on MRI in which diffusion constants of water molecules are measured along many (> 6) orientations and diffusion anisotropy is characterized. It is used to visualize the location, orientation and anisotropy of the brain's white matter tracts, and is sensitive to directional parameters of water diffusion in the brain.

However, it is possible that activity in a human language area during any kind of task might simply reflect covert verbalization. Even though the covert verbalization hypothesis cannot fully explain the overall pattern of activity measured in Broca's area during imitation, execution and observation of action — and also the lateralization of such activity (BOX 3) — a subsequent study tested this hypothesis directly using repetitive TMS (rTMS)[34]. With rTMS, a transient lesion in the stimulated area can be induced and consequent behavioural effects observed. If the activity in Broca's area observed during imitation is simply epiphenomenal covert verbalization, rTMS should not induce imitative deficits. In the rTMS study, participants performed a finger movement imitation task and a control visuomotor task in which the motor output was identical to the imitative task. Participants were stimulated over posterior Broca's area (pars opercularis of the inferior frontal gyrus) and over a control cortical site. The results showed a selective impairment for imitation only (and not for the control task) in response to stimulation of Broca's area only (and not for the control site)[34]. These data clearly indicate an essential role for posterior Broca's area in imitation.

Subsequent imaging studies of imitation in the human MNS have looked at specific types of imitation and at functional aspects of the imitative process. Developmental studies have shown that, early in life, children tend to imitate others as in a mirror[35] (if one raises the right hand, the imitator raises the left hand). Inferior frontal mirror neuron areas respond more when participants imitate as in a mirror, compared with imitating in an anatomically correct way (if one raises the right hand, the imitator also raises the right hand)[36]. This brain–behaviour relationship suggests that the human MNS is especially crucial for imitative behaviour early in life. Moreover, developmental studies also show that children tend to imitate the goal of an action first[37]. Imaging studies have shown that action goals during imitation are also coded by inferior frontal mirror neurons[38,39]. By contrast, the human inferior parietal mirror neuron area seems to be more concerned with the motoric aspects of the action to be imitated[40]. Taken together, the imaging data in humans indicate that the human MNS forms, with higher-order visual areas along the superior temporal sulcus (STS), a 'core circuit' for imitation[41]. In this circuit (FIG. 1), the STS would provide a higher-order visual description of the action to be imitated[42], whereas the parietal component of the MNS would be concerned with the motoric aspects of the imitated action and the frontal component of the MNS would be concerned with the goal of the imitated action[41].

Diffusion tensor imaging (DTI) data clearly show strong patterns of connectivity in humans between these three regions. In fact, while supporting the classic view of the arcuate fasciculus connecting posterior superior temporal areas with the inferior frontal cortex, DTI has recently revealed two white matter tracts running in parallel to the arcuate fasciculus and connecting the superior temporal cortex with the inferior parietal cortex, and the inferior parietal cortex with the inferior frontal cortex[43]. Given the strong anatomical connectivity, it is not surprising that functional connectivity between these areas has been also demonstrated[44].

It is important to keep in mind that this core circuit for imitation is obviously not sufficient to implement all forms of imitative behaviour. Extant data suggest that large-scale interactions between the core circuit for imitation and other neural networks are necessary for the implementation of two main forms of imitative behaviour — imitative learning and social mirroring[41] (the neural correlates of social mirroring are discussed below). Imitative learning has recently been studied using fMRI to examine how musically naïve participants learn to execute guitar chords after observation of another individual performing the same chords. Results showed that the MNS interacts with motor preparation areas and the dorsolateral prefrontal cortex during imitative learning[45].

Finally, recent meta-data from fMRI studies of imitation[46] indicate that there are two functionally segregated sectors in the caudal part of the inferior frontal gyrus. The first is located in the dorsal part of pars opercularis. This dorsal sector is properly 'mirror', in that it is activated during action observation and imitation, with greater activity during imitation. The second functional sector is located in the ventral part of pars opercularis. This ventral sector is not mirror, because it is activated only during imitation and not observation of action. No activation during a control motor task in which the motor output is identical to the imitation task was observed. So, this ventral sector of pars opercularis seems not to be simply a 'motor' area but is instead specifically activated by imitative tasks. Its functional significance might be related to the higher needs during imitation to predict the sensory consequences of one's motor output, in order to match the movement of the model to be imitated (what is known as a forward model)[47].

The MNS and social cognition. Developmental behavioural data clearly show that imitative behaviour is crucial for the development of social cognitive skills[2]. The behavioural links between imitation and social cognition suggest a key role for the human MNS in social cognition, which has been addressed in a series of studies. The first fMRI study that specifically investigated the possible role of the MNS in empathy adopted a paradigm of observation and imitation of facial emotional expressions[48]. It is well known that humans tend to imitate each other automatically when interacting socially[4]. This phenomenon is called the Chameleon effect[49]. The more people tend to imitate others, the more they tend to be empathic[49]. These data indicate that one way of empathizing is through the embodiment of the facial expressions and body postures of other people. Given the role of mirror neurons in imitation and action recognition, it is logical to posit the involvement of the MNS in empathy. Obviously, empathizing also requires emotional processing and therefore the involvement of the limbic system. The MNS and the limbic system are anatomically connected in the primate brain by the insula[50]. Therefore, a large-scale network composed of the MNS, the insula, and some limbic structures could provide the ability to empathize with others through the representation and 'inner imitation' of the actions (facial expressions, body postures) of others[48]. The fMRI study on the role of the MNS in empathy indeed demonstrated that during both observation and imitation of emotional faces the whole network of mirror neuron areas, insula and amygdala was activated. Moreover, the activity throughout the whole network increased during imitation, as is typically observed in mirror neuron areas, a finding that is compatible with the idea that mirror neurons might also be modulating activity in other areas of the network[48]. Other studies support the concept of a mirroring, sensorimotor nature of empathy[51–53].

A key aspect of social interactions is the ability to understand the mental states of other people. Early on, it was proposed that mirror neurons do not simply code the actions of others, but also their intentions[54]. A recent fMRI study demonstrated that human mirror neuron areas respond differently to the observation of the same grasping actions, if the actions are embedded in different contexts that suggest different intentions associated with the grasping actions, such as drinking or cleaning up[55]. This is evidence that the MNS codes not only the action (for example, a grasp) but also the intention associated with it (for example, a grasp to drink). So, mirror neurons seem to be key neural elements in the understanding of the intentions of others associated with everyday actions (FIG. 4).

Another recent finding of interest is related to the modulation of activity in mirror neuron areas while observing social interactions[56]. In this fMRI study, participants observed video clips depicting everyday interactions between people. The clips were structured with a segment in which one actor was doing an everyday activity such as cooking or working at a computer, and with a segment in which that same actor interacted with another actor. Activity in mirror neuron areas increased during observation of social interactions[56]. Although, in principle, this increased activity might simply be due to the presence of two people acting simultaneously compared with one person alone, it is also possible that this increased activity reflects the coding of coordinated actions that typically occur in social interactions.

Finally, recent fMRI[57] and TMS[58] data also implicate the human MNS in self-recognition. The simulation process of others onto self that is enabled by mirror neurons is also likely to be used when individuals (the 'perceiving' selves) are looking at their own picture

Box 3 | **The laterality of the human mirror neuron system**

One general principle that should be kept in mind is that the mirror neuron system (MNS) is a special higher-order motor system. Higher-order motor systems tend to be bilateral, not lateralized as in the primary motor cortex. If one is aware of this concept, one should predict that the MNS is relatively bilateral. Meta-data on the imitation of finger movements do show a strongly bilateral pattern of activity[46].

A recent functional MRI study has controlled for various lateralized factors to investigate the lateralization of the human MNS[109]. Participants were imitating finger movements that were flashed to the left and right visual field. Only left finger movements were presented to the left visual field and only right finger movements were presented to the right visual field. Subjects were instructed to imitate left finger movements in the left visual field with their left hand and right finger movements in the right visual field with their right hand. The control conditions of motor execution and action observation were appropriately controlled for laterality. The results of this study also showed that the human MNS is relatively bilateral[109]. Transcranial magnetic stimulation (TMS) data looking at motor facilitation during action observation in the two hemispheres are also consistent with a bilateral human MNS[110].

So, how does one go from a relatively bilateral system for action observation and imitation to a left-lateralized system for language? A key finding here is provided by another TMS study that looked at motor facilitation in the two hemispheres while listening to action sounds[111]. As mirror neurons also respond to the sound of an action[24,25], the motor system of listeners should be facilitated while listening to sounds produced by actions, due to the activation of the MNS. A TMS study shows that such facilitation occurs only in the left hemisphere[111]. This suggests that the left hemisphere of the human brain has a multimodal (visual, auditory) MNS, whereas the right hemisphere has only a visual MNS. Multimodality is considered an important factor in proto-languages or systems of communication precursors of linguistic systems[112]. In humans, the shift from a purely visual to a multimodal MNS might have determined both functional changes that could have facilitated language, and a left-lateralization of language functions.

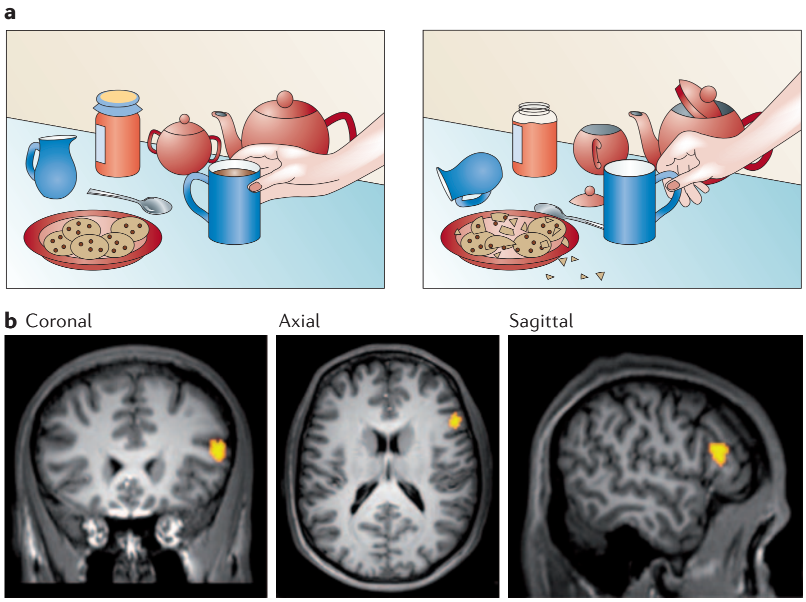

Figure 4 | **Grasping intentions with mirror neurons.** The observation of a grasping action embedded in two different contexts (**a**) that suggest two different intentions — drinking on the left and cleaning up on the right — elicits differential activity (greater for drinking) in the mirror neuron area located in the right posterior inferior frontal gyrus[55] (**b**). This shows that the mirror neuron system does not simply code the observed action ('that's a grasp') but rather the intention associated with the action ('that's a grasp to drink'). Panel **a** modified from REF. 55.

(the 'perceived' selves). In fact, it has been shown that even static pictures seem to activate the MNS[59]. These neural data might provide a functional explanation for developmental data that show functional links between self-recognition and imitation[60]. When 19-month-old children who were unfamiliar with each other were paired according to the ability to self-recognize or not, imitation occurred much more frequently in pairs of those children able to self-recognize[60], which suggests functional links between the development of a sense of self and of social interaction skills provided by imitation. In neural terms, such functional links might be provided by mirror neurons. Some other imaging data are consistent with the idea that the human MNS is more active when the observed actor and the observer are similar to each other: for example, in dancers, the MNS is more active when a dancer observes others performing the type of dance with which they are most familiar[61]. Furthermore, the human MNS is more active when the actions of other humans are observed, rather than those of monkeys or dogs[62].

Development of the MNS and its dysfunction

Typical development. Studies of proactive goal-directed eye movements show that 12-month-old infants can predict the action goals of other people[63]. Also, imitation of facial and hand gestures in human infants has been demonstrated by Meltzoff and Moore[64]. Whether this early predictive ability and the imitative behaviour in infants are both supported by mirror neurons is not proven, but it is not unlikely. Interestingly, recent studies have demonstrated that human early imitative behaviour is not unique. Infant chimpanzees[65] and infant monkeys[20] show imitative behaviour of facial and hand gestures that is similar to humans, therefore providing indirect behavioural evidence of the existence of a functioning MNS early in the life of primates.

A recent electroencephalography (EEG) study on children (less than 11 years old) shows mu rhythm suppression during both execution and observation of hand actions[66]. The suppression of mu rhythm is considered to be an index of motor activation in central areas, and its presence during action observation is considered a probable index of mirror neuron activity[67]. A much younger population — 6–7-month-old infants — was studied with near infrared spectroscopy (NIRS) while the infants were watching live actions and actions shown from a TV monitor. In the adult brain, live actions typically yield much more robust responses than actions shown on a monitor. The infants' NIRS data show a similar pattern of activity. Motor areas were activated by the sight of both live and televised actions, but live actions yielded a much greater response[68]. The EEG and NIRS data suggest that the MNS is functioning early in human life. However, these data do not indicate how crucial the MNS is for the development of social competence. In an fMRI study of observation and imitation of facial emotional expressions in typically developing 10-year-olds, we found that activity in the MNS correlated with empathic concern and interpersonal competence[69]. This correlation strongly supports the hypothesis that the MNS is a key neural system for social cognition[70]. In line with the developmental data, recent fMRI data from adults also show a correlation between the activation of the MNS while listening to action sounds and empathy[71].

Consequences of MNS dysfunction. Given the physiological properties of mirror neurons, the links between the human MNS and imitation, and the key role of imitation in social cognition, it is highly plausible that dysfunctions of the MNS could lead to deficits in social behaviour. It has been suggested that reduced imitation might be a core deficit in autism[72]. Furthermore, it has been proposed that a core deficit of autism, a socially isolating disorder, originates from a MNS dysfunction[73]. This hypothesis has been further developed by suggesting that the MNS enables the modelling of the behaviour of other people through a mechanism of embodied simulation — that is, internal representations of body states associated with actions and emotions. Embodied simulation could provide 'intentional attunement', a direct form of experiential understanding of others[74]. A disruption of MNS activity would preclude such experiential understanding of others, leading to the social deficits of autism[74].

Probably due to its intuitive appeal, the MNS hypothesis of autism has been tested repeatedly in recent years, using various techniques and approaches. A morphometric study has demonstrated structural abnormalities in MNS regions of patients with autism spectrum disorder (ASD), compared with typically developing individuals[75]. Magnetoencephalography (MEG)

Mu rhythm
Ongoing spontaneous electrical activity generated by the primary sensorimotor cortices, consisting of prominent frequencies between 10 and 20 Hz.

Near infrared spectroscopy
(NIRS). Recently developed non-invasive neuroimaging technique based on light in the near infrared, highly applicable to the study of the infant brain in naturalistic settings.

Magnetoencephalography
(MEG). A non-invasive technique that allows the detection of the changing magnetic fields that are associated with brain activity on the timescale of milliseconds.

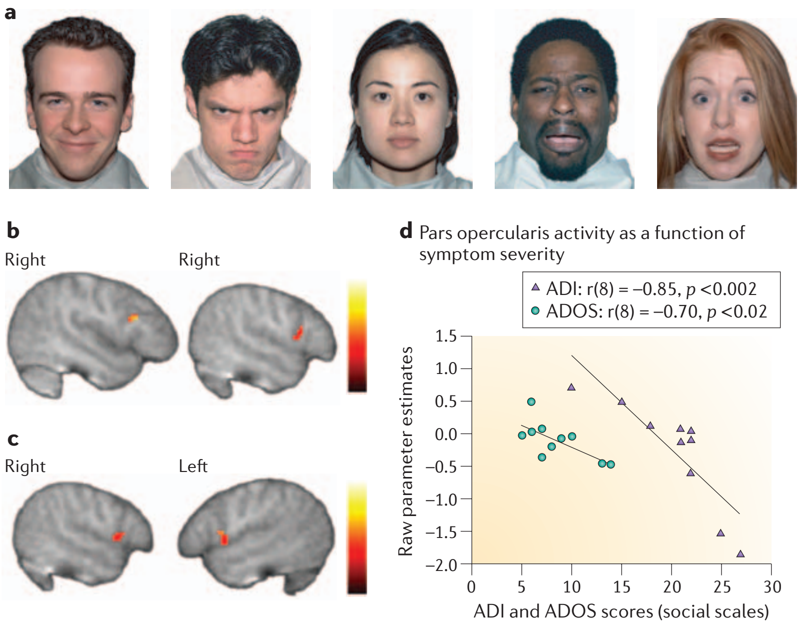

Figure 5 | **The human mirror neuron system and autism.** Typically developing children and children with autism were studied with functional MRI while they observed or imitated facial emotional expressions (**a**). Compared with typically developing children, children with autism demonstrated reduced activity in the frontal mirror neuron system (MNS) area located in the pars opercularis of the inferior frontal gyrus. Moreover, this activity correlated with the severity of disorder as assessed by widely used clinical scales, the Autism Diagnostic Observation Interview (ADI) (**b**) and the Autism Diagnostic Observation Schedule (ADOS) (**c**), such that the higher the severity of disease, the lower the activity in the MNS (**d**)[82]. Images from panel **a** from the MacBrain Face Stimulus Set. Panels **b** and **c** reproduced, and panel **d** modified, with permission, from *Nature Neuroscience* REF. 82 © (2006) Macmillan Publishers Ltd.

data based on imitation of lip movements show that the temporal progression of activation in the core circuit for imitation is delayed in patients with Asperger's syndrome compared with healthy controls[76]. This delayed temporal progression probably reflects a deficit in functional connectivity between the brain regions forming the MNS and its visual input. Furthermore, there is also evidence of disordered functional connectivity between visual and inferior frontal mirror neuron areas[77] and between frontal and parietal areas[78] in patients with ASD.

In patients with ASD compared with healthy controls, EEG data of action observation show reduced mu rhythm suppression[79], and TMS data show reduced corticospinal facilitation during action observation[80]. Furthermore, a recent fMRI study show reduced MNS activity in patients with ASD during the imitation of finger movements[81]. All these data support the idea that the MNS might be impaired in adults with ASD. However, given that the tasks in these studies were primarily motor tasks, the social–emotional domain was not tested directly.

A recent fMRI study has directly tested the function of the MNS in children with ASD during a social mirroring task[82]. Children observed and imitated facial expressions displaying basic emotions. Children with ASD demonstrated reduced MNS activity during imitation and observation of facial emotional expressions compared with typically developing children. Furthermore, the activity measured in mirror neuron areas in children with ASD during the task correlated with the severity of disease, as assessed by widely used clinical scales[82]. These data strongly support the proposal that mirror neuron dysfunction is a core deficit in autism, and suggest that activity in mirror neuron areas during social mirroring could be an effective bio-marker of the impairment of patients with ASD (FIG. 5).

Emerging work on the role of the MNS in autism and the links between the MNS and imitation suggest that imitation could be used as an effective form of treatment in children with autism. Indeed, behavioural data already seem to support this hypothesis. In one study, two groups of children with autism interacted with an adult, and the adult imitated the actions of the children in only one group. Children in the group whose actions were imitated had a higher tendency to initiate social interactions in a later session compared with the group of children that had only a contingent interaction with the adult, with no imitation[83,84].

Conclusions and future perspectives

Although the discovery of mirror neurons is recent, it has already inspired research programmes in social and cognitive neuroscience and in the neurobiology of disease. Complex aspects of social cognition can finally be grounded, at least in part, in a neural system defined in electrophysiological terms. The mirror neuron hypothesis of autism promises to provide further insights into this condition and to inspire novel forms of intervention.

Beyond the research programmes already established, further insights into the MNS will be provided by collaborations between computational neuroscientists and systems neuroscientists[85]. We now have a variety of markers of MNS activity, from single-cell spiking to EEG rhythms. This begs the question of how specific are these markers? Computational models might help to clarify the different degrees of specificity of spikes, local field potential, blood-oxygen-level-dependent (BOLD) signal, mu suppression and so on, as markers of MNS activity. Moreover, in monkeys, mirror neurons are studied with depth electrodes whereas in humans they are largely studied with fMRI, so it is important to reinforce research programmes that combine the study of spiking activity and fMRI in both monkeys[31] and humans[32]. It is also important that individual differences in the MNS are studied. What is the role of the MNS in social forms of affiliation and in disorders of social behaviour beyond autism? Is it possible that hyper-functioning of the MNS could lead to some of the symptoms typically observed in schizophrenia, such as hyper-attribution of mental states to other people? Finally, the possibility of the formation of interactions between the MNS and neural structures beyond the MNS should be investigated. For example, a key issue is how the MNS is controlled and modulated to suppress unwanted imitation or to create a sequence of imitative motor acts in complex forms of imitation. A candidate region for such modulation in monkeys is area F6 in the medial wall of the frontal lobe — which is strongly connected to F5 (REF. 86) — and its human homologue the pre-supplementary motor area. One of the working hypotheses that we are currently investigating is the existence in these regions of 'super mirror neurons' that could potentially modulate activity in the MNS. Determination of how the MNS interacts with other neural systems that seem crucial for social behaviour[87], such as midline structures that belong to the default state network[88], will be essential for advancing our understanding of socially isolating disorders, of which autism is a key example. MNS research has already provided exciting cues with regard to the neural mechanisms at the basis of social behaviour, and promises to give us powerful insights into the neurobiology of disorders affecting the social domain such as autism.

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Competing interests statement

The authors declare no competing financial interests.

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