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# Crossmodal and action-specific: neuroimaging the human mirror neuron system

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The notion of a frontoparietal human mirror neuron system (HMNS) has been used to explain a range of social phenomena. However, most human neuroimaging studies of this system do not address critical 'mirror' properties: neural representations should be action specific and should generalise across visual and motor modalities. Studies using repetition suppression (RS) and, particularly, multivariate pattern analysis (MVPA) highlight the contribution to action perception of anterior parietal regions. Further, these studies add to mounting evidence that suggests the lateral occipitotemporal cortex plays a role in the HMNS, but they offer less support for the involvement of the premotor cortex. Neuroimaging, particularly through application of MVPA, has the potential to reveal the properties of the HMNS in further detail, which could challenge prevailing views about its neuroanatomical organisation.

## Introduction

In the early 1990s a seminal paper [1] reported the existence of neurons in macaque frontal area F5 that showed remarkable tuning properties: these neurons not only fired when the monkey executed a specific action (such as grasping a pellet of food) but also when it observed an experimenter performing the same action. Soon, more reports of this type of visuomotor neurons, later termed 'mirror neurons', followed. Some of the key findings were that, first, neurons with similar properties were found in macaque parietal regions PF and PFG [2,3], which together with F5 [1,4] were termed the frontoparietal 'mirror neuron system' (Figure 1a) [5,6]. Second, mirror neurons also respond when an object is initially viewed but the subsequent reach-to-grasp is obscured by a screen [7], showing an influence of contextual knowledge on mirror neuron activity. Third, some mirror neurons respond differentially to the observation of the same motor act (e.g., grasping) in

the context of different actions (e.g., grasping to eat or placing an object), suggesting a mechanism by which the final goal of a series of actions could be understood [2,3]. Fourth, the class of mirror neurons is heterogeneous with respect to tuning properties of individual neurons on various dimensions including hand and direction preference [4], distance to the observed actor [8], and viewpoint of the observed action [9].

If humans are endowed with such neurons as well, many have argued that this would provide an explanation for how people solve the 'correspondence problem' [4,10] of imitation and of learning and understanding actions performed by others. Given the anatomical location of F5 – in the premotor cortex – a popular interpretation was (and is) that this occurs through a simulation or direct matching mechanism, where observing someone else activates the same motor circuits as when executing that action 'from within', through a 'motor resonance' process [5,6,11]. According to this interpretation, people can understand the actions of others by mapping them directly onto their own motor repertoire. More generally, the idea that visual and motor representations of actions share a common neural 'code' may also help explain findings showing that task-irrelevant spatial [12], symbolic [13], body-related [14], and affordance [15] aspects of stimuli can affect subsequent action responses. Similar effects are also found in more-complex situations, as in the 'chameleon' effect – the tendency of humans to mimic the actions of social partners [16]. Furthermore, such a mirror mechanism [5,6] has also been proposed to underlie more general processes – beyond action representations – such as the automatic understanding of the feelings (i.e., empathy) [17] and thoughts (i.e., mentalising) [18] of others. It is also argued that mirror neurons play a role in language acquisition [19] given the close proximity of macaque F5 and its putative human homologue of Broca's area. Finally, it has been suggested that a dysfunction of mirror neurons is the underlying mechanism of autism [20] (but see [21]).

The putative explanatory power of mirror neurons for this wide range of human social phenomena has led to the prediction that 'mirror neurons will do for psychology what DNA did for biology' [22]. Although not without critics
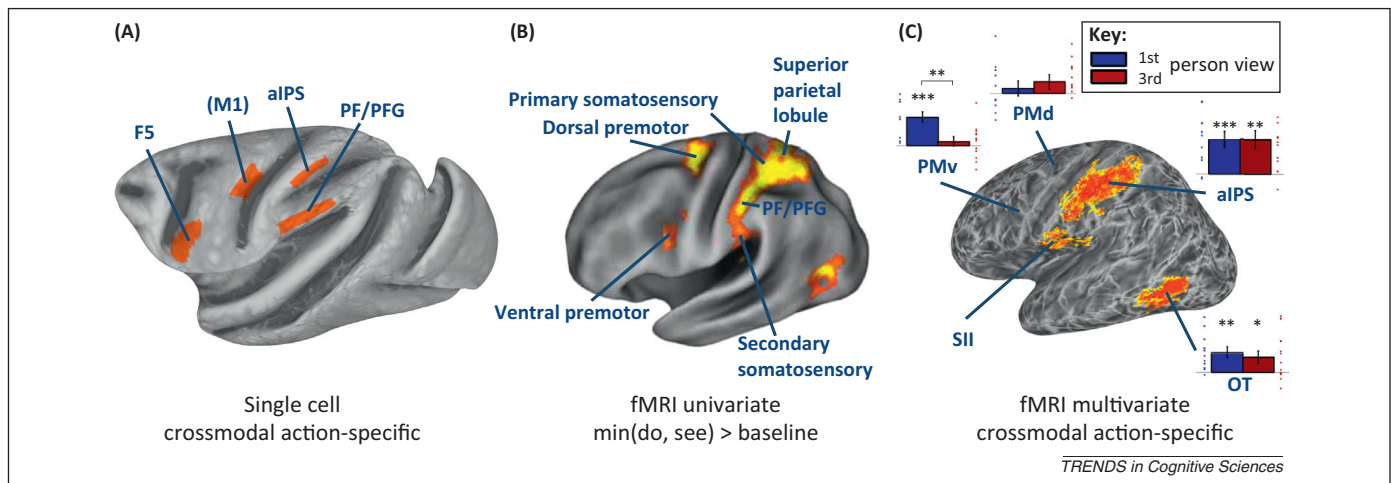
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**Figure 1**. Evidence for mirror neurons in **(A)** macaques using single-cell recordings (adapted, with permission, from [29]), **(B)** humans using univariate conjunction analyses (adapted, with permission, from [29]), and **(C)** humans using multivariate pattern analyses (MVPA; based on data from [58,65]). The inset bar plots in **(C)** show crossmodal action specificity scores for actions observed from a first- (blue bars) and third- (red bars) person perspective (arbitrary units), with dots indicating data from individual participants. Abbreviations: F5, macaque frontal area 5; M1, primary motor cortex; aIPS, anterior parietal cortex; PF/PFG, macaque parietal area F/FG; PMv, ventral premotor cortex; PMd dorsal premotor cortex; SII, secondary somatosensory cortex; OT, occipitotemporal cortex.

[21–27], these thoughts – all resting on the concept of a 'human mirror neuron system' (HMNS) [5,28,29] – make the effort to identify and characterise this system all the more important [30].

## A human 'mirror neuron system'?

Macaque and human brains differ significantly, therefore the findings from macaques do not necessarily extend to humans in a straight forward manner. Indeed, the last-known common ancestor of macaques and humans is estimated to have lived 30 million years ago, resulting in partial but imperfect homology between the species [31]. For example, although early visual areas seem to map well, significant differences have been found between macaques and humans in higher-level associative areas of the intraparietal cortex [32] for tool use [33] and motion processing [34] – functions and regions that may be related to action understanding.

Moreover, the invasive character of neurophysiological recordings has led researchers to turn to other methods to seek evidence for a HMNS (but see [35]). A large body of such studies has employed blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI). The use of fMRI and other systems-level methods, such as transcranial magentic stimulation [36] and magneto- and electro-encephalography [37], introduces important challenges to the study of the HMNS. In varying ways, researchers have identified key properties of mirror neurons determined from single-cell studies and attempted to extrapolate and extend those properties to make systems-level predictions about the activity of large cortical regions. In the following sections of this opinion article, we show that although some of these attempts fall short (and are further limited by the constraints imposed by standard fMRI approaches), more recent studies have extended this logic (and fMRI methods) to paint a more precise picture of the HMNS.

## Crossmodal responses: necessary but not sufficient

Many previous fMRI studies of the HMNS have followed the logic that the presence of mirror neurons in a region can

be inferred when an increased response results from observing and executing actions compared with a baseline condition without a task. In other words: a crossmodal response across the visual and motor modalities. Ostensibly these studies provide overwhelming evidence in support of a HMNS by showing such a response for viewed and executed actions in frontal and parietal regions [6], putative homologues of macaque areas F5 and PF/PFG. Indeed, the idea of a frontoparietal HMNS has become so dominant in human neuroimaging literature that, through reverse inference [38], fMRI responses in these regions have occasionally been taken as evidence for mirror neuron activity [30].

As a recent meta-analysis [39] showed, however, such findings are not specific to canonical frontoparietal regions but extend to many other regions including the early visual cortex, superior temporal cortex, and the cerebellum (Box 1). Another study that used 'unsmoothed' data to reduce artefactual overlap between distinct but adjacent regions reported that 93% of crossmodally responsive voxels were outside the canonical HMNS [40]. It seems likely that general effects of task engagement, attention, or response selection processes – present during action observation or execution but not during baseline periods – are responsible for many of the apparent crossmodal effects found in these studies [30]. Apart from such a baseline explanation, the limited spatial resolution of fMRI – where a single voxel may contain thousands of neurons – means that distinct but spatially overlapping neural populations, with different visual or motor tuning properties, could lead to what has been termed the 'alarming possibility' [40] that many reported crossmodal BOLD responses are not necessarily the result of crossmodal neurons [41]. In other words, such crossmodal responses may be necessary but are not sufficient to make strong inferences on the HMNS (Box 2).

## A crucial ingredient: action specificity

A further key property of mirror neurons is action specificity [30,42]. That is, according to a direct-matching account

**Box 1. Are there mirror neurons everywhere?**

Although a series of studies report evidence for mirror neurons in macaque areas F5 and PF/PFG [1,4], more recent studies have shown neurons with similar tuning properties elsewhere. For example, in a study [87] in which macaques were trained to manipulate a cursor on a screen, certain neurons in primary motor cortex M1 that modulated their firing rate during active cursor manipulation also encoded information during passive observation. Because the modulation of firing rate was similar during performance and observation, these neurons showed evidence for action-specific, crossmodal representations (see also [88]). Other studies have shown crossmodal responses for attended location in lateral intraparietal cortex (LIP) [89], mental rehearsal in dorsal premotor cortex [90], and visuotactile responses in the ventral intraparietal cortex [91]. Furthermore, in humans, recent work in epilepsy patients also revealed neurons with such action-specific, crossmodal neural tuning properties [35]. These neurons were found in the supplementary motor area and in and around the hippocampus and presupplementary motor area – outside the canonical frontoparietal network, perhaps reflecting memory- or emotion-related processes.

Whether or not crossmodal, action-specific neurons found outside the canonical frontoparietal network should be termed 'mirror neurons' is a matter of definition. Some have defined a 'mirror mechanism' based on the requirement that observation of an action is associated with the firing of a set of neurons in the cortical motor system [6], which implies that by definition mirror neurons cannot be found outside the cortical motor system (although neurons in the primary motor cortex presumably would qualify). Alternatively, many would argue that cells or regions that exhibit the key properties reviewed here – irrespectively of anatomical location – should be considered as candidate parts of the HMNS [24,92].

Setting definition issues aside, several studies have shown that different mirror neurons in canonical areas show a wide variety of tuning properties (Box 2). An intriguing possibility is that mirror neurons are not a special category of neurons but rather one example of neurons exhibiting crossmodal tuning properties as found elsewhere in the somatosensory and auditory systems. There is little evidence, however, that neurons with such properties are found everywhere in the brain, and it is likely that other factors, such as brain development constraints and connectivity between functional regions, limit where in the brain such neurons exist [93].

Whether the neurons found outside the canonical areas show similar properties, and/or are associated with different processes such as memory or mental imagery, is an empirical question. For example, one intriguing possibility is that the mirror neurons found in human hippocampus [35] are instances of concept cells that represent actions abstractly [81]. Such questions can ultimately only be resolved by neural recordings.

**Box 2. Interpreting responses from neighbouring locations: a tale of heterogeneous populations**

In many brain regions, spatially neighbouring neurons show remarkably different response profiles. A classic example is orientation columns in macaque primary visual cortex (V1), where different columns show different responses as a function of the orientation of gratings. Such different response profiles are also found in multi-modal areas, where neighbouring neurons may respond more strongly to one of multiple modalities, such as vision and touch [94] or vision and hearing [95].

Further, single neurons can be found that respond to multiple modalities. Crucially, this does not imply, however, that such neurons process information across the different modalities. As an illustration, Lemus et al. [96] measured neural responses in the macaque somatosensory and auditory cortices while the monkeys performed tactile and auditory discrimination tasks. In both cortices neurons were found that responded to their principal modality as well as to their nonprincipal modality (i.e., to tactile stimuli in auditory cortex and to auditory stimuli in somatosensory cortex), which might, ostensibly, challenge the notion of modality-specific cortical areas. When considering discrimination of different stimuli in the same modality, however, in both cortices only stimuli in the principal modality could be distinguished. In other words, although responses were modulated for both modalities, stimulus specificity was limited to the principal modality. This example illustrates that even at a single-cell level – which is not affected by spatial resolution limitations, as in fMRI (Box 3) – an overall increased response for conditions of interest versus some baseline does not imply information processing at a stimulus-specific level. This principle is important for interpreting univariate fMRI studies that identify HMNS regions as those that respond above baseline to visual stimuli and motor behaviour [40].

Interpreting spatially neighbouring responses is complicated further by the heterogeneity of neural responses that can be found in certain areas. Macaque area F5, where the first mirror neurons were found, is a prime example. Most neurons in this area are only involved in executing movements, whereas other neurons are only responsive to observed actions but not executed actions [4]. Indeed, the classic mirror neuron responding strictly congruently to the same action when produced and seen only makes up around 5% of all neurons [4] (Figure 2). Within this class of mirror neurons there is further specialisation with respect to hand and direction preference [4], viewpoint [9], and distance to observed actions [8].

Direct measurement of such fine-grained levels of neural organisation is beyond the resolution of noninvasive imaging methods such as fMRI, which makes interpreting human neuroimaging data even more challenging. One possible avenue is the application of more sophisticated methods such as RS or multivoxel pattern analysis (Box 3) to provide indirect evidence for neural response properties at a population level.

[6], different actions must elicit distinguishable neural signatures, regardless of whether they are seen or executed. Considered at the level of a neural population, one might expect that the response associated with a particular action should be similar whether that action is performed or observed but should be dissimilar for different actions (Figure 2).

The first attempts to address this criterion with fMRI employed BOLD RS to infer neural response properties at a subvoxel level. In these RS studies, a specific action is first observed (or executed) and followed by execution (or observation) of either the same or a different action. According to a neural fatigue interpretation, a reduced response after repeating the same action compared to a different action is evidence for action-specific coding. Apart from interpretational challenges with RS (Box 3), evidence from initial investigations has been mixed. Considering the four recent studies that employed RS and tested visual and motor modalities: one study found action-specific coding within modalities that did not generalise between modalities [43]; two found asymmetric RS, where observed actions followed by executed actions (or vice versa) showed RS but the reverse order did not [44,45]; and one found crossmodal action-specific RS in both directions [46]. Unsurprisingly, this collection of results has not facilitated a consistent view on the HMNS. Interpretation of these findings is further complicated by a recent finding that, at a neural level, neurons in macaque F5 do not adapt to
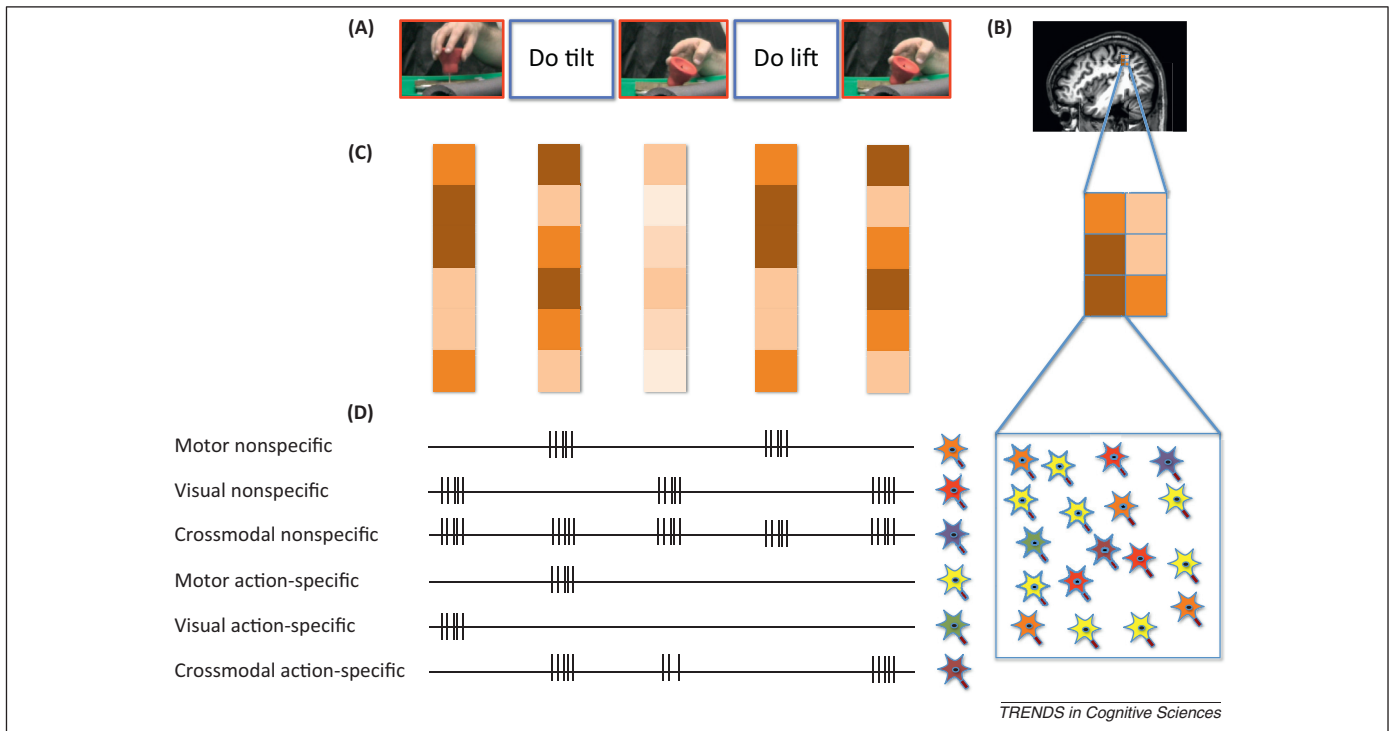
**Figure 2**. Schematic illustration of repetition suppression (RS) and multivariate pattern analyses (MPA). **(A)** During different trials participants view (red boxes) and perform (blue boxes) two different actions: 'lift' and 'tilt'. **(B)** Blood oxygenation level dependent (BOLD) responses from a region in the brain are represented as vectors for each trial. **(C)** The two actions exhibit different response patterns over voxels, and the third action exhibits action-specific repetition suppression (but see also [47]). **(D)** Hypothetical spike response profiles for different classes of neurons that respond either to performed, observed, or both types of actions in either a nonspecific or action-specific manner. The crossmodal action-specific neurons (bottom row) can be termed mirror neurons (Box 1). Size and number of neurons are not to scale.

repeated observed actions [47]. This implies that, if human mirror neurons show similar firing properties to those in macaques, RS is not a suitable technique to study their properties in humans.

**Multivariate pattern analysis**

An alternative approach to study action specificity of neural representations is multivariate pattern analysis (MVPA) [48–51]. This sensitive approach has been used successfully to decode subtle differences between stimulus-evoked activity patterns and even to reconstruct static and dynamic percepts from brain signals [52]. Such sensitivity is important if the proportion of mirror neurons in a region is small, as suggested by macaque (~5% to ~17% [4]) and human (~8% [35]) studies. Importantly for the study of the HMNS, MVPA has also been used to discriminate between spatially overlapping populations [53] (Figure 2). Using this approach, the similarity of patterns evoked across groups of fMRI voxels by specific actions, when viewed and when performed, can be quantified. Areas where the same action (across the visual and motor domains) produces more similar patterns than different actions would be shown to have two key traits for a HMNS: crossmodality and action specificity. A trade off in this approach is that it necessarily considers neither single neurons nor single voxels, but identifies the properties of representations that span across a cortical region.

The first application of MVPA to investigate the HMNS was in the auditory–visual domain, demonstrating effector-specific (hand versus mouth) generalisation across heard and performed sounds in the parietal cortex [54],

although these effects could potentially be explained by large-scale somatotopic organisation of the parietal cortex [55]. A subsequent MVPA study [56] used observed and executed manual actions, and showed action-specific coding within the visual and motor modalities in a set of *a priori* regions of interest. However, no evidence was revealed for the critical case of crossmodal representations. Evidence for such representations was subsequently found using a data-driven searchlight-based mapping approach [57], in which pattern similarity was computed in small disc-shaped regions covering the entire cortical surface (Figure 2c). Two experiments revealed that regions in the anterior intraparietal sulcus (aIPS) and lateral occipitotemporal (OT) cortex showed crossmodal, action-specific patterns of activity [58]. Transitive (object-directed) and intransitive (without object) manual actions implicated similar regions. Likewise, tests with live actions and with pre-recorded videos of actions produced highly similar results. No evidence was found for similar response profiles in the frontal cortex. Interestingly, this data-driven approach pointed to the engagement of OT, a region outside the canonical frontoparietal network, suggesting that areas typically considered part of the visual system can also show motor properties at the action-specific level (see also [35,59] and Box 1).

Aside from identifying candidate HMNS regions that show crossmodal, action-specific activity patterns, it is important to characterise the nature of the representations in these regions and their relationship to psychological variables. One organising principle for describing an action distinguishes between the goal of an action (such as lifting

## Box 3. Interpretation challenges for repetition suppression (RS) and MVPA

It has been claimed that fMRI RS supports inferences about neural populations at a subvoxel resolution [97,98]. In this approach, two trials are presented that share a characteristic of interest (e.g., action type) in rapid succession. Presumably, this results in a (non-time-invariant) response in the neural population that represents the characteristic of interest of the first stimulus. In a neural fatigue interpretation, this prior activation reduces response to a subsequent stimulus possessing this same property [98]. For example, an observed action can be followed by execution of either the same action or a different action. Neural populations that show crossmodal action-specific coding are expected to produce a lower response for executing the same action than a different action.

Interpretations of such results remain challenging, however, because studies suggest that such suppression effects are modulated by stimulus predictability, attention, neural tuning, and the time-scale of stimulus presentation. Other studies have shown that stimulus repetition may enhance (rather than suppress) the BOLD response [99]. Finally, recent findings indicate that effects of repetition on neural and BOLD activity can be distinct [100], which, in the context of the study of mirror neurons in macaque area F5 [47], raises questions about validity.

Multivoxel pattern analysis [48–51] considers data across a spatially extended group of voxels. This approach reflects the assumption that many processes involve neural populations with a spatial extent spanning many voxels and that clusters of voxels, rather than individual voxels, should be treated as the unit of interest in fMRI analysis [101].

Unlike RS, which enforces the use of counterbalanced trial condition sequences and seriously limits the number of trial conditions, the use of MVPA for 'representational similarity' analyses has shown the feasibility of using a large variety of conditions in a single experiment and across modalities (neurophysiology and fMRI) and species (macaques and humans) [76].

Despite these advantages, the neural mechanisms that underlie MVPA are poorly understood. An early proposal suggested that MVPA was based on biased sampling of different neural populations at a subvoxel resolution (hyper acuity) [50], but more-recent work suggests a more complex mechanism that may involve a multiscale organisation and possibly an important role for neural vasculature [102]. Another limitation is that MVPA depends, by definition, on the combined signal of multiple voxels, and several studies have found that increasing the number of voxels increases sensitivity (up to a certain limit). This means that – in particular for data-driven approaches such as information mapping – MVPA entails a compromise between spatial specificity and sensitivity to discriminate between conditions of interest.

a cup) and the implementation of the action (such as using a precision or whole-hand grip). In an MVPA study in which goal and implementation were varied orthogonally, evidence for a posterior-to-anterior goal-to-implementation gradient was found in aIPS [58]. This finding is consistent with earlier suggestions of a more abstract representation of actions in posterior parietal regions, relative to more implementation-related representations in anterior parietal regions [60,61].

A further issue to which MVPA has been applied concerns whether crossmodal effects could be due to mental imagery. For example, earlier work on the visual cortex demonstrated that the lateral occipital complex showed stimulus-specific responses for 'X'- and 'O'-shaped stimuli, irrespectively of whether they were observed or covertly imagined [62]. According to such an interpretation, apparently crossmodal response patterns could be due to visual or conceptual representation of actions that are activated during action execution. To address this question, participants performed actions while receiving visual input of their own actions during some trials, and imagined covertly performing the same actions during other trials [63]. This study found evidence for action-specific coding that generalised across active performing and passive imagery in the anterior parietal cortex, but no such evidence in frontal or occipitotemporal regions. Although speculative, this may be interpreted as evidence for high-level action representations in aIPS that involve modality-independent rather than motor representations or visual representations of specific actions. This interpretation is consistent with its anatomical location between, and functional connections with, the visual and motor cortices.

### Viewpoint invariance

Observing our own actions is typically associated with a particular 'first-person' visual perspective on those actions. By contrast, we typically see others' actions from a variety of different 'third-person' perspectives. A key property of macaque mirror neurons is that they seem to relate the motor aspects of an action (which are inherently personal or 'first person') to the visual aspects of the same action even when that action is performed by others and, hence, seen from a different perspective [64]. This characteristic is considered to underlie the matching of one's own actions to the observed actions of other individuals, which, in turn, ostensibly provides a neural underpinning for relating others' behaviours to one's own.

In another MVPA experiment [65], participants viewed videos showing actions either from a first-person viewpoint (as if they performed actions themselves) or from a third-person viewpoint (as if they observed someone else performing actions). In aIPS and OT regions robust, crossmodal, action-specific patterns of activity were observed for both viewpoints. In the ventral premotor cortex (PMv) – a core region of the canonical frontoparietal HMNS – first-person viewpoints generalised between the visual and motor modalities (Figure 2c), consistent with an earlier RS study [46], but generalisation to third-person viewpoints was not statistically distinguishable from chance. These results are consistent with recordings in macaque area F5 showing that the majority of recorded mirror neurons showed viewpoint-dependent coding [9], with a (nonsignificant) trend for more neurons coding for first-person views than for lateral- or opposite-side-person views. Heterogeneous responses in F5 were also shown at a larger spatial scale using fMRI, showing different response profiles to observed actions and objects across different subregions in area F5 [66]. Taken together, these findings from different scales and levels of analysis raise questions about how the premotor cortex may be involved in understanding the actions of others. At the finest level, many mirror cells appear not to generalise fully to all views of an action; by analogy to the representation of faces and objects, view-dependent local representations may act in concert to produce view-independent properties collectively. However, the MVPA results do not indicate such a

representation at the population level in this region in humans. The question of view (in)dependence is an absolutely central one to the mirror neuron system framework, and more studies are required on single neurons and with MVPA. Meanwhile, an alternative possibility that must be considered is that human premotor areas are engaged for observation of one's own actions (for example in eye–hand coordination required for object manipulation), whereas the more posterior parietal and occipitotemporal regions are involved more in understanding the actions of others [58].

### Concluding remarks and future directions

Recent advances in fMRI methods have been applied to examine the HMNS by extrapolating some of the key properties of mirror neurons to the population level. Already, these first steps paint a picture that differs in some ways from the canonical frontoparietal model of the HMNS (Figure 1) that emerged from the first wave of fMRI studies in this area.

First, with MVPA, PMv shows stronger first-person than third-person view representations of actions, which could mean it is less involved in representing the actions of other individuals [65] than the self. Because one of the purported roles of the HMNS is to understand other people's actions (observed from a third-person viewpoint), further study is required to establish the critical conditions under which PMv generalizes between observed and executed actions. Second, the anterior parietal cortex showed the most consistent coding of actions, with engagement that generalises across the visual, motor, and imagery modalities [67–69]. The consistency of parietal activations across many studies suggests it may be a fundamental hub in the HMNS. These findings are consistent with an abstract representation of action goals in the anterior parietal cortex [60] with a possible extension to effector-related somatosensory properties in the somatosensory cortex [70]. Finally, a region in the lateral occipitotemporal cortex shows crossmodal, action-specific, view-independent action representations [58,59]. Although traditionally this has been considered as a visual region, with neighbouring representations of visual motion [71], body parts [72], and object form [73], numerous recent findings implicate the general region in haptics, motor behaviour, and tool use [59,74,75]. A case is therefore emerging that this OT region should be considered a candidate part of the HMNS.

Although MVPA on fMRI data is subject to limitations (Box 3), we argue that these methods offer tools to test key properties of action representations in ways not accessible to other techniques. They can elucidate not only the existence and location of regions that show crossmodal, action-specific representations but also begin to unpack the nature of their neural coding. Applying MVPA opens the way for similarity-based analysis [76] and investigating shared representations across individuals [77]. Both seem particularly useful to advance our knowledge on how humans represent their own actions and those performed by others. To clarify the population properties of macaque mirror neurons further, MVPA can also be applied to neurophysiology data [78]. More generally, application of representational similarity

**Box 4. Outstanding questions**

- What is the functional role of mirror neurons?
- Is there a mapping from conceptual to neural hierarchical representation of actions?
- How do neurons with mirror properties develop?
- To what extent can hypotheses concerning motor, visual, or conceptual representations be dissociated experimentally?
- To what extent are brain areas and their respective neural representations of action homologous between macaques and humans?
- How do action representations at a neural level change as a function of expertise and training?
- What is the role of forward and feedback connections between mirror areas?

MVPA to fMRI and neurophysiological data in macaques and humans [79] would provide further insights to how information from these modalities can be meaningfully interpreted and integrated.

Mirror neurons were first found in the (pre)motor cortex, which undoubtedly influenced the hypothesis of a direct-matching mechanism in the canonical frontoparietal HMNS, where actions are "understood 'from the inside' as a motor possibility, rather than 'from the outside' as a mere visual description" [6]. More recent findings of crossmodal, action-specific representations far outside the human motor system – in occipitotemporal cortex [58,59,65] and hippocampus [35] – suggest that this hypothesis is incomplete [24]. In these non-motor regions (and possibly in the HMNS as well) actions may be encoded at an abstract level [24–26,61]. Further afield, recent findings point to crossmodal or abstract representations of emotions [80] and of person knowledge [81]. Collectively, these kinds of findings from diverse domains may each represent the result of general associative mechanisms [23,61]. Such an account would be consistent with the claim that crossmodal, action-specific representations are susceptible to effects of action-specific sensorimotor training [82–84]. Thus, a promising avenue for future research is to study how such sensorimotor training affects mirror responses at a single-neuron level in macaques [85] (Box 4).

A priority for future work in macaques would be to study putative homologous regions of the non-motor regions identified in humans, and to compare these to mirror neurons in the premotor and parietal cortices. Finally, to integrate and compare results across humans and macaques, a promising avenue is the application of MVPA – and in particular representational similarity analyses [86] – to fMRI, electrophysiological, and electrocorticographical data, which will also bridge the gaps caused by imperfect brain homologies and different measurement modalities. More generally, as similar approaches are applied to other domains, we may begin to improve our understanding regarding general principles of how the brain integrates primary sensory and motor information to form abstract representations of knowledge [81].

## References

1 di Pellegrino, G. *et al.* (1992) Understanding motor events: a neurophysiological study. *Exp. Brain Res.* 91, 176–180

2 Fogassi, L. *et al.* (1998) Neurons responding to the sight of goal-directed hand/arm actions in the parietal area PF (7b) of the macaque monkey. *Soc. Neurosci. Abstr.* 24

3 Fogassi, L. *et al.* (2005) Parietal lobe: from action organization to intention understanding. *Science* 308, 662–667

4 Gallese, V. *et al.* (1996) Action recognition in the premotor cortex. *Brain* 119, 593–609

5 Rizzolatti, G. and Craighero, L. (2004) The mirror-neuron system. *Annu. Rev. Neurosci.* 27, 169–192

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

7 Umiltà, M.A. *et al.* (2001) I know what you are doing. a neurophysiological study. *Neuron* 31, 155–165

8 Caggiano, V. *et al.* (2009) Mirror neurons differentially encode the peripersonal and extrapersonal space of monkeys. *Science* 324, 403–406

9 Caggiano, V. *et al.* (2011) View-based encoding of actions in mirror neurons of area F5 in macaque premotor cortex. *Curr. Biol.* 21, 144–148

10 Brass, M. and Heyes, C. (2005) Imitation: is cognitive neuroscience solving the correspondence problem? *Trends Cogn. Sci.* 9, 489–495

11 Gallese, V. (2005) Embodied simulation: From neurons to phenomenal experience. *Phenomenol. Cogn. Sci.* 4, 23–48

12 Simon, J.R. and Rudell, A.P. (1967) Auditory S-R compatibility: The effect of an irrelevant cue on information processing, *Journal of. Appl. Psychol.* 51, 300–304

13 Müsseler, J. and Hommel, B. (1997) Blindness to response-compatible stimuli. *J. Exp. Psychol. Hum. Percept. Perform.* 23, 861–872

14 Bach, P. *et al.* (2006) Focusing on body sites: the role of spatial attention in action perception. *Exp. Brain Res.* 178, 509–517

15 Tucker, M. and Ellis, R. (2001) The potentiation of grasp types during visual object categorization. *Vis. Cogn.* 8, 769–800

16 Chartrand, T.L. and Bargh, J.A. (1999) The chameleon effect: the perception-behavior link and social interaction. *J. Perspect. Soc. Psychol.* 76, 893–910

17 Gallese, V. (2001) The shared manifold hypothesis. From mirror neurons to empathy. *J. Conscious. Stud.* 8, 5–7

18 Gallese, V. and Goldman, A. (1998) Mirror neurons and the simulation theory of mind-reading. *Trends Cogn. Sci.* 2, 493–501

19 Rizzolatti, G. and Arbib, M.A. (1998) Language within our grasp. *Trends Neurosci.* 21, 188–194

20 Iacoboni, M. and Dapretto, M. (2006) The mirror neuron system and the consequences of its dysfunction. *Nat. Rev. Neurosci.* 7, 942–951

21 Dinstein, I. *et al.* (2010) Normal movement selectivity in autism. *Neuron* 66, 461–469

22 Ramachandran, V. (2000) Mirror neurons and imitation learning as the driving force behind the great leap forward in human evolution, http://edge.org/conversation/mirror-neurons-and-imitation-learning-as-the-driving-force-behind-the-great-leap-forward-in-human-evolution

23 Heyes, C. (2010) Where do mirror neurons come from? *Neurosci. Biobehav. Rev.* 34, 575–583

24 Hickok, G. (2009) Eight problems for the mirror neuron theory of action understanding in monkeys and humans. *J. Cogn. Neurosci.* 21, 1229–1243

25 Kilner, J.M. (2011) More than one pathway to action understanding. *Trends Cogn. Sci.* 15, 352–357

26 Mahon, B.Z. and Caramazza, A. (2008) A critical look at the embodied cognition hypothesis and a new proposal for grounding conceptual content. *J. Physiol. Paris* 102, 59–70

27 Uithol, S. *et al.* (2012) Hierarchies in action and motor control. *J. Cogn. Neurosci.* 24, 1077–1086

28 Gallese, V. *et al.* (2004) A unifying view of the basis of social cognition. *Trends Cogn. Sci.* 8, 396–403

29 Keysers, C. and Gazzola, V. (2009) Expanding the mirror: vicarious activity for actions, emotions, and sensations. *Curr. Opin. Neurobiol.* 19, 666–671

30 Dinstein, I. *et al.* (2008) A mirror up to nature. *Curr. Biol.* 18, 13–18

31 Sereno, M.I. and Tootell, R.B. (2005) From monkeys to humans: what do we now know about brain homologies? *Curr. Opin. Neurobiol.* 15, 135–144

32 Orban, G.A. *et al.* (2004) Comparative mapping of higher visual areas in monkeys and humans. *Trends Cogn. Sci.* 8, 315–324

33 Peeters, R. *et al.* (2009) The representation of tool use in humans and monkeys: common and uniquely human features. *J. Neurosci.* 29, 11523–11539

34 Orban, G.A. *et al.* (2003) Similarities and differences in motion processing between the human and macaque brain: evidence from fMRI. *Neuropsychologia* 41, 1757–1768

35 Mukamel, R. *et al.* (2010) Single-neuron responses in humans during execution and observation of actions. *Curr. Biol.* 20, 750–756

36 Fadiga, L. *et al.* (1995) Motor facilitation during action observation: a magnetic stimulation study. *J. Neurophysiol.* 73, 2608–2611

37 Hari, R. and Nishitani, N. (2004) From viewing of movement to imitation and understanding of other persons' acts: MEG studies of the human mirror-neuron system. In *Functional Neuroimaging of Visual Cognition. Attention and Performance XX* (Kanwisher, N. and Duncan, J., eds), pp. 463–479, Oxford, Oxford University Press

38 Poldrack, R.A. (2006) Can cognitive processes be inferred from neuroimaging data? *Trends Cogn. Sci.* 10, 59–63

39 Molenberghs, P. *et al.* (2012) Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neurosci. Biobehav. Rev.* 36, 341–349

40 Gazzola, V. and Keysers, C. (2009) The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data. *Cereb. Cortex* 19, 1239–1255

41 Morrison, I. and Downing, P.E. (2007) Organization of felt and seen pain responses in anterior cingulate cortex. *Neuroimage* 37, 642–651

42 Dinstein, I. (2008) Human cortex: reflections of mirror neurons. *Curr. Biol.* 18, 956–959

43 Dinstein, I. *et al.* (2007) Brain areas selective for both observed and executed movements. *J. Neurophysiol.* 98, 1415–1427

44 Chong, T.T-J. *et al.* (2008) fMRI adaptation reveals mirror neurons in human inferior parietal cortex. *Curr. Biol.* 18, 1576–1580

45 Lingnau, A. *et al.* (2009) Asymmetric fMRI adaptation reveals no evidence for mirror neurons in humans. *Proc. Natl. Acad. Sci. U.S.A.* 106, 9925–9930

46 Kilner, J.M. *et al.* (2009) Evidence of mirror neurons in human inferior frontal gyrus. *J. Neurosci.* 29, 10153–10159

47 Caggiano, V. *et al.* (2013) Mirror neurons in monkey area F5 do not adapt to the observation of repeated actions. *Nat. Commun.* 4, 1433–1438

48 Edelman, S. *et al.* (1998) Toward direct visualization of the internal shape representation space by fMRI. *Psychobiology* 26, 309–321

49 Haxby, J.V. *et al.* (2001) Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science* 293, 2425–2430

50 Norman, K.A. *et al.* (2006) Beyond mind-reading: multi-voxel pattern analysis of fMRI data. *Trends Cogn. Sci.* 10, 424–430

51 Haynes, J-D. and Rees, G. (2006) Decoding mental states from brain activity in humans. *Nat. Rev. Neurosci.* 7, 523–534

52 Nishimoto, S. *et al.* (2011) Reconstructing visual experiences from brain activity evoked by natural movies. *Curr. Biol.* 21, 1641–1646

53 Peelen, M.V. and Downing, P.E. (2007) Using multi-voxel pattern analysis of fMRI data to interpret overlapping functional activations. *Trends Cogn. Sci.* 11, 4–5

54 Etzel, J.A. *et al.* (2008) Testing simulation theory with cross-modal multivariate classification of fMRI data. *PLoS ONE* 3, e3690

55 Buccino, G. *et al.* (2001) Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur. J. Neurosci.* 13, 400–404

56 Dinstein, I. *et al.* (2008) Executed and observed movements have different distributed representations in human aIPS. *J. Neurosci.* 28, 11231–11239

57 Oosterhof, N.N. *et al.* (2011) A comparison of volume-based and surface-based multi-voxel pattern analysis. *Neuroimage* 56, 593–600

58 Oosterhof, N.N. *et al.* (2010) Surface-based information mapping reveals crossmodal vision-action representations in human parietal and occipitotemporal cortex. *J. Neurophysiol.* 104, 1077–1089

59 Orlov, T. *et al.* (2010) Topographic representation of the human body in the occipitotemporal cortex. *Neuron* 68, 586–600

60 Grafton, S.T. *et al.* (2007) Evidence for a distributed hierarchy of action representation in the brain. *Hum. Mov. Sci.* 26, 590–616

61 Kilner, J.M. *et al.* (2007) Predictive coding: an account of the mirror neuron system. *Cogn. Process.* 8, 159–166

62 Stokes, M. *et al.* (2007) Imagery for shapes activates position-invariant representations in human visual cortex. *Neuroimage* 56, 1540–1545

63 Oosterhof, N.N. *et al.* (2012) Visuo-motor imagery of specific manual actions: A multi-variate pattern analysis fMRI study. *Neuroimage* 63, 262–271

64 Keysers, C. and Perrett, D.I. (2004) Demystifying social cognition: a Hebbian perspective. *Trends Cogn. Sci.* 8, 501–507

65 Oosterhof, N.N. *et al.* (2012) Viewpoint (in)dependence of action representations: an MVPA study. *J. Cogn. Neurosci.* 24, 975–989

66 Nelissen, K. *et al.* (2005) Observing others: multiple action representation in the frontal lobe. *Science* 310, 332–336

67 Sirigu, A. *et al.* (1996) The mental representation of hand movements after parietal cortex damage. *Science* 273, 1564–1568

68 Sakata, H. *et al.* (1995) Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. *Cereb. Cortex* 5, 429–438

69 Culham, J.C. and Valyear, K.F. (2006) Human parietal cortex in action. *Curr. Opin. Neurobiol.* 16, 205–212

70 Keysers, C. *et al.* (2004) A touching sight: SII/PV activation during the observation and experience of touch. *Neuron* 42, 335–346

71 Tootell, R.B. *et al.* (1995) Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J. Neurosci.* 15, 3215–3230

72 Downing, P.E. and Peelen, M.V. (2011) The role of occipitotemporal body-selective regions in person perception. *Cogn. Neurosci.* 2, 186–203

73 Malach, R. *et al.* (1995) Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. *Proc. Natl. Acad. Sci. U.S.A.* 92, 8135–8139

74 Astafiev, S.V. *et al.* (2004) Extrastriate body area in human occipital cortex responds to the performance of motor actions. *Nat. Neurosci.* 7, 542–548

75 Bracci, S. *et al.* (2012) Closely overlapping responses to tools and hands in left lateral occipitotemporal cortex. *J. Neurophysiol.* 107, 1443–1456

76 Kriegeskorte, N. *et al.* (2008) Representational similarity analysis - connecting the branches of systems neuroscience. *Front. Syst. Neurosci.* 2, 4

77 Haxby, J.V. *et al.* (2011) A common, high-dimensional model of the representational space in human ventral temporal cortex. *Neuron* 72, 404–416

78 Quian Quiroga, R. and Panzeri, S. (2009) Extracting information from neuronal populations: information theory and decoding approaches. *Nat. Rev. Neurosci.* 10, 173–185

79 Kriegeskorte, N. (2009) Relating population-code representations between man, monkey, and computational models. *Front. Neurosci.* 3, 363–373

80 Peelen, M.V. *et al.* (2010) Supramodal representations of perceived emotions in the human brain. *J. Neurosci.* 30, 10127–10134

81 Quiroga, R.Q. (2012) Concept cells: the building blocks of declarative memory functions. *Nat. Rev. Neurosci.* 13, 587–597

82 Cross, E.S. *et al.* (2006) Building a motor simulation *de novo*: Observation of dance by dancers. *Neuroimage* 31, 1257–1267

83 Calvo-Merino, B. *et al.* (2005) Action observation and acquired motor skills: an FMRI study with expert dancers. *Cereb. Cortex* 15, 1243–1249

84 Cook, R. et al. Mirror neurons: from origin to function. Behav. Brain Sci. (in press)

85 Hickok, G. and Hauser, M. (2010) (Mis)understanding mirror neurons. *Curr. Biol.* 20, 593–594

86 Kriegeskorte, N. *et al.* (2008) Matching categorical object representations in inferior temporal cortex of man and monkey. *Neuron* 60, 1126–1141

87 Tkach, D. *et al.* (2007) Congruent activity during action and action observation in motor cortex. *J. Neurosci.* 27, 13241–13250

88 Dushanova, J. and Donoghue, J. (2010) Neurons in primary motor cortex engaged during action observation. *Eur. J. Neurosci.* 31, 386–398

89 Shepherd, S.V. *et al.* (2009) Mirroring of attention by neurons in macaque parietal cortex. *Proc. Natl. Acad. Sci. U.S.A.* 106, 9489–9494

90 Cisek, P. and Kalaska, J.F. (2004) Neural correlates of mental rehearsal in dorsal premotor cortex. *Nature* 431, 993–996

91 Ishida, H. *et al.* (2010) Shared mapping of own and others' bodies in visuotactile bimodal area of monkey parietal cortex. *J. Cogn. Neurosci.* 22, 83–96

92 Keysers, C. and Gazzola, V. (2010) Social neuroscience: mirror neurons recorded in humans. *Curr. Biol.* 20, 353–354

93 Mahon, B.Z. and Caramazza, A. (2011) What drives the organization of object knowledge in the brain? *Trends Cogn. Sci.* 15, 97–103

94 Graziano, M.S.A. and Gross, C.G. (1993) A bimodal map of space: somatosensory receptive fields in the macaque putamen with corresponding visual receptive fields. *Exp. Brain Res.* 97, 96–109

95 Barth, D.S. *et al.* (1995) The spatiotemporal organization of auditory, visual, and auditory-visual evoked potentials in rat cortex. *Brain Res.* 678, 177–190

96 Lemus, L. *et al.* (2010) Do sensory cortices process more than one sensory modality during perceptual judgments? *Neuron* 67, 335–348

97 Krekelberg, B. (2006) Adaptation: from single cells to BOLD signals. *Trends Neurosci.* 29, 250–256

98 Grill-Spector, K. *et al.* (2006) Repetition and the brain: neural models of stimulus-specific effects. *Trends Cogn. Sci.* 10, 14–23

99 Segaert, K. *et al.* (2013) The suppression of repetition enhancement: a review of fMRI studies. *Neuropsychologia* 51, 59–66

100 Sawamura, H. *et al.* (2006) Selectivity of neuronal adaptation does not match response selectivity: a single-cell study of the FMRI adaptation paradigm. *Neuron* 49, 307–318

101 Penny, W. *et al.* (2003) Mixtures of general linear models for functional neuroimaging. *IEEE Trans. Med. Imaging* 22, 504–514

102 Kriegeskorte, N. *et al.* (2010) How does an fMRI voxel sample the neuronal activity pattern: compact-kernel or complex spatiotemporal filter? *Neuroimage* 49, 1965–1976