Motor and cognitive functions of the ventral premotor cortex

Giacomo Rizzolatti*‡, Leonardo Fogassi† and Vittorio Gallese*

Recent data show that the ventral premotor cortex in both humans and monkeys has motor and cognitive functions. The cognitive functions include space perception, action understanding and imitation. The data also show a clear functional homology between monkey area F5 and human area 44. Preliminary evidence suggests that the ventral part of the lateral premotor cortex in humans may correspond to monkey area F4. A tentative map of the human lateral premotor areas founded on the reviewed evidence is presented.

Addresses
*Istituto di Fisiologia Umana and †Dipartimento di Psicologia, Università di Parma, Via Volturno 39, I-43100 Parma, Italy
‡e-mail: fisioum@symbolic.pr.it

Current Opinion in Neurobiology 2002, **12**:149–154

0959-4388/02/$ – see front matter

Abbreviations

AIP	anterior intraparietal area
dPM	dorsal premotor area
FEF	frontal eye field
fMRI	functional magnetic resonance imaging
RFs	receptive fields
SII	secondary somatosensory cortex
VIP	ventral intraparietal area
vPM	ventral premotor area

Introduction

The premotor cortex of the monkey is typically subdivided into two large sectors: the ventral (vPM) and the dorsal (dPM) premotor cortex. In turn, each of these sectors is formed by two areas, one located rostrally and the other caudally (Figure 1a). No distinction between dorsal and ventral premotor cortex has classically been made in humans, the cortex lying on the cortical lateral surface being dubbed lateral area 6. A distinction, however, between rostral and caudal premotor sectors is apparent in humans. The dorsal part of lateral area 6 consists of two areas: 6aα and 6aβ [1]. They are indicated in light pink and blue, respectively, in Figure 1b. Two areas similarly form the ventral sector of lateral area 6: 6aα and area 44. They are indicated in red and dark pink, respectively, in Figure 1b. The homology between area 44 in humans and the rostral part of vPM (or F5) in monkeys was noted by Von Bonin and Bailey [2] and recently confirmed by Petrides and Pandya [3].

Here, we review recent monkey and human studies that address the functional role of ventral sectors of premotor cortex (area 44 included) in action organization, motor imagery, and action understanding. Studies on language are not reviewed.

Caudal ventral premotor cortex in monkeys and humans

Caudal ventral premotor cortex in monkeys: F4

Area F4 is the frontal node of a cortical circuit that includes the ventral intraparietal area (VIP), the intraparietal sector of area PE (PEip), and the secondary somatosensory cortex (SII) [4•]. This circuit transforms specific positions in the space around the monkey (peripersonal space) into arm, neck, and face/mouth movements. This circuit is also involved in space perception [5].

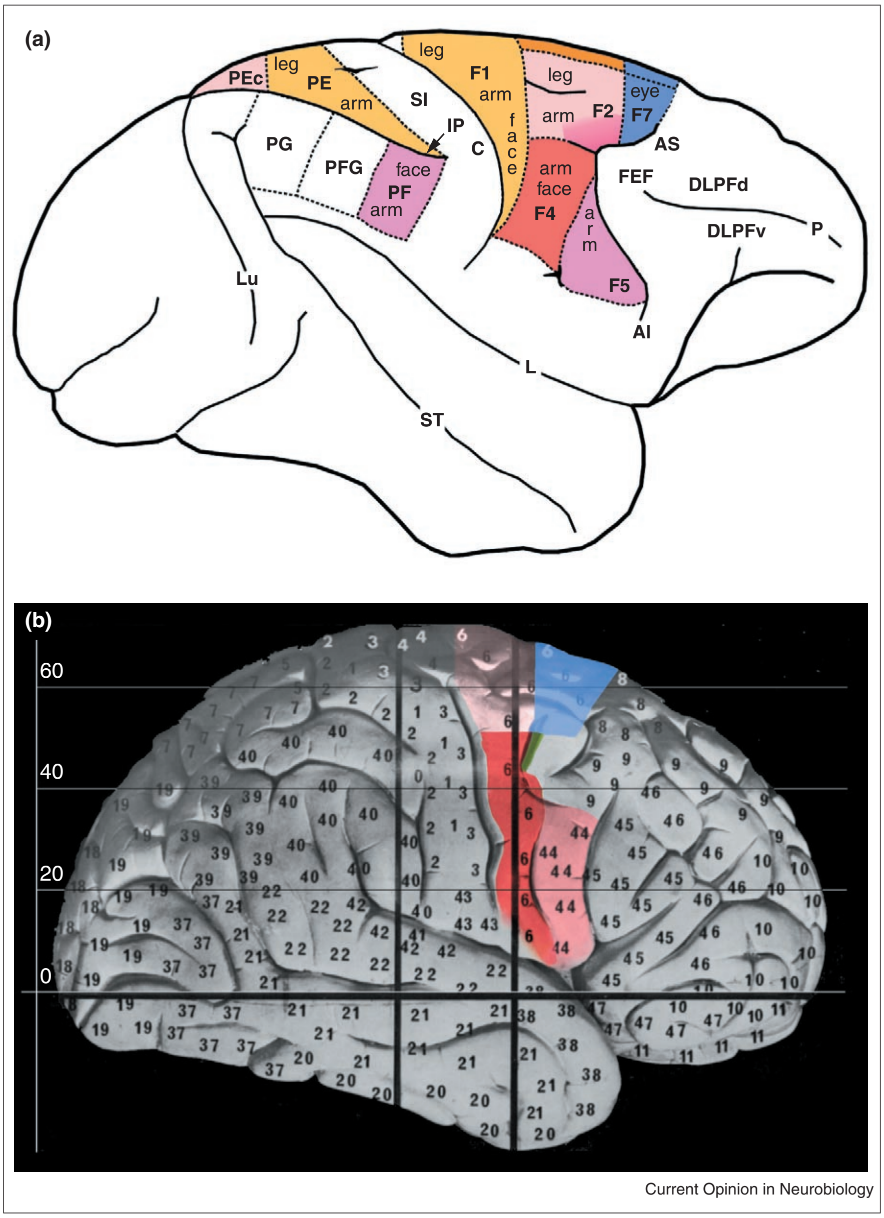
F4 neurons discharge according to specific body part movements. In addition, most of these neurons respond to somatosensory stimuli. Some also respond to visual and auditory stimuli [6–9]. F4 visual receptive fields (RFs) are located around the tactile RF and, typically, extend in depth up to ~30 cm from it [6–8]. Their position is independent of eye position and is anchored to a particular body part [10]. When the body part is moved, the RF moves with it [8]. Recent data showed that F4 contains representations of wrist movements directed to specific space positions [11•]. Interestingly, most F4 neurons that respond to wrist movements code actions in extrinsic (spatial) coordinates, rather than in intrinsic coordinates, as previously described for F1 [12]. This study [11•] elegantly confirmed the notion that area F4 codes goal-directed actions, the goal being represented by spatial locations.

Lesion studies

Ablation of F4 (including portions of F5) produces hemispatial neglect in the monkey, as well as reaching deficits. The neglect is circumscribed to peripersonal space [13]. Selective neglect for peripersonal space may occur also in humans [14]. A recent study by Berti and Frassinetti [15•] confirmed this finding. They described a patient who, after a right hemisphere stroke, exhibited selective peripersonal neglect. The near/far dissociation was clear in line bisection tasks that were impaired in the near space, but virtually normal in the far space. This was observed when the patient bisected lines using a light projection pen. However, when the patient acted on far stimuli using a stick, neglect reappeared. Berti and Frassinetti [15•] explained this result by referring to neurophysiological data obtained by Iriki *et al.* [16••], who showed that the use of a tool extends the monkey peripersonal space. In the case of the patient, the use of a stick extended his peripersonal space so as to include all the space between the body and the stimulus. As a consequence, far space was remapped as near space and the neglect reappeared. Maravita *et al.* [17] and Farnè and Ladavas [18] reported similar findings.

Prompted by the observation that, in the monkey, F4 visual RFs move with the body part to which they are

Figure 1



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Ventral premotor cortex in monkeys and humans. **(a)** Lateral view of the monkey brain showing the cytoarchitectonic parcellation of the motor cortex and the posterior parietal cortex. Matching colors indicate each motor area and its corresponding parietal input (area VIP, buried inside IP, is not shown). The motor area F7, receiving its main input from the prefrontal lobe, is indicated in blue. Areas F2 and F7 are often referred to as dPM; areas F4 and F5 form the vPM. AI, inferior arcuate sulcus; AS, superior arcuate sulcus; C, central sulcus; DLPFd, dorsolateral prefrontal cortex dorsal part; DLPFv, dorsolateral prefrontal cortex ventral part; IP, intraparietal sulcus; L, lateral fissure; Lu, lunate sulcus; P, principal sulcus; SI, primary somatosensory cortex; ST, superior temporal sulcus. Modified with permission from [4•]. **(b)** Lateral view of the human brain showing the cytoarchitectonic parcellation of Brodmann and the basal lines (thick lines) depicted by Talairach and Tournoux [50]. Thin horizontal lines indicate z values. Colored regions indicate: dPM 6aα, light pink; 6aβ (predPM [51•]), blue; vPM (ventral area 6), red; area 44, dark pink; FEF, green. Modified with permission from [50].

anchored, a series of studies investigated cross-modal extinction in patients with mild neglect [19,20]. These experiments showed that the presentation of a visual stimulus near the patients' ipsilesional (normal) arm or hemiface caused an extinction of a tactile stimulus applied on the patients' contralesional (neglected) hand. However, when the visual stimulus was presented in the identical spatial location, but the body part was moved to another position, the extinguishing effect of vision was not observed or was markedly reduced. Peripersonal cross-modal extinction was also recently observed when the ipsilesional visual stimulus was presented near the patient's hand seen in a mirror [21•].

The lesions causing neglect in humans are always very large. Thus, although data supporting the existence of separate systems for peripersonal and extrapersonal space are very robust, the localization of the human homologue of area F4 is difficult to determine on the basis of lesion data alone.

Caudal ventral premotor cortex in humans

Brain imaging experiments, in which the anatomical localization of arm movements was studied, were unsuccessful in localizing F4 in humans. The results showed only a strong activation of the primary motor cortex extending to the dorsal part of area 6 (stereotaxic coordinates z=+52 and above, see [22–25]). Note, however, that these studies used rather simple motor tasks not requiring the spatial transformations that characterize the activity of F4 neurons in monkeys. Furthermore, head and combined head/mouth movements that should also be represented in the human homologue of F4 were never tested, due to the technical limitations of brain imaging techniques.

However, experiments using sensory stimulation suggest that an area homologous to monkey F4 exists in humans. Particularly interesting in this respect is a recent functional magnetic resonance imaging (fMRI) study [26••]. Bremmer *et al.* [26••] attempted to localize the multimodal tactile, auditory and visual cortical areas in humans. Tactile stimuli (applied on the forehead), moving visual stimuli, and auditory stimuli producing the illusion of sound movement were presented to human subjects. Multimodal convergence was found in three sites: the depth of the intraparietal sulcus, SII, and the vPM at the border of ventral areas 6 and 44. The authors propose that the active vPM site probably corresponds to the monkey F4 sector where head movements are represented. Activation of ventral area 6 and area 44 was also recently found in a task in which participants had to judge the position of visual and somatosensory stimuli relative to their body midline [27]. The authors of this study suggested that these two areas intervene in cognitive spatial tasks.

Another experiment that supports the existence of a human homologue of F4 is that of Buccino *et al.* [28••]. Here, participants were asked to observe goal-related foot, hand and mouth actions. The observation of arm reaching to grasp actions led to the activation of two premotor foci, one located in area 44 (see below), and one located ventral (x=–56; y=–4; z=+44) to the activations observed during the execution of intransitive arm movements.

Summing up, it appears that humans may possess an area homologous to monkey area F4 (see Figure 1b). In this area, arm reaching movements are located dorsally [28••], whereas head movements are located ventrally [26••]. Note that this proposed homology is in accord with the location of the frontal eye field (FEF) in the two species. In monkeys, FEF is located immediately rostral to area F4 (see Figure 1a). In humans, the z coordinates of FEF range between +44 and +51 [29]. Our suggestion is that the upper limit of FEF in humans marks the border between vPM and dPM (see Figure 1b).

Rostral ventral premotor cortex in monkeys and humans

Area F5 forms the rostral part of the monkey vPM. It consists of two main sectors: one, F5c, located on the dorsal convexity, the other, F5ab, on the posterior bank of the inferior arcuate sulcus. Both sectors receive afferents from SII and area PF of the parietal lobe. In addition, F5ab is the selective target of the anterior intraparietal area (AIP). Area F5 contains representations of hand and mouth movements. The two representations overlap to a considerable extent [4•,5].

Canonical and mirror neurons

Recordings from single neurons in a natural context were particularly important for our understanding of the function of F5. These studies showed that most F5 neurons code specific actions, rather than the single movements that form them. F5 neurons were thus subdivided into several action classes, for example, ‘grasping’, ‘holding’ or ‘tearing’ neurons [30]. Many F5 neurons respond to the presentation of visual stimuli (visuomotor neurons). Some of these respond to the presentation of graspable objects and were named ‘canonical’ F5 neurons (see [4•] for review). Others discharge when the monkey observes another individual making an action in front of it. These neurons were named F5 ‘mirror’ neurons [31,32]. Canonical neurons are mostly located in F5ab, whereas mirror neurons are found essentially in F5c.

On the basis of the functional properties of canonical F5 neurons, F5 was proposed to play a crucial role in transforming the visual properties of three-dimensional objects into hand shapes appropriate to interact with them. Recent inactivation experiments directly tested this proposal [33•]. Monkeys were trained to reach for and grasp geometric solids of different size, shape and orientation. In separate sessions, F5ab, F5c and the hand field of F1 were reversibly inactivated. The results showed that after inactivation of F5ab (the sector where canonical neurons are located), the hand shaping that relies on the visual properties of the objects was markedly impaired. The monkeys were able to grasp the objects, but only after corrections made under tactile control.

It has been suggested that mirror neurons might be involved in the understanding of actions made by others [31,32]. Usually an action is recognized even when its final part is out of vision. A recent study investigated whether mirror neurons could form the basis of this capacity [34••]. The experiment consisted of two conditions. In one, the monkey was shown a fully visible action directed towards an object. In the other, the same action was presented, but with its final, critical part (hand–object interaction) hidden behind a screen. The results showed that the majority of mirror neurons responded also in the hidden condition. In control experiments, the monkey saw the beginning of the same actions, but also knew that nothing was behind the screen. No response was obtained in this condition. These results clearly support the notion that mirror neurons mediate action understanding.

F5 and area 44 respond to hand actions

As mentioned above, cytoarchitectonically, the most likely human homologue of F5 is area 44 [2,3]. Functionally, however, whereas F5 has both a representation of hand and mouth actions [30], area 44 has been classically considered to be a speech area. Recent brain imaging experiments, by confirming previous indications (e.g. [35]), demonstrated beyond any doubt that area 44 is also related to hand actions [36,37•,38,39•,40,41•].

Binkofski *et al.* [36] asked volunteers to manipulate multifaceted complex objects in one condition and a smooth sphere in another. The complex manipulation task activated area 44 (–52, +8, +28), an area inside the intraparietal sulcus, and SII. This cortical network closely corresponds to the cortical circuit (AIP, SII, F5) for manipulation in the monkey [4•]. Further support for the functional homology between F5 and area 44 comes from the study of Ehrsson *et al.* [37•], in which they compared the cortical areas involved in different types of grips. They found that the focus of representation of precision grip is located in area 44 (–56, +12, +32). This finding fits with monkey data showing that precision grip is largely represented in F5, whereas only few F5 neurons discharge during whole hand prehension [30].

Area 44 motor representation is not only activated by actual movement execution, but also by imaging hand actions [42,43] or by hand mental rotation [44]. Gerardin *et al.* [39•] showed that both transitive hand actions and the imagination of intransitive finger movements activate area 44 (–54, +12, +12). The activation was stronger during imagery than during actual execution. The prolonged effort that imaging a movement requires in comparison with movement execution was probably the reason for this stronger activation.

Object observation

Several brain imaging studies have shown that naming tools, generating action words in response to tool observation, and imaging manipulating objects determine the activation of area 44 (see [45] for review). Recently, Chao and Martin [46••] showed that even the mere observation of tools activates the cortex within the precentral sulcus, most likely in area 44 (–42, +6, +23). In addition, activation was also found in the left inferior parietal lobule, in an area corresponding to the intraparietal sulcus. Control conditions, in which pictures of animals, faces and houses were presented, showed that activation in both these regions was stronger with tools than with the other stimuli. These data show that, as in monkeys [4•], observation of an object without other requirements activates a parietal–premotor circuit formed by area AIP and area 44 (the most likely human homologue of area F5).

In another very recent fMRI study [47•], a parietal–premotor circuit largely overlapping that described by Chao and Martin [46••] was found to be active during observation of bidimensional objects. The activation was particularly strong when the task required object-related attention.

Action observation

A further condition that activates area 44 is action observation ([28••,40,48], see also [49•]). Iacoboni *et al.* [40] tested volunteers while they observed a finger movement, a static finger, or a cross (observation conditions), and when they were required to move their finger in response to these stimuli (observation/execution conditions). The results showed that, in the task in which participants had to move the finger in response to the observation of a similar movement (imitation), the activation of area 44 (–50, +12, +12) was stronger than in all other conditions. These findings demonstrate that an action observation/execution matching system exists in humans, and is used for imitation. Similar results were obtained independently by Nishitani and Hari [41•] using magnetoencephalography.

Activation of area 44 during the observation of hand actions could be interpreted as reflecting verbal mediation. If this interpretation is correct, area 44 should be active regardless of the type of observed action and the effector used. On the other hand, if activation of area 44 reflects a specific localization of hand actions, the activation should be absent when observing actions of other effectors, such as the foot. A recent fMRI experiment [28••] showed that during the observation of hand actions there was an activation in area 44 (–64, +12, +20) and in ventral area 6 (see above). Foot action observation determined the activation of a dorsal site in area 6 (–32, –8, +64), but no activation of area 44. These results demonstrate that action observation activates somatotopically organized sectors of the premotor cortex, and that verbal mediation is not responsible for the activation of area 44 during hand and mouth action observation.

Conclusions

The data reviewed here indicate that the vPM has both motor and cognitive functions. The motor functions transform the intrinsic properties of objects into hand actions and spatial locations into head and arm actions. The cognitive functions include space perception, action understanding and imitation.

There is also convincing evidence of a functional homology between monkey areas F5 and human area 44. Fewer data are available to establish the location of the possible human homologue of area F4. Preliminary evidence suggests that it is located in the ventral sector of area 6, approximately ventral to z=+50.

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