Grezes - Regehr F 15

ACADEMIC
PRESS

Activations related to "mirror" and "canonical" neurones in the human brain: an fMRI study

J. Grèzes,[a,*] J.L. Armony,[a,b] J. Rowe,[a] and R.E. Passingham[a,c]

[a] *Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, London WC1N 3BG, UK*
[b] *Institute of Cognitive Neuroscience, University College London, London WC1N 3BG, UK*
[c] *Department of Experimental Psychology, University of Oxford, Oxford OX1 3UD, UK*

Abstract

In the macaque monkey ventral premotor cortex (F5), "canonical neurones" are active when the monkey observes an object and when the monkey grasps that object. In the same area, "mirror neurones" fire both when the monkey observes another monkey grasping an object and when the monkey grasps that object. We used event-related fMRI to investigate where in the human brain activation can be found that reflects both canonical and mirror neuronal activity. There was activation in the intraparietal and ventral limbs of the precentral sulcus when subjects observed objects and when they executed movements in response to the objects (canonical neurones). There was activation in the dorsal premotor cortex, the intraparietal cortex, the parietal operculum (SII), and the superior temporal sulcus when subjects observed gestures (mirror neurones). Finally, activations in the ventral premotor cortex and inferior frontal gyrus (area 44) were found when subjects imitated gestures and executed movements in response to objects. We suggest that in the human brain, the ventral limb of the precentral sulcus may form part of the area designated F5 in the macaque monkey. It is possible that area 44 forms an anterior part of F5, though anatomical studies suggest that it may be a transitional area between the premotor and prefrontal cortices.
© 2003 Elsevier Science (USA). All rights reserved.

Keywords: fMRI; Mirror neurons; Canonical neurons; Parietal cortex; Premotor cortex; Inferior frontal gyrus

Introduction

The understanding of goal-directed action requires mechanisms by which the subject can understand the action that is appropriate for an object, as well as mechanisms by which the subject can read the intention conveyed by goal-directed actions performed by others. Within the ventral premotor area F5, there are neurones that discharge during goal-directed actions (Rizzolatti et al., 1988). Among these neurones, Rizzolatti and colleagues (1988, 1996a; Gallese et al., 1996) have discovered two populations that have different visual responses, though they are indistinguishable as far as their motor properties are concerned.

The first type, called "canonical neurones," become active when the monkey simply views an object, as well as when the monkey grasps that object. The bank of F5 is the target of projections originating from the anterior intraparietal area (AIP), which has similar functional properties to those of F5 (Taira et al., 1990; Sakata et al., 1995; Murata et al., 2000). On the basis of these common properties, it has been proposed that the AIP-F5 circuit plays a role in transforming the intrinsic properties of objects into the appropriate hand movements (Jeannerod et al., 1995). The description of the object features, in terms of its affordances, is carried out in the parietal area AIP and then transmitted to the premotor area F5, where potential actions are encoded (Murata et al., 1997; Fagg and Arbib, 1998; Rizzolatti and Fadiga, 1998).

The second type, called "mirror neurons," fire both when the monkey observes an agent acting with the hand upon an object and when the monkey grasps the object

---

* Corresponding author. Wellcome Department of Imaging Neuroscience, 12 Queen Square, London, WC1N 3BG, UK. Fax: +44-0-207-813-1420.
E-mail address: jgrezes@fil.ion.ucl.ac.uk (J. Grèzes).

itself. Neurones with similar visual properties to these F5 convexity neurones have been recorded in the superior temporal sulcus (STS, Perrett et al., 1990) and in area 7b/PF located in the rostral part of the convexity of the anterior inferior parietal cortex (Fogassi et al., 1998). This STS-7b-F5 circuit may subserve the internal representation of actions evoked by the observation of the actions of others and may play a role in both imitation and recognition of action (Jeannerod, 1994; Rizzolatti et al., 1996a; Carey et al., 1997; Rizzolatti and Arbib, 1998; Gallese and Goldman, 1998).

Brain imaging experiments have been carried out in humans in order to investigate the existence and the localization of cortical circuits similar to those described in monkey. Subjects have been scanned during (1) the perception of manmade objects (Martin et al., 1995, 1996; Grafton et al., 1997; Perani et al., 1999; Chao and Martin, 2000; Grèzes and Decety, 2002), (2) the manipulation of objects (Grafton et al., 1996; Binkofski et al., 1999), or (3) the perception of simple finger movements (Iacoboni et al., 1999; Hermsdorfer et al., 2001), pantomimes (Decety et al., 1997; Grèzes et al., 1998; Buccino et al., 2001), or object-directed actions (Rizzolatti et al., 1996b; Grafton et al., 1996; Perani et al., 2001; Buccino et al., 2001; Decety et al., 2002; Chaminade et al., 2002). Common activations have been found in premotor and posterior parietal cortex. Activations have also been reported in the region of Broca's area, which some have suggested to be the human homologue of monkey premotor area F5 (Grafton et al., 1996; Rizzolatti et al., 1996b; Iacoboni et al., 1999; Buccino et al., 2001).

However, a recent meta-analysis of PET studies (Grèzes and Decety, 2001) failed to show reliable activation in Broca's areas during action observation, and this led the authors to propose that the ventral premotor cortex, rather than Broca's area, might be homologous to F5. Nonetheless, there could be two reasons for the absence of reliable activations in the ventral premotor cortex and/or Broca's areas during action observation, action execution, and imitation. The first is that PET may be less sensitive than fMRI (see Joliot et al., 1999). Second, it has been shown that the neural network engaged is influenced by the type of action presented and by the tasks required during the observation phase (Grèzes et al., 1998). Finally, none of the studies cited have included conditions within the same paradigm where subjects perceive both objects and gestures, whether for passive observation and for movement execution.

Our experiment uses event-related fMRI to investigate all conditions within the same study in which canonical neurones and mirror neurones fire in the macaque premotor cortex. Humans can imitate gestures whether directed to an object or not. We therefore tested both conditions, even though mirror neurones in monkeys do not respond to the sight of a hand mimicking an action in the absence of an object. Subjects viewed video recordings of objects, grasping movements, or objects being grasped. They were re-

quired either to passively observe or to execute the appropriate grasp toward a manipulandum. The aim of the present experiment was to functionally identify mirror and canonical circuits in humans and to tentatively localize the human homologue of F5. The human brain regions homologous to the monkey canonical and mirror circuits should be active for viewing an object alone (canonical neurones) and for viewing hands grasping objects (mirror neurones), as well as for executing the appropriate grasp (canonical and mirror neurones).

Materials and methods

Subjects

Twelve right-handed male subjects (range, 19–39 years) with no neurological or psychiatric history participated in the imaging study. All gave informed consent according to procedures approved by the Joint Ethics Committee of the National Hospital for Neurology and Neurosurgery (UCLH NHS Trust) and Institute of Neurology (UCL).

Stimuli

The stimuli consisted of color video recordings (3.5 s each) of objects, grasping pantomimes, and objects being grasped. The baseline condition consisted of a stationary background. The videos were viewed by projection onto a mirror mounted onto the head coil in the scanner. The subjects viewed the videos and were required either to passively observe or to execute the appropriate grip on a manipulandum. In the observation context, subjects observed an object (OO), observed a grasp (OG), or observed an object being grasped (OGO); in the baseline condition they observed a stationary background (OB). In the execution conditions, the subjects executed the grasp appropriate for the object that they viewed (EO), imitated the pantomime they viewed (EG), or imitated the hand grasping an object (EGO). In the baseline condition subjects executed the same grasp (power grip) on all trials while viewing a stationary background (EB). This forms a 2 × 2 × 2 factorial design (execute vs observe, presence vs absence of object, presence vs absence of gesture, see Fig. 1A).

Two different objects were used; one had large opposition axes and would normally be grasped with a power grip (between the thumb, the surface of the palm, and all other fingers). The other object was small and would normally be grasped by a precision grip (between the index finger and the thumb). As a consequence, two different video recordings were presented in each condition: small object and large object (object condition), mimicking a precision and a power grip (gesture condition), and actual precision and power grip toward the object (gesture toward object condition). The two types of grasps and their associated object size were not distinguished in the analysis.
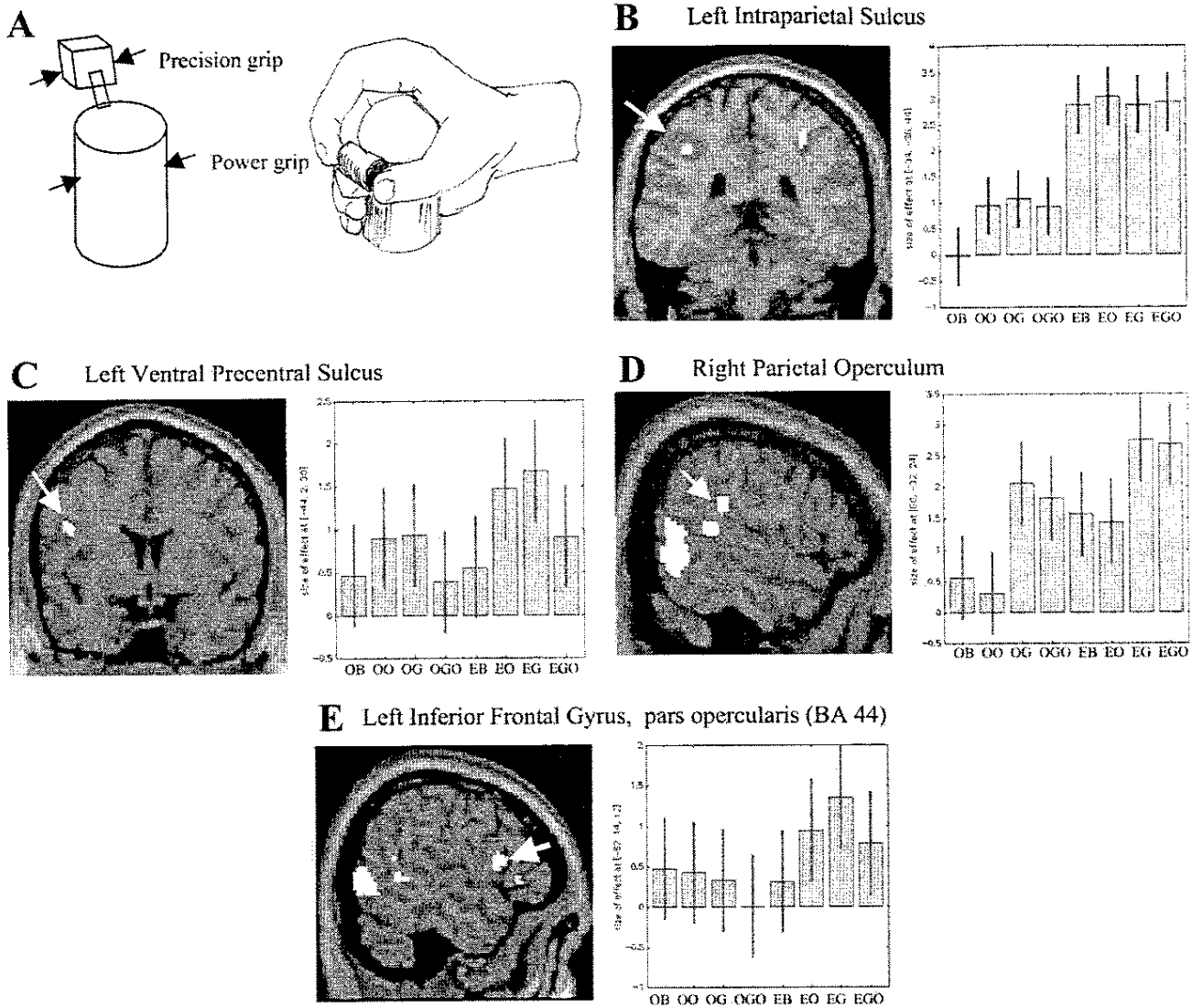
Fig. 1. (A) Response device used during the MRI experiment. (B) Left intraparietal sulcus (−36 −38 42). (Left) Group (n = 12) average activation of the left intraparietal sulcus (indicated by an arrow) superimposed on a coronal section of the MNI brain. (Right) Histograms representing the percentages of signal change at the local maxima in the left intraparietal sulcus across conditions; the first four correspond to the Observation context and the last four to the Execution context. The order of the conditions in the two contexts is identical and as follows Background (B), Object (O), Gesture (G), and Gesture toward Object (GO) in both contexts. (C) Left precentral sulcus activation (−44 2 30). Other conventions as in C. (D) Right parietal operculum activation (58 −32 24). Other conventions as in C. (E) Left inferior frontal gyrus activation (−52 14 12). Other conventions as in C.

The nonmagnetic manipulandum employed for responses had two components (see Fig. 1B). The first component consisted of a wooden cylinder, 7 cm tall and 3 cm in diameter, that was used for the power grip response. Attached to the top part of the cylinder, the second component was made of a 2-cm-square and 1.5-cm-thick piece of wood and was used for the precision grip response. Both components contained a force transducer to record grip responses. Subjects held the manipulandum in their right hand, grasping the square between their thumb and their index finger, and the cylinder between the remaining three fingers and the surface of the palm.

The study was carried out in a single continuous scanning session that was divided into blocks of 28 s. Each block started by a written instruction (3.5 s) followed by seven trials. Within each block, stimuli were equally counterbalanced across conditions and presented in random order. Twenty-one blocks of Observation and twenty-one blocks of Execution were alternated during the single scanning session, and counterbalanced across subjects. Fourteen additional blocks were intermixed between the Observation and Execution blocks, during which subject were shown letters and lexical symbols, but the data for these are not presented in the present paper.

Data acquisition

A 2-T VISION system (Siemens, Erlangen, Germany) was used to acquire 36 T^*_2-weighted transverse echo–planar (EPI) images (FOV, 192 × 192 mm; matrix size, 64 × 64; in-plane resolution, 3 × 3 mm²; flip angle, 90; T_E = 40 ms) with blood oxygenation level-dependent (BOLD) contrast. EPIs comprised 2.4-mm-thick axial slices taken every 3.6 mm, acquired sequentially in a descending direction and continuously during a 26-min session. An automatic shimming procedure was performed before each session. A total of 578 functional volumes were collected for each subject within the single scanning session, with an effective repetition time (T_R) of 2.74 s/vol. The first five volumes were discarded to allow for T_1 equilibration effects. T_1 anatomical volume images (MPRAGE sequence with a high-resolution isovoxel acquisition of 1 × 1 × 1 mm³) were collected for each subject.

Image processing was carried out using SPM99 (Wellcome Department of Imaging Neuroscience, London, UK; see http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 5.3 (Mathworks Inc., Sherborn, MA). Images were realigned to the first volume by rigid body transformation, sinc interpolated over time to correct for phase advance during acquisition, and normalized into standard stereotaxic space using the Montreal Neurological Institute template (MNI). The normalized images of 2 × 2 × 2 mm³ were spatially smoothed by a Gaussian kernel of FWHM 6 mm (Ashburner and Friston, 1997; Friston et al., 1995). Treating the volumes as a time series, the data were high-pass filtered to 1/120 Hz. The anatomical (T_1-weighted) images were coregistered with the subject's corresponding mean realigned EPI volume and normalized with the same deformation parameters.

Data analysis

We analyzed the data in three ways. (1) First we analyzed the simple main effects and main effects. These results are presented only where relevant. (2) Second, we estimated the interactions between contexts so as to find activations that were greater for the execution than the observation context. We also estimated the interactions within contexts so as to test whether there was any difference between gesture alone and gesture toward objects. (3) We used conjunction analyses so to study what effects were common to the contexts of observation and execution.

Data were analyzed using SPM99 employing a random-effects model implemented into a two-level procedure. At the first level, in a subject-specific analysis, we specified a general linear model including eight effects of interest: four events corresponding to the Observation context (OB, OO, OG, OGO) and four events corresponding to the Execution context (EB, EO, EG, EGO). These effects were modeled by convolving a delta function of each event type with the hemodynamic response function to create regressors of in-

terest. For each comparison of interest, for each subject, a contrast of parameter estimates was calculated in a voxel-wise manner to produce a "contrast image." At the second level, the contrast images from all subjects were entered into a one-sample *t* test to assess the population mean effects. In this way, the variance estimates at the second level incorporated appropriately weighted within-subject and between-subject variance effects.

To test for interactions between context for each event of interest, as well as interactions between events within contexts, different second level analyses were performed, including for each subject a contrast image for each event of interest minus the baseline in the Observation and in the Execution contexts and the contrast image for the interactions between object and gesture in each context.

Finally, to examine response commonly evoked by each event of interest (object, gesture, and object related) to both contexts, we carried out a conjunction analysis at the first level on each event of interest in the two contexts versus the corresponding baselines. The conjunction analysis addressed whether activations were jointly significant in a series of task pairs. The conjunction analysis therefore allowed us to demonstrate the context-invariant nature of regional responses.

On the basis of previous studies of observation and imitation of hand actions (meta-analysis by Grèzes and Decety, 2001), we had an a prior hypothesis for differential activity in the superior temporal sulcus, the intraparietal sulcus, the inferior parietal lobule, the premotor cortex, and the inferior frontal gyrus. This meta-analysis was, however, done on PET studies. Therefore, in order to define more specifically the coordinates of the regions of interest, we looked at fMRI papers on action observation and action execution/imitation. For the execution of gesture toward object and imitation of gestures, the following papers were taken: Iacoboni et al. (1999, 2001); Binkofski et al. (1999). For the observation of gestures with and without objects, or of object alone, the following served as references: Buccino et al. (2001) and Chao and Martin (2000). From those references, mean coordinates for each region can been calculated (see table). All the coordinates for our regions of interest are significant within a sphere with a radius of 10 mm on those mean coordinates.

Ba 44	VPMC	AIP	SII	STS
−51 11 13	−50 5 24	−37 −40 44	−62 −22 22	−57 −50 16

Therefore, we report activations for five or more contiguous voxels in the specified regions that survived the threshold of $Z > 3.09$ ($P = 0.001$, uncorrected, $T > 4.02$). Anatomical identification was carefully performed by superimposing the maxima of activation foci both on the MNI template and on the normalized structural images of each subject and labeled using the atlas of Duvernoy (1991). Furthermore, to localize activity changes in the pars oper-

Table 1
Activations found by conjunction analyses between contexts for each event

Anatomic location	Talairach coordinates (MNI template)			
	X	Y	Z	Peak Z score
Object (OO-OB and EO-EB)				
L. ventral precentral sulcus (PMv)	−44	2	26	3.41
Gesture (OG-OB and EG-EB)				
L. precentral gyrus (PMd)	−42	−6	48	5.69
R. precentral gyrus (PMd)	46	0	56	7.08
L. ventral precentral sulcus (PMv)	−42	6	26	3.45
L. intraparietal sulcus	30	−50	52	Inf
R. intraparietal sulcus	−32	−48	52	7.24
R. SII	50	−30	22	3.92
L. superior temporal sulcus	−52	−46	8	Inf
R. superior temporal sulcus	64	−38	12	Inf
Gesture toward object (OGO-OB and EGO-EB)				
L. precentral gyrus (PMd)	−42	−6	46	3.88
R. precentral gyrus (PMd)	40	0	52	6.23
L. intraparietal sulcus	32	−52	58	Inf
R. intraparietal sulcus	−34	−52	58	5.95
R. SII	60	−32	24	4.62
L. superior temporal sulcus	−52	−46	8	7.10
R. superior temporal sulcus	68	−34	12	5.27

cularis of the inferior frontal gyrus (Ba 44), the sulcal landmarks and the probability map of Tomaiuolo et al. (1999) were used.

Results

Conjunction analysis

We performed conjunction analyses in order to describe the neural network common to both contexts (passive observation and execution) elicited by the perception of object, gesture, or object being grasped (Table 1). The observation of object, irrespective of context (OOvsOB and EOvsEB), was associated with activation in the left ventral precentral sulcus. There was no significant activation in the parietal cortex for this conjunction. It is clear from Fig. 1B that this is because the area was highly activated even in the baseline condition in which subjects executed a movement to the background (EB). However, there was significant activation in the left intraparietal sulcus for the simple main effect of passive observation of object vs the baseline (−36 −38 42, Z = 3.14).

During the observation of gesture, specific activations common to both contexts (OGvsOB and EGvsEB) were found bilaterally in the dorsal premotor cortex and in the left ventral precentral sulcus. Activations were detected bilaterally in the intraparietal sulcus and in the superior temporal sulcus and in the right parietal operculum (SII).

The observation of object-related hand actions, irrespective of context (OGOvsOB and EGOvsEB), was associated with specific activations located bilaterally in the dorsal premotor cortex, in the intraparietal sulcus, and in the su-

perior temporal sulcus. In the right hemisphere, the parietal operculum (SII) was also activated.

Interactions between context

In order to identify brain regions (specifically the premotor cortex and the inferior frontal gyrus) that were more active for each event type in the context of Execution compared to the context of Observation, we analyzed interactions between the contexts. The interaction ((EO-EB)–(OO-OB))—showing activity that was specific for the perception of objects in the context of execution—was associated with activation located in the left anterior part of the inferior frontal gyrus, pars triangularis (−38 36 −4, Z = 3.76). The interaction ((EG-EB)–(OG-OB))—showing activity that was specific for gesture alone in the context of execution—was associated with an activation in the inferior frontal sulcus (−36 26 22, Z = 3.35). The interaction ((EGO-EB)–(OGO-OB))—showing activity that was specific for gesture to objects in the context of execution—was associated with activation in the ventral part of the precentral gyrus (−50 −2 32, Z = 3.47) and in the inferior frontal gyrus, pars triangularis (BA 45, −58 22 16, Z = 3.38). No significant brain regions were found in the reverse interactions.

Interactions within contexts

In order to determine brain regions that are more active when subjects imitate an object-related action compared to the imitation of a gesture alone, correcting for the presence of an object, we analyzed the interaction ((EGO-EO)–(EG-EB))—showing activity that was specific for gesture to

objects in the execution context. No significant voxels were detected. However, the opposite interaction ((EG-EB)–(EGO-EO))—showing activity that was specific to gesture alone in the context of execution—was associated with left hemispheric activation in the inferior frontal area BA 44 (−52 14 12, Z = 3.50), in the inferior frontal area 45 (−50 22 12, Z = 3.76), and in the ventral limb of the precentral sulcus (−44 4 26, Z = 3.62).

Discussion

Canonical circuit (OO and EO)

We found a parietopremotor circuit to be active during observation of manipulable objects. This circuit includes an area located in the anterior part of the intraparietal sulcus, at the junction with the postcentral sulcus, as well as the ventral sector of the precentral sulcus, at the junction between premotor area 6 and Broca's area 44.

The left anterior part of the intraparietal sulcus was active during passive observation of manipulable objects, but also during all conditions, including the baseline in the execution context (therefore it could not be detected in the conjunction analysis). The activity was higher during the execution than the observation context (see Fig. 1B). In monkey area AIP, visuomotor neurones discharge during object fixation, manipulation in the light, and manipulation in the dark (Murata et al., 2000). The condition of grasping in the dark has similarities to our baseline condition, where grasping movements are executed without visual perception of objects, in response to the sight of the background. Moreover, in macaques, activity in the AIP during grasping tasks is also higher than during a fixation task. According to Murata et al. (2000) this is due to the enhancement by the motor component, subserved by bidirectional anatomical connections between the premotor area F5 and the AIP (Luppino et al., 1999). In our study, the activation of the human anterior intraparietal sulcus during passive perception of objects and grasping movements (executed both with and without visual cues) seems to closely correspond to the neurophysiological data from monkey area AIP. Thus, the anterior part of the IPS may be the human homologue of monkey area AIP (Taira et al., 1990; Sakata et al., 1995; Choi et al., 2002). Though caution is needed in defining homologous areas in the human and monkey brains, recent data (Bremmer et al., 2001; Rushworth et al., 2001) suggest that the intraparietal sulcus and the surrounding parietal cortex have a similar functional organization to that of the macaque monkey.

Although the activation of the intraparietal sulcus was significant for the simple main effect of object perception compared to the baseline, there was a nonsignificant trend for activation in the ventral precentral sulcus (−42 0 26, Z = 2.77). However, a consistent effect is shown by the result of the conjunction analysis between the two contexts: the

effects of (OO-OB) and (EO-EB) were conjointly significant at Z > 3.09 (see Fig. 1C). Only 20–30% of F5 premotor canonical neurones fire in response to visual stimuli in the absence of movements (Di Pellegrino et al., 1992), while about 50% of AIP visuomotor neurones respond during an object-fixation task (Murata et al., 2000). Those proportions could explain the relative weakness of the activation in the ventral precentral sulcus in the observation context.

Comparing those data with electrophysiological findings in monkeys, the concomitant activation of parietal and premotor areas during passive observation of an object and during execution of a grasp toward that object seems to correspond to the circuit shown in the macaque brain, that is, the parietal area AIP and the premotor area F5, where canonical neurones have been recorded.

Mirror circuit (OGO and EGO)

Common activations between the observation of grasping action toward an object and its imitation were detected bilaterally in the intraparietal sulcus, dorsal premotor cortex, superior temporal sulcus, and right parietal operculum (SII). Similar activations were detected for gestures alone (OG and EG), except for an additional cluster in the left ventral limb of the precentral sulcus.

The left intraparietal sulcus (IPS) was found to be activated not only during the observation of object-related action, but also during the perception of objects and during all conditions of the execution context (see Fig. 1B). Electrophysiological recordings in the IPS of monkeys show that this area is involved both in preparing actual movement (Kalaska and Crammond, 1995) and also in extracting potential motor representations in response to visual stimuli or "motor intentions" (Snyder et al., 1997, 2000). This neural activity is independent of actual execution and anatomically segregated along the IPS according to the effectors (Snyder et al., 1997, 2000). Preparatory activity has also been observed in the anterior and the posterior IPS of the human brain (Toni et al., in press). This activity is related to motor intention since it occurs even on trials in which no movement is executed (Toni et al., 2001). There was a similar pattern of activation in the anterior convexity of the left inferior parietal cortex, but specific to the perception of gestures (G and GO) and not for object. This activation is in area PF (von Economo, 1929), which probably corresponds to area 7b in the macaque monkey (Passingham, 1998). It is in this region that Fogassi et al. (1998) have reported that there are mirror neurones in the macaque brain.

The dorsal premotor cortex is known to play a role in motor preparation. Set-related activity has been recorded in this area both in the macaque brain (Wise and Mauritz, 1985; Crammond and Kalaska, 1996) and in the human brain (Toni et al., 1999a, in press). Therefore, the concomitant activation of the intraparietal parietal cortex and the dorsal premotor cortex may reflect the automatic activation

of motor representations elicited by the perception of gestures.

Several neuroimaging studies have shown that the superior temporal sulcus is involved in the perception of biological motion and of hand, mouth, and eye movements (for a recent review, see Allison et al., 2000). The left STS was, in the present study, also activated when subject had to execute an action in response to a perceived object, suggesting that the perception of biological agents is not necessary for activation if this region. In favor of this argument, the same region is activated during learned arbitrary visuomotor associations (Toni et al., 1999b) as well as during mentalizing tasks (see Frith, 2001, for a review). Therefore, as the superior temporal sulcus receives input from both dorsal and ventral streams (Baizer et al., 1991), it could have a role in the extraction of contextual and intentional cues (Toni et al., 2001; Frith, 2001) which are necessary for various tasks, including visuomotor transformations.

Activity in the parietal operculum (SII) was also detected during the perception of gestures, irrespective of the presence of an object and irrespective of the context (Fig. 1D). Using MEG, Avikainen et al. (2002) have recently reported evidence for the modulation by the observation of action of activity recorded from this area. We propose that the activation within the parietal operculum could reflect the somatosensory consequences of the action that are linked to the activation of a motor representation. The first argument arises from the common coding model which postulates that actions are coded in terms of an anticipatory representation of the intended effects of that action (Prinz, 1997; Elsner and Hommel, 2001). The second argument is provided by developmental psychologists, who suggest that selective imitation in newborn babies (Meltzoff and Moore, 1977; Meltzoff, 1999) indicates the existence of an innate cross-modal matching between visual and proprioceptive information that could internalized through development into motor representations. Therefore, in addition to the activation of a parieto-premotor network, the activation within SII during observation of action (G and GO) may therefore be linked to a representation of the sensory effects of a voluntary action that is associated with the motor plans producing the effects.

Activations in the precentral sulcus and inferior frontal gyrus

In the present study, specific activations were detected in the ventral limb of the precentral sulcus and in the inferior frontal gyrus. Significant activations were found in the inferior limb of the precentral sulcus (BA 6/44) during both contexts, only in response to the perception of object (O) and gesture (G) (see Fig. 1C). The absence of an interaction between observation and execution contexts for object (O) and gesture (G), as well as the conjunction analysis across contexts, demonstrated that the activation in the ventral limb of the precentral sulcus was independent of the con-

texts. For all effects of interest (object, gesture, and gesture toward object), the interactions between contexts were associated with activations in the inferior frontal gyrus (BA 44/45), showing that this region is more activated in the context of execution than in the context of observation (see Fig. 1E). The significant interaction within the context of execution demonstrated that activations in the inferior limb of the precentral sulcus (BA 6/44) and in the inferior frontal gyrus (BA 44/45) were stronger for object (EO) and gesture (EG) than for gesture toward objects (EGO).

It is unclear to what extent the inferior limb of the precentral sulcus (BA 6/44) and the inferior frontal areas (BA 44/45) can be considered functionally independent subregions. However, there are data in favor of possible subdivisions. For example, Schubotz and von Crammond (2001) have recently indicated that certain studies have detected two clusters (mean coordinates $\pm$ 44 -1 28 and $\pm$ 47 16 14) corresponding to the precentral sulcus and the inferior frontal gyrus, respectively. The following sections tentatively discuss possible interpretations of the separate clusters we have found.

Ventral limb of the precentral sulcus

Activation in this area has been discussed previously in the section concerning canonical neurones (see Fig. 1C). Similar activation has been detected in tasks involving the perception of objects or gestures, the execution of hand movements, or the mental simulation of hand movements (Grafton et al., 1997; Lacquaniti et al., 1997; Krams et al., 1998; Binkofski et al., 1999, 2000; Joliot et al., 1999; Chao and Martin, 2000; Ehrsson et al., 2000, 2001; Kollias et al., 2001; Rushworth et al., 2001a; Gerlach et al., 2000, 2002; Simon et al., 2002). Our experiment demonstrates in the same data set that activation within the ventral part of the precentral sulcus can be elicited both by the perception of objects and gestures and by the execution of a grip in response to viewing objects or gestures (OO, OG, EO, EG). Buccino et al. (2001) have reported activation on the left at very similar coordinates when subjects observed gestures toward objects, but for reasons that are not clear, the activation in the present study was significant for observation of gestures alone and not for observation of gestures toward objects.

The inferior frontal gyrus

The patterns of activation within both Brodmann areas 44 and 45/47 are similar during the observation and the execution contexts. The level of activity in the observation context was identical across the four experimental conditions (see Fig. 1E). Using fMRI, Iacoboni et al. (1999) have scanned subjects during observation and observation–execution of simple repetitive finger movements, fingers with a cross, or simply a cross against a gray background. Immediate imitation of simple finger movements was associated with activations in the inferior frontal gyrus. However, no significant differences were found between observing

finger movements, the static hand, or the cross against a gray background. In our study there was similarly no difference between conditions in the observation context. Activation in the inferior frontal gyrus has also been elicited during the performance of visual and visuomotor conditional tasks (Passingham et al., 1998; Toni and Passingham, 1999). Those results are consistent with the fact that in humans there is an input to the inferior frontal gyrus from the ventral visual stream (Di Virgilio and Clarke, 1997).

During the execution context, only the object and the gesture conditions (EO and EG) compared to baseline were associated with significant activation in Broca's area 44 (see Fig. 1E). There was also a trend toward activation in this region for EGO ($P = 0.002$), and there was no significant difference between EO and EGO in this area. Broca's area has been classically thought to be concerned with language, but recent studies have demonstrated that this region is also activated by nonlanguage tasks (Iacoboni et al., 1999; Rushworth et al., 2001). These studies involved copying finger movements. Rushworth et al. (2001) have reported that Broca's area 44 ($-50\ 16\ 26$) was activated more when the subject had to prepare an action in response to a seen gesture; in the same study the same area was activated when subjects prepared to say a letter. A similar activation in the inferior frontal gyrus was detected by Sergent et al. (1992) during a complex visuomotor task consisting of the translation of musical notation into movement patterns. In the present study, this area was activated in executing the movements that are appropriate to objects (EO) as well as imitating gestures (EG) and to a lesser extent gestures to objects (EGO). Based on these results, we suggest that the inferior frontal gyrus is involved in converting what we see into action.

F5 in the human brain

In the macaque monkey brain, area F5 lies within the agranular area 6. Petrides and Pandya (1995) claimed some similarity between the tissue in the posterior bank of the ventral limb of the arcuate sulcus and Broca's area 44 in the human brain. In line with this, in their cytoarchitectonic map of the macaque brain, von Bonin and Bailey (1947) include this posterior bank in the area FCBm, this being the designation of Broca's area in the map of the human brain by von Economo (1929). But in a recent quantitative study using observer-independent methods, Amunts and Zilles (2001) have showed that area 44 is more similar to prefrontal area 45 than to premotor area 6. The evidence is, however, not conclusive since the density of glutamatergic AMPA receptor binding sites of areas 44, 6, and 4 are almost identical in the human brain, whereas area 45 is different with respect to both the absolute concentration and the laminar pattern (Amunts, pers. comm.). Amunts and Zilles (2001) conclude that "area 44 (which is dysgranular) takes a transitional position between area 45 (which is granular) and area 6 (which is agranular)."

On the basis of our results, we suggest that, in the human brain, the ventral limb of the precentral sulcus may form part of the area designated F5 in the macaque monkey. We found activation in this region during both the observation and the execution contexts. However, the spatial resolution of our methods does not allow us to determine whether these activations lay in the posterior or anterior bank of this sulcus. Amunts et al. (1999) report that the posterior border of area 44 can lie within either bank of the precentral sulcus.

Though we also found activations on the convexity cortex of area 44, but only during the execution context, our functional data cannot be used to decide conclusively whether this area should be properly regarded as the anterior part of F5, or a transitional area that differentiated out of F5. One issue is whether area 44 in the human brain has the same anatomical inputs as area F5 in the macaque brain. No projections have been described from the inferotemporal cortex to the ventral premotor cortex in the macaque monkey (Boussaoud et al., 1996; Tanne-Gariepy et al., 2002; Boussaoud, pers. comm.), though projections have been described from the posterior part of the superior temporal sulcus to the dorsal premotor cortex (Luppino et al., 2001). In the human brain, on the other hand, there are projections from the ventral temporal cortex to area 44, as well as to prefrontal area 45 (Di Virgillio and Clarke, 1997). Further evidence is now needed to discriminate whether area 44 is the anterior part of F5 or whether it differentiated out of F5, lying at the transition between the premotor and prefrontal cortices.

References

Allison, T., Puce, A., McCarthy, G., 2000. Social perception from visual cues: role of the STS region. Trends Cog. Neurosci. 4, 267–278.

Amunts, K., Schleicher, A., Burgel, U., Mohlberg, H., Uylings, H.B.M., Zilles, K., 1999. Broca's region revisited: cytoarchitecture and intersubject variability. J. Comp. Neurol. 412, 319–341.

Amunts, K., Zilles, K., 2001. Advances in cytoarchitectonic mapping of the human cerebral cortex, in: Naidich, T.P., Yousry, T.A., Mathews, V.P. (Eds.), Anatomical Basis of Functional Magnetic Resonance Imaging, vol. 11. Harcourt, Philadelphia, pp. 151–169.

Ashburner, J., Friston, K., 1997. Multimodal image coregistration and partitioning—a unified framework. Neuroimage 6, 209–217.

Avikainen, S., Forss, N., Hari, R., 2002. Modulated activation of the human SI and SII cortices during observation of hand actions. Neuroimage 15, 640–646.

Bailey, P., von Bonin, G., McCullogh, W.S., 1950. The Isocortex of the Chimpanzee. Univ. of Illinois Press, Urbana.

Baizer, J.S., Ungerleider, L.G., Desimone, R., 1991. Organisation of visual inputs to the inferior temporal and posterior parietal cortex in macaques. J. Neurosci. 11, 168–190.

Binkofski, F., Amunts, K., Stephan, K.M., Posse, S., Schormann, T., Freund, H.J., Zilles, K., Seitz, R.J., 2000. Broca's region subserves imagery of motion: a combined cytoarchitectonic and fMRI study. Hum. Brain Mapp. 11, 273–285.

Binkofski, F., Buccino, G., Posse, S., Seitz, R.J., Rizzolatti, G., Freund, H., 1999. A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. Eur. J. Neurosci. 11, 3276–3286.

Boussaoud, D., di Pellegrino, G., Wise, S.P., 1996. Frontal lobe mechanisms subserving vision-for-action versus vision-for-perception. Behav. Brain Res. 72, 1–15.

Bremmer, F., Schlack, A., Shah, N.J., Zafiris, O., Kubischik, M., Hoffmann, K., Zilles, K., Fink, G.R., 2001. Polymodal motion processing in posterior parietal and premotor cortex: a human fMRI study strongly implies equivalencies between humans and monkeys. Neuron 29, 287–296.

Buccino, G., Binkofski, F., Fink, G.R., Fadiga, L., Fogassi, L., Gallese, V., Seitz, R.J., Zilles, K., Rizzolatti, G., Freund, H.J., 2001. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. Eur. J. Neurosci. 13, 400–404.

Chaminade, T., Meltzoff, A.N., Decety, J., 2002. Does the end justify the means? A PET exploration of the mechanisms involved in human imitation. Neuroimage 15, 318–328.

Chao, L.L., Martin, A., 2000. Representation of manipulable man-made objects in the dorsal stream. Neuroimage 12, 478–484.

Choi, H.J., Amunts, K., Mohlberg, H., Fink, G.R., Schleicher, A., Zilles, K. 2002. Cytoarchitectonic mapping of the anterior ventral bank of the intraparietal sulcus in humans. Human Brain Mapping Conference, Abstract No. 20038.

Crammond, D.J., Kalaska, J.F., 1996. Differential relation of discharge in primary motor cortex and premotor cortex to movements versus actively maintained postures during a reaching task. Exp. Brain Res. 108, 45–61.

Decety, J., Chaminade, T., Grèzes, J., Meltzoff, A.N., 2002. A PET exploration of the neural mechanisms involved in reciprocal imitation. Neuroimage 15, 265–272.

Decety, J., Grèzes, J., Costes, N., Perani, D., Jeannerod, M., Procyk, E., Grassi, F., Fazio, F., 1997. Brain activity during observation of actions. Influence of action content and subject's strategy. Brain 120, 1763–1777.

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., Rizzolatti, G., 1992. Understanding motor events: a neurophysiological study. Exp. Brain Res. 91, 176–180.

Di Virgilio, G., Clarke, S., 1997. Direct interhemispheric visual input to human speech areas. Hum. Brain Mapp. 5, 347–354.

Duvernoy, H.M., 1991. The Human Brain: Surface, Three-Dimensional Sectional Anatomy and MRI. Springer-Verlag, New York.

Ehrsson, H.H., Fagergren, A., Jonsson, T., Westling, G., Johansson, R.S., Forssberg, H., 2000. Cortical activity in precision- versus power-grip tasks: an fMRI study. J. Neurophysiol. 83, 528–536.

Ehrsson, H.H., Fagergren, E., Forssberg, H., 2001. Differential frontoparietal activation depending on force used in a precision grip task: an fMRI study. J. Neurophysiol. 85, 2613–2623.

Elsner, B., Hommel, B., 2001. Effect anticipation and action control. J. Exp. Psychol. Hum. Percept. Perform. 27, 229–240.

Fagg, A.H., Arbib, M.A., 1998. Modeling parietal-premotor interactions in primate control of grasping. Neural Networks 11, 1277–1303.

Fogassi, L., Gallese, V., Fadiga, L., Rizzolatti, G., 1998. Neurones responding to the sight of goal-directed hand/arm actions in the parietal area PF(7b) of the macaque monkey. Soc. Neurosci. Abstr. 24, 257.5.

Friston, K.J., Frith, C.D., Frackowiak, R.S., Turne, R., 1995. Characterizing dynamic brain responses with fMRI: a multivariate approach. Neuroimage 2, 166–172.

Frith, U., 2001. Mind blindness and the brain in autism. Neuron 32, 969–979.

Gallese, V., Fadiga, L., Fogassi, L., Rizzolatti, G., 1996. Action recognition in the premotor cortex. Brain 119, 593–609.

Gallese, V., Goldman, A., 1998. Mirror neurones and the simulation theory of mind-reading. Trends Cogn. Sci. 2, 493–501.

Gerlach, C., Law, I., Gade, A., Paulson, O.B., 2000. Categorization and category effects in normal object recognition: a PET study. Neuropsychologia 38, 1693–1703.

Gerlach, C., Law, I., Gade, A., Paulson, O.B., 2002. The role of action knowledge in the comprehension of artefacts—a PET study. Neuroimage 15, 143–152.

Grafton, S.T., Arbib, M.A., Fadiga, L., Rizzolatti, G., 1996. Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. Exp. Brain Res. 112, 103–111.

Grafton, S.T., Fadiga, L., Arbib, M.A., Rizzolatti, G., 1997. Premotor cortex activation during observation and naming of familiar tools. Neuroimage 6, 231–236.

Grèzes, J., Costes, N., Decety, J., 1998. Top down effect of the strategy on the perception of human biological motion: a PET investigation. Cogn. Neuropsychol. 15, 553–582.

Grèzes, J., Decety, J., 2001. Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. Hum. Brain Mapp. 12, 1–19.

Grèzes, J., Decety, J., 2002. Does visual perception of object afford action? Evidence from a neuroimaging study. Neuropsychologia 40, 212–222.

Hermsdorfer, J., Goldenberg, G., Wachsmuth, C., Conrad, B., Ceballos-Baumann, A.O., Bartenstein, P., Schwaiger, M., Boecker, H., 2001. Cortical correlates of gesture processing: clues to the cerebral mechanisms underlying apraxia during the imitation of meaningless gestures. Neuroimage 14, 149–146.

Iacoboni, M., Woods, R.P., Brass, M., Bekkering, H., Mazziotta, J.C., Rizzolatti, G., 1999. Cortical mechanisms of human imitation. Science 286, 2526–2528.

Jeannerod, M., 1994. The representing brain: neural correlates of motor intention and imagery. Behav. Brain Sci. 17, 187–246.

Jeannerod, M., Arbib, M.A., Rizzolatti, G., Sakata, H., 1995. Grasping objects: the cortical mechanisms of visuomotor transformation. Trends Neurosci. 18, 314–320.

Joliot, M., Papathanassiou, D., Mellet, E., Quinton, O., Mazoyer, N., Courtheoux, P., Mazoyer, B., 1999. FMRI and PET of self-paced finger movement: comparison of intersubject stereotaxic averaged data. Neuroimage 10, 430–447.

Kalaska, J.F., Crammond, D.J., 1995. Deciding not to GO: neuronal correlates of response selection in a GO/NOGO task in primate premotor and parietal cortex. Cereb. Cortex 5, 410–428.

Kollias, S.S., Alkadhi, H., Jaermann, T., Crelier, G., Hepp-Reymond, M.C., 2001. Identification of multiple non-primary motor cortical areas with simple movements. Brain Res. Rev. 36, 185–195.

Krams, M., Rushworth, M.F., Deiber, M.P., Frackowiak, R.S., Passingham, R.E., 1998. The preparation, execution and suppression of copied movements in the human brain. Exp. Brain Res. 120, 386–398.

Lacquaniti, F., Perani, D., Guigon, E., Bettinardi, V., Carrozo, M., Grassi, F., Rossetti, Y., Fazio, F., 1997. Visuomotor transformations for reaching to memorized targets: a PET study. Neuroimage 5, 129–146.

Luppino, G., Calzavara, R., Rozzi, S., Matelli, M., 2001. Projections from the superior temporal sulcus to the agranular frontal cortex in the macaque. Eur. J. Neurosci 14, 1035–1040.

Luppino, G., Murata, A., Govoni, P., Matelli, M., 1999. Largely segregated parietofrontal connections linking rostral intraparietal cortex (areas AIP and VIP) and the ventral premotor cortex (areas F5 and F4). Exp. Brain Res. 128, 181–187.

Martin, A., Haxby, J.V., Lalonde, F.M., Wiggs, C.L., Ungerleider, L.G., 1995. Discrete cortical regions associated with knowledge of color and knowledge of action. Science 270, 102–105.

Martin, A., Wiggs, C.L., Ungerleider, L.G., Haxby, J.V., 1996. Neural correlates of category-specific knowledge. Nature 379, 649–652.

Meltzoff, A.N., 1999. Understanding the intention of others: reenactment of intented acts by 18-month-old children. Dev. Psychol. 31, 838–850.

Meltzoff, A.N., Moore, M.K., 1977. Imitation of facial and manual gestures by human neonates. Science 198, 74–78.

Murata, A., Fadiga, L., Fogassi, L., Gallese, V., Raos, V., Rizzolatti, G., 1997. Object representation in the ventral premotor cortex (area F5) of the monkey. J. Neurophysiol 78, 2226–2230.

Murata, A., Gallese, V., Luppino, G., Kaseda, M., Sakata, H., 2000. Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. J. Neurophysiol. 83, 2580–2601.

Passingham, R.E. 1998. The specialization of the human cerebral cortex. in: Comparative Neuropsychology, Milner, A.D. Oxford Univ. Press, pp. 271–298.

Passingham, R.E., Toni, I., Schluter, N., Rushworth, M.F., 1998. How do visual instructions influence the motor system? Novartis Found. Symp. 218, 129–141 discussion 141–146.

Perani, D., Cappa, S.F., Schnur, T., Tettamanti, M., Collina, S., Rosa, M.M., Fazio, F., 1999. The neural correlates of verb and noun processing. A PET study. Brain 122, 2337–2344.

Perani, D., Fazio, F., Borghese, N.A., Tettamanti, M., Ferrari, S., Decety, J., Gilardi, M.C., 2001. Different brain correlates for watching real and virtual hand actions. Neuroimage 14, 749–758.

Perrett, D.I., Mistlin, A.J., Harries, M.H., Chitty, A.J., 1990. Understanding the visual appearance and consequences of hand actions, in: Goodale, M.A. (Ed.), Vision and Action: the Control of Grasping. Ablex, Norwood, NJ, pp. 163–180.

Petrides, M., Pandya, D.N., 1995. Comparative architectonic analysis of the human and macaque frontal cortex. In: Grafman, J., Boller, F. (Eds.), Handbook of Neuropsychology, Vol. 9. Elsevier, Amsterdam, pp. 17–58.

Prinz, W., 1997. Perception and action planning. Eur. J. Cogn. Psychol. 9, 129–154.

Rizzolatti, G., Arbib, M.A., 1998. Language within our grasp. Trends Neurosci. 21, 188–194.

Rizzolatti, G., Camarda, R., Fogassi, L., Gentilucci, M., Luppino, G., Matelli, M., 1988. Functional organization of inferior area 6 in the macaque monkey. II. Area F5 and the control of distal movements. Exp. Brain Res. 71, 491–507.

Rizzolatti, G., Fadiga, L., 1998. Grasping objects and grasping action meanings: the dual role of monkey rostroventral premotor cortex (area F5). Novartis Found. Symp. 218, 81–95 discussion 95–103.

Rizzolatti, G., Fadiga, L., Gallese, V., Fogassi, L., 1996a. Premotor cortex and the recognition of motor actions. Cogn. Brain Res. 3, 131–141.

Rizzolatti, G., Fadiga, L., Matelli, M., Bettinardi, V., Paulesu, E., Perani, D., Fazio, F., 1996b. Localization of grasp representations in humans by PET: 1. Observation versus execution. Exp. Brain Res. 111, 246–252.

Rushworth, M.F., Krams, M., Passingham, R.E., 2001. The attentional role of the left parietal cortex: the distinct lateralization and localization of motor attention in the human brain. J. Cogn. Neurosci. 13, 698–710.

Sakata, H., Taira, M., Murata, A., Mine, S., 1995. Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. Cereb. Cortex 5, 429–438.

Schubotz, R.I., von Cramon, D.Y., 2001. Functional organization of the lateral premotor cortex: fMRI reveals different regions activated by anticipation of object properties, location and speed. Cogn. Brain Res. 11, 97–112.

Sergent, J., Zuck, E., Terriah, S., MacDonald, B., 1992. Distributed neural network underlying musical sight-reading and keyboard performance. Science 257, 106–109.

Simon, O., Mangin, J.F., Cohen, L., Le Bihan, D., Dehaene, S., 2002. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron 33, 475–487.

Snyder, L.H., Batista, A.P., Andersen, R.A., 1997. Coding of intention in the posterior parietal cortex. Nature 386, 167–170.

Snyder, L.H., Batista, A.P., Andersen, R.A., 2000. Intention-related activity in the posterior parietal cortex: a review. Vision Res. 40, 1433–1441.

Taira, M., Mine, S., Georgopoulos, A.P., Murata, A., Sakata, H., 1990. Parietal cortex neurons of the monkey related to the visual guidance of hand movement. Exp. Brain Res. 83, 29–36.

Tanne-Gariepy, J., Rouiller, E.M., Boussaoud, D., 2002. Parietal inputs to dorsal versus ventral premotor areas in the macaque monkey: evidence for largely segregated visuomotor pathways. Exp. Brain Res. 145, 91–103.

Tomaiuolo, F., MacDonald, J.D., Caramanos, Z., Posner, G., Chiavaras, M., Evans, A.C., Petrides, M., 1999. Morphology, morphometry and probability mapping of the pars opercularis of the inferior frontal gyrus: an in vivo MRI analysis. Eur. J. Neurosci. 11, 3033–3046.

Toni, I., Passingham, R.E., 1999. Prefrontal-basal ganglia pathways are involved in the learning of arbitrary visuomotor associations: a PET study. Exp. Brain Res. 127, 19–32.

Toni, I., Schluter, N.D., Josephs, O., Friston, K., Passingham, R.E., 1999. Signal-, set- and movement-related activity in the human brain: an event-related fMRI study. Cereb Cortex 9, 35–49.

Toni, I., Shah, N.J., Fink, G.R., Thoenissen, D., Passingham, R.E., Zilles, K., 2002. Multiple movement representations in the human brain: an event-related fMRI study. J. Cogn. Neurosci. 14, 769–784

Toni, I., Thoenissen, D., Zilles, K., 2001. Movement preparation and motor intention. Neuroimage 14, S110–S117.

von Bonin, G., Bailey, P., 1947. The Neocortex of *Macaca mulatta*. Univ. of Illinois Press, Urbana.

von Economo, C., 1929. The Cytoarchitectonics of the Human Cerebral Cortex. Oxford Univ. Press, London.

Webster, M.J., Bachevalier, J., Ungerleider, L.G., 1994. Connections of inferior temporal areas TEO and TE with parietal and frontal cortex in macaque monkeys. Cereb. Cortex 4, 470–483.

Wise, S.P., Mauritz, K.H., 1985. Set-related neuronal activity in the premotor cortex of rhesus monkeys: effects of changes in motor set. Proc. R. Soc. London Ser. B. Biol. Sci. 223, 331–354.