

Modulation of Motor and Premotor Activity during Imitation of Target-directed Actions

Lisa Koski^{1,2}, Andreas Wohlschläger⁶, Harold Bekkering⁷, Roger P. Woods^{1,2}, Marie-Charlotte Dubeau^{1,3}, John C. Mazziotta^{1,2,4} and Marco Iacoboni^{1,3,5}

¹Ahmanson-Lovelace Brain Mapping Center, Neuropsychiatric Institute, ²Departments of Neurology, ³Psychiatry and Biobehavioral Sciences, ⁴Pharmacology and Radiological Sciences, ⁵Brain Research Institute, UCLA School of Medicine, 660 Charles E. Young Drive South, Los Angeles, CA 90095, USA, ⁶Department of Cognition and Action, Max Planck Institute for Psychological Research, Amalienstraße 33, D-80799 Munich, Germany and ⁷Department of Experimental and Work Psychology, Grote Kruisstraat 2/1, 9712 TS Groningen, The Netherlands

Behavioral studies reveal that imitation performance and the motor system are strongly influenced by the goal of the action to be performed. We used functional magnetic resonance imaging (fMRI) to assess the effect of explicit action goals on neural activity during imitation. Subjects imitated index finger movements in the absence and presence of visible goals (red dots that were reached for by the finger movement). Finger movements were either ipsilateral or contralateral. The pars opercularis of the inferior frontal gyrus showed increased blood oxygen level-dependent fMRI signal bilaterally for imitation of goal-oriented actions, compared with imitation of actions with no explicit goal. In addition, bilateral dorsal premotor areas demonstrated greater activity for goal-oriented actions, for contralateral movements and an interaction effect such that goal-oriented contralateral movements yielded the greatest activity. These results support the hypothesis that areas relevant to motor preparation and motor execution are tuned to coding goal-oriented actions and are in keeping with single-cell recordings revealing that neurons in area F5 of the monkey brain represent goal-directed aspects of actions.

Introduction

Recent studies of neurons in the ventral premotor cortex (area F5) of the monkey suggest that this cortical region is important for the representation of actions. Area F5 contains neurons whose activity is modulated during the performance of a particular action, such as grasping or tearing (Rizzolatti *et al.*, 1987a, 1988, 1990, 1996a; Di Pellegrino *et al.*, 1992; Gallese *et al.*, 1996). Within area F5 there is a class of neurons, known as mirror neurons, that respond to the sight of another monkey or experimenter performing the same type of action encoded by that neuron (Di Pellegrino *et al.*, 1992; Rizzolatti *et al.*, 1996a). Thus, the ventral premotor area with its mirror neurons may be an important part of a system that represents actions through the direct matching of observed and executed actions.

Functional neuroimaging and magnetic stimulation studies point to the existence of a similar mirror system in humans. The activity in posterior inferior frontal cortex (Brodmann's areas 44/45) during action observation and motor imagery tasks follows a pattern consistent with that observed in area F5 mirror neurons in monkeys (Grafton *et al.*, 1996; Rizzolatti *et al.*, 1996b; Krams *et al.*, 1998; Parsons and Fox, 1998; Iacoboni *et al.*, 1999; Nishitani and Hari, 2000). Moreover, anatomic considerations suggest a homology between Brodmann's areas 44/45 in the human and ventral premotor area F5 in monkeys (Petrides and Pandya, 1994; Rizzolatti *et al.*, 1996a, 1998).

Mirror neurons are characterized by their response to both observation and execution of the same action. It has been proposed that the human ability to imitate evolved out of the mirror system, with its capacity to match directly observed and

executed actions (Arbib, 2002). A region with properties similar to those of mirror neurons would be active during performance of a specific action, but would show additional activity when this action was guided by observation of the same action performed by another. This pattern of activity has been observed in the posterior inferior frontal gyrus in studies using functional magnetic resonance imaging (fMRI) (Iacoboni *et al.*, 1999) and magnetoencephalography (Nishitani and Hari, 2000).

What specific aspects of an action are encoded by the mirror system? Single-unit studies in the monkey suggest that cortical representations of an action are organized around the goal or target of that action. Many F5 neurons become active during actions that share the same goal but are performed with different effectors, suggesting that actions are represented in this cortical region with respect to their goals, rather than with respect to commands to specific muscle groups (Rizzolatti *et al.*, 1987a; Gallese *et al.*, 1996; Fadiga *et al.*, 2000). Detailed studies of the response properties of mirror neurons during action observation indicate that they are most responsive to the interaction of a hand with an object. They respond maximally when the hand comes in contact with an object and respond less when observing someone grasping the object with a tool, making a grasping movement without an object, or when object and action are spatially separated (Di Pellegrino *et al.*, 1992; Gallese *et al.*, 1996). Thus, activity in area F5 of the ventral premotor cortex appears to encode preferentially object-oriented actions.

Similarly, human imitation seems to be driven by action goals. In a series of developmental studies, children imitated the experimenter reaching with one hand to touch a target on the ipsilateral or contralateral side of space. For contralateral movements, children tend to target the correct location in space, but using the incorrect (i.e. ipsilateral) hand (Schofield, 1976; Bekkering *et al.*, 2000; Gleissner *et al.*, 2000). One study designed to assess the influence of action goals demonstrated that more such errors were made when children had to reach for one of two red dots (the goal) on the table surface than when reaching to the same location when no dots were present (Bekkering *et al.*, 2000). Thus, encoding of the target of an action is a major determinant of imitation performance in children, overriding those aspects of the action representing how the target is reached. Recent behavioural data suggest that normal adults make similar errors during imitation of contralateral movements to a target, albeit with a lesser frequency than is seen in children (Wohlschläger and Bekkering, 2002).

The neurophysiological correlates of the human tendency to imitate the goal of an action are largely unexplored. Functional magnetic resonance imaging (fMRI) data suggest that during simple action observation it is possible to observe the neuro-

physiological effects of visible action goals on the human brain (Buccino *et al.*, 2001). Increased activity was found bilaterally in Brodmann's area 44 for the observation of object-oriented hand/arm movements, compared with observation of hand/arm movements without an object. When observing mouth movements, however, there was a comparable increase in signal in area 44 and also in area 45 in the right hemisphere, whether the action was observed with or without an object (Buccino *et al.*, 2001). These results suggest that the activity observed in human inferior frontal cortex during action observation is driven primarily by goal-oriented actions, as in the macaque brain. To date, however, no studies have used imitation to investigate the effect of goals on inferior frontal cortex activity.

We report here the results of an fMRI study that tested the effect of explicit action goals on neural activity during imitation. As in the developmental and chronometric studies described above (Bekkering *et al.*, 2000; Wohlschläger and Bekkering, 2002), the targets of the imitated action were red dots. Subjects had to imitate the ipsilateral or contralateral finger movement without seeing their own hands. We predicted that, given the reported mirror properties of Brodmann area 44 (Iacoboni *et al.*, 1999, Buccino *et al.*, 2001) the presence of an explicit target in the to-be-imitated action would preferentially engage the frontal operculum. We further hypothesized that the presence of a target in the observed action would elicit a motor plan representing the most direct route to reach the target, i.e. the ipsilateral response. Thus, reaching for a contralateral dot should require the suppression of the ipsilateral movement and the selection of the correct, contralateral movement. This predicts greater activity in areas that are critical to response selection, such as dorsal premotor cortex (Wise, 1985; Passingham, 1993).

The study design used here involved not only action imitation, but also a separate set of action observation conditions. Each type of action presented for imitation was also presented as a separate set of passive observation tasks in which subjects did not imitate but simply observed the actions without response. Thus, the design allowed us to dissociate the effect of goals on imitation from the effect of goals on action observation.

Materials and Methods

Subjects

Fourteen right-handed subjects (10 female) were recruited through

newspaper advertisements. Participants gave informed consent according to the requirements of the Institutional Review Board of UCLA. The average age of the subjects was 26.1 years (SD 8.3). The subjects were right-handed, as indicated by a questionnaire adapted from the Edinburgh Handedness Inventory (Oldfield, 1971). All were screened to rule out medication use, a history of neurological or psychiatric disorders, head trauma, substance abuse or other serious medical conditions. No neurological abnormalities were identified by neurological examination performed just before the scanning session.

Image Acquisition and Processing

Images were acquired using a GE 3.0 T MRI scanner with an upgrade for echo-planar imaging (EPI; Advanced NMR Systems Inc.). A two-dimensional spin-echo image ($T_R = 4000$ ms; $T_E = 40$ ms, 256×256 matrix, 4 mm thick, 1 mm spacing) was acquired in the sagittal plane to allow prescription of the slices to be obtained in the remaining sequences and to ensure the absence of structural abnormalities in the brain. For each subject, two functional EPI scans (gradient-echo, $T_R = 4000$ ms, $T_E = 70$ ms, 64×64 matrix, 26 slices, 4 mm thick, 1 mm spacing) were acquired, each for a duration of 5 min 40 s and covering the whole brain. Each scan consisted of eight task periods of 20 s alternating with nine rest periods of 20 s. A high resolution structural T_2 -weighted echo-planar image (spin-echo, $T_R = 4000$ ms, $T_E = 54$ ms, 128×128 matrix, 26 slices, 4 mm thick, 1 mm spacing) was acquired coplanar with the functional images.

The functional images were aligned with the T_2 -weighted structural image within each subject using a rigid-body linear registration algorithm (Woods *et al.*, 1998a). The images were then registered to a Talairach-compatible MR atlas (Woods *et al.*, 1999) with fifth-order polynomial nonlinear warping (Woods *et al.*, 1998b). Data were then spatially smoothed using an in-plane, Gaussian filter for a final image resolution of $8.7 \times 8.7 \times 8.6$ mm.

Behavioral Conditions

Stimuli consisted of computer presentations of downward movements of the index finger of the left hand (50% movements in each task period) or right hand (50% movements in each task period). The backs of both hands were shown next to each other against a white surface with the index fingers extended and the thumb and other fingers curled under (see Fig. 1). The hands were oriented so that the fingers pointed toward the subject so that s/he would imitate as if looking in a mirror. A series of 10 movements was presented in each 20 s task period. The hands appeared first in the neutral position (index finger up) for 1000 ms, then the index finger moved down to touch the white surface for 1000 ms, returning to the neutral position to begin the next movement. Thus, the total duration of each movement trial was 2 s and there was no interval between one movement trial and the next.

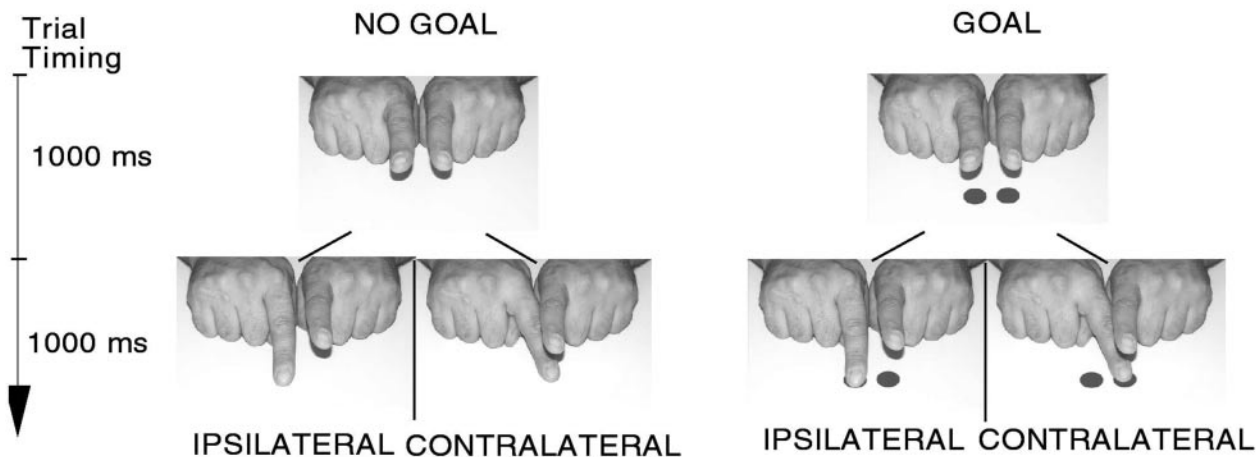


Figure 1. Representation of the images viewed by subjects for action observation and imitation. The first frame showed the hands in the neutral position, with or without dots. Goal-oriented action trials had dots, whereas non-goal oriented action trials did not. The movement type that followed was ipsilateral or contralateral.

The experimental design included two stimulus variables, goals (dots versus no-dots) and direction (contralateral versus ipsilateral), and one instruction variable (imitate versus observe). The combination of the two stimulus factors yielded four different stimulus conditions (ipsilateral, no dots; contralateral, no dots; ipsilateral, dots; contralateral, dots) that were presented in separate 20 s blocks of trials. For 'dots' trials, two red dots were present on the white surface below each finger throughout the block and the index finger was depicted as reaching down to touch a dot (the goal) on the surface. For the 'no-dots' blocks of trials, the dots were absent and thus there was no explicit goal for the action. On 'ipsilateral' trials, the index finger reached directly down to touch the background surface. On 'contralateral' trials, the index finger was abducted slightly to touch the surface beneath the contralateral index finger.

Each of the four stimulus conditions was presented twice within a scanning run, once for each level of the instruction variable. For four blocks, subjects were instructed to imitate the actions observed as if looking in a mirror, whereas for the other four blocks, the subjects were instructed to observe the actions passively. Subjects were told simply to imitate or just observe the finger movements, with no emphasis on the presence of the dots. There were 10 movements (five left index finger, five right index finger) presented in each task block and the laterality of the action (left versus right) was varied from one trial to the next in a counterbalanced order. Two scanning runs were acquired from each subject and the two instruction conditions were counterbalanced across runs and subjects.

Statistical Analyses

All statistical analyses were performed on group data using analysis of variance (ANOVA) (Iacoboni *et al.*, 1996, 1997, 1998, 1999, 2001). For the imitation instruction tasks, a three-way ANOVA model for the between-task comparisons included the following factors: subject ($n = 14$); functional scan ($n = 2$); and stimulus condition ($n = 4$, contralateral dots; ipsilateral dots; contralateral no-dots; ipsilateral no-dots) (Woods *et al.*, 1996). This model factors out the run-to-run variability within subjects as well as the between-subject variability in signal intensity. The dependent variable was the sum of the signal intensity at each voxel throughout each imitation task period. The main effect of 'goals' on BOLD fMRI signal during imitation was tested by subtracting the two no-dots conditions from the two dots conditions. The main effect of 'movement direction' during imitation was tested by subtracting the two ipsilateral conditions from the two contralateral conditions. Behavioral data (Wohlschläger and Bekkering, 2002) showed that the contralateral dots condition differs from the other three conditions in terms of reaction time and errors. Therefore, we also performed a planned contrast, using the following contrast weights: +3 for contralateral-movement-to-dots and -1 for the three other conditions. This allowed us to test our hypothesis that brain regions critical for response selection should be preferentially activated during the condition in which contralateral movements were made toward dots.

The main effect of 'goals' on action observation was tested using the

same three-way ANOVA model applied to the sum of the signal intensity at each voxel throughout each observation instructed task period.

On the basis of the proposed homology between area F5 in the macaque and Brodmann's area 44 in the human brain (Petrides and Pandya, 1994; Rizzolatti *et al.*, 1996a; Rizzolatti and Arbib, 1998), we hypothesized that activity in the pars opercularis of the inferior frontal gyrus would vary as a function of the representation of goals during imitation. The recent analysis and probabilistic map by Tomaiuolo and colleagues indicates that the average volume of the pars opercularis is 3.68 cm³ (Tomaiuolo *et al.*, 1999). Therefore, the statistical threshold for this region was set at $P = 0.05$, corrected for multiple comparisons across the equivalent volume in resolution elements in our study. This corresponds to a critical t -value of 2.47 for 39 degrees of freedom (d.f.). Brain regions outside the pars opercularis of the inferior frontal gyrus that showed activity during imitation task periods compared to rest (at $P = 0.05$ uncorrected) were evaluated at $P = 0.05$, corrected for multiple spatial comparisons (d.f. = 39, $t = 5.69$) (Worsley, 1996).

Results

Main Effect of Goals

The results of this and other task comparisons are presented in Table 1. The comparison of the dots versus no-dots conditions for imitation only yielded significant bilateral increases in the frontal operculum (see Fig. 2). In both hemispheres, the peak of the activity in the frontal operculum was located within the pars opercularis, according to the probabilistic map of Tomaiuolo and colleagues (left, 25–50% probability; right, 50–75% probability) (Tomaiuolo *et al.*, 1999) and thus in Brodmann's area 44, according to probabilistic cytoarchitectonic maps of the human brain (Amunts *et al.*, 1999; Mazziotta *et al.*, 2001).

Increases were also seen bilaterally in the rostral portion of the dorsal premotor cortex (Brodmann's area 6). One other region in the right middle occipital gyrus (Brodmann's area 18/19) showed greater signal in the presence of goals.

The comparison of the dots versus no-dots conditions for observation only did not yield significant increases in signal in the pars opercularis of the inferior frontal gyrus or elsewhere.

Main Effect of Movement Type during Imitation

Subtracting activity in the ipsilateral conditions from activity in the contralateral conditions revealed significant bilateral increases in activity in the rostral portion of the dorsal premotor cortex (Brodmann's area 6) and in the primary motor cortex (Brodmann's area 4). Activity in the left premotor cortex was greater and more extensive than in the right premotor cortex.

Table 1

Brain regions showing significant increases in signal for three between-task comparisons of the imitation conditions

	BA	Goals		Contralateral		Goal × direction	
		X, Y, Z	t	X, Y, Z	t	X, Y, Z	t
Left sensorimotor area	4/3	n.s.		-40, -24, 58	7.1	-40, -23, 58	6.4
Right sensorimotor area	4/3	n.s.		34, -28, 62	6.0	n.s.	
Left dorsal premotor	6	-16, 0, 64	5.7	-18, 0, 64	6.9	-18, 0, 64	6.1
				-10, 8, 60	6.9		
				-28, -10, 60	6.3		
Right dorsal premotor	6	13, -4, 62	5.8	12, -2, 64	5.9	15, 0, 62	6.1
Left pars opercularis	44	-58, 8, 14	3.6	n.s.		n.s.	
Right pars opercularis	44	57, 14, 12	3.6	n.s.		n.s.	
Right middle occipital gyrus	18/19	24, -94, 18	7.7	Fn.s.		25, -98, 18	5.6

BA = Brodmann's area; Goals = dots minus no-dots contrast; Contralateral = contralateral minus ipsilateral finger movement contrast; Goal × direction = contralateral dots minus the average of the other three imitation conditions; X, Y, Z = peak of greatest signal intensity in the t -map, in Talairach coordinates (Talairach and Tournoux, 1988); t = t -statistic value; n.s. = not significant by our statistical thresholds (see text for details).

Figure 2

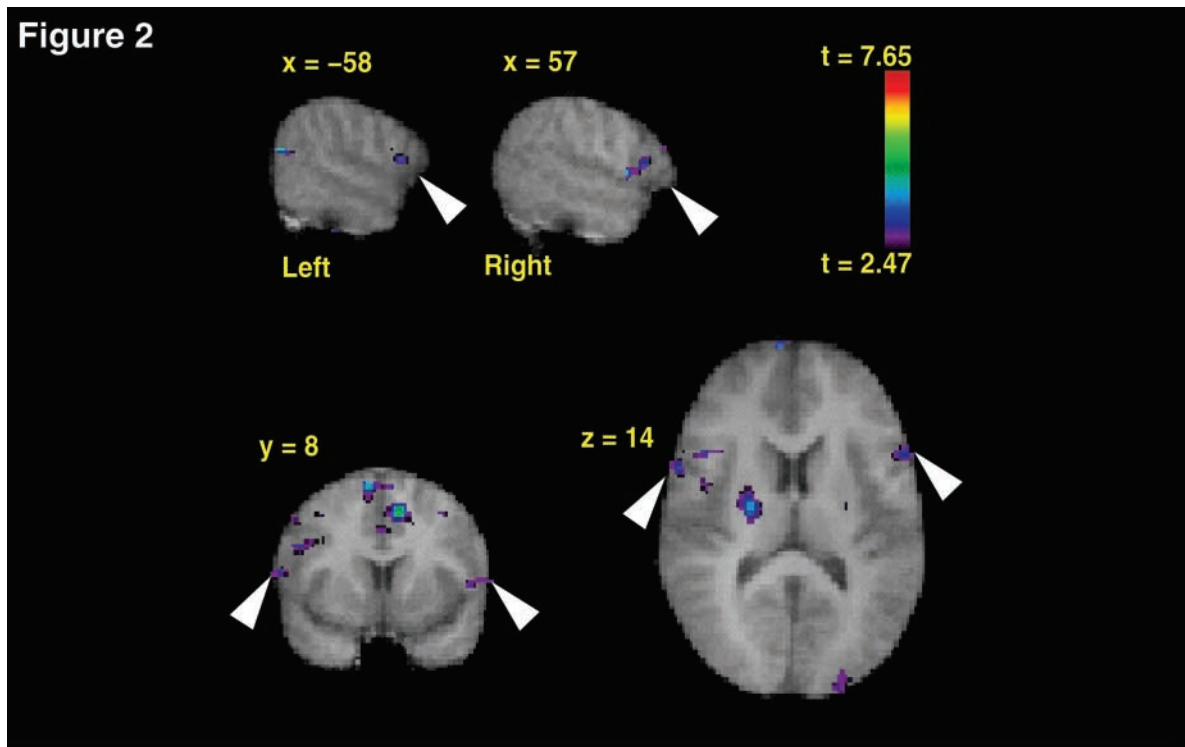
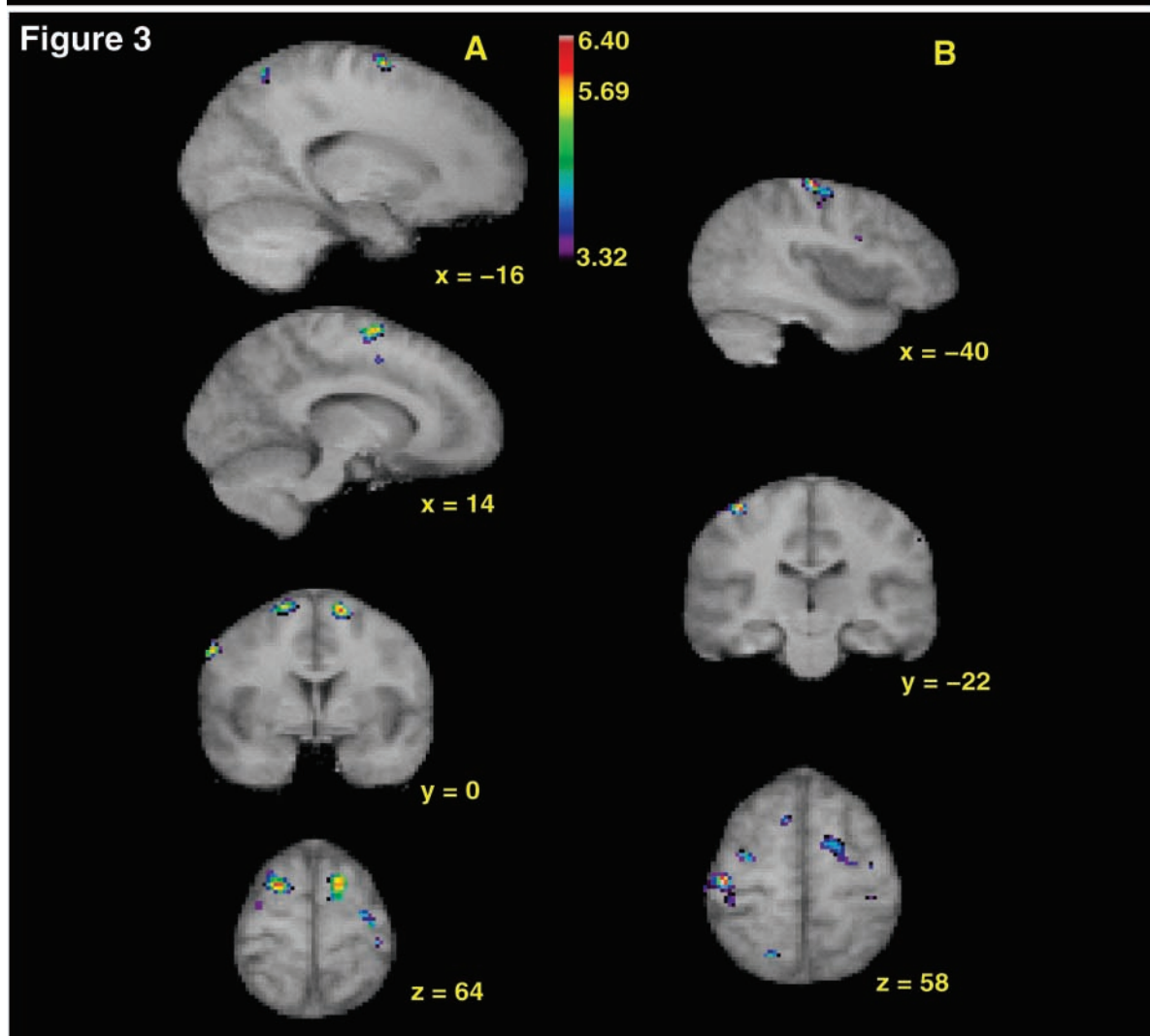


Figure 3



Goals and Movement Type Interaction during Imitation

The results of the interaction analysis revealed that the specific combination of conditions involving both dots and contralateral responses led to significant increases compared with the other three conditions in three regions: left primary sensorimotor cortex; bilateral dorsal premotor cortex; and a small activation in the right occipital cortex (see Fig. 3).

Discussion

The present study yielded two main findings. First, the presence of a visible goal in the observed action during imitation was associated with an increased blood oxygen level-dependent (BOLD) fMRI signal in the frontal operculum and in dorsal premotor cortex. Second, goal-directed imitated actions may require the engagement of dorsal premotor and primary motor systems to overcome prepotent response tendencies. We elaborate on each of these findings in the discussion that follows.

The Role of Brodmann's Area 44 in Imitating Goal-directed Actions

Our data suggest that Brodmann's area 44 is more active during imitation of actions that have a visible goal. This finding is in line with the single-unit recording work in monkeys that demonstrated maximum modulation of F5 mirror neurons when the hand interacted with an object, during either observation or execution (Di Pellegrino *et al.*, 1992; Gallese *et al.*, 1996). It is also consistent with the hypothesis derived from positron emission tomography (PET) studies of action observation that area 44 in the human is important for encoding hand/object interactions (Grafton *et al.*, 1996). Finally, these data suggest that imitation, even in the adult brain, is a behavior largely tuned to replicate the goal of an observed action.

It is interesting to note that the presence of the dots significantly affected the BOLD fMRI signal in Brodmann's area 44 during the imitation condition, but not during action observation only. This suggests that the effect of the presence of the target on inferior frontal cortex activity cannot be simply due to differences in the visual display presented to the subjects. One explanation for the present data would be that subjects only attended to the goals when they were behaviorally relevant. Then, could the pattern of cortical activity observed here be attributed to attentional factors rather than to representation of the action goal? Differences in attention to the visual input in the imitation and observation conditions are certainly possible. We suggest, however, that greater attention to the goals in the imitation condition would predict increased activity throughout

widespread regions of the cortex in areas related to sensory as well as motor processing. Our data do not fit well with such a prediction, as the majority of the increases in signal were observed in motor regions, including the inferior frontal cortex, which is not an area known for its visual sensory processing functions. The attentional hypothesis is still valid, however, if viewed within the framework of a premotor theory of attention (Rizzolatti *et al.*, 1987b, 1994; Craighero *et al.*, 1999). According to this framework, the response requirements of the imitation task drive the emphasis on the action goal. At the cortical level, the task demands requiring representation of action in motor regions could even extend secondarily in a top-down fashion to enhance sensory processing of goal-relevant aspects of the sensory input. This type of attentional mechanism has been termed action-for-perception (Craighero *et al.*, 1999).

Another important factor to consider when comparing the pattern of neural activity during imitation and observation in the present study is the nature of the goals. The target-directed actions observed in previous imaging (Buccino *et al.*, 2001) and single-unit recording studies (Di Pellegrino *et al.*, 1992; Gallese *et al.*, 1996) used three-dimensional, graspable objects as goals. These studies found increased activity in ventral premotor regions during target-directed actions relative to non-target-directed actions. The goals used in the present study, however, were simple two-dimensional red dots, which may have been less ecologically valid as goals than graspable objects. Thus, the relatively impoverished stimuli used as goals in the present study may account for the failure to observe an effect during simple observation, when motor attentional mechanisms are probably reduced.

The concept of 'goals' has been widely used in theories about imitation. In the goal-directed theory of imitation (Bekkering and Wohlschläger, 2002), 'goals' typically refers to physical things such as dots and ears. That is, imitators tend to move to the correct goal, such as an object or a particular ear to reach for. However, this theory also uses the concept of goals at another more functional level, as reflected in the ideomotor principle (Greenwald, 1970). The ideomotor principle states that the selected physical goals elicit the motor program with which they are most strongly associated. In other words, the physical goals are represented in certain neural codes and these representations affect the selection and initiation processes of imitative actions. Thus, 'goals' here refers to a functional mechanism necessary to initiate an imitative action.

The active intermodal mapping theory (Meltzoff and Moore, 1997) also addresses the issue of goal-directed acts. Here, the

Figure 2. Location of the increased signal in the pars opercularis of the inferior frontal cortex during imitation in the presence of the dots (dots versus no-dots contrast). The two images on top are in the sagittal plane and display the left and right pars opercularis, respectively. The bottom-left image is in the coronal plane and the bottom-right image is in the transverse plane. The images for these planes were selected to show the maximal *t*-values for both the left and right pars opercularis and the left side of the images represents the left side of the brain. The *t*-maps are displayed on a T_1 -weighted version of the atlas used for spatial normalization. The color represents the intensity of the *t*-values at each voxel, as indicated by the color bar and *t*-values in the upper right portion of the figure. The maps have been thresholded to display only those regions that showed increased activity at or above the statistical threshold used to correct for multiple comparisons within the region of interest in the pars opercularis ($t = 2.47$, $P = 0.05$ corrected). Transverse, $z = 12$; coronal, $y = 14$; sagittal, $x = -58$ (left) and 56 (right). Arrowheads point to the location of the activity in the pars opercularis in each plane.

Figure 3. Location of the regions of increased signal when comparing the contralateral-dots condition with the other three imitation conditions. (A) Left side of figures: images were selected to show the location of the maximal *t*-values for the dorsal premotor cortex bilaterally [$z = 64$, $y = 0$, $x = -16$ (left) and 14 (right)]. The top two images are in the sagittal plane and display the left and right dorsal premotor cortex, respectively. The second image from the bottom is in the coronal plane and the bottom image is in the transverse plane. The left side of the image in these two planes represents the left side of the brain. (B) Right side of figure: the images for these planes were selected to show the maximal *t*-values for the left sensorimotor cortex [$z = 58$, $y = -22$, $x = -40$]. The top image is in the sagittal plane and displays the location of activity in the sensorimotor cortex in the left hemisphere. The middle image is in the coronal plane and the bottom image is in the transverse plane. The left side of the image in these two planes represents the left side of the brain. The *t*-maps are displayed on a T_1 -weighted version of the atlas used for spatial normalization. The color represents the intensity of the *t*-values at each voxel, as indicated by the color bar and *t*-values in the upper central portion of the figure. The maps have been thresholded to display only those regions that showed increased activity at or above an uncorrected statistical threshold of $P = 0.001$ uncorrected for multiple spatial comparisons ($t = 3.32$). The value $t = 5.69$ is also indicated on the color bar because it represents the level of statistical significance at $P = 0.05$ that resulted after correcting for multiple comparisons outside the region of interest in the pars opercularis.

goal of an infant is to match their own body with the observed model's body organ relations, which clearly refers to the functional action level of the goal concept. In his work, Tomasello has repeatedly emphasized that action goals are understood as something separate from the behavioral means used to obtain them (Tomasello, 1999). He has also proposed the term 'emulation' for imitative behaviors that map more on the action goals than on the motor details of the action. A further elaboration is introduced by Travis, who suggests that a goal, strictly defined, is 'a mental state representing a desired state of affairs in the world' and can therefore only be observed in the outcome of intentional actions (Travis, 1997). Thus, the effect of visible goals during imitation in Brodmann's area 44 appears to link mirror neurons with imitation and intentional states.

Bilateral versus Lateralized Mirror Premotor Systems in Humans

A number of neuroimaging studies have associated action observation, imagery or imitation with left hemisphere increases in inferior frontal cortex activity (Grafton *et al.*, 1996; Rizzolatti *et al.*, 1996b; Iacoboni *et al.*, 1999; Nishitani and Hari, 2000). It is possible that this asymmetry reflects a left hemisphere dominance for the selection of action (Schluter *et al.*, 1998, 2001). When one looks at imaging data, however, one must consider that activation studies typically binarize continuous brain activity, concluding that one region is active while another region is not. Thus, threshold effects may transform a largely bilateral activation with an asymmetry into a lateralized activation. For example, our previously reported left-lateralized activation in the inferior frontal cortex during imitation belongs to this category (Iacoboni *et al.*, 1999). At lower statistical thresholds, bilateral activation in the inferior frontal cortex was observed (unpublished observations).

In this study, the presence of a target in the observed action during imitation was associated with a comparable degree of increased signal in both inferior frontal cortices. Further, the recent action observation study of Buccino and colleagues demonstrated bilateral activity in area 44 for observed actions performed by the right hand only (Buccino *et al.*, 2001). We recently performed a meta-analysis on 58 subjects studied with fMRI in our laboratory during imitation and action observation (Molnar-Szakacs *et al.*, 2002). We observed bilateral activation of Brodmann's area 44. Furthermore, we observed a functional differentiation between a ventral sector of Brodmann's area 44, activated only during imitation, and a dorsal sector activated during both imitation and observation. This suggests that the mirror portion of area 44 is located dorsally in the pars opercularis, as was the area responding to the presence of dots during imitation in the present experiment. Taken together, the evidence suggests that the premotor mirror system in humans is largely bilateral and more active when the imitative behavior maps onto actions with visible goals.

Action Control and the Mirror System

A second finding to emerge from this study concerns the pattern of activity observed in dorsal premotor and primary motor cortex. The dorsal premotor region was associated with a greater BOLD fMRI signal for imitation of target-oriented actions, for imitation of contralateral movements and for an interaction between these two factors, such that contralateral goal-oriented observed actions yielded greater activity than the other kinds of actions studied here. The primary motor cortex showed greater activity for contralateral movements as well as in the interaction contrast.

The effect of visible goals in the to-be-imitated action is similar to that observed in inferior frontal cortex. Thus, it is possible that the greater activity in inferior frontal mirror areas during imitation of target-oriented actions influences activity in premotor and primary motor regions. Indeed, the dorsal premotor regions are anatomically interconnected with the ventral premotor cortex in the monkey (Matelli *et al.*, 1984; Passingham, 1993) and it is plausible that the increased activity in these regions is due to the remote effects of activity originating from the pars opercularis of the inferior frontal cortex.

However, an alternative explanation is that the entire motor system in general is tuned to detecting the goals of imitated actions. The developmental literature suggests that the ability to detect the goal of an action emerges as early as 6 months of age in humans (Woodward, 1998). Indeed, neurons in both dorsal premotor and primary motor cortex show response properties that are sensitive to target-related aspects of an action, such as target location and target size (Shen and Alexander 1997a,b; Johnson *et al.*, 1999a,b; Gomez *et al.*, 2000; Hoshi and Tanji, 2000). This sensitivity to the goal of an action may be a property of widespread regions within the motor system. Thus, the present data may support a non-hierarchical view of the functions of the various motor regions that is in line with the recent single-unit recording studies cited above.

Contralateral movements were also associated with an increased BOLD fMRI signal in dorsal premotor and also in primary motor cortex. This may simply be due to differences in motor parameters between the two movements, the most obvious being amplitude (contralateral movements have greater amplitude than ipsilateral ones) and direction. Neurons coding these parameters have been observed in both dorsal premotor cortex (Crammond and Kalaska, 1994; Kurata, 1994; Messier and Kalaska, 2000) and primary motor cortex (Georgopoulos *et al.*, 1982; Fu *et al.*, 1993).

The interaction of movement type with the presence of visible goals, however, supports our hypothesis that acting on a contralateral target should require greater intervention from regions that control response selection. In the absence of a target, the contralateral action may be encoded simply as a movement of the hand in a contralateral direction. The presence of a target, however, may tend to cue the action that reaches it by the most direct route: an ipsilateral response (Bekkering *et al.*, 2000; Wohlschläger and Bekkering, 2002). This response must be suppressed and the correct movement selected. The importance of the dorsal premotor cortex in the suppression of prepotent response tendencies has been demonstrated previously (Praamstra *et al.*, 1999; Praamstra and Plat, 2001). A wealth of other studies in both monkeys and humans also points to a role for the dorsal premotor cortex in the performance of arbitrary or 'non-standard' (Wise *et al.*, 1996) stimulus-response tasks, in which response selection is determined by an arbitrary rule, rather than by properties of the stimulus itself (Petrides, 1982, 1985, 1987; Kurata and Hoffman, 1994; Iacoboni *et al.*, 1996, 1997, 1998; Wise *et al.*, 1996; Toni and Passingham, 1999).

We wish to clarify that in the present study, subjects performed an imitation task, in which the action produced was identical to the action observed. Therefore, the present data do not represent simply another instance of the effects of arbitrary or incompatible stimulus-response pairing. More accurately, we would state that response suppression and motor control systems are activated in the condition involving contralateral movements toward a goal, as was supported by the observation of increased activity in dorsal premotor cortex. Thus, we might speculate that the activity observed in inferior frontal cortex, along with the

other motor regions, reflects the representation of target-oriented actions, while the dorsal premotor cortex shows additional involvement required to suppress the most direct (ipsilateral) response to the encoded target and facilitate the selection of the correct (contralateral) response.

The interaction observed within the left primary motor cortex has two possible interpretations. The first interpretation is based on a hierarchical model of the functions of the various components of the motor system. Dorsal premotor cortex has often been associated with selection of an appropriate learned response, whereas primary motor cortex is ascribed the function of direct control over the execution of a selected response (Passingham, 1993). In this view, the activity observed here in primary motor cortex would not reflect response selection properties of this region, but may reflect a modulatory role of dorsal premotor regions on primary motor regions. Anatomic connectivity between premotor and primary motor regions is well established in the monkey (Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Godschalk *et al.*, 1984; Matelli *et al.*, 1984; Leichnetz, 1986; Stepniewska *et al.*, 1993), thus providing a possible anatomical substrate for the potential modulatory role of premotor regions on the primary motor cortex. Indeed, recent studies in humans using transcranial magnetic stimulation strongly suggest functional connectivity between these two motor regions. Studies combining TMS and PET point to functional connections from primary motor to dorsal premotor regions (Siebner *et al.*, 2001; Strafella and Paus 2001). More importantly, support for premotor-to-motor connectivity was provided by recent reports in which reduced excitability of primary motor cortex was observed 6 ms after a single conditioning pulse over the premotor cortex (Civardi *et al.*, 2001) and for up to 15 min after a train of pulses over premotor cortex (Gerschlagler *et al.*, 2001).

An alternative interpretation, based on a non-hierarchical model of the functions of the motor system, is suggested by studies of the properties of single neurons in the primary motor cortex. Neurons in the primary motor cortex encode many of the same parameters as neurons in the premotor cortex, including the stimulus-response mapping rule, movement direction and target location (Georgopoulos *et al.*, 1982; Alexander and Crutcher, 1990; Shen and Alexander, 1997a; Zhang *et al.*, 1997). Given these findings, it may be equally plausible to view response selection as a function of both the primary motor and dorsal premotor regions.

The interaction effect in the primary motor cortex showed an asymmetry to the left hemisphere that may reflect the cerebral dominance for motor control and response selection demonstrated in previous studies in humans (Iacoboni *et al.*, 1996, 1998; Schluter *et al.*, 1998, 2001). The cerebral dominance hypothesis could also explain the greater prevalence of activity in the dorsal premotor cortex of the left hemisphere that was most evident during the comparison of the contralateral versus ipsilateral movement conditions.

To conclude, our data converge with developmental (Bekkering *et al.*, 2000) and chronometric data (Wohlschläger and Bekkering, 2002) in suggesting that visible goals modulate human behavior and the motor system during action observation and imitation. A system critically involved in this neural and behavioral mechanism seems to be located in Brodmann's area 44, an area with complex functional properties that seem essential for action understanding and social communication.

Notes

We wish to acknowledge the helpful feedback provided by anonymous

reviewers of an earlier version of this manuscript. This work was supported by the International Human Frontier Science Program and by the following entities: the Brain Mapping Medical Research Organization; the Brain Mapping Support Foundation; the Pierson-Lovelace Foundation; The Ahmanson Foundation; the Tamkin Foundation; the Jennifer Jones-Simon Foundation; the Capital Group Companies Charitable Foundation; the Robson Family; the Northstar Fund; the National Center for Research Resources grants RR12169 and RR08655; and a ROLE National Science Foundation grant to M.I.

Address correspondence to Lisa Koski, Ahmanson-Lovelace Brain Mapping Center, 660 Charles E. Young Drive South, Los Angeles, CA 90095-7085, USA. Email: koski@loni.ucla.edu.

References

- Alexander GE, Crutcher MD (1990) Neural representations of the target (goal) of visually guided arm movements in three motor areas of the monkey. *J Neurophysiol* 64:164-178.
- Amunts K, Schleicher A, Burgel U, Mohlberg H, Uylings HB, Zilles K (1999) Broca's region revisited: cytoarchitecture and intersubject variability. *J Comp Neurol* 412:319-341.
- Arbib MA (2002) The mirror system, imitation, and the evolution of language. In: *Imitation in animals and artifacts* (Nehaniv C, Dautenhahn K, eds). Cambridge, MA: MIT Press (in press).
- Bekkering H, Wohlschläger A (2002) Action perception and imitation. In: *Common mechanisms in perception and action* (Prinz W, Hommel B, eds). Oxford: Oxford University Press (in press).
- Bekkering H, Wohlschläger A, Gattis M (2000) Imitation of gestures in children is goal-directed. *Q J Exp Psychol A* 53:153-164.
- Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, Seitz RJ, Zilles K, Rizzolatti G, Freund HJ (2001) Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur J Neurosci* 13:400-404.
- Civardi C, Cantello R, Asselman P, Rothwell JC (2001) Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. *Neuroimage* 14:1444-1453.
- Craighero L, Fadiga L, Rizzolatti G, Umiltà C (1999) Action for perception: a motor-visual attentional effect. *J Exp Psychol Hum Percept Perform* 25:1673-1692.
- Crammond DJ, Kalaska JF (1994) Modulation of preparatory neuronal activity in dorsal premotor cortex due to stimulus-response compatibility. *J Neurophysiol* 71:1281-1284.
- di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G (1992) Understanding motor events: a neurophysiological study. *Exp Brain Res* 91:176-180.
- Fadiga L, Fogassi L, Gallese V, Rizzolatti G (2000) Visuomotor neurons: ambiguity of the discharge or 'motor' perception? *Int J Psychophysiol* 35:165-177.
- Fu QG, Suarez JI, Ebner TJ (1993) Neuronal specification of direction and distance during reaching movements in the superior precentral premotor area and primary motor cortex of monkeys. *J Neurophysiol* 70:2097-2116.
- Gallese V, Fadiga L, Fogassi L, Rizzolatti G (1996) Action recognition in the premotor cortex. *Brain* 119:593-609.
- Georgopoulos AP, Kalaska JF, Caminiti R, Massey JT (1982) On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J Neurosci* 2:1527-1537.
- Gerschlagler W, Siebner HR, Rothwell JC (2001) Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. *Neurology* 57:449-455.
- Gleissner B, Meltzoff AN, Bekkering H (2000) Children's coding of human action: cognitive factors influencing imitation in 3-year-olds. *Dev Science* 3:405-414.
- Godschalk M, Lemon RN, Kuypers HG, Runday HK (1984) Cortical afferents and efferents of monkey postarcuate area: an anatomical and electrophysiological study. *Exp Brain Res* 56:410-424.
- Gomez JE, Fu Q, Flament D, Ebner TJ (2000) Representation of accuracy in the dorsal premotor cortex. *Eur J Neurosci* 12:3748-3760.
- Grafton ST, Arbib MA, 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.
- Greenwald AG (1970) Sensory feedback mechanism in performance

- control: with special reference to the ideomotor mechanism. *Psychol Rev* 77:73-99.
- Hoshi E, Tanji J (2000) Integration of target and body-part information in the premotor cortex when planning action. *Nature* 408:466-470.
- Iacoboni M, Woods RP, Mazziotta JC (1996) Brain-behavior relationships: evidence from practice effects in spatial stimulus-response compatibility. *J Neurophysiol* 76:321-331.
- Iacoboni M, Woods RP, Lenzi GL, Mazziotta JC (1997) Merging of oculomotor and somatomotor space coding in the human right precentral gyrus. *Brain* 120:1635-1645.
- Iacoboni M, Woods RP, Mazziotta JC (1998) Bimodal (auditory and visual) left frontoparietal circuitry for sensorimotor integration and sensorimotor learning. *Brain* 121:2135-2143.
- Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, Rizzolatti G (1999) Cortical mechanisms of human imitation. *Science* 286:2526-2528.
- Iacoboni M, Koski L, Brass M, Bekkering H, Woods RP, Dubeau M-C, Mazziotta JC, Rizzolatti G (2001) Reafferent copies of imitated actions in the right superior temporal cortex. *Proc Natl Acad Sci USA* 98:13995-13999.
- Johnson MT, Coltz JD, Ebner TJ (1999a) Encoding of target direction and speed during visual instruction and arm tracking in dorsal premotor and primary motor cortical neurons. *Eur J Neurosci* 11:4433-4445.
- Johnson MT, Coltz JD, Hagen MC, Ebner TJ (1999b) Visuomotor processing as reflected in the directional discharge of premotor and primary motor cortex neurons. *J Neurophysiol* 81:875-894.
- Krams M, Rushworth MFS, Deiber M-P, Frackowiak RSJ, Passingham RE (1998) The preparation, execution and suppression of copied movements in the human brain. *Exp Brain Res* 120:386-398.
- Kurata K (1994) Information processing for motor control in primate premotor cortex. *Behav Brain Res* 61:135-142.
- Kurata K, Hoffman DS (1994) Differential effects of muscimol microinjection into dorsal and ventral aspects of the premotor cortex of monkeys. *J Neurophysiol* 71:1151-1164.
- Leichnetz GR (1986) Afferent and efferent connections of the dorsolateral precentral gyrus (area 4, hand/arm region) in the macaque monkey, with comparisons to area 8. *J Comp Neurol* 254:460-492.
- Matelli M, Camarda R, Glickstein M, Rizzolatti G (1984) Interconnections within the postarcuate cortex (area 6) of the macaque monkey. *Brain Res* 310:388-392.
- Matsumura M, Kubota K (1979) Cortical projection to hand-arm motor area from post-arcuate area in macaque monkeys: a histological study of retrograde transport of horseradish peroxidase. *Neurosci Lett* 11:241-246.
- Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, *et al.* (2001) A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philos Trans R Soc Lond B Biol Sci* 356:1293-1322.
- Meltzoff AN, Moore MK (1997) Explaining facial imitation: a theoretical model. *Early Dev Parenting* 6:179-192.
- Messier J, Kalaska JF (2000) Covariation of primate dorsal premotor cell activity with direction and amplitude during a memorized-delay reaching task. *J Neurophysiol* 84:152-165.
- Molnar-Szakacs I, Iacoboni M, Koski L, Maeda F, Dubeau M-C, Aziz-Zadeh L, Mazziotta J (2002) Action observation in the pars opercularis: evidence from 58 subjects studied with fMRI. Annual Meeting of the Cognitive Neuroscience Society, 2002, abstract.
- Muakkassa KF, Strick PL (1979) Frontal lobe inputs to primate motor cortex: evidence for four somatotopically organized 'premotor' areas. *Brain Res* 177:176-182.
- Nishitani N, Hari R (2000) Temporal dynamics of cortical representation for action. *Proc Natl Acad Sci USA* 97:913-918.
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia* 9:97-113.
- Parsons LM, Fox PT (1998) The neural basis of implicit movements used in recognising hand shape. *Cogn Neuropsychol* 15:583-615.
- Passingham RE (1993) *The frontal lobe and voluntary action*. New York: Oxford University Press.
- Petrides M (1982) Motor conditional associative-learning after selective prefrontal lesions in the monkey. *Behav Brain Res* 5:407-413.
- Petrides M (1985) Deficits in non-spatial conditional associative learning after periarculate lesions in the monkey. *Behav Brain Res* 16:95-101.
- Petrides M (1987) Conditional learning and the primate frontal cortex. In: *The frontal lobes revisited* (Perecma E, ed.), pp. 91-108. New York: IRBN Press.
- Petrides M, Pandya DN (1994) Comparative architectonic analysis of the human and the macaque frontal cortex. In: *Handbook of neuropsychology* (Boller F, Grafman J, eds), pp. 17-58. Amsterdam: Elsevier.
- Praamstra P, Kleine BU, Schnitzler A (1999) Magnetic stimulation of the dorsal premotor cortex modulates the Simon effect. *Neuroreport* 10:3671-3674.
- Praamstra P, Plat FM (2001) Failed suppression of direct visuomotor activation in Parkinson's disease. *J Cogn Neurosci* 13:31-43.
- Rizzolatti G, Arbib MA (1998) Language within our grasp. *Trends Neurosci* 21:188-194.
- Rizzolatti G, Gentilucci M, Fogassi L, Luppino G, Matelli M, Ponzoni-Maggi S (1987a) Neurons related to goal-directed motor acts in inferior area 6 of the macaque monkey. *Exp Brain Res* 67:220-224.
- Rizzolatti G, Riggio L, Dascola I, Umilta C (1987b) Reorienting attention across the horizontal and vertical meridians: evidence in favor of a premotor theory of attention. *Neuropsychologia* 25:31-40.
- 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, Gentilucci M, Camarda RM, Gallese V, Luppino G, Matelli M, Fogassi L (1990) Neurons related to reaching-grasping arm movements in the rostral part of area 6 (area 6a beta). *Exp Brain Res* 82:337-350.
- Rizzolatti G, Riggio L, Sheliga BM (1994) Space and selective attention. In: *Attention and performance XV* (Moscovitch M, Umilta C, eds), pp. 232-265. Cambridge, MA: MIT Press.
- Rizzolatti G, Fadiga L, Gallese V, Fogassi L (1996a) Premotor cortex and the recognition of motor actions. *Brain Res 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.
- Rizzolatti G, Luppino G, Matelli M (1998) The organization of the cortical motor system: new concepts. *Electroencephalogr Clin Neurophysiol* 106:283-296.
- Schluter ND, Rushworth MFS, Passingham RE, Mills KR (1998) Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements: a study using transcranial magnetic stimulation. *Brain* 121:785-799.
- Schluter ND, Krams M, Rushworth MF, Passingham RE (2001) Cerebral dominance for action in the human brain: the selection of actions. *Neuropsychologia* 39:105-113.
- Schofield WN (1976) Do children find movements which cross the body midline difficult? *Q J Exp Psychol* 28:571-582.
- Shen L, Alexander GE (1997a) Neural correlates of a spatial sensory-to-motor transformation in primary motor cortex. *J Neurophysiol* 77:1171-1194.
- Shen L, Alexander GE (1997b) Preferential representation of instructed target location versus limb trajectory in dorsal premotor area. *J Neurophysiol* 77:1195-1212.
- Siebner H, Peller M, Bartenstein P, Willech F, Rossmeier C, Schwaiger M, Conrad B (2001) Activation of frontal premotor areas during suprathreshold transcranial magnetic stimulation of the left primary sensorimotor cortex: a glucose metabolic PET study. *Hum Brain Mapp* 12:157-167.
- Stepniewska I, Preuss TM, Kaas JH (1993) Architectonics, somatotopic organization, and ipsilateral cortical connections of the primary motor area (M1) of owl monkeys. *J Comp Neurol* 330:238-271.
- Strafella AP, Paus T (2001) Cerebral blood-flow changes induced by paired-pulse transcranial magnetic stimulation of the primary motor cortex. *J Neurophysiol* 85:2624-2629.
- Tomaiuolo F, MacDonald JD, Caramanos Z, Posner G, Chiavaras M, Evans AC, 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.
- Tomasello M (1999) *The cultural origins of human cognition*. Cambridge, MA: Harvard University Press.
- Toni I, Passingham RE (1999) Prefrontal-basal ganglia pathways are involved in the learning of arbitrary visuomotor associations: a PET study. *Exp Brain Res* 127:19-32.

- Travis LL (1997) Goal-based organization of event memory in toddlers. In: Developmental spans in event comprehension and representation: bridging fictional and actual events (van den Broek PW, Bauer PJ, Bourg T, eds), pp. 111-138. Mahwah, NJ: Erlbaum.
- Wise SP (1985) The primate premotor cortex: past, present, and preparatory. *Annu Rev Neurosci* 8:1-19.
- Wise SP, di Pellegrino G, Boussaoud D (1996) The premotor cortex and nonstandard sensorimotor mapping. *Can J Physiol Pharmacol* 74: 469-482.
- Wohlschläger A, Bekkering H (2002) Is human imitation based on a mirror-neuron system? Some behavioural evidence. *Exp Brain Res* 143: 335-341.
- Woods RP, Iacoboni M, Grafton ST, Mazziotta JC (1996) Improved analysis of functional activation studies involving within-subject replications using a three-way ANOVA model. In: Quantification of brain function using PET (Myers R, Cunningham V, Bailey D, Jones T, eds), pp. 353-358. San Diego, CA: Academic Press.
- Woods RP, Grafton ST, Holmes CJ, Cherry SR, Mazziotta JC (1998a) Automated image registration: I. General methods and intrasubject, intramodality validation. *J Comput Assist Tomogr* 22:139-152.
- Woods RP, Grafton ST, Watson JD, Sicotte NL, Mazziotta JC (1998b) Automated image registration: II. Intersubject validation of linear and nonlinear models. *J Comput Assist Tomogr* 22:153-165.
- Woods RP, Dapretto M, Sicotte NL, Toga AW, Mazziotta JC (1999) Creation and use of a Talairach-compatible atlas for accurate, automated, nonlinear intersubject registration, and analysis of functional imaging data. *Hum Brain Mapp* 8:73-79.
- Woodward AL (1998) Infants selectively encode the goal object of an actor's reach. *Cognition* 69:1-34.
- Worsley KJ (1996) A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp* 4:58-73.
- Zhang J, Riehle A, Requin J, Kornblum S (1997) Dynamics of single neuron activity in monkey primary motor cortex related to sensorimotor transformation. *J Neurosci* 17:2227-2246.