

Functional Segregation within Pars Opercularis of the Inferior Frontal Gyrus: Evidence from fMRI Studies of Imitation and Action Observation

Istvan Molnar-Szakacs^{1,2,3}, Marco Iacoboni^{1,2,3,4,5}, Lisa Koski^{1,6} and John C. Mazziotta^{1,3,4,5,6,7,8}

¹Ahmanson-Lovelace Brain Mapping Center, 660 Charles Young Dr. South, Los Angeles, CA 90095, USA, ²FPR-UCLA Center for Culture, Brain and Development, Los Angeles, CA, USA, ³Brain Research Institute, David Geffen School of Medicine at University of California, Los Angeles, CA, USA, ⁴Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at University of California, Los Angeles, CA, USA, ⁵Neuropsychiatric Institute, David Geffen School of Medicine at University of California, Los Angeles, CA, USA, ⁶Department of Neurology, David Geffen School of Medicine at University of California, Los Angeles, CA, USA, ⁷Department of Pharmacology, David Geffen School of Medicine at University of California, Los Angeles, CA, USA, ⁸Department of Radiological Sciences, David Geffen School of Medicine at University of California, Los Angeles, CA, USA

Recent neuroimaging studies have suggested that the inferior frontal gyrus (IFG) is important for action observation and imitation. In order to further explore the role of IFG in action observation and imitation, we pooled data from seven functional magnetic resonance imaging studies involving observation and imitation of simple finger movements performed in our laboratory. For imitation we found two peaks of activation in the pars opercularis, one in its dorsal sector and the other in its ventral sector. The dorsal sector of the pars opercularis was also activated during action observation, whereas the ventral sector was not. In addition, the pars triangularis was activated during action observation but not during imitation. This large dataset suggests a functional parcellation of the IFG that we discuss in terms of human mirror areas and the computational motor control architecture of internal models.

Keywords: action, Broca's area, internal models, language, mirror neurons

Introduction

Broca's aphasia, a nonfluent aphasia with preservation of comprehension, was described well over a century ago, localizing language function to the left inferior frontal cortex (Broca, 1861; Foundas *et al.*, 1998). Speech arrest produced by direct cortical stimulation, and most recently by transcranial magnetic stimulation (TMS) have also enforced the notion that Broca's area plays a role in the motor aspects of language production (Ojemann and Whitaker, 1978; Ojemann, 1991; Epstein *et al.*, 1999).

Although traditionally considered the most important language area in the brain, functions of Broca's area are not limited to language. Recent neuroimaging studies have demonstrated the importance of this region for grasping, motor sequence learning, motor imagery, observation and preparation of action and imitation (Rizzolatti *et al.*, 1996b; Krams *et al.*, 1998; Binkofski *et al.*, 1999, 2000; Iacoboni *et al.*, 1999; Ehrsson *et al.*, 2000; Grafton *et al.*, 2002; Koski *et al.*, 2002; Mecklinger *et al.*, 2002; Johnson-Frey *et al.*, 2003). One explanation for these findings is that Broca's area is involved in the subconscious mediation of these motor processes by internal speech (Grezes and Decety, 2001). However, a recent study showed that repetitive TMS when applied over the pars opercularis of the inferior frontal gyrus (IFG) in either hemisphere preferentially disrupted an imitation task versus its motor control task

(Heiser *et al.*, 2003). Furthermore, in a functional magnetic resonance imaging (fMRI) study comparing anatomic (actor and imitator both move anatomically congruent hand) versus specular imitation (the actor moves the right hand and the imitator the left hand, as if in a mirror), there was stronger response in the pars opercularis during the latter condition (Koski *et al.*, 2003). It is difficult to imagine why imitation, but not motor execution (and similarly, specular but not anatomic imitation) would require mediation through internal speech. Taken together, this evidence suggests this region's role in imitation is not due to linguistic mediation, but rather is modulated by the imitative behavior itself.

Beyond its traditional role in language, Broca's area appears to anchor a simulation network that provides a link between perceived and executed actions through a 'mirror' like mechanism (Rizzolatti and Arbib, 1998; Iacoboni *et al.*, 1999; Chaminade *et al.*, 2001; Carr *et al.*, 2003). Direct evidence of 'mirror' activity in the macaque brain has been provided through electrophysiological recordings. Neurons located in the ventral premotor area F5 of macaque cortex fire both when the monkey performs a particular action such as grasping, tearing and holding, and when it observes another individual (monkey or human) performing a similar action (Gallese *et al.*, 1996; Rizzolatti *et al.*, 1996a; Ferrari *et al.*, 2001, 2003). This firing pattern may enable an individual to recognize the actions of others by mapping them onto their own internal representation, or motor schema of that action, also encoded by mirror neurons in area F5 (Arbib, 1981; Rizzolatti *et al.*, 1988). These neurons have been proposed to be the neural substrate of an observation-execution matching system. Such a system would serve as a link between perceived and executed actions and as a communicative channel between interacting individuals (Rizzolatti and Arbib, 1998).

Area F5 of the monkey cortex is generally considered to be the homologue of Brodmann's area 44 (BA44) in the human brain (Preuss, 1995; Rizzolatti and Arbib, 1998; Geyer *et al.*, 2000). This is based on the hypothesis that the ventral portion of the arcuate sulcus, which is the superior border of area F5 in the monkey brain, evolved into the inferior frontal sulcus in the human brain. The inferior frontal sulcus is the superior border of the homologous human structure, the pars opercularis (Rizzolatti and Arbib, 1998). Probabilistic data suggest that the

pars opercularis encompasses BA44 within its sulcal borders (Amunts *et al.*, 1999; Mazziotta *et al.*, 2001). The pars opercularis is the caudalmost sector of the IFG, and is located immediately anterior to the ventralmost sector of the precentral gyrus, with the anterior vertical (or ascending) ramus forming its anterior border (Foundas *et al.*, 1998).

Current imaging literature on language defines Broca's area as encompassing both Brodmann areas (BAs) 44 and 45 (Aboitiz and Garcia, 1997; Bookheimer, 2002). The cytoarchitectonic region defined as BA45 roughly encompasses the pars triangularis of the IFG (Mazziotta *et al.*, 2001). This region is bounded by the inferior frontal sulcus dorsally, the anterior horizontal ramus inferiorly and the anterior ascending ramus caudally. This latter sulcus divides pars triangularis from the posteriorly adjacent pars opercularis (Foundas *et al.*, 1998). Regions around Broca's area are also involved in various aspects of motor and linguistic processing. In particular, the neighboring ventral premotor cortex (vBA6) has been shown to be important for motor sequence learning, motor imagery (Rizzolatti *et al.*, 1996b; Grafton *et al.*, 2002; Grezes and Decety, 2002; Koski *et al.*, 2002) and phonological processing (Friederici *et al.*, 2000; Roskies *et al.*, 2001).

Neuroimaging studies on language have provided evidence of a functional segregation within Broca's area, with semantics, syntax, phonological processing and verbal working memory represented in different subregions of the IFG (Paulesu *et al.*, 1993, 1997; Demb *et al.*, 1995; Dapretto and Bookheimer, 1999; Ni *et al.*, 2000b; Chein *et al.*, 2002; for a review, see Bookheimer, 2002). Furthermore, task-dependent functional segregation within the pars opercularis has been shown for semantic processing (Roskies *et al.*, 2001). Thus, a relatively clear picture emerges from the language literature that assigns specific aspects of language processing to subregions of the IFG. An important role for the IFG has also been described for various aspects of motor processing, including motor sequence learning, action observation, motor imagery and imitation (Rauch *et al.*, 1995; Grafton *et al.*, 1996; Rizzolatti *et al.*, 1996b; Iacoboni *et al.*, 1999; Gerardin *et al.*, 2000; Grezes and Decety, 2002), yet there is no emergent functional parcellation of the IFG for motor and imitative behavior that parallels the findings in the language literature. The current evidence regarding motor processing assigns functions to BA45 that are not dissimilar from that of the neighboring BA44, making it difficult to precisely localize neural functions to their anatomical substrates.

The goal of the present study was to look for evidence of a functional parcellation of the IFG during action observation and imitation, with a particular focus on the role of the pars opercularis and pars triangularis. These subregions of the IFG have emerged as important to various aspects of both language and motor function. We pooled together and reanalyzed data from our laboratory of 58 subjects performing action observation tasks, 47 of whom also performed imitation tasks. The advantage of this approach, compared to traditional meta-analytic approaches, is that the data we pooled together were collected on the same scanner and processed using the same analysis tools, thereby avoiding discrepancies in the computation and reporting of spatial coordinates (Fox and Parsons, 1998). In addition, including several studies in the analysis strengthens results by averaging out differences in task requirements of individual studies to provide us with a clear picture of relative blood oxygen level dependent (BOLD) signal change.

These changes in BOLD signal are an indirect measure of relative cerebral perfusion, or 'activations', that are fundamental to basic aspects of observation and imitation of finger movements.

Materials and Methods

Subjects

Combining the subjects from seven studies on imitation and action observation performed in our lab yielded 58 right-handed subjects (27 female) for this analysis. Subjects gave informed consent to participate in each study, according to the requirements of the Institutional Review Board of UCLA. The mean age of subjects was 26.16 years \pm 6.4. Handedness was assessed by a questionnaire adapted from the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects had normal or corrected-to-normal vision. A brief neurological exam and screening questionnaire to rule out medication use, a history of neurological or psychiatric disorders, substance abuse and other medical conditions were completed prior to scanning. For all studies, images were acquired using a GE 3.0 T MRI scanner with an upgrade for advanced nuclear magnetic resonance-echo planar imaging.

Original Data Acquisition

For the purposes of this study we reanalyzed individual subject data from seven fMRI studies conducted in our laboratory, some of which have already been published independently (Iacoboni *et al.*, 1999; Koski *et al.*, 2002, 2003). The stimuli involved images of hands representing simple lifting or side-to-side movements of the index finger or middle finger from a resting position on a flat surface. The hands were oriented with fingers toward the subject and were presented on a uniform background. Some trials contained an animated hand executing an actual movement and other trials represented movement symbolically by a cross appearing on the index or middle finger (control conditions). In some studies, the fingers moved towards dot targets on the flat surface, while other studies contained no such visual targets. Finally, one of the studies used a simple reaching and grasping of a cup as a stimulus. In all of the stimulus sets, the full hand and part of the forearm was visible to subjects, but no other parts of the body.

In these seven studies, conditions required the subjects to use only their right hand, both hands simultaneously or both hands alternating within the same block. Thus, this reanalysis included data for the right hand blocks and mixed blocks, but not for left hand. For subjects that gave bimanual responses, the data from both hands was averaged. This approach was necessitated by the fact that in some of the original studies, the use of alternating hands was intermixed within the same block. We compared the data from the observation and the imitation conditions with a resting baseline condition. The total number of subjects in this analysis was 58 subjects for action observation and 47 subjects for imitation.

In addition, a subset of 24 subjects performed a control motor task and a control visual task, and for this subset of subjects we compared the activity during imitation and action observation with their respective control tasks. The control motor tasks require the same motor output as the imitation tasks, but the movement in this case is cued by a spatial cue, rather than the biological stimulus of a hand. The visual control task for action observation contains the same visual information as the stimulus, but the movement of the hand is replaced by the appearance of a spatial cue.

All studies used a 2-D spin echo sequence ($T_R = 4000$ ms, $T_E = 40$ ms, 256×256 voxel matrix, 4 mm thickness, 1 mm spacing), to rule out any brain abnormalities and allow prescription of the slices to be obtained in the remaining sequences. Functional data were acquired using echo planar T2-weighted gradient echo sequence ($T_R = 4000$ ms, $T_E =$ either 25 ms or 70 ms, flip angle = 90° , 64×64 voxel matrix, 26 slices, 4 mm thickness, 1 mm spacing). Anatomical data in all studies were acquired with a coplanar high-resolution T2-weighted echo planar imaging volume with $T_R = 4000$ ms, $T_E = 54$ ms, flip angle = 90° , 128×128 voxel matrix, 26 axial slices, 3.125 mm in-plane resolution, 4 mm thickness, 1 mm spacing.

Original Data Processing

Functional images were aligned to the coplanar high-resolution EPI volume within each subject with a rigid-body linear registration algorithm (Woods *et al.*, 1998a). Image spatial normalization was performed with fifth-order polynomial nonlinear warping (Woods *et al.*, 1998b) of each participant's images into a Talairach-compatible brain magnetic resonance atlas (Woods *et al.*, 1999). Data were smoothed using an in-plane, Gaussian filter to produce a final image resolution of $8.7 \times 8.7 \times 8.6$ mm.

Post-processing Image Reanalysis

Mean images were made of individual subjects' data for each experiment by averaging the images across a given condition (i.e. imitation, observation, rest) within and across runs. The first and last image volume of each task and rest period were excluded due to the blurred nature of the hemodynamic response (Menon and Kim, 1999). This post-processing procedure resulted in one image per task (imitation, observation, rest) per subject.

Statistical analysis was performed using fixed effects two-way analysis of variance (ANOVA) (Woods *et al.*, 1996) on the signal intensity at each voxel throughout each task for each contrast. We used a two-way ANOVA for the imitation versus rest contrast with factors subjects ($n = 47$) and task (imitation, rest). Similarly for the action observation versus rest contrast we had factors subjects ($n = 58$) and task (action observation, rest). Two additional two-way ANOVAs were performed, for the contrasts of imitation versus action observation with factors subjects ($n = 47$) and task (imitation, action observation), and for the inverse contrast.

The recent probabilistic map constructed by Tomaiuolo and colleagues found the average volume of the pars opercularis to be 3.68 ml (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 (resels) in our study. This corresponds to a critical t -value of 2.44 for 57 degrees of freedom (df) resulting from the analysis of action observation data (subjects = 58) and a critical t -value of 2.45 for 46 df resulting from the analysis of imitation data (subjects = 47). The statistical threshold for brain areas outside pars opercularis was set at $P = 0.001$ uncorrected ($t = 3.24$, $df = 57$; $t = 3.28$, $df = 46$) (Worsley, 1996). In addition to sulcal anatomic landmarks, we also used cytoarchitectonic probabilistic maps of BA44 and BA45 (Amunts *et al.*, 1999), as well as MRI-based probabilistic maps of the pars opercularis (Tomaiuolo *et al.*, 1999), to determine the anatomic location of each peak.

Activity Profile in Significantly Activated Voxels

To further explore the pattern of increased BOLD signal and to rule out the possibility that the change in cerebral blood flow observed during action observation or imitation could be due to lower-level functions

such as visual input or motor output, we compared the pattern of BOLD response during action observation and imitation to two control tasks, a control motor task for imitation and a control visual task for action observation. These tasks were performed only by a subset of subjects ($n = 24$).

Results

Action observation

The results of the contrast of action observation versus rest are presented in Table 1 and Figure 1. Compared with the resting baseline, action observation showed significant increases in BOLD signal bilaterally in the pars opercularis, pars triangularis and ventral premotor cortex (vBA6). Activity in the pars opercularis was confined to its dorsal sector, and was more widespread in the left hemisphere. Activity in the pars triangularis was present mostly in the right hemisphere. In the left hemisphere, only one voxel was significantly above threshold at $P = 0.001$, uncorrected. At lower statistical thresholds however, a large cluster of voxels was identified in the pars triangularis of the left hemisphere.

We performed repeated measures ANOVA on the average percent change in BOLD signal intensity at the peak voxels in the pars triangularis from the left and right hemispheres from the contrast of observation versus rest. Although the pars triangularis shows a stronger BOLD response for action observation than during the imitation task, the main effect of task did not reach significance. This result is likely due to the large variability in the BOLD response during the control motor and visual tasks.

Imitation

The results of the contrast of imitation versus rest are presented in Table 1 and Figure 2. Imitation of action versus resting baseline yields significant bilateral increases in BOLD signal in the pars opercularis, but not in the pars triangularis. The ventral portion of the premotor cortex was also activated bilaterally. The pars opercularis of the left hemisphere contains two distinct peaks of activity, one in the dorsal and one in the ventral sector, whereas in the right hemisphere, a single peak was observed in the dorsal sector.

Table 1
Relative BOLD Signal Changes for Task-Specific Contrasts

Contrast	H	Region	BA	Talairach coordinates			t	Cluster size	Probabilistic location (%)		
				x	y	z			1 PO	2 BA44	BA45
Observation > rest df = 57	L	vPMC	6	-38	6	30	4.46	245		20	
	L	dPO	44	-48	18	24	4.38	176	25-50	30	20
	L	PT	45	-48	24	6	3.28	1		20	30
	R	vPMC	6	46	2	36	6.16	478			
	R	dPO	44	50	10	16	4.3	78	25-50	50	10
	R	PT	45	50	26	4	3.89	61			
Imitation > rest df = 46	L	vPMC	6/9	-50	6	36	5.68	290		10	
	L	dPO	44	-56	10	20	5	178	25-50	50	10
	L	vPO	44	-52	8	8	5	140	25-50	30	10
	R	dPO	44	52	8	20	6.32	336	25-50	40	

Note: H indicates left (L) or right (R) hemisphere; Region refers to areas delineated by sulcal anatomy corresponding to the Brodmann's areas: ventral premotor cortex (vPMC), dorsal pars opercularis (dPO), ventral pars opercularis (vPO) and pars triangularis (PT); x, y, z = peak of greatest signal intensity in the t -map, in Talairach coordinates (Talairach and Tournoux, 1988); Cluster size is the extent of the activation surrounding the reported peaks in voxels; Probabilistic location refers to occurrence frequencies from: (1) the MRI-based probability map of pars opercularis by Tomaiuolo *et al.* (1999) and (2) cytoarchitectonic probability mapping of BA44 and BA45 (Amunts *et al.*, 1999).

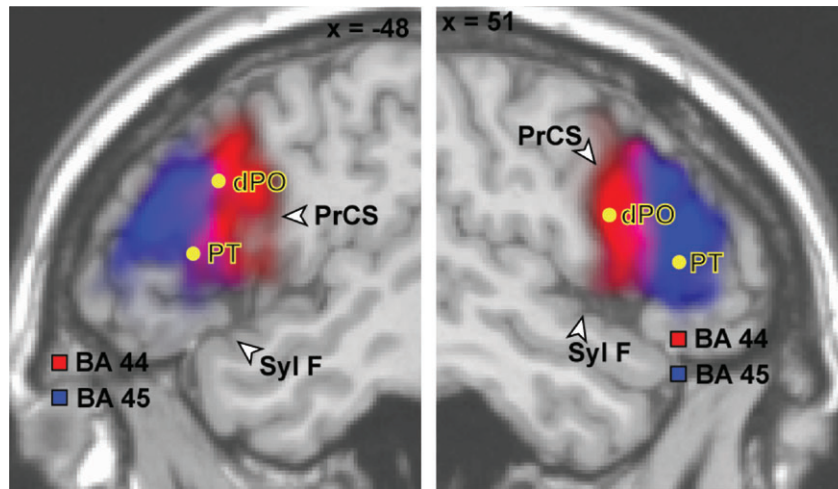


Figure 1. Location of the peak voxels of signal change for the action observation versus rest contrast, overlaid on probabilistic cytoarchitectonic maps of BA44 and BA45 in the left and right hemispheres. The dorsal sector of the pars opercularis (BA44) is activated in both the left (LH) and the right hemisphere (RH). There is also a significant bilateral peak of activation in the pars triangularis (BA45), showing a functional parcellation of the inferior frontal gyrus during action observation. The peaks lay close to the planes shown ($x = -48$) in LH and ($x = 51$) in RH. Coordinates for the peak voxels are listed in Table 1. PrCs, precentral sulcus; SylF, Sylvian fissure, BA, Brodmann's areas.

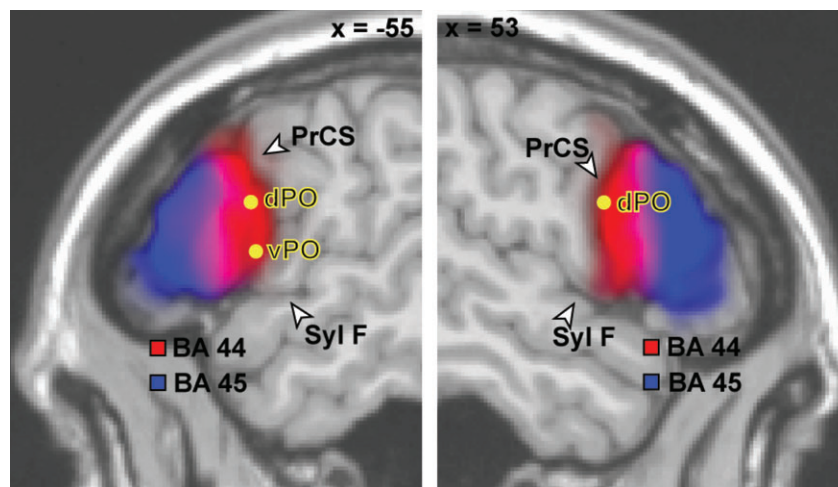


Figure 2. Location of the peak voxels of signal change for the imitation versus rest contrast, overlaid on probabilistic cytoarchitectonic maps of BA44 and BA45 in the left and right hemispheres. The pars opercularis (BA44) of the left hemisphere (LH) shows functional segregation with significant activations in the dorsal and ventral sector. The right hemisphere (RH) contains a peak in the dorsal sector of the pars opercularis. There are no significant activations in the pars triangularis (BA45) in either hemisphere. The peaks lay close to the planes shown ($x = -55$) in LH and ($x = 53$) in RH. Coordinates for the peak voxels are listed in Table 1. PrCs, precentral sulcus; SylF, Sylvian fissure, BA, Brodmann's areas.

To further explore the nature of the response in the dorsal sector of the pars opercularis, we performed a repeated measures ANOVA on the average percent change in BOLD signal intensity at the peak voxels from the imitation versus rest and observation versus rest contrasts. We combined values from peaks in both hemispheres and both contrasts in order to avoid unfairly biasing the pattern of results in favor of either task. With task (imitation, action observation) as the within-subjects factor, we found a significant task effect ($P = 0.025$). The percent change in BOLD response during imitation and action observation is shown in Figure 3. The dorsal sector of the pars opercularis, which was activated bilaterally during both imitation and action observation, shows the predicted BOLD response of a mirror region. It is active during action observation, but significantly more so during imitation, a task which contains both an observation and an execution component.

In addition, we also performed repeated-measures ANOVA on the percent change in BOLD signal during the four experimental conditions in the dorsal sector of pars opercularis active during both imitation and action observation. We used the average percent change at the peak voxels in left and right hemisphere from the contrast of imitation versus rest and observation versus rest. These data did show the predicted trend of largest increase in BOLD signal for imitation, smaller for action observation and lowest for the control conditions; however, the main effect of task was not significant.

A repeated measures ANOVA on the percent change in BOLD response in the ventral sector of the pars opercularis during imitation, action observation and their respective control conditions revealed a significant task effect ($P = 0.04$). Task (imitation, action observation and a control motor task for imitation and a control visual task for action observation) was

used as the within-subjects factor. The percent change in BOLD response during action observation, imitation and their respective control conditions is shown in Figure 4. The ventral sector of the pars opercularis shows a significantly stronger ($P = 0.02$) BOLD response during imitation than during the control motor task in which the motor output is identical to the imitation task. Thus, the increased signal in the ventral pars opercularis may be attributed to processes specific to imitation, rather than to the general requirement to perform a motor response.

Imitation versus Action Observation

A direct contrast between imitation and action observation for those 47 subjects who performed both these tasks revealed bilateral activations in the insula and the dorsal premotor cortex. We do not discuss these findings further, as these activations fall outside our current regions of interest.

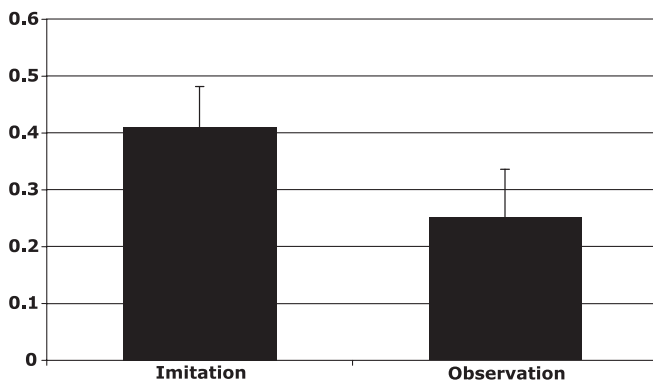


Figure 3. Percent change in BOLD signal during imitation and action observation in the dorsal sector of pars opercularis active during both tasks. The activation profile is for the average values at the peak voxels from both the left and right hemisphere of both the imitation versus rest and action observation versus rest contrasts. Error bars indicate standard error. Data is from the subset of 47 subjects who performed both imitation and action observation. The dorsal sector of pars opercularis shows a significantly stronger BOLD response during imitation than during action observation ($P = 0.025$). This is the predicted pattern of response for a mirror region, showing some response during the observation of action, but significantly more response during its imitation, which also includes an execution component (see text for further details).

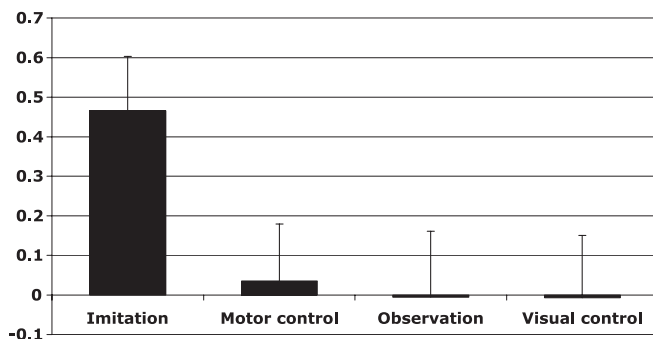


Figure 4. Percent change in BOLD signal during the four experimental conditions in the ventral sector of pars opercularis active during imitation, but not during action observation. The activation profile is for the peak voxel $(-52, 8, 8)$ from the contrast of imitation versus rest. Error bars indicate standard error. Data is only from the subset of 24 subjects who performed a control motor task for imitation and a control visual task for action observation. The ventral sector of pars opercularis shows a significantly stronger BOLD response during imitation than during a control motor task in which the motor output is identical to the imitation task ($P = 0.02$). This suggests that the ventral sector of pars opercularis is not simply a premotor area activated by the motor component of the imitation task (see text for further details).

Action Observation versus Imitation

A direct contrast of action observation and imitation in 47 subjects revealed a significantly higher BOLD response in the right pars triangularis during action observation, which is expected due to the significantly higher response in this region in the action observation versus rest condition, than the imitation versus rest condition described above.

Discussion

The large dataset analyzed here suggests a functional parcellation of the pars opercularis of the inferior frontal gyrus. The dorsal sector of the pars opercularis is active during both action observation and imitation, but significantly more so during imitation. The ventral sector of the pars opercularis is activated only during imitation. Furthermore, this ventral sector shows no activity during a control motor task in which the motor output is effectively identical to the motor output of the imitation task. Finally, the pars triangularis is activated during action observation but not during imitation.

To localize the BOLD signal changes we observed in our study, we adopted multiple criteria. As typically done in brain imaging literature, we assigned the coordinates of activation peaks to specific brain structures, adopting the classical deterministic approach of the Talairach coordinate system (Talairach and Tournoux, 1988). Deterministic localization of a structure on the basis of functional data is, however, problematic, due to known variability among human brains (for a discussion, see Mazziotta *et al.*, 2001). Thus, to localize the observed foci of activation more meaningfully, we also mapped our data onto probabilistic locations at both the morphological and cytoarchitectonic level of description (Amunts *et al.*, 1999; Tomaiuolo *et al.*, 1999). To use both morphological and cytoarchitectonic indicators of localization is essential, since it has been shown that sulcal anatomy is not a reliable indicator of cytoarchitectonic features in Broca's area (Amunts *et al.*, 1999). The combination of standardized coordinates and probability mapping at the cytoarchitectonic and morphological levels provides a better description of the concordance between structure and function in our region of interest, the pars opercularis. Note that our reanalysis was performed on studies in which the individual anatomical data were acquired only for registration purposes and not for individual anatomical localization. Thus, we are unable to report data on the individual variability in the localization of peaks of activation and our results should be interpreted mostly at a probabilistic population level. Hence, some caution is warranted in translating our results in terms of functional localization within the pars opercularis and pars triangularis at the individual level.

Our results can be interpreted in terms of the observation-execution matching system subserved by human mirror areas, and the computational motor control literature of internal models. It appears that the dorsal sector of pars opercularis likely represents the *mirror* region of the IFG, as it is active during both action observation and imitation, but significantly more so during imitation. Human mirror regions show properties similar to those described for mirror neurons in the monkey brain (Gallese *et al.*, 1996). BOLD signal change in a human mirror region is present during action observation, but is larger during imitation, a task that also includes an execution component (Iacoboni *et al.*, 1999; Koski *et al.*, 2002, 2003). This is precisely the pattern of response we observe in this

region. The ventral sector of the pars opercularis cannot be considered simply a premotor area, or we would expect to see a relative increase in cerebral blood flow in this region during a control motor task as well. We propose that the ventral sector of the pars opercularis is the source of the efferent copy of motor plans that is sent to the posterior part of the superior temporal sulcus (STS) during imitation (Iacoboni *et al.*, 2001; Miall, 2003; Iacoboni, 2004). By virtue of this cortico-cortical loop between posterior IFG and STS, likely passing through the rostral part of the posterior parietal cortex, given that direct connections between IFG and STS have not been described in the primate brain (Petrides and Pandya, 1988), a forward model that predicts the sensory consequences of planned imitative actions can be hypothesized.

Internal models are simulators of sensory-motor states and are computationally useful as predictors in motor control and sensory-motor integration (Wolpert *et al.*, 1995; Wolpert and Kawato, 1998). Forward models are extremely useful during imitation as predictors of the output of the motor plan even when simple finger movements are involved, given that the task requires the accurate matching of the observed finger movement. Inverse models calculate the motor commands necessary to achieve a desired trajectory, in this case for the movement of the finger. Based on the pattern of activity in the ventral sector of the pars opercularis, we conclude that the input of the forward model arises here from efferent copies of motor plans during imitation. During the control motor task, however, only finger movement selection based on a spatial cue is required. This difference in task requirements likely necessitates a forward model in the imitation task but not in the control motor task, giving rise to the pattern of activity we see in this ventral region. The output of the forward model results from the matching of the predicted sensory consequences of the planned imitative actions provided by efferent copies and higher-order visual description of the observed action provided by posterior STS (Iacoboni *et al.*, 2001; Iacoboni, 2004).

There is now converging evidence supporting the notion that some internal models are acquired and implemented in the cerebellar cortex (Kawato, 1999; Imamizu *et al.*, 2003), and that these regions of the cerebellum have functional connectivity to the pars opercularis and pars triangularis of the IFG (Tamada *et al.*, 1999). As the target of cerebellar regions that implement these models, it has been proposed that mirror neurons in the ventral premotor cortex may represent the desired state of actions for inverse models (Imamizu *et al.*, 2003). Our data on the ventral pars opercularis is not consistent with a role in implementing an inverse model, as this sub-region is only active during imitation, and an inverse model would be necessary during the motor control condition as well. However, it has been shown that learning establishes a pathway between cerebellar lobules and the pars triangularis and pars opercularis of the IFG, which may be a network involved in tool use associated motor control (Tamada *et al.*, 1999). Such a proposal is interesting and highly relevant, as some theories have proposed that the ability to use tools paved the way for gestural communication and language capability in humans (Hewes, 1973; Kimura and Archibald, 1974).

The activation of the pars triangularis during action observation but not during imitation is most readily explained by the notion that frontal inhibitory mechanisms are involved in suppressing movement execution during action observation or motor imagery, as has been proposed previously (Deiber

et al., 1998). A possible parallel in the language literature is the finding that there is increased IFG activation during silent versus overt reading (Bookheimer *et al.*, 1995). This notion is further supported by the findings that a decision not to execute movement in a GO/NO-GO task was found to be associated with right prefrontal activation (Kawashima *et al.*, 1996). In a recent review, it was suggested that damage to the right inferior frontal cortex disrupts performance in both response inhibition and task-set switching paradigms, but that this region must interact with more posterior cortical regions such as basal ganglia, primary motor cortex and medial temporal lobe memory structures for cognitive inhibition (Aron *et al.*, 2004).

Converging evidence from neuroimaging studies of language function and studies of sensory-motor integration point to a strong link between the brain regions involved in language functions and the mirror system (Rizzolatti and Arbib, 1998). Anatomical evidence shows that both of these functions are subserved by some common neural structures. Our results provide evidence for the basis of a possible functional link between these systems. We have observed a functional segregation in the pars opercularis of the left hemisphere, which distinguishes a dorsal region with mirror properties and a ventral region with motor properties. A similar parcellation, also of the left pars opercularis, has been shown in a meta-analysis of functional imaging studies using language activation tasks, where the BOLD signal change in a dorsal region correlated with task difficulty in verbal working memory, while a more ventral region was sensitive to the lexical status of letter strings (Chein *et al.*, 2002). Although it is difficult to make clear and interpret the common principles underlying the functional segregation of pars opercularis in language and motor tasks, the evidence for similar functional segregation is compatible with the notion that both language and motor control use similar computations.

We have proposed that the ventral sector of the pars opercularis is the source of the efference copy during imitation. The recruitment of a common region by a language task and imitation may indicate that this region is an important predictor of sequence in language production and comprehension just as the forward model is a predictor of the sensory consequences of manual action during imitation. In support of this assertion, Kimura and colleagues have proposed that apraxic deficits associated with deficits in speech may be related through the motor sequencing involved in both of these abilities, rather than because of deficits in symbolic linguistic representation. They have shown that in right-handers, speaking interferes with performance of sequential movements of the right hand (Kimura and Archibald, 1974; Lomas and Kimura, 1976). More recently, an fMRI study looking at semantic and syntactic processing in the pars triangularis and pars opercularis found that the latter was more involved in syntactic processing, whereas the pars triangularis was involved in thematic processing (Newman *et al.*, 2003). More specifically, the pars opercularis was sensitive to noun-verb agreement violations, rather than extra verb violations, which indicates that it may have a predictive role in processing incoming linguistic information to integrate the syntactic structure of sentences.

Let us now discuss the possible link between our finding that the dorsal sector of the pars opercularis shows mirror properties and the finding of Chein and colleagues that verbal working memory tasks recruit this same region. It was found that a majority of mirror neurons in area F5 of the macaque cortex respond during action observation, also when the final part of

the action is invisible (Umiltà *et al.*, 2001). This finding implies that mirror neurons have a 'working memory'-like representation for actions or trigger an internal representation of the observed action. It is perhaps this internal retrieval process that is common to action recognition, imitation and language tasks of verbal working memory that recruits the dorsal region of the pars opercularis. Binkofski *et al.* (2000) have reported activation of the pars opercularis during imagery of abstract movement, and concluded that this region may hold both motor and linguistic representations relevant to human communication. Taken together, the evidence presented regarding the role of the pars opercularis, dorsal and ventral, to language and motor tasks shows that the role of this region should be interpreted in terms of the fundamental functions it serves in diverse cognitive tasks such as motor control and language, as such functional parallels are likely not coincidental.

A final point to address in relation to language is the question of laterality. Traditionally, the language functions of Broca's area are described as being lateralized to the left hemisphere. However, data from our laboratory and others have shown that various aspects of motor processing recruit Broca's area and the corresponding region of the IFG in the right hemisphere. For example, mirror imitation, imitation of goal directed actions, motor imagery, motor sequence learning all recruit various regions of the IFG bilaterally and TMS to left and right BA44 has been shown to disrupt imitation (Binkofski *et al.*, 2000; Grafton *et al.*, 2002; Koski *et al.*, 2002, 2003; Heiser *et al.*, 2003). Speech arrest occurs reliably from stimulation of the IFG immediately anterior to the inferior end of the precentral gyrus of the left hemisphere (Rasmussen and Milner, 1975) and lesions to the homologous region of the right hemisphere rarely produce lasting speech deficits (Tonkonogy and Goodglass, 1981). On the other hand, several studies also show bilateral activity in the pars opercularis during language processing tasks, such as detection of semantic errors (Ni *et al.*, 2000a), detection of grammatical errors (Embick *et al.*, 2000) and discourse processing (St. George *et al.*, 1999). Thus, it appears that several aspects of language processing engage parts of the same neural network, bilateral IFG, involved in processing actions.

To conclude, our study provides evidence of a functional parcellation within the pars opercularis of the IFG related to action observation and imitation. Its dorsalmost sector shows mirror properties that may allow one to understand an observed action by matching it to one's own neural representation of that action and its ventralmost sector likely contains neurons with functional properties that allow forward modeling in a network with posterior, higher order visual neurons in STS. In addition, the pars triangularis could serve to decouple action observation from execution, by exerting an inhibitory influence over the more posterior premotor regions of the IFG. The evolution of such a system may facilitate communication among individuals by allowing them to predict and understand the actions of others and react accordingly. It is this property of the action observation-execution matching system that makes it an ideal substrate for the evolution of a communication system like language.

Notes

The authors would like to thank Lisa Aziz-Zadeh and Stephen Wilson for their contribution. Generous support was given by the Brain Mapping Medical Research Organization, Brain Mapping Support Foundation, Pierson-Lovelace Foundation, The Ahmanson Foundation,

Tamkin Foundation, Jennifer Jones-Simon Foundation, Capital Group Companies Charitable Foundation, Robson Family, William M. and Linda R. Dietel Philanthropic Fund at the Northern Piedmont Community Foundation, Northstar Fund, the National Center for Research Resources grants RR12169, RR13642 and RR08655, and National Science Foundation grant REC-0107077.

Address correspondence to Istvan Molnar-Szakacs, Ahmanson-Lovelace Brain Mapping Center, 660 Charles Young Dr. South, Los Angeles, CA 90095, USA. Email: imolnar@ucla.edu.

References

- Aboitiz F, Garcia GL (1997) The evolutionary origin of language areas in the human brain. A neuroanatomical perspective. *Brain Res Rev* 25:381-396.
- 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 (1981) Perceptual structures and distributed motor control. In: *Handbook of physiology*, section 2 (Brooks VB, ed.), pp. 1449-1480. Bethesda, MA: American Physiological Society.
- Aron AR, Robbins TW, Poldrack RA (2004) Inhibition and the right inferior frontal cortex. *Trends Cogn Sci* 8:170-177.
- Binkofski F, Buccino G, Stephan KM, Rizzolatti G, Seitz RJ, Freund HJ (1999) A parieto-premotor network for object manipulation: evidence from neuroimaging. *Exp Brain Res* 128:210-213.
- Binkofski F, Amunts K, Stephan KM, Posse S, Schormann T, Freund HJ, Zilles K, Seitz RJ (2000) Broca's region subserves imagery of motion: a combined cytoarchitectonic and fMRI study. *Hum Brain Mapp* 11:273-285.
- Bookheimer S (2002) Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci* 25:151-188.
- Bookheimer SY, Zeffiro TA, Blaxton T, Gaillard W, Theodore W (1995) Regional cerebral blood flow during object naming and word reading. *Hum Brain Mapp* 3:93-106.
- Broca P (1861) Remarques sur le siege de la faculte de langage articule, suivies d'une observation d'aphemie. *Bull Soc Anat Paris* 2:330-357.
- Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL (2003) Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci USA* 100:5497-5502.
- Chaminade T, Meary D, Orliaguet JP, Decety J (2001) Is perceptual anticipation a motor simulation? A PET study. *Neuroreport* 12:3669-3674.
- Chein JM, Fissell K, Jacobs S, Fiez JA (2002) Functional heterogeneity within Broca's area during verbal working memory. *Physiol Behav* 77:635-639.
- Dapretto M, Bookheimer SY (1999) Form and content: dissociating syntax and semantics in sentence comprehension. *Neuron* 24:427-432.
- Deiber MP, Ibanez V, Honda M, Sadato N, Raman R, Hallett M (1998) Cerebral processes related to visuomotor imagery and generation of simple finger movements studied with positron emission tomography. *Neuroimage* 7:73-85.
- Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JD (1995) Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. *J Neurosci* 15:5870-5878.
- Ehrsson HH, Fagergren A, Jonsson T, Westling G, Johansson RS, Forssberg H (2000) Cortical activity in precision- versus power-grip tasks: an fMRI study. *J Neurophysiol* 83:528-536.
- Embick D, Marantz A, Miyashita Y, O'Neil W, Sakai KL (2000) A syntactic specialization for Broca's area. *Proc Natl Acad Sci USA* 97:6150-6154.
- Epstein CM, Meador KJ, Loring DW, Wright RJ, Weissman JD, Sheppard S, Lah JJ, Puhlovich F, Gaitan L, Davey KR (1999) Localization and characterization of speech arrest during transcranial magnetic stimulation. *Clinical Neurophysiology* 110:1073-1079.
- Ferrari PF, Gallese V, Rizzolatti G, Fogassi L (2003) Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. *Eur J Neurosci* 8:1703-1714.

- Ferrari PF, Gallese V, Rizzolatti G, Fogassi L (2003) Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. *Eur J Neurosci* 17:1703-1714.
- Foundas AL, Eure KF, Luevano LF, Weinberger DR (1998) MRI Asymmetries of Broca's area: the pars triangularis and pars opercularis. *Brain Lang* 64:282-296.
- Fox PT, Parsons LM (1998) Beyond the single study: function/location metanalysis in cognitive neuroimaging. *Curr Opin Neurobiol* 8: 178-187.
- Friederici AD, Opitz B, von Cramon DY (2000) Segregating semantic and syntactic aspects of processing in the human brain: an fMRI investigation of different word types. *Cereb Cortex* 10:698-705.
- Gallese V, Fadiga L, Fogassi L, Rizzolatti G (1996) Action recognition in the premotor cortex. *Brain* 119:593-609.
- Gerardin E, Sirigu A, Lehericy S, Poline JB, Gaymard B, Marsault C, Agid Y, Le Bihan D (2000) Partially overlapping neural networks for real and imagined hand movements. *Cereb Cortex* 10:1093-1104.
- Geyer S, Matelli M, Luppino G, Zilles K (2000) Functional neuroanatomy of the primate isocortical motor system. *Anat Embryol (Berl)* 202: 443-474.
- 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.
- Grafton ST, Hazeltine E, Ivry RB (2002) Motor sequence learning with the nondominant left hand. A PET functional imaging study. *Exp Brain Res* 146:369-378.
- Grezes 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.
- Grezes J, Decety J (2002) Does visual perception of object afford action? Evidence from a neuroimaging study. *Neuropsychologia* 40: 212-222.
- Heiser M, Iacoboni M, Maeda F, Marcus J, Mazziotta JC (2003) The essential role of Broca's area in imitation. *Eur J Neurosci* 17:1123-1128.
- Hewes G (1973) Primate communication and the gestural origin of language. *Curr Anthropol* 14:5-24.
- Iacoboni M (2004) Understanding others: Imitation, language, empathy. In: *Perspectives on imitation: from mirror neurons to memes* (Hurley S, Chater N, eds). Cambridge, MA: MIT Press (in press).
- 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 LM, Brass M, Bekkering H, Woods RP, Dubeau MC, Mazziotta JC, Rizzolatti G (2001) Reafferent copies of imitated actions in the right superior temporal cortex. *Proc Natl Acad Sci USA* 98:13995-13999.
- Imamizu H, Kuroda T, Miyauchi S, Yoshioka T, Kawato M (2003) Modular organization of internal models of tools in the human cerebellum. *Proc Natl Acad Sci USA* 100:5461-5466.
- Johnson-Frey SH, Maloof FR, Newman-Norlund R, Farrer C, Inati S, Grafton ST (2003) Actions or hand-object interactions? Human inferior frontal cortex and action observation. *Neuron* 39: 1053-1058.
- Kawashima R, Satoh K, Itoh H, Ono S, Furumoto S, Gotoh R, Koyama M, Yoshioka S, Takahashi T, Takahashi K, Yanagisawa T, Fukuda H (1996) Functional anatomy of GO/NO-GO discrimination and response selection — a PET study in man. *Brain Res* 728:79-89.
- Kawato M (1999) Internal models for motor control and trajectory planning. *Curr Opin Neurobiol* 9:718-727.
- Kimura D, Archibald Y (1974) Motor functions of the left hemisphere. *Brain* 97:337-350.
- Koski L, Wohlschlagger A, Bekkering H, Woods RP, Dubeau MC, Mazziotta JC, Iacoboni M (2002) Modulation of motor and premotor activity during imitation of target-directed actions. *Cereb Cortex* 12: 847-855.
- Koski L, Iacoboni M, Dubeau MC, Woods RP, Mazziotta JC (2003) Modulation of cortical activity during different imitative behaviors. *J Neurophysiol* 89:460-471.
- Krams M, Rushworth MF, Deiber MP, Frackowiak RS, Passingham RE (1998) The preparation, execution and suppression of copied movements in the human brain. *Exp Brain Res* 120:386-398.
- Lomas J, Kimura D (1976) Intrahemispheric interaction between speaking and sequential manual activity. *Neuropsychologia* 14:23-33.
- Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B, Holmes C, Collins L, Thompson P, MacDonald D, Iacoboni M, Schormann T, Amunts K, Palomero-Gallagher N, Geyer S, Parsons L, Narr K, Kabani N, Le Goualher G, Boomsma D, Cannon T, Kawashima R, Mazoyer B (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.
- Mecklinger A, Gruenewald C, Besson M, Magnie MN, Von Cramon DY (2002) Separable neuronal circuitries for manipulable and non-manipulable objects in working memory. *Cereb Cortex* 12: 1115-1123.
- Menon RS, Kim S-G (1999) Spatial and temporal limits in cognitive neuroimaging with fMRI. *Trends Cogn Sci* 3:207-216.
- Miall RC (2003) Connecting mirror neurons and forward models. *Neuroreport* 14:2135-2137.
- Newman SD, Just MA, Keller TA, Roth J, Carpenter PA (2003) Differential effects of syntactic and semantic processing on the subregions of Broca's area. *Cogn Brain Res* 16:297-307.
- Ni W, Constable RT, Mencl WE, Pugh KR, Fulbright RK, Shaywitz SE, Shaywitz BA, Gore JC, Shankweiler D (2000a) An event-related neuroimaging study distinguishing form and content in sentence processing. *J Cogn Neurosci* 12:120-133.
- Ni W, Constable RT, Mencl WE, Pugh KR, Fulbright RK, Shaywitz SE, Shaywitz BA, Gore JC, Shankweiler D (2000b) An event-related neuroimaging study distinguishing form and content in sentence processing. *J Cogn Neurosci* 12:120-133.
- Ojemann GA (1991) Cortical organization of language. *J Neurosci* 11:2281-2287.
- Ojemann GA, Whitaker HA (1978) Language localization and variability. *Brain Lang* 6:239-260.
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia* 9:97-113.
- Paulesu P, Frith CD, Bench CJ, Bottini G, Grasby G, Frackowiak SJ (1993) Functional anatomy of working memory: the articulatory loop. *J Cereb Blood Flow Metab* 13:551.
- Paulesu E, Goldacre B, Scifo P, Cappa SF, Gilardi MC, Castiglioni I, Perani D, Fazio F (1997) Functional heterogeneity of left inferior frontal cortex as revealed by fMRI. *Neuroreport* 8:2011-2017.
- Petrides M, Pandya DN (1988) Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. *J Comp Neurol* 273:52-66.
- Preuss TM (1995) *The argument from animals to humans in cognitive neuroscience*. Cambridge, MA: MIT Press.
- Rasmussen T, Milner B (1975) Clinical and surgical studies of the cerebral speech areas in man. In: *Cerebral localization* (Zulch KJ, Creutzfeldt O, Galbraith GC, eds), pp. 238-257. Berlin: Springer-Verlag.
- Rauch SL, Savage CR, Brown HD, Curran T, Alpert NM, Kendrick A, Fischman AJ, Kosslyn SM (1995) A PET investigation of implicit and explicit sequence learning. *Hum Brain Mapp* 3:271-286.
- Rizzolatti G, Arbib MA (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, 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.
- Roskies AL, Fiez JA, Balota DA, Raichle ME, Petersen SE (2001) Task-dependent modulation of regions in the left inferior frontal cortex during semantic processing. *J Cogn Neurosci* 13:829-843.

- St. George M, Kutas M, Martinez A, Sereno MI (1999) Semantic integration in reading: engagement of the right hemisphere during discourse processing. *Brain* 122:1317-1325.
- Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. New York: Thieme.
- Tamada T, Miyauchi S, Imamizu H, Yoshioka T, Kawato M (1999) Cerebro-cerebellar functional connectivity revealed by the laterality index in tool-use learning. *Neuroreport* 10:325-331.
- 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.
- Tonkonogy J, Goodglass H (1981) Language function, foot of the third frontal gyrus, and rolandic operculum. *Arch Neurol* 38: 486-490.
- Umiltà MA, Kohler E, Gallese V, Fogassi L, Fadiga L, Keysers C, Rizzolatti G (2001) I know what you are doing. A neurophysiological study. *Neuron* 31:155-165.
- Wolpert DM, Kawato M (1998) Multiple paired forward and inverse models for motor control. *Neural Netw* 11:1317-1329.
- Wolpert DM, Ghahramani Z, Jordan MI (1995) An internal model for sensorimotor integration. *Science* 269:1880-1882.
- 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.
- Worsley KJ (1996) A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp* 4:58-73.