Behavioral/Systems/Cognitive

Lateralization of the Human Mirror Neuron System

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A cortical network consisting of the inferior frontal, rostral inferior parietal, and posterior superior temporal cortices has been implicated in representing actions in the primate brain and is critical to imitation in humans. This neural circuitry may be an evolutionary precursor of neural systems associated with language. However, language is predominantly lateralized to the left hemisphere, whereas the degree of lateralization of the imitation circuitry in humans is unclear. We conducted a functional magnetic resonance imaging study of imitation of finger movements with lateralized stimuli and responses. During imitation, activity in the inferior frontal and rostral inferior parietal cortex, although fairly bilateral, was stronger in the hemisphere ipsilateral to the visual stimulus and response hand. This ipsilateral pattern is at variance with the typical contralateral activity of primary visual and motor areas. Reliably increased signal in the right superior temporal sulcus (STS) was observed for both left-sided and right-sided imitation tasks, although subthreshold activity was also observed in the left STS. Overall, the data indicate that visual and motor components of the human mirror system are not left-lateralized. The left hemisphere superiority for language, then, must be have been favored by other types of language precursors, perhaps auditory or multimodal action representations.

Key words: **motor; sensorimotor; premotor; language; hemisphere; lateralization**

Introduction

Several studies indicate a shared representation for the execution of actions and for their observation. This finding was first observed in monkeys, where a group of neurons in the F5 region, called mirror neurons, responded to both actions made by the monkey herself and to observing the same action made by the experimenter (di Pellegrino et al., 1992; Gallese et al., 1996). Brain-imaging studies have expanded the findings to humans (Fadiga et al., 1995; Grafton et al., 1996; Rizzolatti et al., 1996b; Grezes et al., 1998, 2003; Binkofski et al., 1999; Iacoboni et al., 1999, 2005; Nishitani and Hari, 2000; Buccino et al., 2001; Aziz-Zadeh et al., 2002; Johnson-Frey et al., 2003; Koski et al., 2003; Molnar-Szakacs et al., 2005). These studies indicate that Brodmann area 44 (BA44), which is located in the pars opercularis of the inferior frontal gyrus (probabilistic atlas) (Mazziotta et al., 2001) and is considered the human homolog of monkey area F5 (Geyer et al., 2000), may be part of the human mirror neuron system (MNS). The data further indicate that the superior temporal sulcus and the inferior parietal lobule, together with the pars opercularis, may serve as a core neural network for action understanding (Rizzolatti et al., 2000; Carr et al., 2003; Iacoboni, 2005).

Several investigators have speculated about the ties between MNS and language evolution (Rizzolatti and Arbib, 1998; Corballis, 2002; Iacoboni, 2005). Some of this speculation is based on the anatomical location of the pars opercularis of the inferior frontal gyrus: it is a component of Broca's area, a predominant speech area in the human brain. Some have claimed that the human MNS is specialized to the left hemisphere (Corballis, 2002), the dominant hemisphere for language (Zaidel, 1978). However, this claim has not been properly tested. In the monkey, mirror neurons have been found in the F5 region of both hemispheres (Gallese et al., 1996). In humans, functional imaging studies used to examine the system have not properly controlled for laterality. For example, where a motor response is required of a participant, most studies use the right hand. Furthermore, observation of actions is often limited to watching one hand perform an action. Thus, greater activity reported in the left hemisphere MNS areas may simply reflect the laterality of either the responding hand or the observed hand.

To investigate more systematically the lateralization of the human MNS, we performed a functional magnetic resonance imaging (fMRI) study where participants were asked to observe, execute, or imitate a finger action toward a target. Because we were interested in MNS lateralization as it relates to language, we focused our analysis on lateralized patterns of activity in the pars opercularis. Stimuli were flashed to each visual hemifield and the response hand was ipsilateral to the hemifield of presentation, a method widely used to investigate behavioral differences between the two hemispheres. To our knowledge, this is the first fMRI

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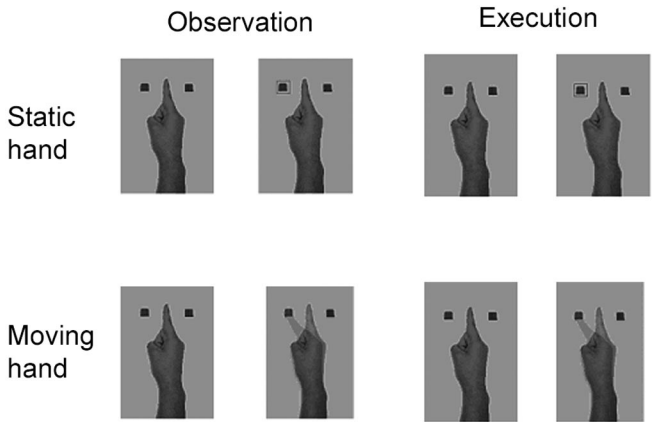

Figure 1. Stimuli used in fMRI study of action observation, execution, and imitation. Stimuli consisted of two frames of right or left hands, consecutively flashed for a total of 150 ms to the right or left visual field. Participants participated in four task conditions: observation of a static hand, observation of a moving hand, execution to a static hand, or imitation. The right-hand stimuli shown here all appeared to the right of a fixation cross. Left-hand stimuli appeared to the left of a fixation cross. Both left- and right-hand stimuli were presented in color.

study that controls for laterality while investigating action observation, execution, and imitation.

Materials and Methods

Participants

Twelve right-handed healthy volunteers (six men, six women; mean age, 29; range, 18–45) screened by questionnaire to have no history of brain damage, participated in the study. Participants gave informed consent, according to the requirements of the Institutional Review Board of the University of California, Los Angeles. Handedness was assessed by a questionnaire adapted from the Edinburgh Handedness Inventory (Oldfield, 1971). A minimum handedness score of 12 out of 15 on this inventory was needed to participate in the study. All participants reported to have normal or corrected-to-normal vision. Before scanning, participants completed a screening questionnaire to rule out medication use, a history of neurological or psychiatric disorders, substance abuse, and other medical conditions. Images were acquired using a General Electric 3.0T MRI scanner with an Advanced Magnetic Resonance Imaging upgrade for echo planar imaging (EPI).

Stimuli

Stimuli were presented in counterbalanced blocks, beginning with a rest block consisting of a fixation cross at the center of the screen. Stimuli were still images of a left or right hand on its side in an egocentric perspective with the index finger pointing forward (Fig. 1). Because data indicate that MNS activity is stronger for goal-oriented actions (Koski et al., 2002), our stimuli included a target for the hand action. Thus, a red button was present on either side of the index finger. In one-half of the blocks, the index finger moved toward either the left or right button. In the other half, the finger was still and a black box appeared around one of the buttons. Stimuli appeared for 150 ms in either the left visual field (LVF) or the right visual field (RVF) while participants focused on a fixation cross. Right hand stimuli were always presented to the RVF, and left hand stimuli to the LVF. Stimuli were presented in blocks, interleaved with rest blocks consisting of a center fixation cross. The order of the task blocks was counterbalanced.

Task

Participants were asked to observe, imitate, or execute actions in different blocks while their eyes remained focused on the fixation cross. Specifically, there were four conditions, two involving only observation, and two involving making a movement. In one observation condition, participants observed a goal-oriented action made by an index finger (action observation). In the other observation condition, they observed a still image of a hand (static hand observation). In one movement condition, participants imitated the action made by an index finger (imitation condition). In the other movement condition, the same action was indicated by an abstract cue (execution condition). In both movement conditions, the participant always used the right hand to respond when the right-hand stimulus was presented to the RVF and the left hand to respond when the left-hand stimulus was presented to the LVF.

fMRI

Four scans of 5 min 56 s were performed with each participant. Each scan consisted of eight task periods (LVF observation of moving left hands, LVF observation of static left hands, RVF observation of moving right hands, RVF observation of static right hands, execution during LVF presentation of static left hands, execution during RVF presentation of static right hands, imitation of LVF presented left hands, imitation of RVF presented right hands) of 20 s alternating with nine rest periods of 20 s. To rule out any brain abnormalities and allow prescription of the slices to be obtained in the remaining sequences, we performed a two dimensional spin echo sequence with repetition time (TR) = 4000 ms, echo time (TE) = 40 ms, 256 × 256 voxel matrix, 4 mm thickness, and 1 mm spacing. Functional data were acquired using an echo planar T2-weighted gradient echo sequence (TR = 4000 ms, TE = 25 ms, flip angle = 90°, 64 × 64 voxel matrix, 26 slices, 4 mm thickness, 1 mm spacing). For anatomical normalization purposes, anatomical data were acquired with a coplanar high-resolution T2-weighted echo planar imaging volume with TR = 4000 ms, TE = 54 ms, flip angle = 90°, 128 × 128 voxel matrix, 26 axial slices, 3.125 mm in-plane resolution, 4 mm thickness, and 1 mm spacing.

Image processing

Functional images were aligned to the coplanar high-resolution EPI volume within each participant using 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 mm by 8.7 mm by 8.6 mm.

Statistical analysis was performed using an ANOVA (Woods et al., 1996). There is now a considerable body of evidence implicating the pars opercularis of the inferior frontal gyrus in action simulation, observation, execution, and imitation (Gallese et al., 1996; Grafton et al., 1996; Rizzolatti et al., 1996a; Decety et al., 1997, 2002; Krams et al., 1998; Grezes et al., 1999; Iacoboni et al., 1999, 2005; Binkofski et al., 2000; Nishitani and Hari, 2000; Buccino et al., 2001; Koski et al., 2002; Molnar-Szakacs et al., 2004). This region was characterized cytoarchitectonically and named by Brodmann as area 44 (Brodmann, 1908). It is anatomically delimited rostrally by the vertical ramus of the Sylvian fissure, dorsally by the inferior frontal sulcus, caudally by the inferior portion of the precentral sulcus, and ventrally by the Sylvian fissure. The recent analysis and probabilistic map constructed by Tomaiuolo et al. (1999) found the average volume of the pars opercularis to be ~4 ml. Therefore, the statistical threshold for the pars opercularis, our primary region of interest, was set at $p = 0.05$, corrected for multiple comparisons across the equivalent volume in resolution elements in our images (Worsley, 1996). The statistical threshold for brain areas outside this region of interest was set at $p = 0.001$, uncorrected for multiple spatial comparisons. To circumvent the problem of blood oxygen level-dependent (BOLD) signal autocorrelation, we used as the dependent variable the sum of the signal intensity at each voxel throughout the experimental blocks (Iacoboni et al., 1999, 2001; Koski et al., 2002; Carr et al., 2003; Koski et al., 2003).

Task-related activity for all tasks minus rest. Two separate maps were generated to identify those brain regions that show task-related activity over all conditions (action execution, observation of moving hands, observation of static hands, and imitation) as compared with rest. The first map considered LVF presentations only, whereas the second map considered RVF presentations only. Each map was created from a contrast of the main effect of task minus rest using an ANOVA model with the following factors: participant ($n = 12$), run ($n = 4$), phase (task, rest), task (observation, execution), and stimulus type (moving, static).

Task-related activity contrasting between hemispheres. Two maps were generated to identify brain regions that show task-related activity over all task conditions together (observation of static hands, observation to moving hands, execution, imitation) when stimuli are presented to the RVF as compared with the LVF or, similarly, when they are presented to the LVF as compared with the RVF. Each map was created from a contrast of the LVF (or RVF) presentation task blocks minus RVF (or LVF, respectively) presentations task blocks, using an ANOVA model with the following factors: participant ($n = 12$), run ($n = 4$), task (execution, observation), visual field (LVF, RVF) stimulus type (moving, static).

MNS-related activity. We have previously proposed an empirical way to test for MNS activity during observation, execution of action, and imitation (Iacoboni et al., 1999, 2005). Single-unit recordings in macaques show that mirror neurons respond more strongly to execution of action than its observation. During imitation, there is both observation and execution of action. Thus, one can conceptualize MNS activity as expressed by BOLD signal as progressively increasing from observation, to execution, to imitation of an action (Iacoboni et al., 1999, 2001, 2005; Koski et al., 2002, 2003). We tested this pattern with a linear contrast in frontoparietal areas known to be involved in the MNS: the pars opercularis and the posterior parietal cortex. The superior temporal sulcus (STS) is a higher order visual area, but it seems to receive efference copies of motor plans from frontoparietal mirror areas (Iacoboni et al., 2001); thus, even in STS, one might expect to find a similar pattern of activity.

MNS-related activity contrasting between hemispheres (LVF-RVF; RVF-LVF). We further aimed to find the areas that show an increased MNS pattern of activity when comparing laterality effects. Thus, we performed a linear contrast, comparing the areas in which BOLD signal increased progressively from observation, to execution, to imitation of an action for RVF trials more than LVF trials and vice-versa.

Mean percentage signal change in probabilistic BA44 for each condition. Because we are interested specifically in laterality for MNS areas as they relate to laterality for language, in this final analysis, we focused on BA44. We analyzed the mean percentage signal change for each task condition (imitation, execution, observation, static control) separately for each hemisphere and the stimulus/response hand in this region. We defined BA44 using probabilistic cytoarchitectonic maps (Amunts et al., 1999). These maps show, for each voxel, the percentage of subjects for whom that voxel lay in BA44. Our BA44 region of interest (ROI) included voxels in which this probability was >20%. Repeated measures ANOVA with task (imitation, execution, observation, static), cerebral hemisphere (left; right), and visual field/response hand (left; right) was also conducted to look for a main effect of hemisphere for each condition, as well as an interaction between hemisphere and response hand.

Table 1. Peaks of activation for brain areas active during all task conditions as compared to rest during LVF trials

Hemisphere	Region	BA	Tal-coordinates			*T*
			x	*y*	*z*	
LH	Ant cingulate	32	−2	28	−8	4.16
LH	Inferior frontal gyrus	45	−32	28	2	4.64
LH	Inferior parietal lobule	40	−47	−38	36	4.53
LH	Pars opercularis (medial)	44	−36	14	24	4.27
LH	Pars opercularis (lateral)	44	−47	8	6	2.93
LH	Middle frontal gyrus	9	−37	43	22	3.95
LH	Middle frontal gyrus	9	−41	10	34	5.59
LH	Premotor cortex	6	−32	−2	58	4.74
LH	Premotor cortex	6	−42	−0	48	4.90
LH	Putamen		−19	10	2	4.43
LH	Supplementary motor area	6	−2	7	52	4.35
LH	Striate/middle occipital gyrus	19	−42	−68	6	6.72
LH	Superior parietal lobule		−16	−66	56	4.27
RH	Fusiform gyrus		40	−48	−18	4.30
RH	Pars opercularis	44	44	8	21	4.85
RH	Primary motor cortex	4	39	−14	56	6.40
RH	Premotor cortex	6	36	−4	56	6.72
RH	Postcentral gyrus		55	−24	22	3.58
RH	Primary visual area	17	11	−94	8	4.27
RH	Supplementary motor area	6	4	4	60	4.56
RH	Striate	18	22	−76	−10	3.58
RH	Striate	19	28	−90	16	4.53
RH	Striate	19	51	−70	6	5.93
RH	Striate	19	46	−80	4	6.43
RH	Striate/angular gyrus		27	−72	36	4.11

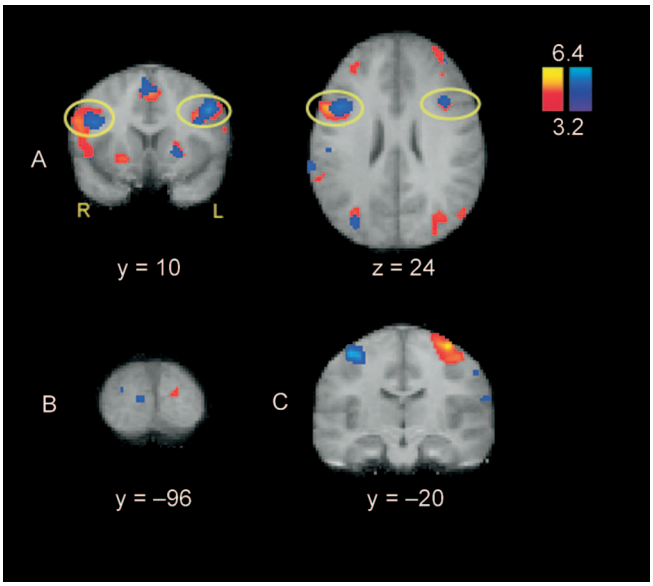

Figure 2. All activations are for the comparisons LVF-rest (blue range of voxels) and RVF-rest (red range of voxels). Activations are given as *t* values, with the left hemisphere on the right side. Here, we show bilateral activations in pars opercularis for both comparisons (***A***). ***B***, Lateralization of the input: activation of the contralateral visual areas. ***C***, Lateralization of the output: activation of the contralateral motor areas.

Results

LVF presentations: task minus rest

This contrast examined voxels that yielded reliable signal increases during all task periods (observation, execution, and imitation) compared with rest, when stimuli were presented to the LVF/right hemisphere. The pars opercularis in both hemispheres had reliable signal increases (df = 33; $t > 2.49$; $p < 0.05$, corrected for multiple spatial comparisons). Two peaks were observed in the left pars opercularis, a dorsomedial one and a ventrolateral one. A single peak was observed in the right pars opercularis. (Table 1, Fig. 2*A*). Other areas that showed signal increases (df = 33; $t = 3.36$; $p = 0.001$, uncorrected) included the right primary motor cortex, right primary visual areas, right primary somatomotor areas, right supplementary motor area (SMA), bilateral extrastriate areas, and left striatum. (Table 1, Fig. 2*B*,*C*).

RVF presentations: task minus rest

This contrast examined brain areas that yielded reliable signal increases during task periods (observation, execution, and imita-

Table 2. Peaks of activation for brain areas active during all tasks as compared to rest for RVF trials

Hemisphere	Region	BA	Tal-coordinates			*T*
			x	*y*	*z*	
RH	Supramarginal gyrus	40	62	−45	24	3.87
RH	Striate	19	48	−74	4	5.80
RH	Pars opercularis	44	54	7	26	5.45
RH	Amygdala		36	19	4	4.16
RH	Striate	19	38	−62	−12	5.64
RH	Cerebellum		39	−62	−12	5.64
RH	Inferior frontal gyrus	46	41	35	12	4.30
RH	Putamen		21	12	−4	4.43
RH	Middle frontal gyrus	46	40	47	18	4.82
RH	Middle frontal gyrus	10	38	47	−2	4.69
RH	Premotor cortex	6	38	−0.3	54	6.03
RH	Striate	19	33	−70	32	4.90
RH	Premotor cortex	6	38	0	54	6.03
RH	Premotor cortex	6	41	−1	38	5.09
RH	Precuneus	7	28	−56	50	5.40
RH	Precuneus	7	17	−62	58	5.24
RH	Cerebellum		35	−44	−26	4.80
RH	Supplementary motor area	6	12	2	66	6.69
LH	Supplementary motor area	6	1	6	52	5.96
LH	Premotor cortex	6	−16	0	64	5.82
LH	Primary motor cortex	4	−46	2	48	5.69
LH	Premotor cortex	6	−30	−5	60	6.72
LH	Primary motor cortex	4	−33	−22	62	6.69
LH	Putamen		−22	4.3	10	4.72
LH	Inferior parietal lobule	40	−27	−52	56	6.14
LH	Striate	19	−24	−84	38	6.32
LH	Striate	19	−41	−61	−8	6.51
LH	Pars opercularis (lateral)	44	−35	11	30	4.66
LH	Pars opercularis (medial)	44	−58	10	16	3.32
LH	Striate	18/19	−45	−79	12	6.72

tion) compared with rest, when stimuli were presented to the RVF/left hemisphere. As in the previous contrast, we found bilateral signal increases in the pars opercularis (df = 33; $t = 2.49$; $p = 0.05$, corrected for multiple spatial comparisons). A single peak in each pars opercularis was observed (Table 2, Fig. 2*A*). Other signal increases (df = 33; $t = 3.36$; $p = 0.001$, uncorrected) were located in the left primary motor cortex, left primary visual area, bilateral SMA, premotor, posterior parietal, and extrastriate areas, and the bilateral striatum. (Table 2, Fig. 2*B*,*C*).

LVF task minus RVF task

This contrast examined brain areas that yielded a higher signal during LVF/right hemisphere presentations across task conditions (observation, execution, imitation) than during RVF/left hemisphere presentations across all task conditions. As in the previous LVF minus rest analysis, two peaks were found in the ipsilateral, left pars opercularis, a dorsomedial one and a ventrolateral one (df = 33; $t = 2.49$; $p = 0.05$, corrected for multiple spatial comparisons). Other differentially activated areas (df = 33; $t = 3.36$; $p = 0.001$, uncorrected) included the right primary motor cortex, right visual areas, and left cerebellum.

RVF task minus LVF task

This contrast examined brain areas that yielded a higher signal during the RVF/left hemisphere presentations across task conditions (observation, execution, imitation) than during the LVF/right hemisphere presentations across all task conditions. In keeping with the previous analysis, the ipsilateral, right pars opercularis was activated (df = 33; $t = 2.49$; $p = 0.05$, corrected for multiple spatial comparisons). Other activated areas (df = 33; $t = 3.36$; $p = 0.001$, uncorrected) included the left primary motor areas, left posterior parietal, bilateral extrastriate visual areas, and right cerebellum.

MNS-related activity

Our study design included three conditions known to activate the MNS: action observation, action execution, and imitation. We looked for areas that show a pattern of activation consistent with the properties of the MNS, responding most strongly to imitation, followed by execution, then observation of actions, and minimally to observation of static images of a hand. This trend in activation pattern was explored for each VF condition as compared with rest as well as with the contralateral VF (LVF task minus RVF task, and RVF task minus LVF task conditions).

Task minus rest

As expected, the pars opercularis showed activation consistent with MNS properties. This mirror-like pattern of activity was observed not only in the left but also in the right pars opercularis. This was true both for LVF task conditions as compared with rest and for RVF task conditions as compared with rest. We also found this trend bilaterally in the posterior parietal cortex as well as in the right STS.

Hemispheric contrast

As Figure 3 shows, again the pars opercularis, posterior parietal cortex, and STS show a pattern of activity that is consistent with MNS properties. This analysis shows that when exploring for laterality, each pars opercularis is activated more strongly by the ipsilateral visual stimulus and response hand. That is, the LVF-RVF contrast for MNS activity shows the left pars opercularis only and the RVF-LVF contrast shows the right pars opercularis only. This means that the pars opercularis yields reliably higher signal for ipsilateral, rather than contralateral, visual stimuli and response hands. Furthermore, like the pars opercularis, the posterior parietal cortex is more strongly activated by the ipsilateral stimulus and response hand. Other significantly active areas include the contralateral primary motor cortex and the contralateral SMA. Finally, we found the right hemisphere STS to be activated in both laterality contrasts.

Because the STS is thought to be an important region for action understanding, the right hemisphere activation observed by this contrast motivated us to investigate the laterality of this area further. Thus, we conducted a *post hoc* analysis in which we took the voxels in the right STS as our ROI and flipped this ROI onto the left hemisphere. Next, we extracted the mean "trends" coefficient for each subject in these two ROIs (i.e., $3 \times$ imit $+ 1 \times$ exec $- 1 \times$ obs $- 3 \times$ static) averaged over all the voxels in the ROI. This coefficient was compared in the left and right over the 12 subjects with a paired *t* test (df = 11), which indicated that the difference between the two ROIs was not significant ($p = 0.52$). Thus, although there was greater activation in the right STS, there must also be subthreshold activation in the left STS that also follows a mirror-like pattern of activation.

Mean percent signal change in probabilistic BA44 for each condition

Figure 4 shows mean percent signal change as compared with rest for imitation, execution, action observation, and the control static condition for each hemisphere (left/right BA44 ROI) and each hand (left; right). The ANOVA for the signal change in probabilistic BA44 demonstrated a main effect of hemisphere, only for the execution condition ($F_{(1,11)} = 5.76$; $p = 0.035$), with the right hemisphere yielding greater signal changes than the left hemisphere. The imitation and observation conditions showed no significant differences ($p = 0.46$ and $p = 0.37$, respectively). Nor were there any significant main effects for visual field/response hand for the imitation, execution, or the observation condition [$p = 0.47$, $p = 0.26$, $p = 0.81$, not significant (NS), respectively].

When we tested for interactions between hemisphere and visual field/response hand, we found a highly significant interaction in the imitation condition only. The left hand shows stronger activation in the left hemisphere ROI and the right hand shows stronger activation in the right hemisphere ROI ($F_{(1,11)} = 10.94$; $p = 0.0070$). For execution and observation, the interactions were not significant ($p = 0.91$, $p = 0.67$, NS, respectively). No other significant effects were observed. In particular, to test whether the three experimental conditions (imitation, execution, and observation) recruited similar or different processes in probabilistic BA44, we ran an additional ANOVA, excluding the static control condition. We found no main effect of condition ($p = 0.86$; NS), and no interaction between condition and laterality (i.e., ipsilateral vs contralateral; $p = 0.39$; NS).

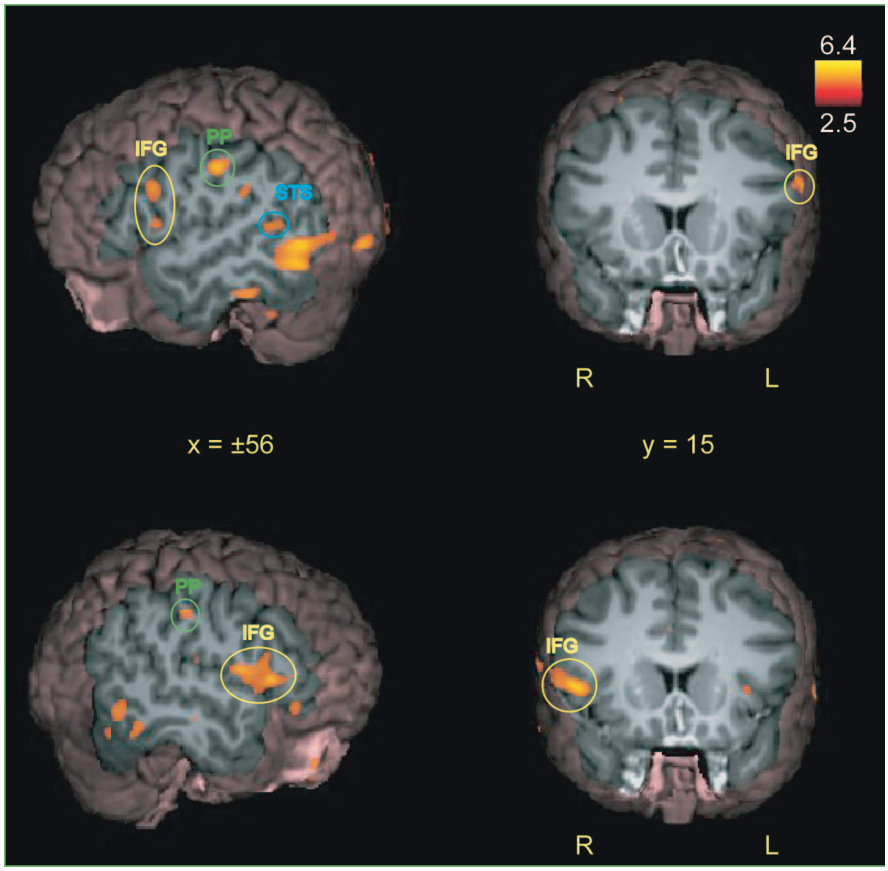

Figure 3. Views of the activation for areas that are activated in a mirror-like pattern (imitation>execution>observation> observation of static hands) for LVF-RVF trials (top) and RVF-LVF trials (bottom). The pars opercularis of the inferior frontal gyrus (IFG) is activated ipsilaterally. Furthermore, we show activation in areas associated with the human mirror system: the right STS ($x = -58$; $y = -58$; $z = 6$) and bilaterally the posterior parietal (PP) areas ($x = -56$; $y = -26$; $z = 36$; $x = 52$; $y = -30$; $z = 38$).

Discussion

We found bilateral activations in the pars opercularis, independent of the visual field of presentation and the laterality of the response hand or observed hand during task trials as compared with rest trials. In both hemispheres, this area also showed an MNS-like activation pattern, with strong signal increase to imitation, less so to execution and observation, and finally even less to observation of a static hand. Thus, it seems that both the left and right pars opercularis have MNS properties and that both hemispheres contribute to the processing of action observation and imitation. This finding is further supported by an fMRI meta-analysis of 58 participants showing bilateral activation in the pars opercularis during action observation and imitation tasks (Molnar-Szakacs et al., 2005). It should be noted that when we used probabilistic BA44 to look at signal changes in this region during the tasks, this pattern did not emerge clearly (Fig. 4). This is because the large intersubject variability in cytoarchitecture results in probabilistic maps that spread into neighboring regions, making these analyses less sensitive than voxel-by-voxel analyses.

Despite the bilateral activations, when we analyzed our data by comparing LVF and RVF blocks, we found greater signal increase in the ipsilateral pars opercularis. That is, our data indicate that the pars opercularis of the inferior frontal gyrus in each hemisphere is more activated for observed, executed, or imitated ipsilateral distal finger movements. The ROI analysis of signal

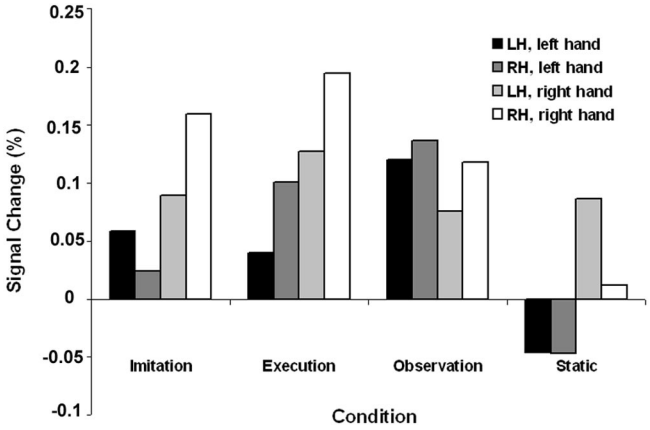

Figure 4. Mean percentage signal change as compared with rest for imitation, execution, action observation, and the control static condition for each ROI (left BA44; right BA44), and each hand (left; right). The BA44 ROI was selected using probabilistic cytoarchitectonic maps. An ANOVA indicates a significant interaction for hemisphere and hand for the imitation condition. No main effect for hemisphere was observed except for the execution condition.

changes in BA44 based on probabilistic maps of the region, however, indicated that the ipsilateral pattern is reliable only in the imitation condition.

This ipsilateral pattern of activity, albeit seemingly paradoxical, is indeed consistent with findings in previous fMRI studies in ventral premotor regions involved in distal finger movements. These studies indicate that performing a precision grip is associated with greater signal in the inferior frontal gyrus ipsilateral to the responding hand (Ehrsson et al., 2000), and that the ventral premotor cortex has ipsilateral finger representations (Cramer et al., 1999; Hanakawa et al., 2005). Furthermore, both left- and right-brain damaged patients show grasping deficits with the ipsilesional hand (Hermsdorfer et al., 1999). Together, these studies indicate that there is a greater ipsilateral response in ventral premotor cortex during finger movements, and such a pattern emerges more readily during imitation of finger movements, as our data suggest.

The ipsilateral activation in pars opercularis may be attributed to the visual field, laterality of the observed hand, laterality of the response hand, or any combination of these three variables. Because the laterality of the activation is influenced by the laterality of the hand used or observed, the data indicate quite clearly that caution must be used in designing and interpreting action observation/imitation studies where laterality is of theoretical importance. The laterality of the effector, of the stimulus, and of the side of space in which the stimulus is presented may show differentially lateralized activations in the system. The perspective of the observed action (egocentric or allocentric orientations) may also influence laterality patterns and should be explored in future studies.

The inferior frontal cortex has prominent connections with the STS via the arcuate fasciculus and with the inferior parietal lobule (Catani et al., 2005). Although the STS is not considered a mirror neuron area because it is not activated for action execution, it is thought to provide a visual description of the action that is critical for the process of imitation, and therefore considered to be strongly associated with mirror neuron areas. Together, these three areas are thought to constitute a network critical for imitation (Nishitani and Hari, 2002; Carr et al., 2003; Miall, 2003; Iacoboni, 2005). We found activation in the rostral section of the inferior parietal lobule to be stronger in the hemisphere ipsilateral to the hand observed, imitated, or moved. It appears that this area, which seems to correspond to area PF in the monkey brain (Iacoboni et al., 2006), also has stronger ipsilateral than contralateral representation. Furthermore, our data indicate that the STS bilaterally shows a mirror-like pattern of activation, although the activation is stronger in the right hemisphere. However, such pattern is unlikely caused by motor activity originating from STS, and likely reflects efferent copies of motor commands from MNS areas back to STS (Iacoboni et al., 2001).

A previous study also found differing lateralized activations in the inferior parietal cortex and superior temporal gyrus based not on the effector used (only right hands were manipulated) but on whether one is imitating another person or another person is imitating them (Decety et al., 2002). It is difficult to interpret those results in relation to the current ones because the former study only manipulated the right hand, whereas our data focus on differences between manipulating either the left or right effector. However, it is possible that, although the effector observed, imitated, or moved contributes to ipsilateral activations, other task demands, such as focus on the self or other [or, as in another study, possibly deficits in mentalization (Nishitani et al., 2004)], may also have strong contributions to lateralized findings.

To conclude, these data suggest that the human frontoparietal mirror neuron system is bilaterally distributed in its activity. Aspects of left lateralization of language, then, must be accounted for by other factors. Recently, auditory mirror neurons have been discovered in the macaque brain (Kohler et al., 2002). In our lab, using transcranial magnetic stimulation, we observed a left-lateralized corticospinal facilitation to action sounds (Aziz-Zadeh et al., 2004). A recent fMRI study has also found stronger left ventral premotor activation to action sounds (Gazzola et al., 2005). Thus, one possibility is that the progression toward left lateralization of language functions may have been facilitated by a left-lateralized auditory component of a multimodal mirror neuron system.

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