The Mirror-Neuron System and Handedness: A “Right” World?

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Abstract: To assess the relationship between the mirror-neuron system (MNS), an observation-execution matching system, and handedness, we acquired functional magnetic resonance imaging from 11 right-handed (RH) and eight left-handed (LH) subjects to identify regions involved in processing action (execution and observation) of the right and left upper limbs. During the execution tasks, LH subjects had a more bilateral pattern of activation than RH. An interaction between handedness and hand observed during the observation conditions was detected in several areas of the MNS and the motor system. The within- and between-groups analyses confirmed different lateralizations of the MNS and motor system activations in RH and LH subjects during the observation tasks of the dominant and nondominant limbs. The comparison of the execution vs. observation task demonstrated that during the execution task with their dominant limbs, RH subjects activated areas of the motor system in the left hemisphere, whereas LH subjects also activated areas of the MNS. During the execution task with the nondominant limbs, both groups activated regions of the MNS and motor system. Albeit this study is based on a small sample, the patterns of MNS activations observed in RH and LH subjects support the theory that suggests that this system is involved in brain functions lateralization. In LH people, this system might contribute to their adaptation to a world essentially built for right-handers through a mechanism of mirroring and imitation. *Hum Brain Mapp* 29:1243–1254, 2008. © 2007 Wiley-Liss, Inc.

Key words: functional MRI; handedness; mirror-neurons; movement

INTRODUCTION

Approximately 90% of the population show a left-hemispheric dominance for processing speech and motor acts [Annett 1973]. This has led people to assume a relation

between language lateralization and handedness [Knecht et al., 2000]. Several morphometric studies identified a relationship between asymmetries of the pars triangular and the planum temporale and language dominance [Foundas et al., 1994, 2001], whereas studies investigating the relationship between handedness and structural cerebral asymmetries have yielded conflicting results [Foundas et al., 2002; Good et al., 2001a]. Similarly, several studies have described asymmetries of the functional organization of the human brain by using different activation techniques. Speech- and motor-related activations are usually lateralized to the left hemisphere in right-handers and bilateralized or lateralized to the right hemisphere in left-handers [Kim et al., 1993; Singh et al., 1998; Solodkin et al., 2001; Verstynen et al., 2005]. However, the definition of the

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TABLE I. Main demographic characteristics and results of functional assessment of upper limbs from right- and left-handed healthy individuals

	Right-handed subjects	Left-handed subjects
Sex (F/M)	8/3	5/3
Mean age (range)	29 (25–41)	30 (22–43)
Mean EHI laterality quotient (range)	0.96 (0.90–100)	−0.93 (−100 to −0.90)
Right upper limb mean time to complete the nine-hole peg test (SD) [s]	19.7 (3.2)	21.5 (1.9)
Right upper limb mean maximum finger tapping rate (SD) [s]	3.6 (0.4)	3.7 (0.5)
Left upper limb mean time to complete the nine-hole peg test (SD) [s]	21.9 (2.7)	20.3 (1.7)
Left upper limb mean maximum finger tapping rate (SD) [s]	3.0 (1.2)	3.0 (0.9)

F, female; M, male; EHI, Edinburgh Handedness Inventory; SD, standard deviation.

brain networks associated to such a lateralization of functions is still very limited. In this study, we hypothesized a relationship between the function of the mirror-neuron system (MNS) and handedness. The MNS is an observation-execution matching system activated, in humans, during internally generated actions, action observation, motor learning, and imitation of action [Iacoboni, 2005; Iacoboni et al., 1999; Rizzolatti and Craighero, 2004]. It has also been thought to be recruited in speech generation [Arbib, 2005]. One of the main roles of the MNS is thought to be the understanding of actions. Neurons of the MNS have been located in the inferior frontal gyrus (IFG), the adjacent premotor cortex, and the parietal lobe [Rizzolatti et al., 2001]. The MNS is connected with the superior temporal sulcus (STS), which provides a higher-order visual description of the observed action [Iacoboni, 2005].

We used functional magnetic resonance imaging (fMRI) to test how actions performed by others are represented in the brains of right-handed (RH) and left-handed (LH) subjects and the possible relationship between this action representation processed by the MNS and the processing of a simple motor act.

MATERIALS AND METHODS

Subjects

We studied 11 RH (eight females, three males; mean age = 29 years, range = 25–41) and eight LH (five females, three males; mean age = 33 years, range = 22–51) subjects with no previous history of neurological dysfunction and a normal neurological exam. Handedness was established according to the 10-item version of the Edinburgh Handedness Inventory (EHI) scale [Oldfield, 1971]. The mean laterality quotient at the EHI was 0.96 (range = 0.90, 100) in RH subjects and −0.93 (range = −100, −0.90). Local Ethical Committee approval and written informed consent from all subjects were obtained prior to study initiation.

Functional Assessment

Motor functional assessment was performed for all the subjects on the same day of MRI acquisition. The nine-hole

peg test (9-HPT) and the maximum finger tapping frequency were used to assess upper limbs function. The maximum finger tapping rate was observed for two 30-s trial periods outside the magnet and the mean frequency to the nearest 0.5 Hz entered the analysis. No differences were found in the performance of these tests between RH and LH individuals (Table I).

Experimental Design

Using a block design (ABAB), the subjects were scanned while performing two experiments. During the first experiment (right-hand experiment), regions involved in processing action of the right hand were investigated. This was obtained by investigating the performance of two different tasks. The first consisted of repetitive flexion-extension of the last four fingers of the right hand moving together alternated to epochs of rest (hand-execution/right). The movements were visually cued at a 1 Hz frequency. The second task consisted of observation of a movie showing the hand of another subject while performing the same simple task alternated to epoch of static hand (hand-observation/right). During the second experiment (left-hand experiment), regions involved in processing action of the left hand were investigated. This was obtained by investigating the performance of two different tasks. The first consisted of repetitive flexion-extension of the last four fingers of the left hand moving together alternated to epochs of rest (hand-execution/left). The movements were visually cued at a 1 Hz frequency. The second task consisted of observation of a movie showing the hand of another subject while performing the same simple task alternated to epoch of static hand (hand-observation/left). During the observations conditions, video-clips were showed from a 3rd person visual perspective. The handedness of the production and the hand observed in the video-clips were fully crossed in all the experiments. Subjects were trained before performing the experiments. They were also monitored visually during scanning to ensure accurate task performance and to assess for additional (e.g., mirror) movements. Tasks were performed equally well by all the subjects.

fMRI Acquisition

Brain MRI scans were obtained using a 3.0 Tesla scanner (Intera, Philips Medical Systems, Best, The Netherlands). Functional MR images were acquired using a T2*-weighted single-shot echo-planar imaging (EPI) sequence (echo time [TE] = 35 ms, flip angle = 85°, matrix size = 128 × 128, field of view [FOV] = 240 mm², repetition time [TR] = 3.7 s). Thirty axial slices, parallel to the AC-PC plane, with a thickness of 4 mm, covering the whole brain were acquired during each measurement. Shimming was performed for the entire brain using an auto-shim routine, which yielded satisfactory magnetic field homogeneity.

Structural MRI Acquisition

On the same occasion and using the same magnet, the following images of the brain were also obtained from all subjects: (1) dual-echo turbo spin echo (TSE) sequence (TR/TE = 3000/45–120 ms; echo train length = 5; flip angle = 90°; 30 contiguous, 4 mm-thick, axial sections, matrix size = 256 × 256; FOV = 230 × 230 mm²); (2) 3D T1-weighted fast-field echo (FFE) sequence (TR/TE = 25/4.6 ms; flip angle = 90°; 220 contiguous, axial slices with voxel size = 0.89 × 0.89 × 1 mm, matrix size = 256 × 256; FOV = 230 × 230 mm²); (3) pulsed-gradient SE echo planar (EP) with SENSE (acceleration factor = 2.5; TE/TR = 80/8283.2 ms; 55 contiguous, 2.5-mm thick axial slices; acquisition matrix size = 96 × 96; FOV = 240 × 240 mm²; after SENSE reconstruction, the matrix dimension of each slice was 256 × 256, and in-plane pixel size 0.94 × 0.94 mm) and diffusion gradients applied in 32 noncollinear directions, using a gradient scheme, which is standard on this system (gradient overplus) and optimized to reduce echo time as much as possible. To optimize the measurement of diffusion only two b factors were used ($b_1 = 0$, $b_2 = 1000$ s/mm²). Fat saturation was performed to avoid chemical shift artifacts. All slices were positioned to run parallel to a line that joins the most infero-anterior and infero-posterior parts of the corpus callosum.

fMRI Analysis

All image post-processing was performed on an independent computer workstation (Sun Sparcstation, Sun Microsystems, Mountain View, CA). fMRI data were analyzed using the statistical parametric mapping (SPM2) software developed by Friston et al. [1995]. Prior to statistical analysis, all images were realigned to the first one to correct for subject motion, spatially normalized into the standard space of SPM, and smoothed with a 10-mm, 3D-Gaussian filter.

Structural MRI Post-Processing

All the structural MRI analysis was performed by a single experienced observer, unaware to whom the scans

belonged and blinded to the fMRI results. Dual-echo scans were visually inspected for the presence of macroscopic visible lesions.

For DT MRI images, the DT was estimated by using a nonlinear regression (Marquardt–Levenberg method), assuming a mono-exponential relationship between signal intensity and the b-matrix components [Basser et al., 1994]. After diagonalization of the estimated tensor matrix, the two scalar invariants of the tensor, mean diffusivity (MD) and fractional anisotropy (FA), were derived for every pixel. Then, using the VTK CISG Registration Toolkit [Hartkens et al., 2002], the rigid transformation needed to correct for position between the $b = 0$ images (T2-weighted, but not diffusion weighted) and T2-weighted images was calculated. Normalized Mutual Information [Studholme et al., 1999] was the similarity measure chosen for the matching. The same transformation parameters were then used to coregister the MD and FA images to the T2-weighted images. By using SPM2 and maximum image inhomogeneity correction [Ashburner and Friston, 1997], gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) were then automatically segmented from the T2-weighted images. Each pixel was classified as GM, WM, or CSF, depending on which mask had the greatest probability (maximum likelihood) at that location. This pixel classification generated mutually exclusive masks for each tissue. The resulting masks were superimposed onto the MD and FA maps and the corresponding MD and FA histograms of the WM and GM were produced. FA histograms were derived only for the WM, since no preferential direction of water molecular motion is expected to occur in the GM, because of the absence of a microstructural anisotropic organization of this tissue compartment. For each histogram, the average MD and FA values and the peak heights (i.e., the proportion of pixels at the most common MD and FA values) were measured.

Normalized brain volumes (NBV) were measured using 3D-FFE images and the cross-sectional version of the fully automated Structural Imaging Evaluation of Normalized Atrophy (SIENAX) software [Smith et al., 2001]. Regional volumetry measurements were performed using an optimized VBM approach, as described by Ashburner and Friston [2000], and Good et al. [2001b], using the 3D-FFE images and SPM2 software [Friston et al., 1995]. Full details of the steps involved in the optimized method of VBM analysis have been presented extensively elsewhere [Ashburner and Friston, 2000; Good et al., 2001b]. Briefly, a customized T1 template, together with the corresponding probability maps of GM, WM and CSF, were first created using 3D-FFE scans of six of the subjects of the study, who were selected randomly. This procedure involved spatial normalization of the original images to the standard SPM T1 template, segmentation into WM and GM, averaging of the images and smoothing with an 8-mm FWHM Gaussian kernel. Then, the same 3D-FFE data were segmented and normalized to the customized template using the GM tissue maps driving this transformation. After a new segmen-

tation step in the SPM stereotaxic space, the GM normalized maps obtained were modulated to incorporate the point-wise volume expansion/contraction induced by the transformation [Ashburner and Friston, 2000] and smoothed with a 12 mm³ FWHM Gaussian kernel. Prior to statistical analysis, the scans were thresholded at 20% of global intensity to reduce the influence of any remaining nonGM tissue.

Statistical Analysis

Changes in blood oxygenation level dependent (BOLD) contrast associated with the performance of the different tasks were assessed on a pixel-by-pixel basis, using the general linear model and the theory of Gaussian fields [Friston et al., 1995]. Specific effects were tested by applying appropriate linear contrasts. Significant haemodynamic changes for each contrast were assessed using *t* statistical parametric maps (SPM_t). The intra-group activations and comparisons between groups were investigated using a random-effect analysis [Friston et al., 1999]. To test the hypothesis of an interaction between the MNS and handedness during the observation conditions, a 2 × 2 factorial design was defined in an ANOVA model to assess the main effect of hand observed, the main effect of handedness and their interaction (34 degrees of freedom). A non-sphericity correction was applied for variance differences between conditions or subjects. To define the behavior of the MNS and the motor system in the two groups of subjects according to their handedness and the task investigated, an analysis of within-group task-related activations and between-groups task-related differences were also performed, using a one-sample *t* test (10 degrees of freedom for RH and 7 degrees of freedom for LH subjects), and a two sample *t*-test (17 degrees of freedom), respectively. We report activations below a threshold of $P < 0.05$ corrected for multiple comparisons (family-wise error). Differences of structural MR-derived metrics between RH and LH subjects were assessed using a two-tailed Student *t* test for not-paired data. The comparison of GM maps between RH and LH subjects was performed on a voxel-by-voxel basis using SPM2 and a two-sample *t* test. The GM densities were compared as absolute units. The SPM were thresholded at $P < 0.05$, corrected for multiple comparisons at a voxel level.

TABLE II. Brain volumes, MD, and FA histogram-derived metrics of the white and gray matter from RH and LH healthy volunteers

	RH subjects	LH patients	<i>P</i> values
Normalized brain volume (SD)	1648 (78)	1642 (67)	n.s.
WM average MD (SD)	0.79 (0.02)	0.79 (0.03)	n.s.
WM MD peak height (SD)	14.6 (1.8)	13.6 (1.2)	n.s.
GM average MD (SD)	1.01 (0.05)	0.99 (0.06)	n.s.
GM MD peak height (SD)	6.5 (1.1)	6.5 (1.3)	n.s.
WM average FA (SD)	0.39 (0.02)	0.37 (0.02)	n.s.
WM FA peak height (SD)	2.3 (0.1)	2.2 (0.1)	n.s.

WM, white matter; GM, gray matter; SD, standard deviation; MD, mean diffusivity; FA, fractional anisotropy; MS, multiple sclerosis; n.s., not significant.

Note: brain volume is expressed in ml, average MD of the diffusivity histogram is expressed in units of mm²s⁻¹ × 10⁻³, FA is a dimensionless index, peak heights are %.

RESULTS

No structural differences were found between the LH and RH groups in terms of brain volumes, GM densities, and WM and GM diffusivity characteristics (Table II).

All subjects performed the tasks correctly and no additional movements were observed during fMRI acquisition. We will not describe in detail the movement-associated brain pattern of cortical activation during the performance of the two “execution tasks” (right and left hand) in the two groups of subjects separately because this was not the main topic of this study. During both the experiments, LH subjects had a more bilateral pattern of activation than RH ones. These results were confirmed by the between group comparisons (data not shown). In addition, during hand-execution/left, RH subjects showed a cluster of activation in the right IFG (SPM coordinates: 58, 6, 20). Conversely, LH subjects showed a cluster of activation in the left IFG (SPM coordinates: -56, 8, 30) during hand-execution/right and in the bilateral IFG (SPM coordinates: -62, 16, 22 and 62, 8, 24) during hand-execution/left.

The factorial analysis showed the main effect of hand observed in the superior frontal sulcus (SFS), bilaterally (SPM coordinates: 12, 60, 30 and -24, 56, 34), the middle occipital gyrus (MOG), bilaterally (SPM coordinates: 28, -86, 8 and -34, -92, -8), the left IFG (SPM coordinates: -32, 22, -20), the left basal ganglia (SPM coordinates:

Figure 2.

Cortical activations on a rendered brain from RH (A, C) and LH healthy subjects (B, D) during the performance of an observation task involving the right (A, B) and left (C, D) upper limbs (within-group analysis, one-sample *t* tests, $P < 0.05$ corrected for multiple comparisons). During hand-observation right, the activation of areas of the MNS is mainly located in the left cere-

bral hemisphere in RH subjects and in the right cerebral hemisphere in LH subjects. During hand-observation left, the activation of areas of the MNS is mainly located in the right cerebral hemisphere in both groups of subjects. Blue circles identify the inferior frontal gyrus activation. Images are in neurological convention.

Figure 1.

Results of the analysis of interaction between handedness (RH or LH) and hand observed (right or left) during the observation conditions, on a rendered brain. The superior frontal sulcus, bilaterally (A, C, D), the left supplementary motor area (A), the inferior frontal gyrus, bilaterally (C, D), the left basal ganglia (B), the right cerebellum (D), and the middle occipital gyrus, bilaterally (C, D) are shown ($P < 0.05$ corrected for multiple comparisons). Images are in neurological convention.

–24, 2, –6), the left angular gyrus (SPM coordinates: –49, –70, 35), and the right cerebellum (SPM coordinates: 28, –46, –50). The main effect of handedness was detected in the left supplementary motor areas (SMA) (SPM coordinates: –2, 0, 56), the right primary sensorimotor cortex (SMC) (SPM coordinates: 40, –24, 52), the right IFG (SPM coordinates: 40, 28, –10), the left secondary sensorimotor cortex (SPM coordinates: –64, –54, 8), the left MOG (SPM coordinates: –26, –96, –12), and the right cerebellum (SPM coordinates: 36, –46, –40). The interaction analysis showed an effect of handedness and hand observed in the SFS, bilaterally (SPM coordinates: –38, 50, 12 and 12, 60, 30), the left SMA (SPM coordinates: –2, 0, 56), the IFG, bilaterally (SPM coordinates: –38, 50, –12 and 40, 28, –10), the left basal ganglia (SPM coordinates: –26, 4, 2), the right cerebellum (SPM coordinates: 30, –46, –48), and the MOG, bilaterally (SPM space coordinates: –36, –92, –8 and 34, –90, 6) (Fig. 1).

The within-group assessment of whole brain activations associated to the observation task of the right hand revealed the activation of areas of the MNS and motor systems mainly located in the left cerebral hemisphere in RH subjects and in the right cerebral hemisphere in LH subjects (Fig. 2). During this condition, LH subjects showed an activation of the left IFG, while RH subjects had an activation of the right IFG (Fig. 2). These results were confirmed by the between-group comparison (Fig. 3). In particular,

Figure 2.

Figure 3.

Relative cortical activations in RH and LH subjects during the observation task in right-hand Experiment. Compared with LH subjects, RH showed increased recruitment of the anterior portion of the left precentral gyrus (A), the left inferior parietal lobule (B), the left middle frontal gyrus (C), and the left culmen

of the cerebellum (D). Compared with RH subjects, LH showed increased recruitment of the right supplementary motor area (E), the precentral gyrus, bilaterally (F), the putamen, bilaterally (G), and the left inferior frontal gyrus (G). Images are in neurological convention.

Figure 4.

Cortical activations on a rendered brain from RH (A, C) and LH healthy subjects (B, D) showing the results of the within-group comparison of execution vs. observation task during the two experiments: right hand = A, B; left hand = C, D. During both experiments, while RH subjects had exclusively an increased activation of areas of the motor system (primary and secondary

sensorimotor cortices, supplementary motor areas, and cerebellum) in the left cerebral hemisphere, LH subjects tended to have a bilateral activation of these regions as well as the activation of additional areas of the frontal and parietal lobes. Blue circles identify the inferior frontal gyrus activation. Images are in neurological convention.

TABLE III. Within-group comparison of execution vs. observation task (right and left hands, separately) activations in RH and LH healthy volunteers (paired t test in each group)

Activation sites	Right-handed hand-execution vs. observation right		Left-handed hand-execution vs. observation right		Right-handed hand-execution vs. observation left		Left-handed hand-execution vs. observation left	
	SPM coordinates X Y Z	t	SPM coordinates X Y Z	t	SPM coordinates X Y Z	t	SPM coordinates X Y Z	t
Primary SMC	-40, -22, 54	14.8	-40, -20, 56	8.1	46, -16, 46	10.4	30, -26, 52	12.8
SMA	-6, -8, 54	9.2	-10, 0, 60	5.1	-2, -2, 52	4.6	—	—
CMA	—	—	—	—	0, 14, 34	4.65	—	—
R cerebellum	16, -64, -30	12.7	16, -50, -30	7.4	—	—	24, -40, -34	14.5
L cerebellum	—	—	-24, -72, -28	7.1	-20, -46, -36	8.5	-24, -60, -28	4.9
					-4, -58, -6	18.4	-4, -66, -20	4.5
R putamen	22, 8, -6	4.2	—	—	32, -4, -10	6.9	28, -8, -6	3.9
	22, 8, 14	3.9	—	—	—	—	—	—
L putamen	-30, -4, -8	7.9	—	—	—	—	—	—
R thalamus	—	—	—	—	18, -12, -4	11.9	16, -18, 6	8.8
L thalamus	-14, -18, -8	8.2	-14, -20, -6	3.7	—	—	—	—
R insula	—	—	-42, 2, 6	10.1	—	—	—	—
L insula	—	—	—	—	—	—	-36, 4, 12	4.6
R SII	—	—	—	—	—	—	58, -18, 16	4.2
L SII	-50, -18, 16	8.7	-64, -18, 18	4.5	—	—	—	—
R precentral gyrus	—	—	30, -6, 56	6.1	—	—	—	—
R postcentral gyrus	—	—	58, -32, 52	3.8	—	—	—	—
L postcentral gyrus	—	—	-18, -60, 70	3.7	—	—	—	—
R IFG	—	—	—	—	60, 6, 22	6.1	58, 10, 34	6.9
L IFG	—	—	-60, 12, 24	6.8	—	—	—	—
R SPL	—	—	24, -58, 66	3.4	—	—	—	—
L IPL	—	—	-50, -44, 54	8.9	—	—	—	—

SMC, sensorimotor cortex; SMA, supplementary motor area; CMA, cingulate motor area; SII, secondary sensorimotor cortex; SPL, superior parietal lobule; IFG, inferior frontal gyrus; IPL, inferior parietal lobule.

during the observation task in right-hand experiment, when contrasted with LH subjects, RH subjects had more significant activations of the precentral gyrus (SPM space coordinates: -42, 6, 40), the inferior parietal lobule (IPL) (SPM space coordinates: -54, -38, 44), the MFG (SPM coordinates: -30, 46, 16), and the cerebellum (SPM space coordinates: -14, -38, -12) in the left side of the brain. Conversely, LH subjects had more significant activations of the precentral gyrus, bilaterally (SPM space coordinates: 36, -14, 40 and -34, -16, 42), the putamen, bilaterally (SPM space coordinates: 28, 8, -6 and -24, 12, -6), the right SMA (SPM space coordinates: 8, -6, 54), and the left IFG (SPM space coordinates: -58, 26, 10) (Fig. 3). Since, with the exception of the IFG, all these areas were not detected at the within-group one-sample t test analysis, the results of such an analysis were reassessed by evaluating the deactivations during this task. This analysis showed that the SMA, the precentral gyrus, bilaterally, and the putamen, bilaterally, were deactivated in RH subjects and not in LH subjects.

The within-group assessment of whole brain activations associated to the hand-observation/left task revealed the activation of areas of the MNS, including the IFG, mainly located in the right cerebral hemisphere in both groups of subjects (Fig. 2). The between-group comparison showed and increased activation of the right primary SMC (SPM

coordinates: 36, -18, 64) in RH subjects when compared with the LH ones, and of the SMA (SPM coordinates: 4, 0, 56) and the right superior temporal sulcus (SPM coordinates: 58, -24, 0) when the opposite contrast was run.

The within-group comparison of the execution vs. observation tasks during right-hand experiment showed that during the execution task, RH subjects had exclusively an increased activation of areas of the motor system (primary SMC, SII, SMA, and cerebellum) in the left cerebral hemisphere, whereas LH subjects tended to have a bilateral activation of these regions as well as of additional areas in the frontal (precentral gyrus and IFG) and parietal (postcentral gyrus, SPL and IPL) lobes (Fig. 4) (Table III). The opposite contrast showed that, during right-hand experiment, RH subjects had an increased activation of areas of the MNS located in the frontal and parietal lobes, bilaterally, whereas LH subjects tended to have an increased activation of areas of the MNS located in the temporal and occipital lobes, bilaterally.

The within-group comparison of the execution vs. observation tasks during left-hand experiment demonstrated that during the execution task, both groups of subjects had activation of areas of the motor system (primary SMC, thalamus, SMA) of the right cerebral hemisphere in addition to an activation of the left cerebellum and the right IFG. RH subjects also showed an activation of the SMA

TABLE IV. Within-group comparison of observation vs. execution task (right and left hands, separately) activations in RH and LH healthy volunteers (paired t test in each group)

Activation sites	Right-handed hand-observation vs. -execution right		Left-handed hand- observation vs. -execution right		Right-handed hand-observation vs. -execution left		Left-handed hand-observation vs. -execution left	
	SPM coordinates X Y Z	t	SPM coordinates X Y Z	t	SPM coordinates X Y Z	t	SPM coordinates X Y Z	t
R MOG	28, -84, -20	13.2	38, -60, -16	6.7	30, -86, -18	14.5	34, -94, -10	8.7
L MOG	-26, -92, -10	4.5	-24, -92, 10	8.2	-42, -88, -12	12.2	-48, -70, -4	4.7
			-36, -76, 2	6.6				
R CMA	12, 54, 2	9.3	—	—	12, 44, 12	7.1	-6, 18, 32	3.01
	10, -42, 24	5.7	—	—				
R SFG	22, 60, 8	6.7	—	—	20, 60, 20	3.4	8, 44, 52	3.5
	14, 40, 48	5.1					32, 52, 26	3.5
L SFG	—	—	-8, 60, 30	7.6	-8, 62, 24	5.1	-24, 42, 50	3.4
R precentral gyrus	46, 6, 44	8.3	42, -12, 40	6.92	—	—	48, 0, 34	5.6
R MFG	40, 24, 34	6.9	6, 64, -4	7.2	—	—	—	—
R IFG	—	—	—	—	—	—	48, 20, -6	3.5
L IFG	—	—	-52, 26, 12	3.6	-50, 26, -4	3.5	—	—
L precuneus	-2, -42, 54	7.0	-4, -30, 60	4.3	-10, -38, 62	8.6	-12, -66, 56	4.3
	-8, -58, 52	6.9						
R IPL	56, -46, 26	6.8	—	—	54, -60, 26	5.5	30, -86, 26	5.1
R STG	58, -40, 8	5.4	—	—	54, -12, -10	7.9	46, -52, 8	5.1
L STG	—	—	-54, -40, 22	6.6	-54, -28, -6	10.0	-56, -10, -6	6.8
R MTG	—	—	—	—	—	—	50, -66, -6	5.4
L MTG	—	—	—	—	-56, -70, 10	12.1	—	—

MOG, middle occipital gyrus; CMA, cingulated motor area; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; STG, superior temporal gyrus; MTG, middle temporal gyrus.

that was not detected in LH individuals (Fig. 4). The opposite contrast showed widespread activations of areas of the MNS located in the frontal, parietal and temporo-occipital lobes in both groups of subjects (Table IV and Fig. 5).

DISCUSSION

A large amount of theories has been proposed to explain hand preference and dominance in humans, including inheritance of handedness as a uni/multi- dimensional trait [Annett 1972; Healey et al., 1986], hormone influences [Geschwind et al., 1985], and anatomical and morphological differences in specific brain structures [Foundas et al., 1994, 2001, 2002; Good et al., 2001a]. Theories supporting a role of asymmetries of functional specialization of brain networks suggest that the MNS might constitute a bridge between action and language processing and might represent the neuronal substrate from which human language evolved [Arbib 2005; Rizzolatti and Arbib, 1998]. Assuming that the acquisition of language is related to the MNS evolution in humans, it is tempting to speculate that “intermediate changes” in the function of the system occurred before reaching such a role. This hypothesis is strengthened by the observation that in humans the MNS is active not only during the execution and observation of object-related transitive actions [Rizzolatti and Craighero, 2004; Rizzolatti et al., 1996], but also in case of intransitive actions [Buccino et al., 2001; Iacoboni et al., 1999].

Although the sample size studied was relatively small, and as a consequence, our findings should be considered as preliminary, this is the first study suggesting a different lateralization of the MNS in RH and LH subjects (within-group analysis), providing evidence to the theory of the involvement of this system in the lateralization of brain functions in humans. The absence of any difference in structural MRI metrics between RH and LH subjects allows us to rule out a possible influence of diversity in brain symmetries on our fMRI results. Using fMRI, a previous study [Aziz-Zadeh et al., 2006] focused the analysis on selected regions of the system, in particular the IFG, exclusively in RH subjects and found that the activation of this region, albeit more marked in the hemisphere of the response hand, was nevertheless bilateral. This suggested that motor components of the MNS are not left-lateralized. However, it is difficult to compare our findings with the previous ones for several reasons, including the fact that the previous results were detected during an imitation task (thus not allowing to rule out the bias associated to task execution), while in our paradigm we analyzed exclusively action observation, which can be viewed as a sort of “passive task,” which is another and different feature of this system. Furthermore, the previous study compared activations between right and left hands, while we also compared activations between RH and LH subjects.

The analysis of interaction between handedness and hand observed during the observation condition confirmed our working hypothesis by showing a complex interplay

Figure 5.

Cortical activations on a rendered brain from RH (A, C) and LH healthy subjects (B, D) showing the results of the within-group comparison of observation vs. execution task during the two experiments: right hand = A, B; left hand = C, D. During right-hand experiment, RH subjects had an increased activation of areas of the MNS located in the frontal and parietal lobes, bilat-

erally, while LH subjects tended to have an increased activation of areas of the MNS located in the temporal and occipital lobes, bilaterally. During left-hand experiments, both groups of subjects had a widespread and bilateral activation of areas of the MNS system. Images are in neurological convention.

between the activity of areas of the motor system (SMA, basal ganglia and cerebellum) and those of the MNS (IFG, SFS and MOG). It is worth noting that MOG is part of the dorsal visual pathway, which takes part to visual guidance of action. In addition, it shows a selective response to human bodies and body parts [Downing et al., 2001] and has a prominent role in the construction of gesture visual representation, available for subsequent recognition or imitation [Peigneux et al., 2000]. MOG neurons are supposed to code the goal of actions rather than the specific hand-object interactions used for attaining it and forward this information to IFG neurons coding the details of the hand-object interaction [Fogassi and Luppino, 2005; Iacoboni et al., 2005].

To characterize the different behavior of the motor and MNS in the two groups of subjects during the different experimental conditions, a detailed assessment of within- and between-groups activation was also performed. The between-group comparison demonstrated that during right-hand experiment, when performing the observation task, LH subjects had increased activation of areas that are considered typical of the MNS (including several region in the frontal and parietal lobes), as well as of other areas of

the motor network, including the primary and secondary sensorimotor cortices, the SMA, and the basal ganglia. It is worth noting that, with the exception of the IFG, the different activations of the remaining areas were due to a lack of “deactivation” in LH subjects. The areas previously described were found to be activated by studies with paradigms involving action execution/imitation. Basal ganglia activity has been associated with motor program selection and suppression at early stages of motor planning, as well as with control of movement simulation [Kessler et al., 2006]. Basal ganglia exert their influence for learned movements mainly via thalamus. To our knowledge, no study assessed so far areas of “deactivation” during MNS tasks. The term “deactivation” usually refers to activity that is greater during rest than during task performance. Recently, a relationship has been shown between the negative BOLD signal change, reduced oxygen consumption and neuronal inhibition, probably originating at a presynaptic level [Shmuel et al., 2006; Stefanovic et al., 2004]. The lack of “deactivation” of areas of the motor network in LH subjects suggests an upregulation of this system in these subjects during the observation task. Alternatively, the temporal sequence of brain activations during hand move-

ment might be different between the two groups [Nishitani et al., 2000]. Modulation of connections between the motor and other systems devoted to processing the motor acts might be one of the evolutionary mechanisms that led to the preservation of one system and to its functional specialization. If this is the case, these results suggest that increased cross-talk between the MNS and the motor system might be one of the processes related to establishment of hand preference/dominance in humans. This hypothesis is supported by the demonstration by Kessler et al. [2006] that premotor, temporal and parietal areas of the MNS mediate imitation of biological movements in close interaction with motor areas (cerebellum, basal ganglia and sensorimotor cortex). The analysis of the observation task during left-hand experiment, showed a similar brain pattern of cortical activations between RH and LH subjects, with the activation of several areas of the motor system and the MNS, including the IFG, mainly located in the right cerebral hemisphere. The between-group comparison demonstrated that LH subjects had an increased activation of the SMA and the STS, when compared with RH subjects. The STS is thought not only to be involved in the recognition of body postures, but also to provide a visual description of the action that is critical for the process of imitation, one of the main roles of the MNS [Iacoboni, 2005].

The analysis of interaction between the execution and observation conditions in the two experiments provided important information for the understanding of the brain circuits involved in simple act performance and handedness. In particular, RH subjects activated exclusively areas of the motor network, mainly in the contralateral (left) cerebral hemisphere, during simple act performance with their dominant, right, upper limb, while during the same task with their nondominant left upper-limb they showed, in addition to an activation of areas of the motor network, mainly located in the right cerebral hemisphere, also an activation of the right IFG. This region, which is a critical node of the MNS, was activated by LH subjects during movement of both the dominant and the nondominant upper limbs, with a lateralization of activation similar to that of the motor network. These findings suggest that independently from handedness, the activation of regions of the MNS, in particular the activation of the IFG, might have an important role for performing a simple motor act with the nondominant upper limbs. It is tempting to speculate that the MNS activation in this case might be related to the need to manipulate the internal repertoire of motor acts usually carried out with the dominant limbs, thus rendering the performance of a task with the nondominant hand as a sort of imitative task of what is usually done with the dominant-hand. Previous studies [Kim et al., 1993; Solodkin et al., 2001; Verstynen et al., 2005] assessing functional representation of simple motor acts in RH and LH subjects did not describe such an activation of areas of the MNS. This discrepancy is likely to be due to the fact that the majority of the previous studies performed a region-of-interest analysis focused on the main areas of the

motor system (primary SMC, SMA), and did not consider areas of the MNS.

Contrary to RH subjects, LH subjects showed an activation of the IFG also during the performance of a simple motor act with their dominant, left, upper limb. Although definitive conclusions regarding IFG lateralization, handedness and simple hand movement can not be derived from our study, our results seems to indicate that the lateralization of the motor components of the MNS, that is represented by the IFG, follows the same lateralization of the motor network with handedness. The IFG contains a representation of the distal movements [Binkofski and Buccino, 2006; Krams et al., 1998] and it is considered the human homologue of monkey areas F5 [Rizzolatti and Arbib, 1998], in which an action observation-execution matching system has been described. Previous studies showed activation of this region not only during observation-execution of simple finger movements, but also during observation only [Grezes et al., 2002; Iacoboni et al., 1999]. The activation of regions that are part of the MNS in LH subjects during the performance of a simple movement with their dominant, upper, left limbs suggests that even a simple motor task might be experienced by LH subjects as a sort of imitative task. Imitation is a fundamental aspect of evolution. This mechanism has been described not only in monkeys [Rizzolatti et al., 2001], but also in human newborns [Meltzoff and Decety, 2003]. In particular, in line with previous studies on imitation of face expressions [Meltzoff and Decety, 2003], a recent study demonstrated the existence of imitation of finger movements in neonates. It is worth noting that in this study neonatal imitation was more frequently LH [Nagy et al., 2005]. Considering that different theories propose that handedness might be under genetic control [Annett, 1972; McManus, 1985] and that several studies suggest that handedness is present prior to birth [Hepper et al., 1991; Trevarthen, 1996], it is tempting to speculate that handedness in the adult life might be the result of a complex interaction between genetic and environmental factors and that the MNS might play a role in this interaction through its role in imitation. In particular, our findings support the notion that left-handers act adapting their actions to a world that has been essentially built for RH people; this is indeed the case for the vast majority of common tools of daily-life activity. Our results suggest that LH subjects are able to deal with this "right" world essentially by mirroring RH.

Obviously, our study is not without limitations, including the relatively small number of subjects studied and the fact that we did not assess the brain patterns of cortical activations during a condition involving imitation, which is one of the main role of the MNS. In addition, considering the variability of fMRI findings, our results need to be replicated. Nevertheless, considering that, to our knowledge, this is the first study dealing with the topic of MNS and handedness, it was not possible to include, in a single analysis all the conditions/variables possibly related to the investigated tasks. Further studies are now warranted to confirm and advance our findings.

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