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Dominance of the Right Hemisphere and Role of Area 2 in Human Kinesthesia


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INTRODUCTION

Somatic perception of limb position or limb movement depends to a large extent on the central processing of kinesthetic information originating from the receptors in muscles. With eyes closed, vibration stimuli at ∼80 Hz on the tendon of a limb can elicit a kinesthetic illusory movement of the limb in the absence of actual movements (Goodwin et al. 1972a,b; Naito and Ehrsson 2001; Naito et al. 1999, 2002a,b). The vibration stimuli mainly excite the muscle spindle afferents signaling that the vibrated muscles are stretched although the limb remains immobile (Burke et al. 1976; Collins and Prochazka 1996; Gandevia 1985; Roll and Vedel 1982; Roll et al. 1989). We have consistently demonstrated by positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) that the contralateral motor cortex (M1), cytoarchitectonic areas 4a and 4p), primary somatosensory cortex (SI), dorsal premotor cortex (PMD), supplementary motor area (SMA), cingulate motor area (CMA) (Naito and Ehrsson 2001; Naito et al. 1999, 2002a,b), and the ipsilateral cerebellum (Naito et al. 2002a,b) are active during illusionary movements of arm or hand. In particular, M1 appears to be primarily responsible for the kinesthetic processing of muscle spindle input, and its activity is associated with the perception of limb movements (Naito 2004; Naito et al. 2002b). The general aim of the present study was to investigate the brain regions, in addition to the motor areas described in the preceding text, which may be active during kinesthetic illusions. We examine three specific hypotheses.

First, we examine the hypothesis that area 2 is involved in kinesthetic illusions. A large number of studies in non-human primates suggest that neurons in cytoarchitectonic area 2 respond to sensory input during passive or active limb movements (Burchiel and Duffy 1972; Costanzo and Gardner 1981; Gardner 1988; Gardner and Costanzo 1981; Iwamura 2000; Iwamura and Tanaka 1996; Iwamura et al. 1993, 1994; Jennings et al. 1983; Mountcastle and Powell 1959; Pons et al. 1992; Salimi et al. 1999; Schwarz et al. 1973; Taoka et al. 1998, 2000; Wolpaw 1980). As there seem to be no obvious anatomical differences between area 2 in monkeys and humans (Zilles and Palomero-Gallagher 2001), one may expect that human area 2 would be involved in the processing of kinesthetic information. One possible reason for the apparent discrepancy between our imaging results and the non-human primate literature is the differences in afferent input during kinesthetic illusions and passive limb movement. During tendon vibration illusions, the muscle spindle afferent is the only sensory source signaling limb movements (see references in the preceding text), whereas during passive limb movements, the brain receives multiple somatosensory inputs from muscle receptors, joint receptors, and skin receptors (Burke et al. 1988; Collins and Prochazka 1996; Hulliger et al. 1979). As neurons
in area 2 respond to input from cutaneous receptors (Costanzo and Gardner 1980; Gardner 1988; Hyvärinen and Poranen 1978; Iwamura and Tanaka 1978; Iwamura et al. 1993, 1994; Warren et al. 1986), area 2 may receive a greater amount of somatosensory input during passive limb movement than during tendon vibration. Nevertheless, if human area 2 is genuinely involved in kinesthetic processing, we would expect to detect area 2 activity during the kinesthetic illusions if we used a sensitive imaging method.

If this is the case, it is important to know the functional differences between M1 and area 2 during kinesthetic illusion. This brings us to our second hypothesis that area 2 should be active not only during illusion of the contralateral limb but also during illusion of the ipsilateral limb, whereas M1 should be active only during illusion of the contralateral limb (Naito and Ehrsson 2001). Neurons in monkey’s area 2 are known to respond to the afferent input not only from the contralateral limbs but also from the ipsilateral limbs (Iwamura 2000; Iwamura et al. 1994; Taoka et al. 1998, 2000). Thus we predicted that area 2 would be active no matter whether subjects experience illusions of the right or the left limb.

Our third hypothesis was that the right hemisphere would have a dominant role in kinesthetic processing. It is a common view in clinical neurology that the right hemisphere is specialized for bodily perception (Berlucchi and Aglioti 1997; Critchley 1953; Devinsky and D’Esposito 2004). This notion is based on human lesion studies (e.g., Halligan et al. 1993; McGonigle et al. 1953; Devinsky and D’Esposito 2004). This notion is based on human lesion studies (e.g., Halligan et al. 1993; McGonigle et al. 1953; Devinsky and D’Esposito 2004). This notion is based on human lesion studies (e.g., Halligan et al. 1993; McGonigle et al. 1953; Devinsky and D’Esposito 2004). This notion is based on human lesion studies (e.g., Halligan et al. 1993; McGonigle et al. 1953; Devinsky and D’Esposito 2004). This notion is based on human lesion studies (e.g., Halligan et al. 1993; McGonigle et al. 1953; Devinsky and D’Esposito 2004). This notion is based on human lesion studies (e.g., Halligan et al. 1993; McGonigle et al. 1953; Devinsky and D’Esposito 2004).

We utilized fMRI to measure the brain activity when subjects experienced an illusory palmar flexion of the wrist that was elicited by the tendon vibration of the wrist extensor muscles. We used fMRI rather than PET because fMRI allowed us to collect a significantly greater number of brain scans per subject and hence provides a better statistical power than PET to detect relatively weak but significant brain activities. Furthermore, we vibrated the tendon of the right or left hand respectively in the same group of subjects. This allowed us to directly investigate a possible lateralization of the activations during kinesthetic illusions. Finally, we used cytoarchitecturally defined areas from 10 postmortem human brains to describe the topography of each area in a probabilistic fashion.

**METHODS**

**Subjects**

Ten right-handed (Oldfield 1971) male subjects (21–33 yr) with no history of neurological or other disease participated in the study. All subjects had given their informed consent and the Ethical Committee of the Karolinska Hospital had approved the study. The fMRI experiment was carried out following the principles and guidelines of the Declaration of Helsinki (1975).

**fMRI measurement and tasks**

A 1.5 T General Electric scanner with head-coil provided T1-weighted anatomical images (3D-SPGR) and functional T2*-weighted echoplanar images (64 × 64 matrix, 3.4 × 3.4 mm, TE = 60 ms). A functional image volume comprised 30 slices of 5-mm thickness (with 0.4-mm interslice gap); this ensured that the whole brain was within the field of view.

The subjects were blindfolded and their ears were plugged. They rested comfortably in a supine position in the MR scanner. The extended arms were oriented in a relaxed supine position parallel to the trunk. The arms were supported proximal to the wrist. The hands were completely relaxed in this position. During the experimental conditions, the subjects were instructed to completely relax (and make no movements) and to be aware of the sensation from the wrist.

We vibrated the tendon of wrist extensor muscles (the extensor carpi ulnaris; ECU) to elicit an illusory palmar flexion of the wrist (illusion). To control for the effect of the skin vibration, we applied the identical stimuli to the skin over the processus styloideus ulnae, which does not elicit any illusion (vibration). A rest condition where the subjects relaxed completely was also included. We used a non-magnetic vibrator that was driven by constant air pressure provided by an air-compressor (Biltema Art. 17–635; Linköping, Sweden). The frequency of the air_current was ~80 Hz. The vibration site was ~1 cm². For each subject, we performed six fMRI sessions: in three of these the right wrist was vibrated alternating with three sessions in which the left wrist was vibrated (e.g., left session, right session, left session, and so forth). A total of 6 × 128 functional image volumes were collected for each subject. In each session, there were six conditions. The subjects were tested on illusion, vibration, and rest when right and left hands were separated and also when right and left hands were in contact palm to palm. The results from the latter three conditions have been reported elsewhere (Naito et al. 2002b). Thus in the present paper, we only describe the results from the conditions where right and left hands were separated, i.e., illusion, vibration, and rest. Each condition lasted for 32 s (8 functional images, TR = 4 s) and was repeated twice during each session. The order of conditions was randomized according to a balanced schedule.

In the training session before fMRI, we selected 10 of 16 subjects, who experienced vivid illusory palmar flexion (>20° wrist flexion) (see METHODS sections in Naito and Ehrsson 2001; Naito et al. 2002a,b). An electromyogram (EMG) from the skin surface of the vibrated ECU muscle showed slight increase of the activity. The EMG activity was present during illusion. These EMG results confirmed those in the previous study (Naito et al. 2002a). During the fMRI scanning, we observed no overt hand movements in any of the conditions. After the fMRI, all subjects reported that they vividly experienced the sensation of a palmar flexion of the vibrated hand.

**fMRI data analysis**

The fMRI data were analyzed with the Statistical Parametric Mapping software (SPM99; http://www.fil.ion.ucl.ac.uk/spm; Wellcome Department of Cognitive Neurology, London, U.K. (Friston et al. 1995a,b)). The functional images were realigned to correct for head movements (Ashburner and Friston 1997), co-registered with each subject’s anatomical MRI, and transformed (linear and nonlinear transformations) into the reference system of Talairach and Tournoux (Ashburner and Friston 1997; Talairach and Tournoux 1988), using the Montreal Neurological Institute (MNI) reference brain (Naito et al. 2002b). The functional images were scaled to 100 to correct for global changes in the MR signal to eliminate the effects of global changes in the signal and were spatially smoothed with a 8-mm full width at half-maximum (FWHM) isotropic Gaussian kernel and smoothed in time by a 4-s FWHM Gaussian kernel. We fitted a linear regression model (general linear model) to the pooled data from all subjects to increase the sensitivity of the analysis (fixed effects model) (Naito et al. 2002b). The validity of this approach, in terms of consistency of effects across all subjects in the group, was confirmed by conducting single-subject volume-of-interest (VOI) analyses (see further in the following text). Each condition was modeled with a boxcar function.
delayed by 4 s and convoluted with the standard SPM99 hemodynamic response function.

To identify the brain areas that are active during the kinesthetic illusion we performed pair-wise contrasts of the conditions i.e., (illusion–vibration). To identify the areas that were active during illusion of the right hand, we used the contrast of (right illusion–right vibration). We used the contrast of (right illusion–right rest) as an inclusive mask to exclude voxels that were not at all active during the illusions as compared with the rest condition. This masking procedure was done to remove voxels that only showed deactivation during vibration. The threshold for the mask was set at the very liberal threshold of \( P < 0.05 \), uncorrected so that no relevant areas were excluded. For the left hand, we used the contrast of (left illusion–left vibration). We also used the contrast of (left illusion–left rest) as an inclusive mask \( (P < 0.05, \text{uncorrected}) \). We used a significant threshold of \( P < 0.05 \) (\( t > 4.58 \)) corrected for multiple comparisons in the whole brain space.

To depict the areas that are commonly active during illusions of right and left hand, we used the SPM99 conjunction analysis of \([\text{right illusion–right vibration}] \cap \) (left illusion–left vibration). Similarly to identify the areas that are commonly active during skin vibration over the bone, the conjunction analysis of \([\text{right vibration–right rest}] \cap \) (left vibration–left rest) was performed. This latter conjunction was done so that we could determine whether the illusion conditions activated quantitatively different areas from the vibration conditions. For the conjunction analysis (Price and Friston 1997; Worsley and Friston 2000), we used the same \( t \) threshold (4.58) for each of the two contrasts because we only wanted to depict those voxels that were significantly active during right illusions as well as left illusions. This means that the threshold of the conjunction analysis corresponds to \( P < 0.00000025 \) for two contrasts after a correction of the number of multiple comparisons in the whole brain space. Because of this conservative threshold in the conjunction analysis, one should bear in mind that we do not report areas that showed a statistical trend for activation during illusion of one hand and a significant activation during the illusion of the other hand. Finally, we only report the clusters whose sizes were >10 voxels in this analysis.

Testing of dominance of the right-sided regions that are commonly active during illusions of right and left hands

The conjunction analysis showed that right-sided areas were active in common during right illusions and left illusions (see Results). This could indicate lateralization of the right hemisphere for kinesthetic processing during tendon vibration. However, to directly test if this reflects a genuine dominance of the right hemisphere, one has to compare the activities in the right areas with those in the corresponding areas in the left hemisphere. In other words, one has to test if the right-sided areas are significantly more activated than the corresponding areas in the left hemisphere. In other words, one has to test if the right-sided areas are significantly more activated than the corresponding areas in the left hemisphere. We did this by flipping (a right-to-left transformation in the \( x \) axis) the functional images from all scans of all subjects (the smoothed and normalized images). The right and the left hemispheres were reversed (flipped images). As just pointed out, this method allowed us to directly compare an activity in a voxel in the right hemisphere with the corresponding voxel in the left hemisphere. We defined a new general linear model that included both the flipped and the unflipped data. To test whether the blood oxygenation level-dependent (BOLD) signals of the right hemisphere during illusion of the right hand were significantly greater than those registered in the left hemisphere, we defined the contrast of \([\text{right illusion–right vibration}] \cap \) (right flipped illusion–right flipped vibration). The contrast (right illusion–right vibration) was used as an inclusive mask to exclude the areas that were not active during illusion of right hand \( (P < 0.05, \text{uncorrected}) \). The corresponding contrasts were defined to test the right-sided dominance during illusion of the left hand. For these tests, we chose a threshold of \( P < 0.05 \) after a correction for multiple comparisons in the right regions.

Single-subject VOI analyses

FUNCTIONAL DIFFERENCES BETWEEN M1 AND AREA 2 DURING ILLUSSIONS OF THE RIGHT AND LEFT HAND. To investigate functional differences between M1 and area 2 during illusions of the right and left hand, a post hoc single-subject analysis was done (see Methods in Naito et al. 2002b). When the right illusion was contrasted with the right vibration, we found peak activities in the left M1 (–36, –24, 51) and in the left area 2 (–30, –36, 60). When the left illusion was contrasted with the left vibration, we found peak activities in the right M1 (36, –18, 51) and in the right area 2 (48, –27, 51). Two peaks of (–30, –36, 60) and (48, –27, 51) were located in the caudal part of the postcentral gyrus in all subjects (of the anatomically standardized T1-weighted MR image of each subject). Similarly, peaks of (–36, –24, 51) and (36, –18, 51) were located in the precentral gyrus in all subjects.

We extracted the fMRI data from the four peaks of activities. We then calculated the mean percent increase of BOLD signal for each epoch of illusion compared with vibration conditions. The mean activity was calculated from six functional images: we excluded the first two functional images. This was done for all epochs on either hand in each subject. The percent increase was calculated for each epoch by using the following formula: \( \text{Mean in illusion} – \text{Mean in the corresponding vibration} \times 100 \text{Mean in the corresponding vibration} \). Finally, the mean value for each individual subject was calculated from the six values from six epochs. The right- and left-hand conditions were separately treated. We performed a two-factorial ANOVA [vibrated side (right or left) \( \times \) MI, area 2 \( \times \) repeated measurement design] for the mean of individual subject (see Fig. 3). The ANOVA was done separately for the right and the left hemisphere.

Dominance of right-sided areas during illusions of right and left hand

To investigate activities in the regions that are commonly active during illusions of the right and the left hand, another post hoc single-subject analysis was done. We extracted the fMRI data from eight peaks of clusters that were commonly active during illusions of the right and the left hand (see Table 3 and Fig. 5). We calculated the mean percent increase for each epoch of the illusion compared with the rest condition. We also calculated the mean for each epoch of the vibration compared with the rest condition.

The mean activity was calculated from six functional images: we excluded the first two functional images. This was done for all epochs on either hand in each subject. The percent increase was calculated for each epoch by using the following formula: \( \text{Mean in illusion or vibration} – \text{Mean in the corresponding rest} \times 100 \text{divided by Mean in the corresponding rest} \). Finally, the mean value for each individual subject was calculated from the six values from six epochs. The right- and left-hand conditions were separately treated. We performed a two-factorial ANOVA [vibrated side (right or left) \( \times \) MI, area 2 \( \times \) repeated measurement design] for the mean of each individual subject for each peak (Fig. 5).

Anatomical definitions

We used cytoarchitecturally defined areas from 10 postmortem brains to describe in a probabilistic way the topography of cytoarchitectonic areas 4a, 4p (Geyer et al. 1996; Schleicher et al. 1999), 2 (Grefkes et al. 2001), 6 (dorsal premotor cortex (PMD), and supplementary motor area (SMA)) (Geyer 2004; Geyer et al. 2002), 44 and 45 (Amunts et al. 1999), areas in the intraparietal sulcus region (IP1 and IP2) (Choi et al. 2002), and areas in the parietal opercular region (OP1, OP2, OP3 and OP4) (Eickhoff et al. 2002) in the standard anatomical space (Roland et al. 2001). The brains were corrected for deformations attributable to histological processing and the images.
were warped to the same standard anatomical format (Roland et al. 2001) by using the full-multigrid (FMG) method (Schormann and Zilles 1998).

A population map was generated for each area (Roland and Zilles 1998). The population maps describe, for each voxel, how many brains have a representation of one particular cytoarchitectonic area. In the case of anatomically adjacent areas, the individual variation in the location and extent of each cytoarchitectural area led to population maps overlapping each other and thus to voxels representing more than one area. In these cases, the voxel was allocated to the cytoarchitectural area with the highest number of postmortem brains associated with it (Roland and Zilles 1996a, 1998). For example, one voxel could correspond to area 4a in 5 of the 10 brains and simultaneously to area 4p in 1 of 10 brains. This voxel was then assigned to area 4a. The result was a probability map of the cytoarchitectural areas (Roland et al. 2001).

At the “outer” border of a cytoarchitectural area (i.e., where the area abuts on a cortical region for which microstructural data and thus a population map was not available, e.g., anterior border of area 6 toward the prefrontal cortex), a threshold of 3 of 10 (30%) brains was applied. This means that voxels with a representation of a given area in n ≥ 3 brains were assigned to this area, whereas voxels with a representation of this area in n < 3 brains were discarded. This criterion has been used before (see e.g., Bodegard et al. 2001; Naito et al. 2002b). The result of this procedure is a probability map that provides a working definition of each area’s most probable location in the standard anatomical space (Roland et al. 2001). The probability map was finally transformed into the MNI reference brain space (Ashburner and Friston 1997). This procedure allowed us to relate the locations of fMRI activation peaks to the cytoarchitectural probability maps (Mohlberg et al. 2003: www.bic.mni.mcgill.ca/cytoarchitectonics/). This technique provided us with an observer-independent possibility to localize activations in the cytoarchitectonic areas. However, some cautions are required when interpreting results. Because the cytoarchitectural areas are probability maps, a voxel in the standard space can correspond to more than one area, i.e., individual postmortem brains can have different areas located at this particular location. Thus the anatomical localizations of activations in the cytoarchitectonic areas should be considered as “probabilistic indicators.” For further discussion of the technique of combining functional imaging and cytoarchitectural mapping, see Bodegard et al. (2001), Ehrsen et al. (2003), Mohlberg et al. (2003), Naito et al. (2002b); Roland et al. (2001), Roland and Zilles (1998), and Young et al. (2004).

We adopted the definition of the functional areas of rostral cingulate motor area (CMAr) and caudal cingulate motor area (CMAc) in the cortical motor system as defined by Roland and Zilles (1996b).

RESULTS

All subjects verbally reported that they experienced vivid illusions of wrist flexion in the illusion condition and no illusion in the vibration condition during fMRI scanning. When the tendon on the right wrist extensor muscles (the ECU) was vibrated, all subjects felt the illusory flexion of the right wrist. Similarly when the tendon on the left muscle was vibrated, all subjects felt the illusion of the left wrist. They also reported that there was no difference in vividness of illusory experience between the right and left hand. No overt wrist movement was observed in any of the experimental sessions.

Brain activation during kinesthetic illusion of right hand movement

When right illusion was contrasted with right vibration, we found significant activations in cortical motor areas, right parietal cortex, bilateral inferior frontal cortices, bilateral prefrontal cortices and right cerebellum (Fig. 1 and Table 1).

In the cortical motor areas, one cluster was located in the left cytoarchitectonic areas 4a, 4p (M1), and 6 (PMD). This cluster further extended rostrally into cortex rostral to area 6 (PMD) and caudally into areas 3a, 3b, and 2. In this cluster, we found three peaks of activation in areas 4p, 6 (PMD), and 2. The second cluster was located in the bilateral medial walls of the frontal lobes. We found three peaks in the left area 6 (SMA/CMAc) and in the right CMAr and CMAc. The third cluster was located in the right area 6 (PMD). The peak was located in the border between area 6 (PMD) and cortex rostral to PMD.

In the right parietal cluster, we found three peaks of activation in areas 2, IP1, and OP1. The bilateral inferior frontal clusters extended ventrally into the tip of superior temporal gyrus (STG). In the right cluster, we found four peaks of activation in areas 44, 45, STG, and anterior insula. In the left cluster, we found a peak in STG.

Brain activation during kinesthetic illusion of left-hand movement

When left illusion was contrasted with left vibration, we found significant activations in cortical motor areas, right parietal cortices, right inferior frontal cortices, right putamen, and left cerebellum (Fig. 2 and Table 2).

In the cortical motor areas, one cluster was located in the right areas 4a, 4p, 6 (PMD). This cluster further extended rostrally into cortex rostral to area 6 (PMD) and caudally into areas 3a, 3b, 2, IP1, and OP1. In this cluster, we found peaks of activation in areas 4a, 6 (PMD), 2, IP1, and OP1, respectively. The second cluster was located in the bilateral medial walls of the frontal lobes. We found three peaks in the left area 6 (SMA/CMAc) and in the right area 6 (SMA/CMAc and pre-SMA).

In the right inferior frontal cluster, we found peaks in areas 44 and 45 and in the STG. Right superior parietal cortex was also activated.

Differences between right- and left-hand illusions

To identify areas that are specifically active during the illusions of right hand movements we contrasted [(right illusion–right vibration) - (left illusion–left vibration)]. The left M1 was significantly activated (−36, −21, 51; area 4p; P < 0.05 corrected for whole brain space). Similarly, the right M1 (36, −18, 51; area 4a) was specifically activated during the illusion of left hand movement [(left illusion–left vibration) - (left illusion–left vibration)].

Activities in M1 and area 2 during illusions of right- or left-hand movement

Figure 3 shows the mean percent increase of the BOLD signal in M1 and area 2 when illusion was compared with vibration. The signal in M1 only increased when the subjects experienced illusory movements of the contralateral hand, whereas the signal in area 2 also increased when they experienced illusions of the ipsilateral hand as well (Fig. 3). A two-factorial ANOVA [vibrated side (right or left) (2) × areas (M1, area 2) (2); repeated measurement design] of the percent increase in each area and hemisphere showed significant inter-
action between these two factors \( F(1,9) = 17.7, P < 0.005 \) for the left hemisphere; \( F(1,9) = 6.8, P < 0.05 \) for the right hemisphere]. This suggests that M1 participates only in the processing of kinesthetic illusions of the contralateral hand, whereas area 2 is involved in the illusions of both right and left hands.

FIG. 1. Active regions during kinesthetic illusion of right-hand movement. Right illusion was contrasted with right vibration \((P < 0.05 \text{ corrected})\). All clusters are displayed on an anatomical T1-weighted MRI from a representative single subject. A: horizontal section \( z = +58 \); B: \( z = +51 \); C: \( z = +34 \); D: \( z = +18 \); E: \( z = +4 \); F: \( z = -24 \). Right hemisphere is shown to the right.
Finally, in the right inferior frontal cluster, we found peaks in areas 44, 45, and STG. From these findings, it is evident that the commonly active areas were predominantly located in the right hemisphere.

In contrast, when we identified the brain areas that were active in common during skin vibration over the right- and left-sided bone (right vibration–right rest) ∩ (left vibration–left rest), we only found activations in the bilateral parietal opercular regions (areas OP1 and OP4). It is noteworthy that none of the regions that were active in common during illusions of right- and left-hand movement was commonly activated during vibration stimuli over the skin (minimum t value of 4.58 in the conjunction analysis). This suggests that there are qualitative differences in the activation patterns during kinesthetic illusions and during skin vibration with no illusions.

**Dominance of the right-sided regions that are commonly active during illusions of right- and left-hand movement**

As described in the preceding text, we found activations in the frontal and parietal areas that were active in common during illusions of the right and left hand. This finding appears to suggest a right-hemisphere dominance in the processing of kinesthetic illusions. However, to statistically test this hypothesis, one has to directly compare the activities in the right-sided areas with those in the corresponding areas in the left hemisphere. Therefore we compared the activities of the clusters in the right hemisphere as detected by the conjunction analysis with those of the corresponding regions in the left hemisphere (see Methods).

We found that when the subjects experienced illusions movements of the right hand, right area 6 (PMD)/cortex rostral to PMD, area 45, IP1/OP1, and STG were significantly more activated than the corresponding left regions (Table 4). In contrast, right SMA and area 2 did not show significantly stronger activity than the corresponding left regions during illusions of right-hand movement. During illusions of the left hand, right area 6 (PMD)/cortex rostral to PMD, 44, 4p, 2, IP1, and STG were significantly more activated than the corresponding left regions. These results demonstrate a right-hemisphere dominance in the processing of kinesthetic illusions elicited by the tendon vibration.

### Single-subject analysis for a dominance of right-sided areas during illusions of right- and left-hand movement

To investigate activities in those regions that are active in common during illusions of right- and left-hand movement, another post hoc single-subject analysis was done (see Methods). One purpose of this analysis was to confirm that the activities in the right-sided regions that were commonly active during illusions of right- and left-hand movement were not biased by the data from a few subjects. We tested if the mean percent increase of the BOLD signal across subjects in the illusion condition is greater than that in the vibration condition (see Methods). Another purpose was to test whether the levels of activities in the right-sided areas differ between right and left illusions.

Figure 5 shows that the mean percent increase of the BOLD signal was greater in the illusion condition than in the vibration condition in all commonly activated areas [main effect of
tendon vibration in the ANOVA, see METHODS; left SMA/CMAc: $F(1,9) = 14.5, P < 0.005$; right SMA/CMAc: $P < 0.025$; right area 2: $P = 0.11$; right PMD/cortex rostral to PMD: $P < 0.025$; right IP1: $P < 0.05$; right area 45: $P < 0.1$; right area 44: $P < 0.025$; right STG: $P < 0.025$. In addition, the left-hand stimulation activated right SMA/CMAc, area 2.

**FIG. 2.** Active regions during kinesthetic illusion of left hand movement. Left illusion was contrasted with left vibration ($P < 0.05$ corrected). A: horizontal section $z = +63$; B: $z = +55$; C: $z = +34$; D: $z = +18$; E: $z = +4$; F: $z = -27$. For other conventions, see legend of Fig. 1.
and PMD/cortex rostral to PMD significantly more than the right-hand stimulation [main effect of the vibrated side in the ANOVA; SMA/CMAc: F(1,9) = 5.5, P < 0.05; area 2: P < 0.025; PMD/cortex rostral to PMD: P < 0.005]. In contrast, there were no significant differences between right- and left-hand stimulation in right IP1, areas 44 and 45, and STG (P > 0.33 for all regions).

**Discussion**

We measured brain activities by fMRI when healthy human subjects experienced kinesthetic illusory flexions of the right or left wrist elicited by tendon vibration. There were three main findings.

First, in the absence of actual limb movements, we found robust activations in the contralateral cortical motor areas [areas 4a and 4p (M1) and 6 (PMD)]. We also found strong activity in bilateral medial area 6 (SMA/CMAc) and in the ipsilateral anterior cerebellum. These results corroborate those from our earlier studies that the motor system participates in the processing of kinesthetic illusions (Naito 2004; Naito and Ehrsson 2001; Naito et al. 1999, 2002a,b).

Second, as suggested by electrophysiological studies in monkeys, cytoarchitectonic area 2, especially right area 2, was also involved in the processing of kinesthetic signals in human subjects. However, the engagement of area 2 in kinesthetic illusions was different from that of M1 in that M1 was strictly active during illusions of the contralateral limb, whereas area 2 was also active during illusions of the ipsilateral limb (Fig. 3). This suggests functional differences in the processing of kinesthetic signals between M1 and area 2.

Third, we found a dominance of the right hemisphere in brain activation during kinesthetic illusions. Right area 6 (PMD)/cortex rostral to PMD, areas 44, 45, IP1, OP1, anterior insula, and STG were all activated in common during illusions of right and left hand (Fig. 4). These right-sided areas were significantly more activated than the corresponding areas in the left hemisphere (Table 4). This provides the first neurophysiological evidence for a dominant role of the right hemisphere in human kinesthetic processing.

**Methodological considerations**

In the illusion and vibration conditions, we vibrated the skin surface at two sites of the wrist. Because the size of skin area that was contacted by the vibrator was identical (~1 cm²) and we used the same frequency (80 Hz) of vibration stimuli, similar sets of skin receptors would probably be recruited in these two conditions (Naito and Ehrsson 2001). It is very unlikely that the conspicuous differences in brain activations observed during the illusion and vibration conditions were due to the fact that we vibrated the different skin areas around the wrist. The distance between the two stimulation areas was small [3.6 ± 0.5 (SD) cm], and therefore the cutaneous afferent input should be very similar. The difference in activation between these two conditions arose from the fact that the tendon of the wrist extensor muscle was only vibrated in the illusion condition. This tendon vibration is an optimal stimulus to excite muscle spindle afferents and elicit kinesthetic illusions (Naito and Ehrsson 2001; Naito et al. 1999, 2002a,b; Roll and Vedel 1982; Roll et al. 1989). In contrast, when we vibrated the skin surface over the nearby bone, the subjects did not experience any reliable illusions because the tendon was not directly stimulated. Although muscle spindles are highly

**FIG. 3.** Mean percent increase of the blood oxygenation level-dependent (BOLD) signal in M1 and area 2 when illusion was compared with vibration (single-subject analysis). The signal in M1 only increased when the subjects experienced illusory movements of the contralateral hand, whereas the signal in area 2 also increased when they experienced illusions of the ipsilateral hand as well. Bars indicate SE.
FIG. 4. Active regions shared by illusions of right- and left-hand movement. All clusters and cytoarchitectonic maps are displayed on an anatomical T1-weighted MRI from a single subject. Right hemisphere is shown to the right. Blue voxels indicate cytoarchitectonic probability map of area 6. Yellow voxels: area 2; orange voxels: area IP1; dark blue voxels: IP2; green voxels: area 45; white voxels: area 44; light yellow voxels: area OP1; light blue voxels: area OP4; light green voxels: area OP2; pink voxels: area OP3. Superimposed clusters encircled by red voxels are the results of the conjunction analysis (right illusion–right vibration) ∩ (left illusion–left vibration). We employed the same $t$ threshold of 4.58 as used in the contrast of (illusion–vibration). The bilateral medial area 6 (SMA/CMAc), right cortex rostral to PMD (area 6), areas 2, 44 and 45, IP1, and OP1, anterior insula and tip of STG were commonly activated. The right hemisphere was predominantly activated no matter whether the subjects experienced illusions of the right or left hand.
sensitive and some spindles in the hand would be activated by the spread of the vibration from the bone to the surrounding tissue, this spread was not strong enough to elicit any clear illusions. In a previous study, we found that when we vibrated the skin surface over the tendon, we never elicited any illusions nor found any motor activations (10 and 220 Hz) unless we used optimal vibration frequency (70 and 80 Hz) (Naito et al. 1999). Thus the present brain activations detected when illusion was contrasted with vibration is most likely to be associated with kinesthetic illusions elicited by afferent information from muscle spindles excited by tendon vibration at an optimal frequency (80 Hz). We did not measure the attention to the stimuli in the different conditions. However, we think it is unlikely that differences in attention could explain our results. First, the subjects did not perform any active task, they were just instructed to relax and be aware of the sensation from their wrists. Second, the subjects were instructed to be aware of their wrists both in the illusion and in the vibration conditions. This suggests that the participants were attending slightly to the stimulated hand in both conditions.

Cytoarchitectonic area 2 and parietal cortex

Area 2 was more strongly activated when the tendon was vibrated over the skin (illusion) than when only the skin was vibrated without directly involving the tendon (vibration; Fig. 5C). Hence, the activity in this area probably reflects the processing of kinesthetic afferent input from muscle spindles. This result fits well with results from earlier single-unit studies in non-human primates that neurons in area 2 react to kinesthetic afferent input during passive limb movements (see references in the introduction).

Area 2 was active during illusory movements of not only the contralateral but also the ipsilateral hand (Fig. 1, A and B) even though the activity in area 2 was larger when the contralateral hand was stimulated (Fig. 3). This finding is in good agreement with findings in non-human primates that neurons in area 2 respond to somatosensory afferent input from not only the contralateral but also the ipsilateral limb (Iwamura 2000; Iwamura et al. 1994; Taoka et al. 1998, 2000). The bilateral involvement of area 2 in the central processing of kinesthetic illusions is different from the strictly contralateral engagement of M1 (Fig. 3). This difference implies that M1 and area 2 might participate in different stages of neuronal processing of kinesthetic information and suggests that human area 2 is a high-order somatosensory area (Bodegard et al. 2001; Roland et al. 1998).

In addition, we found peaks of activation in areas IP1 and OP1 in the right hemisphere when the subjects experienced illusory wrist movements. Area IP1 is caudally located to area 2, lining the rostral part of the intraparietal sulcus and also extending into supramarginal gyrus (SMG; Fig. 4B). Area OP1 is located laterally in the parietal operculum (PO; Fig. 4D) and also extending into SMG (Fig. 4C) (see also Young et al. 2004). These areas are considered to be high-order somatosensory areas in humans in a sense that they are engaged in somatosensory tasks but less somatotopically organized (Young et al. 2004). Indeed, identical section in the right areas IP1 and OP1 was commonly engaged in illusions of right- or left-hand movements.

The precise homology between the cytoarchitectural areas of the human and monkey inferior parietal lobe is still unknown (Eidelberg and Galaburda 1984). In the present study, the activation (areas IP1 and OP1) associated with kinesthetic illusion was located in the lateralmost part of the inferior parietal cortex (Fig. 4, Table 1). Similarly, the lateral and posterior part of the monkey inferior parietal cortex (area 7b/PF) contains neurons that predominantly respond to somesthetic input (Hyvärinen 1981; Hyvärinen and Shelepov 1979). In fact, it has been suggested that the inferior parietal cortex in monkeys (area 7b/PF) corresponds to the SMG in the human brain (Passingham 1998). In the monkey brain, this somasthetic section of the inferior parietal cortex has ipsilateral cortical connections with areas 2, 4, 5, 45, PO (Hyvärinen 1982a,b; Neal et al. 1987, 1990b), ventral premotor cortex (Ghosd and Gattera 1995; Godschalk et al. 1984; Neal et al. 1990a), SMA (Cavada and Goldman-Rakic 1989), and insular cortex (Neal et al. 1987, 1990b 1990b). In our present study, we observed activations in all these areas in conjunction with

### Table 3. Common active areas during right illusion and left illusion

<table>
<thead>
<tr>
<th>Structures</th>
<th>Coordinates of Peak</th>
<th>t-Value</th>
<th>Cluster Size Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral medial wall cluster</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R area 6 (SMA/CMAc)</td>
<td>3 0 51</td>
<td>7.93</td>
<td>176</td>
</tr>
<tr>
<td>L area 6 (SMA/CMAc)</td>
<td>−6 −3 48</td>
<td>6.65</td>
<td></td>
</tr>
<tr>
<td>Right areas 2-IP1-OP1 cluster</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area 2</td>
<td>39 −36 57</td>
<td>7.46</td>
<td>134</td>
</tr>
<tr>
<td>Area IP1</td>
<td>63 −27 42</td>
<td>5.94</td>
<td></td>
</tr>
<tr>
<td>Areas IP1/OP1</td>
<td>57 −27 33</td>
<td>5.85</td>
<td></td>
</tr>
<tr>
<td>Right areas 44-45-STG-insular cluster</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STG</td>
<td>51 24 −15</td>
<td>7.36</td>
<td>207</td>
</tr>
<tr>
<td>Area 45</td>
<td>57 21 24</td>
<td>6.17</td>
<td></td>
</tr>
<tr>
<td>Area 44</td>
<td>60 6 3</td>
<td>6.42</td>
<td></td>
</tr>
<tr>
<td>STG/areas 44/45</td>
<td>57 18 −6</td>
<td>6.32</td>
<td></td>
</tr>
<tr>
<td>Right area 6 (PMD)/cortex rostral to PMD</td>
<td>33 −3 54</td>
<td>6.57</td>
<td>42</td>
</tr>
</tbody>
</table>

See Table 1.

### Table 4. Comparing activation in the right hemisphere and the left hemisphere (flip analysis)

<table>
<thead>
<tr>
<th>Structures</th>
<th>Coordinates of Peak</th>
<th>t-Value</th>
<th>Cluster Size Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right illusion: unflipped vs flipped</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R STG</td>
<td>48 27 −15</td>
<td>6.87</td>
<td>91</td>
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<tr>
<td>R cortex rostral to PMD/area 6 (PMD)</td>
<td>36 3 51</td>
<td>5.17</td>
<td>24</td>
</tr>
<tr>
<td>R area 45</td>
<td>57 24 18</td>
<td>4.6</td>
<td>41</td>
</tr>
<tr>
<td>R area IP1/OP1</td>
<td>63 −24 33</td>
<td>3.9</td>
<td>17</td>
</tr>
<tr>
<td>Left illusion: unflipped vs flipped</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R STG</td>
<td>51 27 −12</td>
<td>3.86</td>
<td>12</td>
</tr>
<tr>
<td>R cortex rostral to PMD/area 6 (PMD)</td>
<td>33 3 54</td>
<td>3.95</td>
<td>12</td>
</tr>
<tr>
<td>R area 44</td>
<td>57 15 21</td>
<td>5.99</td>
<td>71</td>
</tr>
<tr>
<td>R area 4p</td>
<td>36 −30 57</td>
<td>6.02</td>
<td>119</td>
</tr>
<tr>
<td>R area 2</td>
<td>48 −24 48</td>
<td>5.18</td>
<td></td>
</tr>
<tr>
<td>R IP1</td>
<td>60 −24 39</td>
<td>4.8</td>
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</tr>
</tbody>
</table>

See Table 1.
activation in SMG (areas IP1 and OP1); this indicates that the human SMG could be an important node in the network of fronto-parietal sensorimotor-related areas that represent limb movements.

The involvement of the right PO (area OP1) in kinesthetic illusions is consistent with the early observation that the right PO was activated during passive movements of the right arm (Weiller et al. 1996). Although PO seems to be activated by a wide range of somatosensory stimuli (Bodegard et al. 2000; Ledberg et al. 1995; Naito et al. 1999; Roland et al. 1998), our results indicate that the right PO is active when we sense limb movements. Although the role of the right inferior parietal areas in kinesthetic processing is still unclear, the present results fit well with human brain lesion studies demonstrating that damage to the right inferior parietal cortex impairs perception of one’s own body (Berlucchi and Aglioti 1997; Damasio 1999; Hyvärinen 1982b; Sellal et al. 1996).

**Frontal areas**

Kinesthetic illusions activated the contralateral areas 4a, 4p, and 6 (PMD), bilateral SMA (area 6), CMA, and pre-SMA (area 6), and the ipsilateral cerebellum. The contralateral cluster extended into areas 3a and 3b, but we could not find any significant peaks in these areas. The activity in M1 (areas 4a and 4p) was strictly related to the illusions of the contralateral hand (Fig. 3), whereas SMA and CMA were bilaterally engaged in illusions. The evidence that SMA and CMA participate in the kinesthetic processing of muscle spindle afferent input fits with the finding that many neurons in the SMA and CMA respond to proprioceptive input during joint rotation and muscle stretch (Cadoret and Smith 1995). The bilateral activation pattern in these areas irrespective of illusions of right- or left-hand movement (Fig. 4) is most probably due to interconnection between right and left SMA as has been well established by non-human primates studies showing that neurons in two SMAs are strongly interconnected (Rouiller et al. 1994; Tanji 1994).

One of the new observations in the present study was that kinesthetic illusions activated the border between area 6 (PMD) and cortex rostral to PMD in the right hemisphere no matter if the participants experienced illusions of right or left hand (Fig. 4). In the present study, the blindfolded subjects were instructed to be aware of the hand movements with no intention of executing movement. When we sense limb movement, we are not only aware of the changes in joint angle, but we also sense the changes of limb location in extrapersonal space. We speculate that the activity in this area is related to the somatic monitoring of positional changes of the limb in extrapersonal space because this area is associated with spatial-cognitive processes in primates (Boussaoud 2001; Picard and Strick 2001).

In addition, we found a large active cluster that was located in the inferior frontal cortex and that extended into the anterior insula and superior temporal cortex. We know that lesions that damage this region impair the normal perception of one’s own body (Berlucchi and Aglioti 1997; Sellal et al. 1996), and thus...
it is possible that the activity in these areas is related to kinesthetic perception. The inferior frontal peak was located in the right-sided equivalent of Broca’s area (areas 44 and 45) (Amunts et al. 1999). Previously, right areas 44 and 45 were activated during motor imagery of the right hand (Binkofski et al. 2000; Ehrsson et al. 2003) and when visually observing hand actions (Buccino et al. 2001). Right area 44, together with right PMv (ventral part of area 6), is also active during the performance of skilled finger movements of the right hand (Ehrsson et al. 2001). Thus right areas 44 and 45 appear to be related both to kinesthetic and motor representations of hand actions.

Activation in the anterior insular cortex is commonly observed during painful and unpleasant stimulation, and it has been suggested that these regions contain a representation of the physical condition of one’s body (Craig 2002). Finally, a distinct peak of activity was found in the right tip of the STG during illusions. The superior temporal gyrus is a multimodal sensory area that receives somatosensory input (Jones and Powell 1970; Seltzer and Pandya 1978), and human lesion studies suggest that this region may be involved in functions related to spatial awareness (Karnath et al. 2001).

How does the muscle spindle information reach the nonprimary frontal and parietal areas? In non-human primates neurons in M1 (Asanuma et al. 1980; Brinkman et al. 1985; Colebatch et al. 1990; Petz et al. 1980; Hore et al. 1976; Huerta and Pons 1990; Lemon 1981; Lemon et al. 1976; Lemon and Porter 1976; Lemon and Van Der Burg 1979; Porter and Lemon 1993; Rosén and Asanuma 1972; Strick and Preston 1982; Wong et al. 1978), area 3a (Hore et al. 1976; Huerta and Pons 1990; Iwamura et al. 1983; Philips et al. 1971; Schwarz et al. 1973), and area 2 (Burchiel and Duffy 1972; Costanzo and Gardner 1981; Gardner and Costanzo 1981; Iwamura et al. 1993, 1994; Jennings et al. 1983; Mountcastle and Powell 1959; Schwarz et al. 1973) respond to muscle spindle afferent input. It is well established that M1 is connected with cytoarchitectonic area 2 (Darian-Smith et al., 1993; Ghosh and Gattera 1995; Godschalk et al. 1984; Ghosh et al. 1987; Jones et al. 1978; Leichnetz 1986; Leichnetz 1986; Stepeniewska et al. 1993). Area 2 is also connected with SMA and PDM (Pons and Kaas 1986). The inferior parietal cortex has ipsilateral connections with areas 2, 4, 45, PO (Hyvärinen 1982a,b; Neale et al. 1987, 1990b), ventral premotor cortex (Ghosh and Gattera 1995; Godschalk et al. 1984; Neale et al. 1990a, SMA (Cavada and Goldman-Rakic 1989), and the insular cortex (Neale et al. 1987, 1990b). In addition, fronto-parietal opercular regions and insular cortex are connected with sensory-motor areas (Cipolloni and Pandya 1999; Darian-Smith et al. 1993; Guldin et al. 1992; Preuss and Goldman-Rakic 1989). This evidence suggests that also in humans the kinesthetic information from muscle spindles is spread from “primary” motor and sensory areas to “nonprimary” fronto-parietal association areas. However, it should be stressed that future studies are needed to elucidate the exact roles of these nonprimary areas in kinesthetic perception. So far we only have conclusive evidence that activity in the primary motor cortex reflect the perception of limb movement per se (Naito 2004; Naito et al. 2002b).

**Right hemispheric dominance for kinesthetic processing**

An important observation was that right area 6 (PMD/cortex rostral to PDM, areas 44, 45, IP1, OP1, anterior insula, and STG were statistically more activated than the corresponding regions in the left hemisphere no matter whether the subjects experienced illusions of the right or left hand. Importantly, none of these right-sided areas was activated in common when the skin surface over the nearby bone of right or left hand was vibrated. Thus it is unlikely that the activity in these right-sided areas reflects the somatosensory processing of skin vibration or attention to somatosensory stimuli. Rather, the activities in these right-sided areas seem to be related to the processing of kinesthetic information, which is consistent with the results from human brain lesion studies (Halligan et al. 1993; McGonigle et al. 2002; Sellal et al. 1996).

Claims of hemispheric dominance of brain functions have rarely been statistically supported with the exception of language dominance in the left hemisphere (Binder et al. 1997; Springer et al. 1999; Vikingstad et al. 2000; Wada and Rasmussen 1960). Here a hemispheric dominance for human kinesthesia has been statistically demonstrated for the first time in a neuroimaging experiment of intact brains, though a dominance of the right hemisphere for somatosensory functions has been suggested (thermal pain: Coghill et al. 2001; tactile and proprioception: Kawashima et al. 2002). The reason for this right-sided dominance in right-handed subjects is unknown. However, one may conjecturally suggest a developmental arrangement of the functional organization of language and body functions, permitting simultaneous use of language and motoring of somatic functions (e.g., Chiron et al. 1997; Corballis et al. 2000; Geschwind and Galaburda 1985; Karnath 2001). This would give the brain a benefit of avoiding interference between language and somatic functions (Roland 2002; Roland and Zilles 1998).

As stated, our results suggest that the right hemisphere is specialized for the perception of one’s own body. Interestingly, this conclusion fits well with the observation that patients that undergo preoperative evaluation lose awareness and memory of arm weakness during amytal inactivation of their right hemisphere (Carpenter et al. 1995; Meador et al. 2000). During such inactivation testing, these patients no longer feel the weakness of their arm, they lose the ability to visually recognize the weak arm as their own, and they become poor in pointing to different parts of their arm. Thus our results that, in healthy subjects, perception of an illusory limb movement engages a right-sided network of frontal and parietal areas, provides a neurophysiological basis for these perceptual deficits in patients after inactivation of the right hemisphere.

**GRANTS**

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