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I Feel My Hand Moving: A New Role of the Primary Motor Cortex in Somatic Perception of Limb Movement

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Summary

The primary motor cortex (MI) is regarded as the site for motor control. Occasional reports that MI neurons react to sensory stimuli have either been ignored or attributed to guidance of voluntary movements. Here, we show that MI activation is necessary for the somatic perception of movement of our limbs. We made use of an illusion: when the wrist tendon of one hand is vibrated, it is perceived as the hand moving. If the vibrated hand has skin contact with the other hand, it is perceived as both hands bending. Using fMRI and TMS, we show that the activation in MI controlling the nonvibrated hand is compulsory for the somatic perception of the hand movement. This novel function of MI contrasts with its traditional role as the executive locus of voluntary limb movement.

Introduction

When the tendon of the biceps muscle (which flexes the elbow) is vibrated, one gets the illusion that the arm stretches (the elbow extends), despite the arm being absolutely immobile (Craske, 1977; Goodwin et al., 1972a, 1972b; Naito and Ehrsson, 2001; Naito et al., 1999). This kinesthetic illusion is elicited because the vibration of the tendon excites the muscle spindles in a manner similar to when the muscle actually stretches (Burke et al., 1976; Collins and Prochazka, 1996; Gandevia, 1985; Roll and Vedel, 1982; Roll et al., 1989). When subjects experience such kinesthetic illusions, the contralateral somatosensory cortex receiving the signals from the muscle spindles is moderately activated (Naito and Ehrsson, 2001; Naito et al., 1999). Surprisingly, however, the primary motor cortex (MI) is more strongly activated (MI; cytoarchitectonic areas 4a and 4p) (Naito and Ehrsson, 2001; Naito et al., 1999). MI is also active during passive limb movements in humans (Weiller et al., 1996) and in nonhuman primates (Colebatch et al., 1990; Fetz et al., 1980; Lemon, 1981; Lemon et al., 1976; Lemon and Porter, 1976; Porter and Lemon, 1993; Strick and Preston, 1982). This suggests that MI also receives input from the muscle spindles (Colebatch et al., 1990) and suggests a possible role for the MI in the somatic perception of limb movement (Fetz et al., 1980).

There is another type of illusion, created by two different kinds of afferent inputs to the brain. For example, when the tendon of the right biceps muscle is vibrated at the same time that a subject holds her nose between the right thumb and index finger, she feels the nose becoming increasingly elongated (Lackner, 1988; Lackner and Taublieb, 1983). In this case, the brain gets the sensory information about the skin contact between the hand and the nose and the information from the muscle spindles that the arm is stretching. The brain *interprets* this as the nose becoming increasingly longer. The neurobiological mechanisms of this type of illusion are not known. Here, we examine the brain mechanisms and the network of active neurone populations underlying this second type of illusion. However, it is more important to know whether MI activity is necessary for the illusory sensation of limb movement (kinesthesia). If it is, MI should be active when humans sense a limb movement, even in the situation when the brain receives no direct muscle spindle afferents signaling the limb movements and in the situation when subjects do not intend, plan, or mentally simulate the movements. This is important, because the traditional role assigned to MI is that of controlling voluntary movements or preparing for movements, and if sensory input has activated the neurons in MI, this has hitherto been interpreted mainly in this motor context (Sanes and Donoghue, 2000).

We vibrated the tendons of the wrist extensor muscles of either the right or left hand while both hands had mutual skin contact. In this situation, the illusion transfers from the vibrated hand to the nonvibrated hand, and the subjects feel that the nonvibrated hand is also moving in the same direction as the vibrated hand. First, we measured the brain activity with functional magnetic resonance imaging (fMRI) in order to identify the brain areas that are associated with the transfer of illusion and to determine whether activation of the MI controlling the nonvibrated hand was necessary to sense the transfer of the kinesthetic illusion. Second, we tested the neuronal excitability in this MI by transcranial magnetic stimulation while the subjects experienced the transfer of the illusion to the nonvibrated hand.

Results

fMRI Experiment

Muscle Spindle Inputs into the Cerebral Cortex

We vibrated the tendon of a wrist extensor muscle in normal volunteers so as to produce an illusion of movement while we measured the brain activity with fMRI (see Experimental Procedures). Thus, the tendon of the right or left *extensor carpi ulnaris* (ECU) was vibrated at

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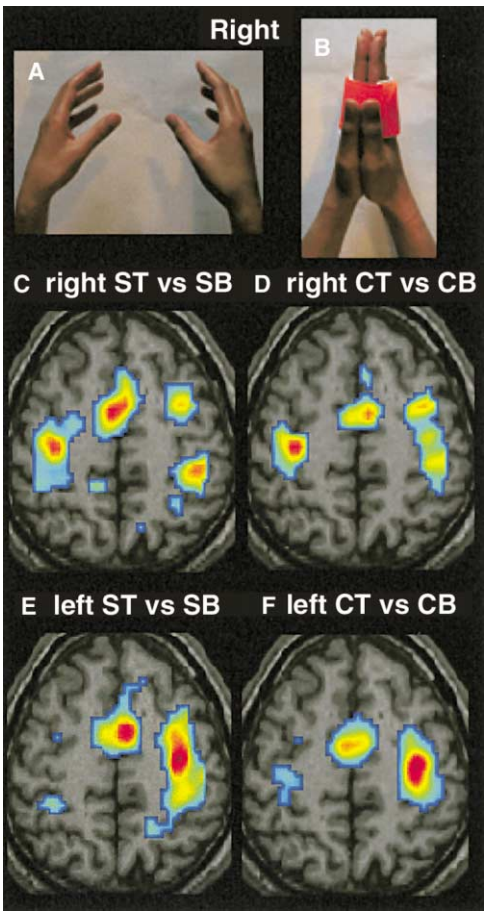

Figure 1. Hand Positions in the fMRI Experiment and Brain Fields Active during Unilateral Illusion and during Transfer of Illusion

(A and B) Hand positions during the fMRI experiment. The hands were separated ("S") (A) or in contact palm-to-palm ("C") (B).
(C) Significant clusters active from the contrast of (separated hands, tendon vibration ["ST"] – separated hands, bone vibration ["SB"]) on the right hand. The clusters were superimposed on the standardized MR from a single subject. Horizontal section $z = +51$.
(D) Clusters active from the contrast of (skin contact, tendon vibration ["CT"] – skin contact, bone vibration ["CB"]) on the right hand.
(E) Clusters active from the contrast of (ST – SB) on the left hand.
(F) Clusters active from the contrast of (CT – CB) on the left hand. The left hemisphere is shown to the left.

80 Hz. When the hands were separated (Figure 1A) and the tendon on the right muscle was vibrated, the left MI was activated, and all subjects felt the unilateral illusion of a flexion of the right wrist immediately after the start of vibration (Figure 1C). Similarly, when the tendon on the left muscle was vibrated, the right MI was activated, and all subjects felt the illusion of a flexion of the left wrist (Figure 1E). The peak of the activations was located to the left area 4p (-36, -21, 51) when the right tendon was vibrated or to the right area 4p (36, -18, 51) when the left tendon was vibrated (Geyer et al., 1996), confirming earlier results that the contralateral MI is more activated than surrounding somatosensory areas (Naito and Ehrsson, 2001; Naito et al., 1999). The MI on the right side was never active when the tendon on the right side was vibrated (see Figure 1C; $p > 0.10$ without a correction for multiple comparisons), nor was the MI on the left side active when the tendon on left side was vibrated (Figure 1E; $p > 0.10$ without a correction for multiple comparisons). This suggests that information originating from muscle spindles reaches the opposite MI only, as was suggested but not substantiated in earlier experiments on animals (Landgren and Silfvenius, 1969, 1970, 1971). As apparent from Figures 1C and 1E, the supplementary motor area (SMA), the right premotor cortex, the right area 8, and a right somatosensory area, which proved to be area 2 when coregistered with the cytoarchitectural probability map, were active no matter whether the right or the left tendon was vibrated when the hands were separated.

The Primary Motor Cortex Is Active during Transfer of Illusion

When there was close skin contact between the right and the left hand (Figure 1B) and the right extensor tendon was again vibrated, after a 4 s delay, all subjects felt *both* hands bending leftward—as if the illusion of the right hand bending was transferred to the left hand ("transferred kinesthetic illusion"). Similarly, when the left extensor tendon was vibrated and the hands were in skin contact, the subjects felt both hands bending rightward. Our prediction was that if MI was necessary for the perception of limb movements, both MIs now should be active, no matter whether the right tendon or the left tendon was vibrated. This was indeed so—the right and the left MI were active, no matter whether the right tendon or the left tendon was vibrated, compared to the controls of vibrating the nearby bone (see Experimental Procedures) (i.e., skin contact, tendon vibration – skin contact, bone vibration) (Figures 1D and 1F). Since there was no BOLD signal in MI opposite to the nonvibrated hand when the hands were separated (and even when the hands were in contact and the bone was vibrated), the ipsilateral MI activation was exclusively related to the conditions of skin contact and ipsilateral tendon vibration, or, put in another way, the ipsilateral MI activation only occurred when the subjects experienced that the nonvibrated hand was moving.

To directly test for brain activity that was exclusively associated with the sensation of the nonvibrated hand moving (transferred illusion), we defined a contrast using a factorial design (skin contact, tendon vibration – skin contact, bone vibration) – (separated hands, tendon vibration – separated hands, bone vibration) (see Experimental Procedures). Importantly, in this contrast, the effects related to the positions of the hands and the vibration stimuli applied on the skin are matched. The results are seen in Figures 2A and 2B, which show the primary motor cortex significantly activated opposite to the nonvibrated hand ($p < 0.01$ after correction for multiple comparisons). There was an additional activation of the right cerebellum (Talairach coordinates 21, -81, -21) when the left wrist was vibrated. The MI activations, however, were the only consistent activations for the transfer of the illusion and had their peaks of activation (42, -18, 51 in the right area 4p and -42, -21, 45 in the left area 4p) (Figures 2C and 2D). Figures 2C and 2D further demonstrate that the MI activation obtained by the transferred illusion was located in the same wrist-arm sector of the MI as was the activations evoked by the

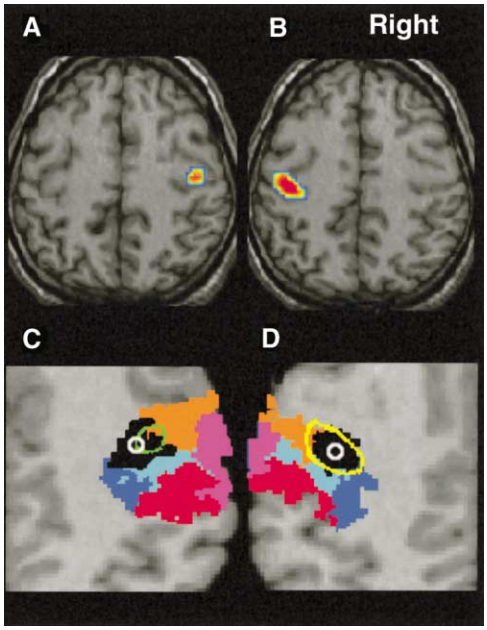

Figure 2. Fields Exclusively Active during Transfer of Illusion and Their Most Probable Locations in the Cytoarchitectonic Areas

(A and B) Significant clusters active from the contrast of (CT – CB) – (ST – SB) on the right hand (A) and on the left hand (B). These clusters were superimposed on the standardized MR image from a single subject.

(C and D) The MI active fields were superimposed on the cytoarchitectonic maps (Roland et al., 2001). Orange areas represent the cytoarchitectonic area 4a, black, area 4p; blue, area 3a; light blue, area 3b; pink, area 1; and red, area 2. The green contour represents the area active described in (A), and the yellow contour corresponds to the active field defined in (B) (see the text). White circles indicate the locations of peaks of the activations from the contrast of (ST – SB) on the left hand (C) and on the right hand (D), signifying the target for the afferent input from muscle spindles. These clusters were superimposed on the standard brain format to which all subjects' fMRI and anatomical MR scans were transformed.

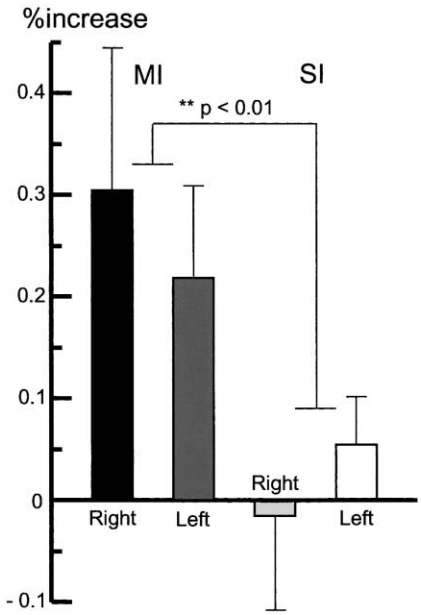

Figure 3. Percent Increase of BOLD Signal in the Contralateral MI and SI to the Nonvibrated Hand during Transferred Illusion

The percent increase of BOLD signal in the ipsilateral MI and SI to the vibrated hand (= contralateral to the transferred illusion) during transferred illusion. The fMRI data were smoothed by using only a 4 mm FWHM Gaussian filter (see Experimental Procedures). Black bar represents data from right MI; dark gray, left MI; light gray, right SI; and white, left SI. Bars indicate SEM. A two-factorial ANOVA revealed that the ipsilateral MI was significantly more activated than the ipsilateral SI, no matter whether the subjects experienced the illusion from the right or the left hand.

muscle spindle input, that is, the part of MI controlling movements of the wrist (Ehrsson et al., 2000).

Thus, the motor cortex controlling the nonvibrated wrist was active, despite the fact that subjects had no intention to move and despite the fact that there were absolutely no movements of either hand nor any electromyographic (EMG) activity of the flexor or extensor muscles in the nonvibrated arm. Only when the hands were mutually in contact and the tendon was vibrated did the subjects experience the kinesthetic illusion of both hands moving. Thus, the ipsilateral MI was active whenever the subjects felt that the nonvibrated hand was moving and was not active when they felt that the hand was not moving. The skin input from the palms, verifying the contact between the hands, and the muscle spindle afferents reaching the hemisphere contralateral to the vibrated hand, informing that the hand was flexing at the wrist, were *interpreted* by the brain as both hands being bent in the direction of the vibrated hand. The increase in the BOLD signal in the MI when the subjects experienced the transfer of the kinesthetic illusion indicates that the neurons representing the nonvibrated hand depolarized (Logothetis et al., 2001).

Possible Contribution of the Primary Somatosensory Cortex in the Transfer of the Illusion

Since the somatosensory cortex and not the MI is usually associated with kinesthetic sensations (Mountcastle and Powell, 1959), we examined the possible engagement of somatosensory areas 3 and 1 in the transfer of the illusion (see Experimental Procedures). Using the voxels corresponding to the peak of the activations from the contrast of bone vibration, skin contact versus rest (33, −33, 57 and −33, −30, 57), both localized to the contralateral area 3b, as the representatives of SI, we calculated the percent increase in SI during tendon vibration, skin contact from bone vibration, skin contact in the ipsilateral hemisphere to the vibrated hand. Similarly, the voxels showing the peak activity from the contrast of tendon vibration, skin contact versus bone vibration, skin contact, localized in the right (33, −24, 54) or left (−33, −24, 54) MI area 4p, were used as the representatives of MI, and the percent increase of tendon vibration, skin contact from bone vibration, skin contact was calculated in the ipsilateral hemisphere. The results are seen in Figure 3, showing that the right ipsilateral SI had no increase, whereas there was a minor increase in the left SI. A two-factorial ANOVA revealed that the ipsilateral MI was significantly more activated than the ipsilateral SI, no matter whether the subjects experienced the illusion from the right or the left hand [$F_{(1,9)} = 11.8$, $p < 0.01$].

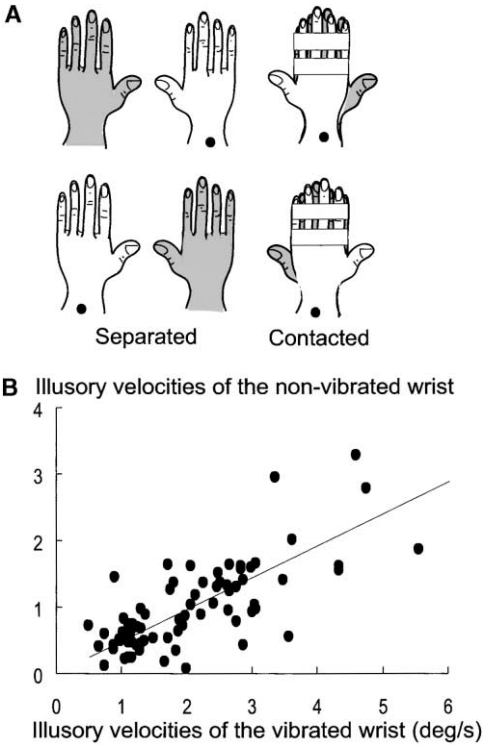

Figure 4. Hand Positions during the TMS Experiment and Psychophysical Features of Transfer of Illusion

(A) Positions of hands (when hands were separated and contacted) during the TMS experiment. In the contacted condition, the vibrated hand was placed on the dorsal surface of the nonvibrated hand. The dots indicate the sites of vibration on the right or left hand. We recorded motor-evoked potentials from the nonvibrated hand (dark hands).

(B) Correlation between calculated velocities of illusory movement of the vibrated hand and those of the nonvibrated hand. All 72 observations were from six trials of the right and six of the left hands in six subjects. The velocity of the nonvibrated hand was approximately half of that of the vibrated hand. Strong positive correlation was observed between illusory movement velocities of the vibrated hand and those of the nonvibrated hand ($r = 0.73$; $n = 72$, $p < 0.01$).

TMS Experiment

Facilitation of Motor-Evoked Potentials during Transfer of Illusion

To further explore the mechanisms of this MI activation, a second experiment was done in a second group of eight healthy subjects in whom the excitability of the motor cortex controlling the nonvibrating hand was examined by transcranial magnetic stimulation (TMS) (see Experimental Procedures). Either the tendon of the ECU was vibrated with an 83 or a 12.5 Hz stimulus or there was no vibration stimulus. When a 12.5 Hz stimulus was used, the subjects experienced no kinesthetic illusion (Naito et al., 1999; Roll and Vedel, 1982). To make sure that the activations of the MI related to the transferred illusion were not due to the particular position of the hands, we made the modification of the fMRI paradigm that the vibrated hand was placed on the dorsal surface of the nonvibrated hand (Figure 4A). The subjects now experienced that both hands were flexing, but only when both hands had skin contact and the tendon was vibrated at 83 Hz. Thus, the perception of movement of the nonvibrated hand is always determined by the illusion of the movement for the vibrated hand. Ergo, the transferred illusion cannot be explained by the spread of vibrations from one hand to another.

The subjects felt the illusory movement slightly stronger from the vibrated hand than from the nonvibrated hand, but there was a strong positive correlation between the experienced velocities of illusory movement of the vibrated hand and those of the nonvibrated hand, in each subject as well as in the population as a whole ($r = 0.73$; $p < 0.01$) (Figure 4B). This means that there is a tight relationship between the illusory movement of the vibrated hand and the transferred illusory movement. This also indicates that the transfer of illusion is a passive sensory process that is somehow regulated by the amount of illusion of the vibrated hand.

By TMS stimulating the motor cortex contralateral to the nonvibrated hand during transfer of illusion, we found a strong facilitation of the motor-evoked potential (MEP) (Figure 5A) in the muscle flexing the wrist of the nonvibrated hand in the same direction as the illusory flexion of the vibrated hand. This shows that the MI excitability for the wrist flexor muscles was enhanced. When the subjects, after some 4–12 s (total range) from the onset of vibration stimulus, experienced both hands flexing, the MEP amplitudes of the flexor muscles increased markedly (Figure 5B), and the MEP onsets became shorter when compared to the control conditions (Figure 5C).

The MEP of the flexor muscles was facilitated only after the subjects experienced illusory flexion of the nonvibrated wrist (Figures 6A and 6B). It took, on average, 9 s (mean 9 s $\pm$ 4 s SD) after the start of vibration for the transfer of the illusion to the nonvibrated hand to occur. In these 9 s, the subjects experienced no illusory movement of the nonvibrated wrist. In contrast, the MEP amplitude of the extensor muscles was reduced only after the subjects experienced illusory flexion of the nonvibrated wrist (Figure 6A). As a corollary, the subjects afterward reported that their feeling of the nonvibrated hand bending suddenly "went blank" for a second when the TMS was given after the illusion had transferred.

This delayed effect of MEP facilitation of the flexor and concomitant reduction of the extensor MEP (Figure 6A) and the fact that the MEP was not enhanced when the hands were separated (Figure 5B) demonstrated that the MEP changes were specifically confined to the period of the subject experiencing the illusion of both hands flexing. Furthermore, the MEP amplitude was correlated with the experienced angle of movement of the nonvibrated hand ($r = 0.52$, $p < 0.05$) (Figure 6C) and negatively correlated with the onset time of the MEP ($r = -0.51$, $p < 0.05$) (Figure 6D).

Discussion

The results presented above show that the MI is active when humans passively experience movement of their own limbs, even in situations when this area does not receive any direct sensory (muscle spindle) afferents signaling limb movements. The increased excitability of

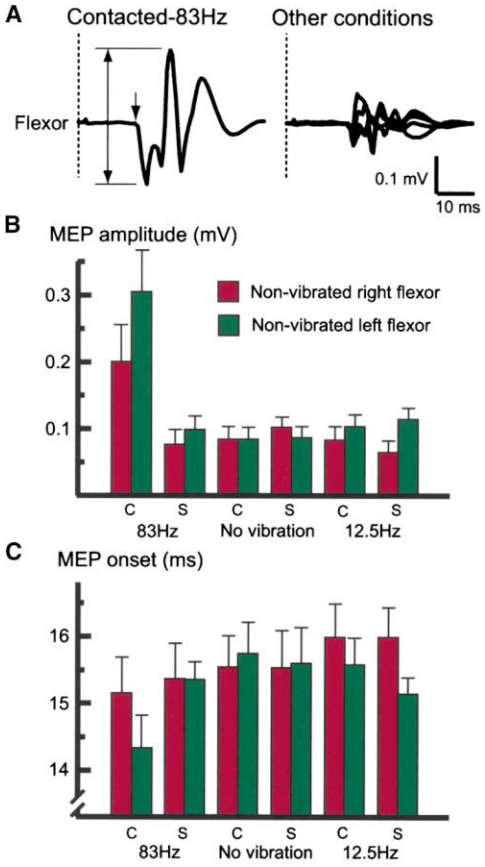

Figure 5. Temporal Profiles of Motor-Evoked Potentials and Changes of MEP Amplitudes and Onsets in the Six Different Conditions

(A) Motor-evoked potential (MEP) from the wrist flexor (the *flexor carpi ulnaris*) muscle. The MEP amplitude was measured between the two largest peaks of opposite polarity in each single event corresponding to single TMS (↕) (Rossini et al., 1994). The MEP $< 5\mu V$ was excluded from the following analyses. The latency of the MEP was also determined by the deflection of the baseline (↓).

(B) MEP amplitude of six conditions. "C," contacted condition; "S," separated condition. Analysis of variance (ANOVA) for MEP amplitude and onset was performed. Number of subjects (n) was six. Mean value of 18 MEPs (three TMS events $\times$ six trials in each condition) was calculated per subject. The MEP amplitude in the C condition (skin contact, 83 Hz vibration) was significantly larger than those in the other five conditions [two factorial (Conditions (6) $\times$ right, left (2)) repeated measurement; $F_{(5, 25)} = 9.3$, $p < 0.001$].

(C) MEP onset. The identical ANOVA for onsets of MEPs also showed significant conditional differences [$F_{(5, 25)} = 4.9$, $p < 0.005$]. There was no significant difference in MEP amplitude and onset between right and left hands.

the section of MI that controls the nonvibrated wrist is confined to the period when the subjects experience illusory movement of the nonvibrated hand, and the degree of MI activity is correlated with the amplitude of the movement sensation. Moreover, the increased BOLD signal in MI controlling the nonvibrated hand shows that the neurons in MI presumably depolarize so as to facilitate the muscle that would be an agonist of the direction of the illusory movement.

It is likely that vibration stimuli may transmit from the vibrated hand to the nonvibrated hand. However, the spread of vibration to the nonvibrated hand is not a prerequisite to elicit the transferred illusion. Before the TMS experiment, we did a psychophysical experiment to examine if the spread of the vibration could produce the transfer of illusion. Sixteen subjects (12 males and 4 females, aged 20–33 years old) participated in this psychophysical experiment. In this experiment, one hand was placed on the dorsal surface of the other hand. In one condition, as we did in the TMS experiment, the tendon of the wrist extensor muscles of the upper hand was vibrated (see Figure 4). In the other condition, the tendon of the wrist extensor muscles of the lower hand was vibrated. In the former case, the vibrations should transmit through the dorsal surface of the nonvibrated hand; in the latter, it should transmit through the palm of the nonvibrated hand. If the spread may produce the transfer of illusion, the direction of the illusory movement of the nonvibrated hand should be determined according to whether the putative transmission of vibration takes place through the palm or the dorsum of the hand. However, in both cases, the nonvibrated hand was always perceived to flex. Furthermore, in the fMRI experiment, the hands were placed palm-to-palm. And in this case, the nonvibrated hand was perceived to extend. Thus, the direction and perception of movement of the nonvibrated hand is always determined by the direction of illusory movement of the vibrated hand. Finally, if the spread of the vibration should elicit the illusion, the illusion of the nonvibrated hand must be experienced during bone vibration when the hands are in contact as well. However, in more than 53 subjects tested, there has never been an illusion in the nonvibrated hand when the hands were in contact and the bone was vibrated. Thus, these effects cannot be explained by the spread of vibrations from one hand to another.

Traditionally, cytoarchitectonic areas 3a and 2 have been held responsible for the sense of kinesthesia (Iwamura et al., 1983, 1993; Mountcastle and Powell, 1959; Phillips et al., 1971; Pons et al., 1992). However, recent studies in humans have all consistently shown that the activation of areas 3a, 3b, and 1 is minor, if at all detectable, when the perception of kinesthesia results from vibration of a muscle tendon (Naito et al., 1999, 2002; Naito and Ehrsson, 2001). The present results are in accordance with these recent results (Figure 3). In the present fMRI experiment, as in Naito and Ehrsson (2001), we have used vibration over the styloid process of the ulna as the control condition. We cannot exclude the possibility that joint receptors also could be excited by the spread of vibration from the bone to surrounding joints when the skin over the styloid process is vibrated. In any case, the use of tendon vibration at 80 Hz to excite muscle spindles in immobile limbs clearly deviates from the investigation of kinesthesia in previous studies in monkeys in which the limbs were moved by the experimenter (Iwamura et al., 1983, 1993; Mountcastle and Powell, 1959; Phillips et al., 1971; Pons et al., 1992).

In the present study, there was also activation of the supplementary motor area (SMA), the right dorsal premotor cortex (PMd), the right area 8, and the right cytoarchitectonic area 2, no matter whether the right hand tendon or the left hand tendon was vibrated (Figures 1C and 1E). Thus, the right hemisphere area 2 was activated (not the primary somatosensory cortex, which is best

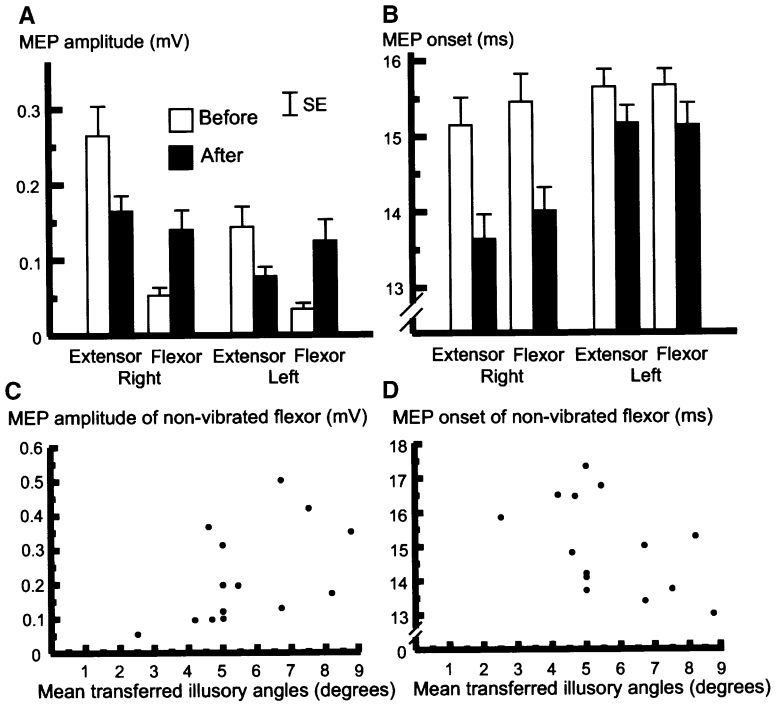

Figure 6. Changes of MEP Amplitudes and Onsets before and after the Transfer of Illusion and Correlation between Transferred Illusory Angle and MEP Amplitude and Onset

(A) Changes of MEP amplitude before (Before transfer) and after (After) the illusion transferred. The MEP amplitude in the flexor muscles was significantly more enhanced after the illusion transferred to the nonvibrated side than before, whereas the MEP in the extensor muscles was reduced after the transfer ($n = 3$) [Three factorial ANOVA (Before, After) $\times$ (extensor, flexor) $\times$ (right, left); interaction between (Before, After) $\times$ (extensor, flexor); $F_{(1, 181)} = 27.2$, $p < 0.001$].

(B) Changes of MEP onset before or after the illusion transferred. The onsets both in the flexor and extensor muscles were also significantly shorter after than before [main effect $F_{(1, 181)} = 22.4$, $p < 0.001$].

(C) Correlation between mean illusory angles and mean MEP amplitudes. We calculated mean MEP amplitude, mean MEP onset, and mean transferred illusory angle of six trials per subject. Each dot represents a mean value from one subject. Since there was no significant difference between the right and left hands, we pooled the data from both hands (giving 14 observations, $n = 14$) to increase the statistical power.

(D) Correlation between mean transferred illusory angles and mean MEP onsets.

defined as areas 3 and 1). The right (ipsilateral) premotor cortex, area 2, and SMA can often be active together in the absence of any movement, vibration, or muscle tension, simply through somatosensory stimulation of the immobile hand (for example, see Bodegard et al., 2001). Activation of these areas, however, is not sufficient to elicit the illusion. The illusion appears only if the MI contralateral to the tendon vibration is active. This is the consistent experience from examining 78 subjects (Naito et al., 1999, Figure 3; Naito and Ehrsson, 2001; Naito et al., 2002; this experiment; our unpublished data). In the present study, the illusion transfers to the nonvibrated hand only if the hands are in contact and if one tendon is vibrated and the ipsilateral and contralateral MIs are active (Figures 1D, 1F, and 2). The MI activation is thus a compulsory activation to be present in order for the subjects to experience the illusion. The crucial point from the present results, however, is that the experience of the illusion is dependent on the activation of the MI but is not dependent on the sensory input from the muscle spindles.

But as the MI hand areas in primates are said to have few, if any, connections across the corpus callosum (Gould et al., 1986; Jenny, 1979; Jones et al., 1979; Rouiller et al., 1994), how then does the ipsilateral MI become depolarized? If one examines the contrasts (right tendon vibrated, skin contact – right bone vibrated, skin contact) and (left tendon vibrated, skin contact – left bone vibrated, skin contact) (Figures 1D and 1F), the two supplementary motor areas (bilateral SMA), the two frontal opercular areas, the right dorsal premotor area, the right area 8, the right cytoarchitectonic area 2 (Grefkes et al., 2001; Iwamura et al., 1994), and the right supramarginal gyrus are active in addition to both the MIs. The MI controlling the nonvibrated wrist is therefore part of this bilateral network of active fields that are interconnected in other primates (Darian-Smith et al., 1993; Gould et al., 1986; Jenny, 1979; Jones et al., 1979; Rouiller et al., 1994; Stepniewska et al., 1993). This evidence is in agreement with the notion that MI neurons on the sets of distributed interconnected cortical neurons could contribute to the perception of passive movement (Fetz et al., 1980).

One plausible scenario is that from the start of the vibration to the transfer of the illusion the above mentioned network of sensorimotor structures (Figures 1D and 1F) will have to reconcile the information that one wrist is bending with the information that the hands are mutually in contact. After awhile, when both of these types of sensory information have been shown to be consistent, the facilitation of the MI controlling the nonvibrated wrist takes place. The network then, by recursive within area-between area computation (Roland, 2002), resolves the issue by activating the MI controlling the nonvibrating hand. This activation targets the part of MI controlling the muscle that would be the agonist of the direction of the illusory movement such that this muscle is more facilitated than is the antagonist. This gives the illusory sensation of movement, for which the MI (and the cerebellum) are primarily responsible. Thus, the MI, not the somatosensory areas, has a major role in somatic perception of limb movement.

This role in kinesthetic perception also prevails under conditions during which MI does not receive any commands to move (no intention to move) nor any direct information from muscle spindles that the wrist is moving. Parenthetically, imagery of slow flexion or extension of the wrist activates the contralateral SMA, PMd, post-

parietal cortex, and the ipsilateral cerebellum, but neither the contralateral nor the ipsilateral MI were activated (see Naito et al., 2002). This new role of MI in somatic sensation is in contrast to MI's traditional role as the executive locus for voluntary movements but is presumably meaningful in the sense that the internal representation of one's own limb position and limb movement is best conveyed to the neurons in MI that control limb movements.

Experimental Procedures

fMRI Experiment

Experimental Conditions

Ten healthy blindfolded right-handed (Oldfield, 1971) male subjects (21–33 years old) 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 and TMS experiments were carried out following the principles and guidelines of the Declaration of Helsinki (1975). A 1.5 T General Electrics scanner with head-coil provided T1-weighted anatomical images (3D-SPGR) and functional T2*-weighted echoplanar images (64 $\times$ 64 matrix, 3.4 $\times$ 3.4 mm, TE = 60 ms). A functional image volume comprised 30 slices of 5 mm thickness (with 0.4 mm interslice gap), which ensured that the whole brain was within the field of view.

The subjects 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 relax completely (and make no movements). We used a nonmagnetic vibrator that was driven by constant air pressure provided by an air compressor (BILTEMA Art. 17-635, Linköping, Sweden). The frequency was approximately 80 Hz. Each subject had six sessions: in three of these, the right wrist was vibrated, alternating with three sessions in which the left wrist was vibrated. A total of 6 $\times$ 128 volumes were collected for each subject. For each session, there were six conditions: (1) separated hands, tendon vibrated (ST); (2) separated hands, bone vibrated (SB); (3) separated hands, rest (no vibration) (SR); (4) palm contact, tendon vibrated (CT); (5) palm contact, bone vibrated (CB); (6) palm contact, rest (CR). Each condition lasted for 32 s (eight 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 rest condition, the vibrator was held in the air close to the right or left wrist ($\sim$5 cm) but did not touch the skin. In the bone vibration conditions, we vibrated the skin surface over the *processes styloideus ulnae* at 80 Hz by placing the vibrator in contact with the skin. This stimulus did not elicit an illusory wrist movement, no matter whether the hands were in skin contact or were separated. In the more than 53 subjects tested, this procedure has never elicited any illusory movements. In the tendon vibration conditions, we vibrated the surface of the skin over the tendon of the right *extensor carpi ulnaris* at 80 Hz. This stimulus elicited a vivid illusion of palmar flexion of the wrist. The contact surface on the skin was approximately 1 cm^2 for both vibration conditions and was marked on the surface of the skin. The mean distance between this tendon site and the *processes styloideus ulnae* was 3.6 $\pm$ 0.5 cm. An experienced experimenter applied the vibrator at these sites with a constant pressure.

In the training session before fMRI, out of 16 subjects, we selected ten who experienced reliable unilateral illusion (more than 20 degrees wrist flexion) when hands were separated and vivid transfer of illusions of the nonvibrated wrist (reporting more than 10 degrees wrist flexion) when hands were contacted. Prior to the fMRI experiments, we took an electromyogram (EMG) from the skin surface of the wrist extensor (represented by the *extensor carpi ulnaris* [ECU]) and flexor (the *flexor carpi ulnaris* [FCU]) and confirmed that no EMG activity was present on the nonvibrated side in any of the subjects when they experienced the transferred illusions. After each fMRI session, the subjects were asked if they experienced illusion or not. All subjects reported that they vividly experienced that both hands were moving when the hands were in contact and one tendon was vibrated.

Data Analysis

The fMRI data was analyzed with the Statistical Parametric Mapping software (SPM99; http//:www.fil.ion.ucl.ac.uk/spm; Wellcome Department of Cognitive Neurology, London) (Friston et al., 1995a, 1995b). The functional images were realigned to correct for head movements, coregistered with each subject's anatomical MRI, and transformed (linear and nonlinear transformation) to the format of the standard brain of the Neurogenerator and Talairach coordinates (Roland et al., 2001). The functional images were scaled to 100 and were spatially smoothed with an 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). Each condition was modeled with a boxcar function delayed by 4 s and convoluted with the standard SPM99 hemodynamic response function. In the central sulcus region, where we had an apriori anatomical hypothesis of activation, we report clusters of active voxels and local maxima of activity that correspond to $p < 0.01$ after a small-volume correction (SPM99). The location of the center of the small volume was defined from an active cluster in an independent PET study (Naito and Ehrsson, 2001). The small volume was defined as spheres with 12 mm radii and centers of (−36, −18, 52) and of (36, −18, 52). The radius was selected according to the final smoothness of the present data. For the rest of the brain, we used a threshold of $p < 0.05$ or better after a correction for multiple comparison in the whole brain space.

To assess condition-specific activations, we performed pairwise contrasts of the conditions (e.g., skin contact, tendon vibration). To detect activity that specifically reflected the transferred kinesthetic illusion, we examined the interaction between the factors of hand position (skin contact or separated hands) and site of vibration (tendon or bone) in a 2 $\times$ 2 factorial design. Importantly, in this contrast, the effects of the hand position and tendon vibration are matched [(skin contact, tendon vibration – skin contact, bone vibration) – (separated hands, tendon vibration – separated hands, bone vibration)].

To specifically address the issue of possible SI activation, we reanalyzed the fMRI data, which this time were smoothed by using only a 4 mm FWHM Gaussian filter. When the right bone was vibrated when the palms were in contact and this condition was contrasted with rest, we found an activity in the left SI, with a peak (−33, −33, 57) located in the postcentral gyrus (cytoarchitectonic area 3b). When the left bone was vibrated when the palms were in contact and this condition was contrasted with rest, we found a peak of the activity in the right SI (33, −30, 57) (cytoarchitectonic area 3b). These peaks were clearly located in the postcentral gyrus in all subjects (of the anatomically standardized T1-weighted MR image of each subject).

When the right tendon was vibrated under the skin contact condition (tendon vibration, skin contact) and was contrasted with the right bone vibration, skin contact condition, we found an activity in the right MI, with a peak (33, −24, 54) located in the precentral gyrus (cytoarchitectonic area 4p). Similarly, when the left tendon vibration, skin contact condition was contrasted with the left bone vibration, skin contact condition, we found an activity in the left MI, with a peak (−33, −24, 54) located in the cytoarchitectonic area 4p. These peaks were clearly located in the precentral gyrus in all subjects (of the anatomically standardized T1-weighted MR image of each subject).

We extracted the fMRI data (4 mm filtered) from the four peaks of activities in the right MI (33, −24, 54), the right SI (33, −30, 57), the left MI (−33, −24, 54), and the left SI (−33, −33, 57) (see above). We then calculated the mean percent increase for each epoch of CT compared to CB 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.

$$\frac{(\text{Mean in CT} - \text{Mean in the corresponding CB}) \times 100}{\text{Mean in the corresponding CB}}$$

Finally, the mean value for each individual subject was calculated from the six values from six epochs. The right hand and left hand conditions were separately treated. Only activity in the ipsilateral side to the vibrated hand (= contralateral side to the transferred illusion) was calculated. We performed a two-factorial analysis of variance (ANOVA) [vibrated side (right or left) (2) x MI, SI (2) repeated measurement] for the mean of individual subject (Figure 3).

Anatomical and Cytoarchitectonic Mapping

The findings were related to cytoarchitectonically defined areas in the postcentral and precentral gyri (Geyer et al., 1996, 1999; Grefkes et al., 2001; Schleicher et al., 1999). Somatosensory areas 3a, 3b, 1, and 2 and primary motor areas 4a and 4p were delineated in ten postmortem brains. The borders between different cytoarchitectonic areas were determined on the basis of statistically significant differences in the neuronal cell bodies (Schleicher et al., 1999). The brains were corrected for deformations due to histological processing and were warped to the same reference brain of the computerized atlas as the fMRI images (Roland et al., 2001) using the FMG method (Schormann and Zilles, 1998). A population map was generated for each area (Roland and Zilles, 1998) (Figures 2C and 2D). The population maps describe, for each voxel, how many brains have a representation of one particular cytoarchitectonic area. The individual variation in the location and extent of each cytoarchitectural area led to voxels representing more than one area. In these cases, the voxel was allocated to the cytoarchitectural area to which most of the brains represented in the voxel belonged. The result was a probability map of the cytoarchitectural areas (Roland et al., 2001). In the case that a cytoarchitectural area did not abut another area on one side (as area 2), a 30% threshold was used to delimit the unabuted part (i.e., 30% of all brains had area 2 represented at this border).

The localization of the central sulcus in each subject was determined from the standardized single-subject MR image (the T1-weighted anatomical image). This was compared to the position of the cytoarchitectural probability map (Roland and Zilles, 1998). In each subject, there was separation of areas 4a and 4p from areas 3a, 3b, and 1 by the central sulcus. Furthermore, we compared the anatomical MR image of each subject with the functional MRI of each subject ($p < 0.05$ uncorrected). We found that the peak of activity in each subject of vibrating the contralateral tendon was always located in the anterior bank (area 4p) of the sulcus.

TMS Experiment

Eight blindfolded subjects (age 23–33 years) who experienced vivid transfer of the kinesthetic illusion participated. The TMS study was approved by the Local Ethics Committee of the Kyoto University. We used two vibrators (Sasuri-Vib EV258-A, Matsushita Electronics, Osaka, Japan, for 83 Hz vibration; and Tanton EV258-A, Matsushita Electronics, Osaka, Japan, for 12.5 Hz) with an identical plastic cap that contacted the skin. In six subjects, we tested the right and the left hand, and in two subjects, we tested the left hand. Each of the six conditions (tendon vibration of 83 Hz or 12.5 Hz or no vibration when both hands were contacted [C] or separated [S]) was repeated six times (Figure 4A). The order of conditions was randomized. The blindfolded subjects sat on a comfortable chair with their arms and hands relaxed. The forearms were put on a table and hands hung freely. We measured the wrist angles with the aid of two small bars attached laterally to the surface of the skin over the wrist. The angle of these bars was read on a transparent protractor, which was placed adjacent to the wrist (Naito et al., 2002). The mean angle of palmar flexion was $50° \pm 6.2°$ for right wrist and $48° \pm 8.4°$ for left wrist during relaxation. Before the TMS experiment, we tested the accuracy and reliability with which the subjects could evaluate and replicate passively flexed wrist angles on both right and left sides (Naito et al., 2002). The subjects could precisely detect angle differences of 2.5°, as shown in the previous study (Clark et al., 1985), demonstrating a high reliability for the subjects' ability to detect illusory angles experienced during the experiment.

We vibrated the tendon of the ECU muscle for 30 s. The subjects were instructed to be aware of the sensation from the wrist and reminded of the requirement to report the angles of any illusory movements after each trial. The subjects were requested to say "start" after the subjects started experiencing transfer of illusion or unilateral illusion. The subjects were also required to say "start" in the control conditions, after the vibration started when the 12.5 Hz stimuli were applied, and after a few seconds in the rest conditions. Three consecutive single TMSs at intervals of 3 s were delivered immediately after the subjects said "start." After each vibrating trial, the subjects were asked if they experienced an illusion or not. When they experienced an illusion, they were requested to replicate the illusory movement by actually moving the wrist at the averaged illusory speed (Naito et al., 2002). The maximum angles and its movement times were measured to estimate the angular velocity of illusion (maximum angles divided by its movement times). We measured the wrist angles from the original relaxed position (Naito et al., 2002). The mean transferred illusory palmar angle across the subjects was about 5° in both sides.

In another experiment, we tested changes of cortical excitability before and after the transfer of illusion (83 Hz vibration when hands were contacted) on three out of eight subjects. One single TMS was delivered after the start of the vibration but before the transfer or immediately after the transfer of illusion had started. Eight trials were performed in each condition. Identical experiments were performed on the right and left sides.

The TMS experiment was done with a figure-eight coil (YM-131B, Nihon Kohden, Tokyo, Japan) powered by a magnetic stimulator with 0.67 Tesla at 100% intensity (SMN-1200, Nihon Kohden, Tokyo, Japan). The coil was placed over the optimal position over the scalp for evoking motor-evoked potentials (MEPs) from the FCU muscle, which is the agonistic muscle for the direction of the transfer of illusion. The optimal position was determined as 4–6 cm laterally located from Cz in the international 10/20 system (Naito and Matsumura, 1994) as the lowest intensity of TMS which could generate an MEP (50μV–100μV) in the target muscle when subjects were totally resting with their eyes closed (Rossini et al., 1994). This threshold intensity was used throughout the experiment. The surface EMG was recorded during the TMS experiment from the nonvibrated FCU muscle and from the nonvibrated ECU muscle with surface electrodes (Ag/AgCl) (Neuroline 70010-K, Medicotest, Olstykke, Denmark) over the muscle bellies. The signal was low-cut filtered (1.5 Hz) and amplified 2000 times (MEG6100-M, Nihon Kohden, Tokyo, Japan). The sampling rate in MEP recording was 2 kHz.

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