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Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions

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Received 26 August 2002; revised 17 February 2003; accepted 14 April 2003

Abstract

Distal, unilateral hand movements can be associated with activation of both sensorimotor cortices on functional MRI. The neurophysiological significance of the ipsilateral activation remains unclear. We examined 10 healthy right-handed subjects with and without activation of the ipsilateral sensorimotor area during unilateral index-finger movements, to examine ipsilateral, uncrossed-descending pathways and interhemispheric interaction between bilateral motor areas, using transcranial magnetic stimulation (TMS). No subject showed ipsilateral activation during right hand movement. Five subjects showed ipsilateral sensorimotor cortical activation during left hand movement (IpsiLMI). In these subjects, paired-pulse TMS revealed a significant interhemispheric inhibition of the *left* motor cortex by the *right* hemisphere that was not present in the 5 subjects without IpsiLMI. Neither ipsilateral MEPs nor ipsilateral silent periods were evoked by TMS in any subjects. Our observation suggests that IpsiLMI is not associated with the presence of ipsilateral uncrossed-descending projections. Instead, IpsiLMI may reveal an enhanced interhemispheric inhibition from the right hemisphere upon the left to suppress superfluous, excessive activation.

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Keywords: Interhemispheric inhibition; Ipsilateral activation; Functional MRI; Transcranial magnetic stimulation; Motor cortex

Introduction

Functional imaging studies in stroke subjects recovering from a hemiparesis often show activation of ipsilateral, unaffected motor cortex during motor tasks with their paretic hand (Weiller et al., 1992; Marshall et al., 2000). Such activation ipsilateral to the hand movement could be related to ipsilateral, uncrossed projections (corticospinal or corticobrain stem descending pathways (Ziemann et al., 1999)) or interhemispheric interactions. Several studies report that

in patients with unilateral stroke motor-evoked potentials (MEPs)¹ for paretic hand muscles can be obtained by transcranial magnetic stimulation (TMS) of the ipsilateral, unaffected motor cortex more frequently than in normal subjects (Trompetto et al., 2000; Caramia et al., 2000; Alagona et al., 2001). However, induction of MEPs in the paretic hand by TMS of the ipsilateral, unaffected motor cortex is inconsistently found and does not indicate favorable outcome in stroke patients (Netz et al., 1997; Caramia et al., 2000; Alagona et al., 2001).

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¹ Abbreviations used: ANOVA, analysis of variance; FDI, first dorsal interosseous muscle; fMRI, functional magnetic resonance image; IpsiLMI, activation of the left primary motor cortex during left index finger movement; MEP, motor-evoked potential; MNI, Montreal Neurological Institute; TMS, transcranial magnetic stimulation.

Activation of the ipsilateral, unaffected motor cortex in stroke patients during movements of their paretic hand might be related to mechanisms similar to those accounting for activation of the ipsilateral primary motor area during certain more challenging and difficult unimanual motor tasks in normal subjects (Roland et al., 1980; Kim et al., 1993). Positron emission tomography (PET) and functional MRI (fMRI) studies have shown activation of the primary motor area during an ipsilateral, unilateral motor task in normal subjects, although not in all of them (Roland et al., 1980; Rao et al., 1993; Singh et al., 1998; Cramer et al., 1999; Allison et al., 2000). Such ipsilateral activation is more frequently observed when a simple motor task is performed with the nondominant hand (Kawashima et al., 1998). During simple movements with the dominant hand, the activation in the motor cortex is generally limited to the contralateral hemisphere or, if any, sparse in the ipsilateral primary motor cortex (Kim et al., 1993; Beltramello et al., 1998). Performing or learning complex motor tasks with the nondominant hand can also evoke activation of the ipsilateral primary motor cortex in many, although not in all subjects (Beltramello et al., 1998; Hund-Georgiadis and von Cramon, 1999).

fMRI and PET reflect regional changes of cerebral blood flow and provide only indirect measures of synaptic and neuronal activity. Therefore, the neurophysiological mechanisms underlying ipsilateral motor cortex activation during unimanual tasks remain unclear. Interhemispheric transcallosal interactions between both motor areas have been studied in animals using direct electrical cortical stimulation (Asanuma and Okamoto, 1962; Matsunami and Hamada, 1984) and more recently in humans using TMS (Ferber et al., 1992; Hanajima et al., 2001). These studies show that stimulation of one motor cortex can induce facilitatory and mostly inhibitory effects in the contralateral motor cortex. Therefore, it is possible that activation of the ipsilateral motor cortex on fMRI during unilateral hand movements might be related to interhemispheric interactions. Such interhemispheric interactions might be engaged during complex motor tasks in normal subjects and might account for similar findings in stroke patients.

In the present study we used TMS to address two possible explanations for the activation of the ipsilateral motor cortex during unimanual movements. The activation of the motor cortex ipsilateral to the hand movement could be due to the contribution of ipsilateral descending pathways for unimanual movements. Alternatively, the activation of the ipsilateral motor cortex could be related to interhemispheric, transcallosal interactions. We investigated 10 healthy right-handed subjects using fMRI during unilateral movements of their index finger. During nondominant (left) finger movements, 5 of the 10 subjects showed significant activation on their ipsilateral (left) sensorimotor hand area. Dominant (right) finger movement did not activate the sensorimotor area of the ipsilateral side in any subject. TMS was then used to assess the feasibility of inducing ipsilateral

motor-evoked potentials or silent periods as markers of corticospinal projections. Interhemispheric interaction was assessed by paired-pulse TMS (Ferber et al., 1992).

Subjects and methods

Subjects

Ten healthy volunteers (7 men and 3 women; 25 to 55 years old; mean age 36.5 ± 12.3 years) were recruited into this study. None of them had any psychiatric or significant past medical history or any contraindications to fMRI or TMS (Wassermann, 1998). Subjects were excluded if they had any pathological findings on their T1 or T2 weighted MRI scanning. All subjects were strongly right-handed according to a hand preference questionnaire (Oldfield, 1971). Importantly, none of the subjects had a history of mirror movements or was noted to have mirror movements during a focused neurological examination. The study was approved by the local institutional review board and written informed consent was obtained from each participant

Experimental design

This study consisted of two parts: an fMRI experiment and a TMS experiment. These two experiments were done on different days.

Functional MRI experiment

Activation tasks

The motor task used in the current study was a metronome-paced index finger abduction/adduction. The task was performed by either the right or the left hand and was briefly rehearsed prior to scanning. During scanning each task was performed continuously, paced by a metronome at 1 Hz. During the nonmovement rest condition the metronome continued to beat at 1 Hz. Movements of the other digits or hand movements were restricted by placing the hand and forearm in a sturdy foam splint and taping the hand and fingers (except for the index finger). Electromyogram recording and careful observation were completed during the motor task in order to rule out involuntary or mirror movement of the other hand and arm. It was confirmed that all subjects performed the unilateral motor task without cocontraction or mirror movements of the other hand and arm.

Each of the two motor epochs, right index finger and left index finger movements, was repeated five times and their order was randomized with the nonmovement rest condition (each epoch lasted 35 s). Participants lay in the supine position and were asked to keep their eyes open and fixate on a spot at the scanner ceiling. During the experiment an examiner continually observed them to monitor task performance (for further details see Hutchinson et al., 2002).

MR scanning

We used a 1.5-T whole body MR system (Magnetom Vision, Siemens, Erlangen, Germany). Participants' heads were positioned in a standard radiofrequency head coil with tape and cushioning to minimize head motion. A three-dimensional magnetization prepared, rapid acquisition gradient echo pulse sequence was used for anatomical volume acquisition and localization of functional images (voxel size 1 mm³; FOV 240 mm). A gradient-echo T2* weighted echo-planar MR sequence was used for fMRI with the following parameters: TE (echo time) = 50 ms, FOV (field of view) = 240 mm, matrix = 128 × 128, voxel size: 2.5 × 2.5 × 6 mm. Using a midsagittal scout image, we acquired 22 slices contiguous without gap, parallel to the anterior–posterior commissure plane covering the entire brain. There were five acquisitions per epoch, with a TR of 5 s. T2 weighted and susceptibility weighted scans were also acquired on each subject to screen for pathological findings.

Data preprocessing and analysis

Off-line data processing was performed using SPM'99 (<http://www.fil.ion.ucl.ac.uk/spm>) for preprocessing and analysis (Friston et al., 1994, 1995, 1997), and Matlab (Mathworks, Natick, MA, USA) for calculations and matrix manipulations. The first two acquisitions of each series were discarded to account for T1-saturation effects. All volumes were realigned to the first volume corrected for motion artifacts and mean adjusted by proportional scaling, followed by coregistration with the subject's corresponding anatomical image. Subsequently they were normalized (2 mm³) into standard stereotactic space (template provided by the Montreal Neurological Institute (MNI, Evans et al., 1992)) and smoothed using an 8-mm full-width-at-half-maximum Gaussian kernel.

In addition, the time series of hemodynamic responses were high-pass filtered to eliminate low-frequency components, temporarily smoothed, and adjusted for systematic differences across trials. These adjusted measures were subjected to the statistical analyses. Voxels associated with movement conditions were searched for by using the General Linear Model approach for time-series data suggested by Friston and colleagues (Friston et al., 1995). For this, we defined a design matrix comprising contrasts modeling the alternating periods of motor tasks and the between groups differences for this contrast using a boxcar reference vector. Two conditions were defined for each of right and left index finger movements; the nonmovement control condition was not explicitly modeled. Voxels were identified as significant if they passed a statistical threshold of $P < 0.005$ (corrected for multiple comparisons).

The location of the central sulcus and primary motor cortex was identified referring to their anatomical MR images by reliable sulcal markers (Yousry et al., 1997; Ono et al., 1990). The most significantly activated voxel in the precentral gyrus was identified within a cluster of voxels

and its spatial coordinate was given in MNI stereotactic space. A paired t test was used to determine whether the coordinates between ipsilateral and contralateral activation sites in the primary motor cortices were significantly different. The subjects were then divided into two groups according to the presence or absence of significant activation in the primary motor cortex ipsilateral to the hand movements. The differences in the coordinates of each group were examined using analysis of variance (ANOVA) and unpaired t test. The cluster sizes in the supplementary motor area and contralateral motor cortex were also calculated in each subject and compared between the two groups of subjects using nonparametric statistics.

TMS experiment

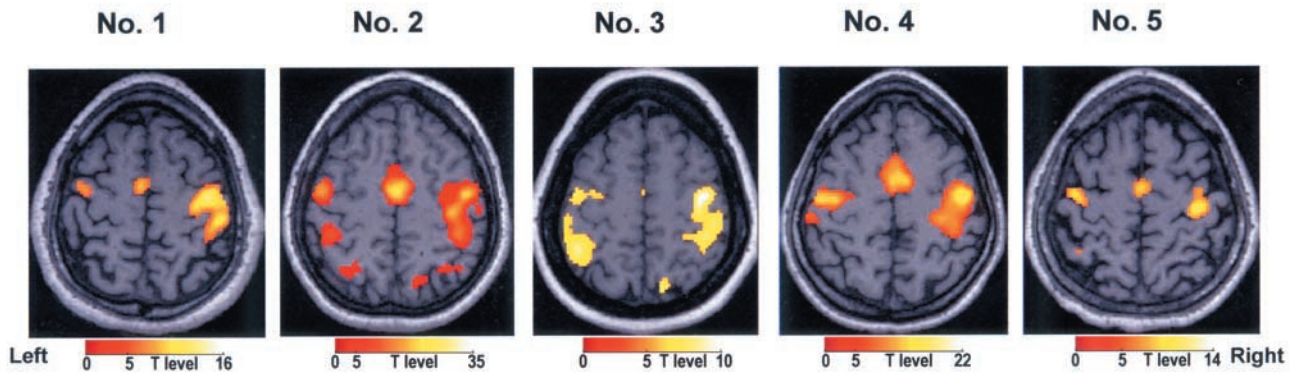
General preparation and data acquisition

Subjects were seated in a reclining chair and were instructed to keep arms and hands relaxed during the TMS experiment. A tight-fitting white lycra swimming cap was placed on their head in order to mark the position for a TMS coil. MEPs induced by TMS were recorded from the right and left first dorsal interosseous muscle (FDI). Silver/silver chloride surface electrodes were placed over the muscle belly (active electrode) and over the tendon of the muscle (reference electrode). A circular ground electrode with a diameter of 30 mm was placed on the dorsal surface of the right wrist. The MEPs were amplified and filtered using a Dantec Counterpoint electromyograph (Dantec, Skovlunde, Denmark) with a bandpass of 20–2000 Hz. Signals were then digitized (digitization rate 5 kHz) through a CED 401 laboratory interface (Cambridge Electronic Design, Cambridge, UK) and fed to a personal computer for off-line analysis.

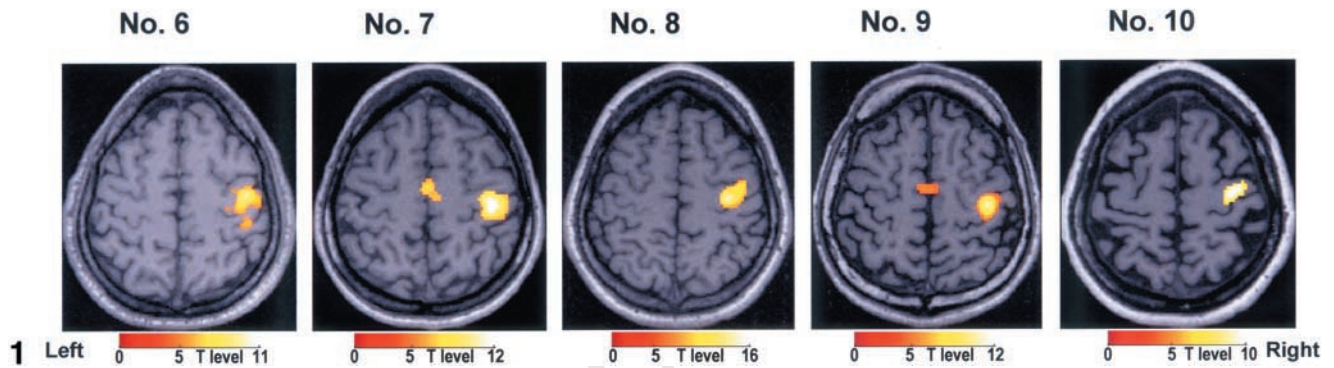
TMS was performed with two sets of 70-mm figure-eight coils and two Magstim 200 stimulators that could be interfaced using a Bistim device (Magstim Company, Dyfed, UK). Stimulation was delivered to the “optimal scalp site,” i.e., the scalp position from which TMS induced MEPs of maximal amplitude in the contralateral FDI. The coil was positioned tangentially to the scalp, pointing anteriorly, 135° from the midsagittal axis. Initially, the motor threshold for evoking MEPs in the FDI was determined. Motor threshold was defined as the minimum TMS intensity which could induce MEPs of >50 μ V peak-to-peak amplitude in >50% of eight successive trials in the FDI, under complete muscle relaxation (Rossini et al., 1994).

The placement of the TMS coil on each subjects' scalp was also monitored using the frameless stereotaxy method (Gugino et al., 2001) with anatomical and functional information derived from the MRI study. We used a Polaris (Northern Digital, Ontario, Canada) infrared device to track the position of the subject's head and the TMS stimulation coil and coregistered the subject's head with the subject's anatomical scan using Brainsight software (Rogue Research, Montreal, Canada).

(A) Subjects with ipsilateral activation during Left finger movement



(B) Subjects without ipsilateral activation during Left finger movement



Interhemispheric inhibition

To assess interhemispheric interaction, TMS was delivered over the hand representation in the primary motor

Anatomical and functional MRI of Subject No. 4.

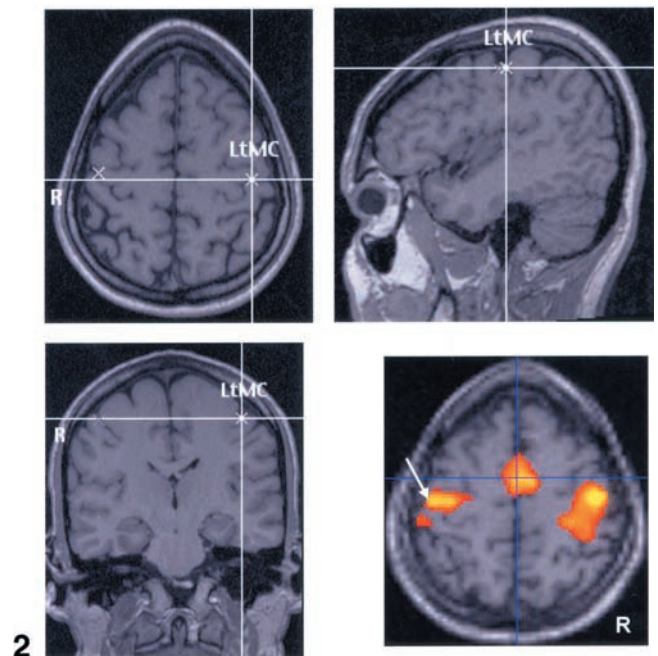


Fig. 1. Functional MR images of all subjects who did (A) and did not (B) demonstrate activation of the ipsilateral primary motor cortex while moving the left index finger. Functional images were superimposed onto the anatomical MR at the level of hand representation in the primary motor cortex, which was indicated with a knob- or omega-like shape of the central sulcus (Yousry et al., 1997). Significant voxels ($P < 0.005$, corrected for multiple comparisons) are indicated on the red color spectrum where in each the height threshold is $T = 5.46-5.78$. Ipsilateral activation was observed in five subjects when they moved their left index fingers, whereas no ipsilateral activation was detected with right index finger movements. Fig. 2. Anatomical (upper row and lower left) and fMRI (lower right) of Subject No. 4. Functional images were superimposed onto the anatomical MR at the level of hand representation in the primary motor cortex, which was indicated with a knob- or omega-like shape of the central sulcus (Yousry et al., 1997). Significant voxels ($P < 0.005$, corrected for multiple comparisons) are indicated by a red color spectrum. The anatomical MRI scan was coregistered with visible landmarks on the subject's head so that the position of the TMS coil could be located relative to the subject's brain. The white cross lines indicate the position approximately 25 mm deep from the center of the coil. The fMRI, obtained during the left index finger movement, showed the ipsilateral activation (white arrow). R, right side in each image. LtMC, the site indicated by stereotactic system when TMS coil was placed on the optimal scalp site on the left side.

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cortex on both sides using two figure-eight coils. A conditioning stimulus to one hemisphere was followed by a test stimulus applied to the other side. Both conditioning and test stimulus were given at the optimal scalp site to evoke motor responses in their respective contralateral FDI. The intensity of conditioning TMS was set at an intensity of 10% above motor threshold. The test stimulus was adjusted to evoke MEPs of peak-to-peak amplitude of approximately 1 mV in contralateral FDI muscle. This resulted in an average stimulation intensity for the test TMS across subjects of approximately 30% above the individual motor threshold. The conditioning–test interstimulus intervals were varied as follows: 5, 7, 8, 9, 10, 12, 15, and 20 ms.

A total of 10 MEPs per each interval were recorded from the FDI contralateral to the test TMS. We also recorded 10 MEPs induced by test TMS alone as baseline data and also added 10 trials with only conditioning TMS to each block of the study. Therefore, in each block of the study, 100 trials were performed in pseudorandom order varied by the CED interface. After one block of the experiment was completed, the conditioning and test sides were changed and the other block was performed after a 10-min rest period.

Involvement of motor area in the motor control of ipsilateral hand

To examine involvement of the primary motor area in the control of ipsilateral hand muscles, additional studies on motor response and silent period were performed. In eight subjects we applied TMS at increasing intensity up to maximal stimulator output. The other two subjects were tested with TMS at an intensity of up to 200% of their motor threshold (90% of stimulator output), but not maximal stimulator output due to discomfort. The TMS coil was located on the optimal scalp site for the MEPs of the right FDI (on the left hemisphere) and TMS was delivered at maximal stimulator output intensity to examine the ipsilateral corticospinal motor pathway. For the silent period, subjects were asked to press a force transducer (Sensotec, Inc., Columbus, OH, USA) by abducting their left index finger and sustaining 10–15% of their maximum voluntary force. TMS was applied to the left primary motor cortex at increasing intensities from 130% of each subject's motor threshold intensity up to maximal stimulator output. In this manner, we also examined whether ipsilateral MEPs could be induced under background contraction, which could enhance activation of ipsilateral corticospinal tracts (Ziemann et al., 1999).

Data analysis for TMS study

Motor thresholds for both hemispheres and interhemispheric difference according to subject groups (present or absent ipsilateral activation on fMRI) were analyzed using ANOVA with repeated measures.

Mean MEP areas under the curve for each condition were calculated for the study of interhemispheric inhibition. The baseline was the mean MEP area calculated from trials with test TMS alone, and all values for the different condi-

tions were expressed as percentages of the baseline for each subject. The results were reported as means \pm standard error. The effect of conditioning TMS was subjected to ANOVA with repeated measures. Post hoc analysis, using a paired *t* test with Bonferroni correction or Scheffe's test, was conducted on the control data and the data obtained for each time interval.

Result

Ipsilateral activation in the functional MRI study

No subject showed significant activation of the ipsilateral (right) sensorimotor cortex during movements of his or her right (dominant) index finger. However, half of subjects showed ipsilateral activation when moving their left (non-dominant) index fingers. Fig. 1 shows the fMRI images of all subjects while moving their left index fingers. Five of the 10 subjects showed ipsilateral activation, i.e., the activation of the left primary motor cortex during their left index finger movement (IpsiLMI) using a threshold of $P < 0.005$ (corrected) (Fig. 1A). The other 5 subjects did not show IpsiLMI with the same threshold (Fig. 1B). Subject Nos. 6 and 8 showed small activation in the lower, lateral part of the ipsilateral frontal lobe (frontoparietal operculum) but not in the ipsilateral primary motor cortex. In order to determine that the absence of IpsiLMI was not due to the relatively conservative threshold used for the fMRI analysis, we also generated images with a threshold of $P < 0.05$ (not shown). None of these 5 subjects showed any activation in the ipsilateral primary motor cortex at these less thresholded images. All subjects performed the motor task successfully as instructed, without any excess movements.

The group of subjects with IpsiLMI consisted of one woman and four men with a mean age of 34.4 ± 10.9 years (range 27 to 53 years). The group of subjects without IpsiLMI consisted of two women and three men with a mean age of 38.6 ± 14.5 years (range 25 to 55 years). Table 1 summarizes the details of our subjects. There was no significant difference in age, gender, or handedness between these two groups.

Table 2 shows the spatial coordinates of the activation in ipsi- and contralateral motor cortex during left or right index finger movements. Ipsilateral activation was shifted relative to contralateral finger site in the same hemisphere, laterally in three of five subjects (mean 2.2 mm), anteriorly in three of five subjects (mean 2.0 mm), and ventrally in four of five subjects (mean 1.2 mm). However, the paired *t* test detected no significant differences between activated sites in the left motor cortex during ipsi- and contralateral finger movements.

The coordinates of the activation in the contralateral motor cortex were also compared between the two groups. There were no significant differences in the *x* and *z* values of the coordinates between the two groups with and without

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Table 1
Subjects' characterization

No	Age	Sex	LQ/handedness	Musical instruction (instrument/year)	Ipsilateral activation ^a	Motor threshold (%)	
						Right	Left
1	27	M	100/R	Piano/3 years	Yes	51	54
2	27	M	100/R	No	Yes	44	45
3	35	F	100/R	No	Yes	59	61
4	53	M	89.5/R	No	Yes	63	64
5	30	M	100/R	No	Yes	35	35
6	25	F	89.5/R	No	No	42	43
7	25	M	100/R	No	No	34	32
8	35	M	100/R	Piano/2 years	No	62	61
9	53	M	100/R	No	No	47	64
10	55	F	100/R	No	No	31	29

Note. LQ, Laterality Quotient by Oldfield Handedness Questionnaires (Oldfield, 1971).

^a Activation on the left primary motor area while moving the left index finger.

IpsiLMI. Repeated measures ANOVA detected a significant difference of the *y* value of the coordinates between these two groups ($F(1, 8) = 16.45, P < 0.005$), but without significant effect of the side of activation ($F(1, 8) = 0$) or interaction between groups and side ($F(1, 8) = 1.09$). The subjects with IpsiLMI had a more anterior activation of the motor cortex contralateral to the hand movement than those without ($P < 0.05$, unpaired *t* test, difference of mean *y* value: 4.80 mm).

The differences of cluster sizes in the supplementary motor area and contralateral motor cortex were examined between the two groups. The average cluster size for both of these regions was larger in the group with IpsiLMI than in the group without. However, there was no statistically significant difference between two groups.

Motor threshold

The motor threshold to evoke MEPs in the contralateral FDI was compared between the two groups of subjects, with or without IpsiLMI. There were no significant differences in

motor threshold between these two groups ($F(1, 8) = 0.57, P = 0.82$, ANOVA with repeated measures) and sides (left versus right, $F(1, 8) = 1.23, P = 0.30$) and no interaction between them ($F(1, 8) = 0.44, P = 0.52$). In the TMS experiments, the image-guided frameless, stereotactic system was used to localize the sites for TMS on the motor cortex (Fig. 2). The site of TMS (optimal scalp site) was confirmed to be overlapped with the activation in the motor cortex detected by fMRI during ipsilateral and contralateral motor tasks.

Interhemispheric inhibition

All subjects demonstrated strong inhibition of MEPs in the left FDI evoked by test TMS of the right hemisphere after the conditioning TMS of the left hemisphere. However, significant inhibition of MEPs in the right FDI evoked by test TMS of the left hemisphere after the conditioning TMS of the right hemisphere was seen only in the subjects with IpsiLMI (Fig. 3).

Table 2
Activation of contra- and ipsilateral motor cortex during left hand movement

Subject No.	MNI coordinates								
	Left index finger movement						Right index finger movement, contralateral (left) side		
	Contralateral (right) side			Ipsilateral (left) side			x	y	z
	x	y	z	x	y	z			
1	32	-16	72	-40	-8	64	-38	-14	60
2	46	-12	60	-48	-16	54	-42	-16	58
3	42	-12	58	-46	-10	56	-42	-12	58
4	36	-20	68	-40	-14	62	-40	-14	64
5	40	-20	64	-48	-10	56	-48	-12	58
6	34	-18	60				-40	-24	52
7	40	-24	64				-40	-12	56
8	42	-22	54				-38	-22	64
9	44	-12	60				-40	-24	52
10	36	-16	56				-40	-22	52

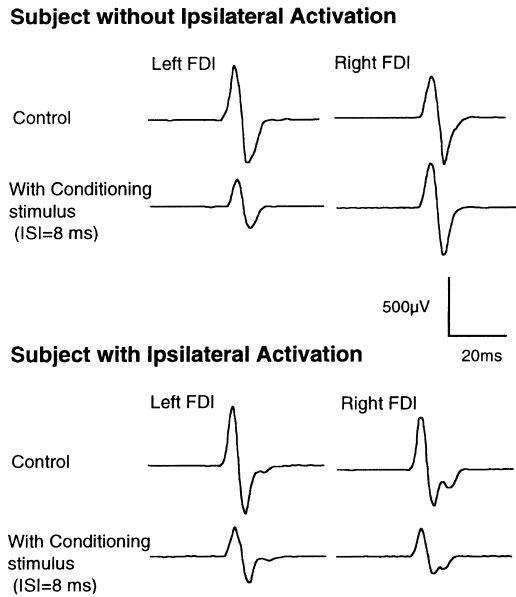


Fig. 3. Representative examples of the MEPs of right and left FDI recorded during the paired-pulse paradigm assessing interhemispheric inhibition. Results are presented for two subjects, one with and one without activation of ipsilateral (left) motor cortex on fMRI during the left index finger movement (IpsiLMI). *Left*: MEPs of the left FDI, evoked by test TMS applied to the right hemisphere. The conditioning TMS on the left hemisphere suppressed MEPs of the left FDI in both subjects. *Right*: MEPs of the right FDI, evoked by test TMS applied to the left hemisphere. In the subject without ipsilateral activation, the conditioning TMS on the right hemisphere did not affect the MEP of the right FDI. Contrarily, in the subject with ipsilateral activation, the MEP of the right FDI was suppressed by the conditioning TMS on the right hemisphere, indicating a suppression of the dominant hemisphere by the nondominant hemisphere. IpsiLMI, activation of ipsilateral (left) motor cortex on fMRI during left index finger movement.

Fig. 4A shows the effects of a conditioning TMS to the left motor area on the MEPs evoked in the left FDI by TMS to the right motor cortex. Repeated measures ANOVA demonstrated a significant effect of the interstimulus intervals ($F(7, 56) = 7.31, P < 0.0001$) but no significant difference or interaction between the two groups of subjects. Post hoc analysis demonstrated that conditioning TMS on the left side suppressed MEPs evoked by test TMS over the right motor area at the interstimuli intervals of 7, 8, 9, 10, and 12 ms ($P < 0.05$, paired t test with Bonferroni correction). Therefore, it appears that the dominant hemisphere suppressed the nondominant side in all subjects.

Fig. 4B demonstrates the effects of conditioning TMS over the right side on the MEPs induced in the right FDI by the test TMS of the left hemisphere. Repeated measures ANOVA showed a significant difference in the effects of the conditioning stimulus between the two groups of subjects ($F(1, 56) = 32.32, P < 0.001$) without significant effect of interstimuli intervals or interaction between interval and subject groups. Post hoc testing revealed a significant difference between the changes in MEPs between the two groups of subjects, those with versus those without

IpsiLMI (Scheffe's test, $P < 0.001$). Therefore, only subjects with IpsiLMI showed significant interhemispheric inhibition of the left motor cortex by the right i.e., MEPs induced by test TMS of left hemisphere were reduced significantly after the conditioning stimulus of the right hemisphere. The group of subjects without IpsiLMI did not show such an effect. Although the average effect of the interhemispheric interaction did not appear to be inhibitory in this group, four of five subjects without IpsiLMI showed 51 to 94% reduction of the MEP sizes not constantly but at some interhemispheric intervals between 7 and 12 ms. Thus, both groups were found to have interhemispheric inhibition from the right hemisphere to the left, but there were striking quantitative differences depending on the presence or absence of IpsiLMI.

Ipsilateral, uncrossed descending projection

TMS of the left motor cortex failed to induce MEPs in the left, ipsilateral hand of all subjects, even when TMS was applied at 100% (90% for Subjects 5 and 6) of stimulator output intensity. Subjects 5 and 6 (one with and one without IpsiLMI on fMRI) were tested with TMS at an intensity of up to 200% of their motor threshold (90% of stimulator output), but not maximal stimulator output due to discomfort. Similarly, when subjects were pressing a force transducer with their index fingers and generating at least 10% of their maximal voluntary force, neither silent periods nor MEPs of the left FDI were induced by TMS of the left (ipsilateral) hemisphere regardless of stimulation intensity in any of the subjects.

Discussion

Half of our subjects showed IpsiLMI, i.e., activation of their left (ipsilateral) motor cortex when performing a relatively simple motor task with their nondominant (left) hands. In these subjects, TMS of the left motor cortex failed to evoke MEPs or silent periods in the left, ipsilateral hand, and the motor threshold for induction of contralateral MEPs was not different between the right and left hemispheres. Therefore, activation of the ipsilateral motor cortex on fMRI does not seem to be related to ipsilateral, uncrossed-descending projections. The paired-pulse TMS study suggests that interhemispheric, transcallosal influences may account for the activation of the motor cortex ipsilateral to the hand movement. Specifically, inhibitory influences of the right, nondominant hemisphere onto the left, dominant hemisphere appear to be reflected in IpsiLMI. IpsiLMI may be related to an enhanced interhemispheric inhibition in order to suppress excessive motor cortical activity and prevent redundant, mirror movements.

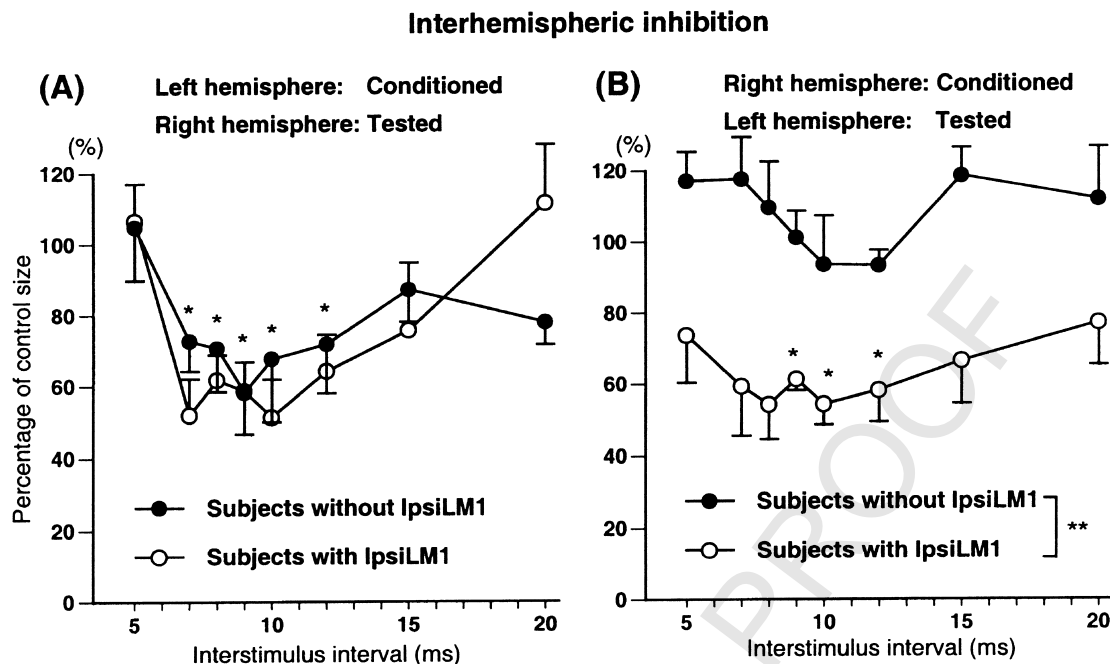


Fig. 4. (A) This chart shows changes in MEP size of left FDI evoked by test TMS over the right motor area, conditioned by preceding TMS on the left motor area. Each chart shows averages for five subjects in each group. The significant inhibition was found at the interstimulus interval of 7 to 12 ms ($*P < 0.05$). There was no significant difference between two groups of subjects. (B) The chart demonstrates changes of MEP size of right FDI evoked by test TMS over the left motor area, conditioned by preceding TMS on the right motor area. Each chart shows averages for five subjects in each group. The changes of MEP sizes were significantly different between two groups and MEPs of right FDI were significantly suppressed in the subjects with IpsiLM1 ($**P < 0.001$). In this group, the significant inhibition was found at the interstimulus interval of 9 to 12 ms ($*P < 0.05$). Error bars represent standard errors. IpsiLM1, activation of ipsilateral (left) motor cortex on fMRI during left index finger movement.

Ipsilateral activation of functional MRI

In fMRI and PET studies, the activation of the sensorimotor area can be observed during an ipsilateral, unilateral motor task in some normal subjects (Roland et al., 1980; Singh et al., 1998). A complex, precise movement in normals or a motor task performed by the paretic hand in subjects following stroke can produce activation of the ipsilateral motor cortex on fMRI much more frequently (Hund-Georgiadis and von cranon, 1999; Ehrsson et al., 2000; Yoshiura et al., 1997), suggesting a recruitment for the ipsilateral hemisphere to assist with difficult and complex movements. During a simple motor task, however, such activation of the ipsilateral motor cortex is not observed in all participants (Boecker et al., 1994; Rao et al., 1993; Allison et al., 2000); it is much more likely to occur during unilateral motor tasks with the nondominant hand (Kawashima et al., 1998, Bastings et al., 1998). In our fMRI study, our subjects were instructed to perform abduction/adduction with their index fingers and their other finger and wrist movements were restricted. This simple motor task, requiring movement of only a few intrinsic hand muscles, might result in our observation that only half of our subjects showed activation in the ipsilateral motor cortex during nondominant hand movement.

Cramer and colleagues (1999) reported that the location of the most significantly activated pixel in the motor cortex

during ipsilateral hand movement was shifted laterally, anteriorly, and ventrally compared with that during contralateral hand movement. In our study, a similar shift was observed in more than half of our subjects, but did not reach statistical significance. The difference in the result might be related to a smaller number of subjects or differences in the motor task employed. Regardless, it is important to note that the shifts observed in our subjects were small so that during TMS the areas of maximal activation on fMRI during ipsilateral and contralateral hand movements were equally affected.

It is noteworthy that the activation contralateral to the hand movement in the subjects with IpsiLM1 was located more anterior than that in the other group of subjects without IpsiLM1. These results suggest that during their hand movement subjects with IpsiLM1 recruit the anterior part of the motor area, possibly including the premotor area. Further studies must be done to evaluate possible behavioral correlates of these differences.

Ipsilateral, uncrossed descending projection

To account for the IpsiLM1, one of the candidate systems may be the ipsilateral uncrossed corticospinal or corticobrainstem-descending pathway (Ziemann et al., 1999) (Fig. 5, III or IV). In humans, 8–10% of the pyramidal tract fibers may be uncrossed corticospinal fibers (Kuypers,

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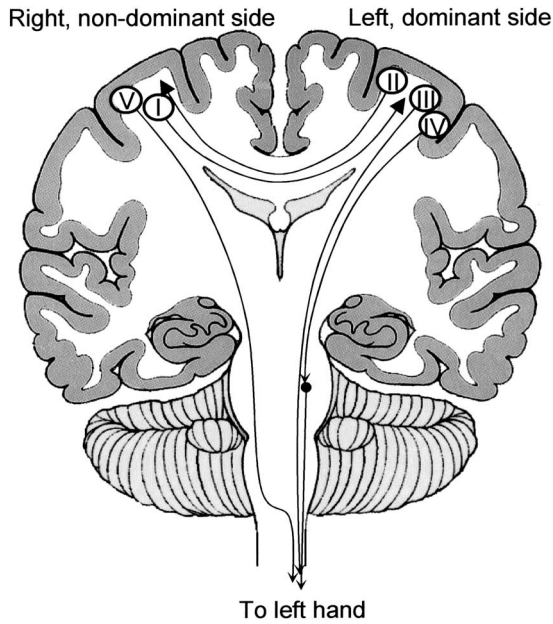


Fig. 5. Schematic illustration of crossed and uncrossed corticospinal tracts and transcallosal tracts.

1981; Brodal, 1981; Nathan et al., 1990; Yakolev and Rakie, 1966). However, such ipsilateral corticospinal fibers reach preferentially proximal, rather than distal hand muscles (Colebatch and Gandevia, 1989).

In previous studies, TMS of the motor cortex failed to elicit MEPs of the ipsilateral hand muscles in most normal adult subjects under resting conditions (Netz et al., 1997; Müller et al., 1997; Caramia et al., 1998). Bastings et al. (1998) used a coregistration system of fMRI and TMS and delivered TMS precisely above the fMRI activation. They failed, however, to induce MEPs in the ipsilateral, left hand with TMS of the left primary motor area even though it was applied just above the fMRI activation that was observed during ipsilateral, left hand movement. Activation of the spinal segmental level by strong voluntary contraction of the target muscle and placement of the TMS coil 3–5 cm anterior to the primary motor area can facilitate ipsilateral MEPs, which are, however, usually small and inconsistent (Ziemann et al., 1999; Caramia et al., 2000; Alagona et al., 2001). Other studies have demonstrated that suppression of voluntary muscle contraction can be induced in ipsilateral hand muscles maintaining 50% or maximal voluntary contraction by high-intensity TMS (Wassermann et al., 1991; Meyer et al., 1998). This suppression of EMG activity has a 10- to 20-ms longer onset latency than contralateral MEPs, suggesting a transcallosal mechanism (Fig. 5, II and V) or a pathway via the corticoreticulospinal tract (Brodal, 1981), rather than ipsilateral direct innervation.

In our study, TMS of the primary motor area failed to induce MEPs or obvious silent periods in the ipsilateral hand muscle despite TMS at maximal stimulator intensity and background contraction at least 10% of maximum power. We used a figure-eight coil to deliver focal stimuli

just over the optimal scalp site and did not apply as strong a background muscle contraction as in previous reports (Ziemann et al., 1999). These different methods might account for the absence of ipsilateral MEPs, but also allow examination of the effect of TMS delivered over the IpsiLM1, avoiding spread of TMS out of the targeted primary motor cortex and activation of the descending pathways that might not involve IpsiLM1. In addition to these results, there was no significant difference between the two groups of subjects in the interhemispheric inhibition of the right by the left hemisphere (Fig. 4A), implying that all subjects have similar transcallosal interactions from the dominant hemisphere to the nondominant side (Fig. 5, II). Therefore, despite clear activation of the ipsilateral motor cortex on fMRI during left, unilateral finger movement, we found no evidence of ipsilateral direct or indirect corticospinal innervation to the hand muscles (Fig. 5, III, IV, or II and V).

Transcallosal interaction

Anatomically, commissural fibers from the primary motor cortex are presumed to exist in the second quarter of the trunk of the corpus callosum in humans (Meyer et al., 1995, 1998). According to animal studies (Asanuma and Okamoto, 1962; Matsunami and Hamada, 1984), the interhemispheric interaction between hand representations in the primary motor cortices is strong and effective. Stimulation of one motor cortex can cause facilitatory as well as inhibitory effects on the contralateral cortex, and the areas that produce excitatory effects may be small and surrounded by wide areas that cause inhibition. Thus, facilitation cannot be always observed and is easily masked by suppression when strong conditioning stimuli are applied (Chang, 1953). These observations are in line with the conception that most movement-related neurons are sensitive to GABAergic inhibition during voluntary movements (Matsumura et al., 1992) and that the interaction between the cerebral hemispheres is mainly inhibitory (Cook, 1986).

Simple unimanual movements can evoke the activation of both sensorimotor areas in high-resolution electroencephalogram (Urbano et al., 1996) and difficult unilateral motor tasks may evoke contraction of the homologous muscles of the other side, i.e., mirror movements, even in normal adults. Mirror movements are produced by simultaneous activation of both left and right cortices rather than transcallosal activation (Mayston et al., 1999) and transcallosal inhibitory control is important during unimanual or asynchronous movements to prevent undesirable mirror movements and interference from the opposite hemisphere (Danek et al., 1992; Mayston et al., 1999).

The predominantly inhibitory nature of transcallosal interactions is further supported by the finding of large ipsilateral MEPs induced by unilateral TMS in a patient with complete agenesis of the corpus callosum (Ziemann et al.,

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1999). In addition, patients with hemispheric damage can show ipsilateral MEPs to TMS of the unaffected hemisphere more frequently than normal subjects (Carr et al., 1993; Netz et al., 1997). In patients with stroke of the unilateral hemisphere, hyperexcitability of the unaffected motor cortex has been observed (Cicinelli et al., 1997; Traversa et al., 1997; Liepert et al., 2000; Shimizu et al., 2002). Shimizu and colleagues (2002) showed decreased intracortical inhibition with disrupted transcallosal inhibition after unilateral cortical stroke. These observations suggest unmasking of uncrossed, ipsilateral corticospinal pathways and disinhibition of the unaffected motor cortex, presumably because of decreased interhemispheric, transcallosal interaction.

Interhemispheric interaction studied by TMS

Interhemispheric interaction in the human brain has been studied with paired-pulse TMS, also emphasizing the inhibitory interaction between the primary motor areas of both sides (Ferber et al., 1992). Ferbert et al. (1992) proposed that the inhibition occurs at the level of the cerebral cortex, because no inhibition was evoked in motor responses by an anodal electrical test stimulus. Direct recording of the descending corticospinal volleys through cervical epidural electrodes also confirmed that this inhibition occurs at the cortical level (Di Lazzaro et al., 1999). Studies on subjects with lesions in their corpus callosum demonstrated that this inhibition is mediated transcallosally (Meyer et al., 1995, 1998; Boroojerdi et al., 1996). While this inhibition could also be mediated subcortically to some extent (Gerloff et al., 1998), our results are in line with the former studies, showing the correlation between cortical activity and interhemispheric inhibition.

The magnitude of interhemispheric inhibition can vary according to the conditioning stimulus intensity. The interhemispheric inhibition can be equal in both sides with a strong conditioning TMS (Ferber et al., 1992; Ugawa et al., 1993). However, applying a lower intensity of conditioning stimulus, the transcallosal inhibition can be demonstrated to be asymmetrical; the inhibition is stronger after left-side conditioning stimulation than after stimulation of the right, nondominant hemisphere in right-handed subjects (Netz et al., 1995). Such an asymmetry was also shown in our results on subjects without IpsiLM1 (Fig. 4).

Using paired-pulse TMS, interhemispheric facilitation can also be observed at ISIs of 4–6 ms (Hanajima et al., 2001). Slight, but not statistically significant, interhemispheric facilitation was observed at 5 ms after left conditioning TMS in all subjects and also at 5 ms after right conditioning TMS in the subjects without IpsiLM1 (Fig. 4A and B). However, the subjects with IpsiLM1 demonstrated inhibition rather than facilitation at the ISI of 5 ms (Fig. 4B), implying a prominent interhemispheric inhibition of the dominant hemisphere by the nondominant hemisphere.

Correlation between ipsilateral activation and interhemispheric inhibition

One possible way to interpret IpsiLM1 is that the right (contralateral and nondominant) motor cortex promotes the activation in the left (ipsilateral and dominant) hemisphere via transcallosal pathways (Fig. 5, I). Since we found remarkable interhemispheric inhibition in the subjects with IpsiLM1, this ipsilateral activity in the dominant hemisphere could be an inhibitory process relayed from the nondominant side suppressing the dominant hemisphere. This speculation, however, might not be consistent with the observation that the activation of the right motor cortex during ipsilateral right hand movement was not observed in any subject even though the interhemispheric inhibition of the right motor cortex after the TMS on the left motor cortex was remarkable in all subjects (Fig. 4A).

Alternatively, IpsiLM1 might indicate excitatory activity instead of inhibition, since fMRI may demonstrate the deactivated area as a region of decreased cerebral blood flow (Allison et al., 2000). In addition nondominant (left) hand movements may facilitate cortical excitability on the dominant (ipsilateral) motor area of the homologous muscle while opposite may occur during dominant, right hand movements (Leocani et al., 2000; Ziemann and Hallett, 2001). It is possible that the ipsilateral activation in the fMRI study reflects an increased excitability of the ipsilateral (dominant) hemisphere and that strong interhemispheric inhibition is developed in order to suppress such excessive excitability in the subjects with ipsilateral activation. This presumption might account for our observation that right hand movements did not produce ipsilateral activation in any subject, while the interhemispheric inhibition of the right motor cortex after the TMS on the left motor cortex was remarkable in all subjects (Fig. 4A).

Our study can neither provide definite evidence for the etiology of the ipsilateral activation in fMRI during unilateral hand movement nor resolve the question of whether the ipsilateral activation in fMRI is inhibitory or excitatory. However, our findings suggest that IpsiLM1 is not associated with the presence of particularly strong or hyperexcitable ipsilateral uncrossed, descending projections, but rather related to enhanced interhemispheric interaction of the nondominant hemisphere onto the dominant one. It would appear that some subjects with ipsilateral activation during nondominant hand movements would have increased transcallosal inhibition, possibly to suppress excessive activation in the ipsilateral, dominant hemisphere that might lead superfluous movements with the dominant hand.

Acknowledgments

We dedicate this paper to the memory of Dr. Berndt-Ulrich Meyer who, along with his wife, Dr. Simone Röricht, and their two young sons, tragically died in the CrossAir

flight accident near Zürich on Saturday, November 24, 2001. This work was conducted at the Harvard–Thorndike General Clinical Research Center, supported by the National Center for Research Resources (MO1 RR01032). In addition, support is acknowledged from the National Institutes of Health (RO1MH57980, RO1MH60734, RO1EY12091), the Goldberg Foundation (APL), the Dana Foundation (GS), the Lawrence J. and Anne Rubenstein Foundation (GS), and the Mochida Memorial Foundation for Medical and Pharmaceutical Research (MK) and Brain Science Foundation (MK). Dr. Hutchinson was supported by the Clinical Investigator Training Program at Beth Israel Deaconess Medical Center and Harvard Medical School. Dr. Schlaug was supported in part by a Clinical Scientist Development award from the Doris Duke Charitable Foundation.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

1

AQ1—AUTHOR: Pls update

AQ2—AUTHOR: title? OK
