

SUPPRESSION OF THE NON-DOMINANT MOTOR CORTEX DURING BIMANUAL SYMMETRIC FINGER MOVEMENT: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY

Y. ARAMAKI,^{a,b} M. HONDA^{a,c,d} AND N. SADATO^{a,b,e,*}

^aNational Institute for Physiological Sciences, 38 Nishigo-naka, Myodaiji, Okazaki, Aichi 444-8585, Japan

^bResearch Institute of Science and Technology for Society, Japan Science and Technology Agency, Kawaguchi, Japan

^cSolution Oriented Research for Science and Technology, Japan Science and Technology Agency, Kawaguchi, Japan

^dDepartment of Cortical Function Disorders, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Japan

^eDepartment of Functional Neuroimaging, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

Abstract—Patterns of bimanual coordination in which homologous muscles are simultaneously active are more stable than those in which homologous muscles are engaged in an alternating fashion. This may be attributable to the stronger involvement of the dominant motor cortex in ipsilateral hand movements via interaction with the non-dominant motor system, known as neural crosstalk. We used functional magnetic resonance imaging to investigate the neural representation of the interhemispheric interaction during bimanual mirror movements. Thirteen right-handed subjects completed four conditions: sequential finger tapping using the right and left index and middle fingers, bimanual mirror and parallel finger tapping. Auditory cues (3 Hz) were used to keep the tapping frequency constant. Task-related activation in the right primary motor cortex was significantly less prominent during mirror than unimanual left-handed movements. This was mirror- and non-dominant side-specific; parallel movements did not cause such a reduction, and the left primary motor cortex showed no such differential activation across the unimanual right, bimanual mirror, and bimanual parallel conditions. Reducing the contralateral innervation of the left hand may increase the fraction of the force command to the left hand coming from the left primary motor cortex, enhancing the neural crosstalk. © 2006 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: bimanual coordination, neural crosstalk, functional MRI, primary motor cortex, cerebellum, ipsilateral control.

Patterns of bimanual coordination in which homologous muscles are active simultaneously are more stable than those in which homologous muscles are alternately engaged (Swinen et al., 1997). This is demonstrated dramatically by the

*Correspondence to: N. Sadato, 38 Nishigo-naka, Myodaiji, Okazaki, Aichi 444-8585, Japan. Tel: +81-564-55-7841; fax: +81-564-55-7786. E-mail address: sadato@nips.ac.jp (N. Sadato).

Abbreviations: BM, bimanual mirror; BOLD, blood oxygen level-dependent; BP, bimanual parallel; fMRI, functional magnetic resonance imaging; ITI, inter-tap interval; M1, primary motor cortex; UL, unimanual left; UR, unimanual right; 3D, three-dimensional.

0306-4522/06/\$30.00+0.00 © 2006 IBRO. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuroscience.2006.05.030

phase transition during bimanual movement: if a subject performs a movement in the asymmetrical mode, increasing the movement frequency ultimately results in a phase transition toward the more stable mirror-symmetrical mode, but the opposite transition does not occur (Kelso, 1984). This phenomenon has been formalized by the concept of inter-manual crosstalk assuming two independent motor plans (Marteniuk and MacKenzie, 1980). The crosstalk consists of dispatching a fraction of the force command sent to one hand as a mirror image to the other hand (Cattaert et al., 1999).

Interactions between the movements of the hands are assumed to result from crosstalk at multiple levels between the signals controlling them. For low-level crosstalk (Cattaert et al., 1999), the movement parameters of the muscles common to both hands are probably derived via both contralateral and ipsilateral corticospinal tracts to the homologous muscles. The ipsilateral innervation might enhance mirror movement, which is more stable than the asymmetrical parallel movement because there are common parameters for the homologous muscles. Behavioral studies revealed greater ipsilateral deficits in stroke patients with left hemisphere damage than those with right hemisphere damage (Wyke, 1971; Kimura, 1977; Haaland et al., 1987; Haaland and Harrington, 1994). The effects of repetitive transcranial magnetic stimulation (rTMS) on the performance of ipsilateral finger sequences suggest a stronger involvement of the dominant motor cortex in ipsilateral hand movements (Chen et al., 1997). Hence the more stable bimanual mirror movement is attributed to the stronger involvement of the dominant motor cortex in ipsilateral hand movements.

Interhemispheric interaction through the corpus callosum is important for symmetrical movements, as callosotomy patients cannot perform in-phase symmetrical bimanual circle drawing (Kennerley et al., 2002). Paired transcranial magnetic stimulation (TMS) studies provided evidence for clear interhemispheric facilitatory (Ugawa et al., 1993) and inhibitory effects (Ferbert et al., 1992) of the motor cortex, probably through the corpus callosum (Di Lazzaro et al., 1998). The trans-callosal inhibition is asymmetric in right-handers with a stronger inhibition from the left-to-right motor cortex than vice versa (Netz et al., 1995). These findings raise the possibility that the non-dominant M1 is where the high-level cortico-cortical interference from the dominant hemisphere occurs during bimanual mirror movement.

The purpose of the present study was to investigate the neural representation of the crosstalk during mirror

movement. Our hypothesis was that if a fraction of a force command is derived through the ipsilateral pathway from the left M1 during mirror movement, the force command from the right M1 may decrease, as indicated by a decrease in neural activity compared with during unimanual left-hand movement, in which the right M1 can no longer rely on the left M1. As the crosstalk consists of dispatching a fraction of the force command sent to one hand as a mirror image to the other hand (Cattaert et al., 1999), no reduction of right M1 activity was expected during parallel movement. We used functional magnetic resonance imaging (fMRI) to measure the task-related activity and compared the neural activation during unimanual movement with that during bimanual mirror movements.

EXPERIMENTAL PROCEDURES

Participants

Thirteen subjects (age range, 25–38 years; mean age \pm S.D., 30.2 ± 4.41 ; seven men and six women) participated in this study. The subjects were all right-handed according to the Edinburgh handedness inventory (0.89 ± 0.16 , mean \pm S.D.) (Oldfield, 1971). None of the subjects had a history of psychiatric or neurological illness. The protocol was approved by the ethical committee of the National Institute of Physiological Sciences, Japan. All subjects gave their written informed consent for the study.

Experiment

Subjects completed four conditions: sequential finger tapping using the unilateral index and middle fingers of the right (UR) and left (UL) hands, and bimanual finger tapping in the mirror (BM) and parallel (BP) modes. In this study, we defined the mirror condition as symmetric or in-phase movement from homologous effectors; the synchronous tapping of both index fingers alternating periodically with the synchronous tapping of both middle fingers: ($_I \times _I$), ($_M \times _M$), ($_I \times _M$), and so on. The parallel condition was defined as asymmetric or anti-phase movement from homologous effectors; the synchronous tapping of the left middle and the right index fingers, which alternated periodically with the synchronous tapping of the left index and the right middle fingers: ($_M \times _I$), ($_I \times _M$), ($_M \times _I$), and so on (Mechsner et al., 2001). Auditory cues of 3 Hz were used to keep the tapping frequency constant. We confirmed that there was no transition from the parallel to mirror mode at this frequency (Aramaki et al., in press).

Two USB MRI-compatible 10-key pads (TK-UYGT; Elecom, Osaka, Japan) were used to record the finger taps. For right-handed finger taps, keys “1” (for the index finger) and “3” (for the middle finger) of the 10-key pad were used. For the left hand, keys “7” (for the index finger) and “9” (for the middle finger) of another 10-key pad were pressed.

The fMRI sessions consisted of alternating four resting and three task epochs. Each epoch lasted 30 s. Each task condition (BM, BP, UL, UR) was performed during separate sessions. To minimize head motion, we used tight but comfortable foam padding placed around the subject's head. An LCD projector (DLA-M200L; Victor, Yokohama, Japan) located outside and behind the scanner projected a crosshair through another waveguide to a translucent screen, which the subjects viewed via a mirror attached to the head coil of the MRI scanner. The subjects were required to fixate the crosshair on the screen, and hence could not see their hands. The color of the fixation point in turn appeared green (“go”) and red (“stop”) every 30 s. The auditory cue was provided continuously throughout the scanning session. The session was repeated twice for each condition. The order of the conditions in the experiment was counterbalanced across the

subjects. Presentation software (Neurobehavioral Systems, Albany, CA, USA) was used to provide the auditory cues and to record the timing of the key presses at 1000 Hz.

Calculation of the deviation of the inter-tap interval (ITI)

To evaluate the accuracy of the tapping rhythm in each condition, the deviation of the ITI from an identical ITI (333 ms) was calculated for each hand. For the right hand tapping, we excluded two subjects from the performance analysis because of technical difficulties in the measurement of their tapping timing.

fMRI data acquisition and analysis

A time-course series of 71 volumes was acquired in one session using T2*-weighted gradient echo-planar imaging (EPI) sequences with a 3.0 Tesla MR imager (Allegra; Siemens, Erlangen, Germany). Each volume consisted of 44 axial slices with a slice thickness of 3 mm and no gap, to include the entire cerebral cortex and cerebellum. The time-interval between two successive acquisitions of the same image was 3000 ms, the echo time 30 ms, and the flip angle was 85 degrees. The field of view (FOV) was 192 mm and the in-plane matrix size was 64×64 pixels, with a pixel dimension of 3×3 mm.

For anatomical reference, T1-weighted images were obtained from each subject with location variables identical to those of the EPIs. In addition, three-dimensional (3D) high-resolution T1-weighted images were obtained. A total of 192 transaxial slices were acquired. The in-plane matrix size was 256×256 pixels, the slice thickness was 1 mm and the pixel size was 0.898×0.898 mm.

The first six volumes of each fMRI session were discarded because of unsteady magnetization and the remaining 65 volumes per subject were used for the analysis. The data were analyzed using statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995a,b) implemented in Matlab (Mathworks, Sherborn, MA, USA). Following realignment of the fMRI data, the 3D high-resolution T1-image was coregistered to the fMRI data using the anatomical T1-weighted image with identical locations to the fMRI data. The parameters for affine and nonlinear transformation into the Montreal Neurological Institute (MNI) T1-template image were estimated using the 3D high-resolution T1-image with least-squares means (Friston et al., 1995a). The parameters were then applied to the realigned fMRI data. The anatomically normalized fMRI data were filtered using a Gaussian kernel of 6 mm (full width at half maximum) in the x, y, and z axes.

Statistical analysis was conducted on the imaging data of all 13 subjects at two levels. First, individual task-related activation was evaluated using a general linear model (Friston et al., 1995b). Second, in order to make inferences at the population level, individual data were summarized and incorporated into a random-effect model (Friston et al., 1999). The spatial extent of the activation foci depicted by the height threshold of $P < 0.001$ (uncorrected for multiple comparisons) was then tested, based on the theory of Gaussian random fields, which considers clusters as “rare events” that occur in a whole brain according to the Poisson distribution (Friston et al., 1996). This procedure is used to control the family-wise error rate (or to correct for multiple comparisons) at the cluster level. The statistical threshold was set at $P < 0.05$.

RESULTS

Behavior of the hand movement

When the average deviations of the ITI from the ideal ITI (333 ms) for the left hand were compared, there were no significant differences between them ($F(2,24) = 2.45$; $P =$

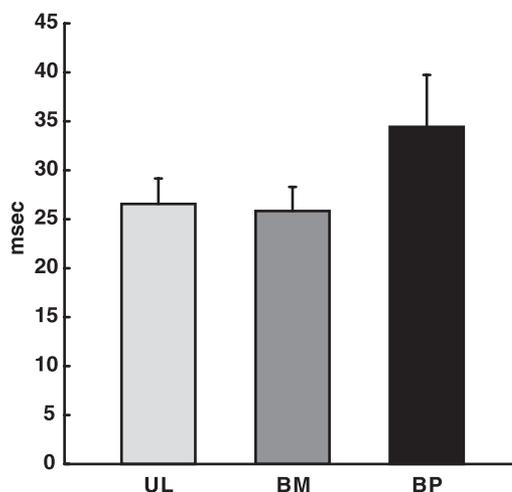


Fig. 1. Deviation of the left hand inter-tap-interval from the ideal ITI (333 ms) in each condition: UL (light gray), BM (dark gray), and BP (black). There is no significant difference between the conditions, indicating that the left hand movement itself does not differ between the three conditions.

0.108; repeated measures ANOVA, Fig. 1). There was also no significant difference between the conditions for the right-hand tapping deviation from the ideal ITI ($F(2,20)=1.068$; $P=0.362$, repeated measures ANOVA).

The primary sensorimotor cortex

As shown in Fig. 2, the task-related activation in the right primary motor cortex (M1) and in the left cerebellum during the BM condition was significantly weaker than during the UL condition ($P<0.05$ corrected at the cluster level). To investigate whether this effect was specific to the mirror mode, we plotted the increment of the brain activity in the right M1, defined as the local maximum highlighted by the UL-BM contrast, in each condition using beta values. The beta value is a regression coefficient in a general linear model. Using the block design employed in this experiment, the amplitude and form of the regressors are common to all conditions. Hence the beta values can be compared between conditions to indicate the increment of the brain activity from the baseline condition. The beta value of the right M1 in the UL condition was significantly larger than that in the BM condition (Fig. 3, upper right, $UL=0.927\pm0.200$ (mean \pm S.E.), $BM=0.479\pm0.191$; $F(1,12)=51.781$, repeated measures ANOVA with a predefined contrast, $P<0.001$). In contrast, the BP condition did not show such a reduction ($UL=0.927\pm0.200$, $BP=0.785\pm0.257$; $F(1,12)=1.178$, $P=0.299$). Thus, this effect in the right M1 was BM-specific. Moreover, the activation of the right M1 in the BP condition was significantly larger than in the BM condition ($BP=0.785\pm0.257$, $BM=0.479\pm0.191$; $F(1,12)=6.459$, $P=0.026$). The left M1, the coordinates of which were defined as those that were mirror-symmetric to those of the right M1, was activated by the UR, BM, and BP conditions to a similar degree ($UR=1.170\pm0.377$, $BM=1.134\pm0.241$, $BP=1.392\pm0.252$). There was no significant reduction during the BM condition compared with

the UR condition ($F(1,12)=0.011$, $P=0.918$) or with BP ($F(1,12)=3.794$, $P=0.075$) (Fig. 3, upper left). Thus, the effect can also be shown to be specific to the non-dominant hand. The right M1 was suppressed by UR ($P=0.046$, one-sample *t*-test), whereas the left M1 did not show such suppression during the UL condition. Fig. 4 shows the typical fitted time courses of the activity of the right M1 in three subjects, clearly demonstrating that the task-related response in the BM condition was smaller than that in the UL and in the BP conditions.

Cerebellum

The same phenomenon was observed in the cerebellum contralateral to M1 (Fig. 3, lower left). The beta value of the left cerebellum in the UL condition was significantly larger than that in the BM condition ($UL=1.352\pm0.319$, $BM=0.788\pm0.194$; $F(1,12)=26.657$, $P<0.001$). On the contrary, the BP condition did not cause such a reduction ($UL=1.352\pm0.319$, $BP=1.447\pm0.273$, $F(1,12)=0.206$, $P=0.658$). The beta value of the left cerebellum in the BP condition was significantly larger than in the BM condition ($BP=1.447\pm0.273$, $BM=0.788\pm0.194$; $F(1,12)=11.049$, $P=0.006$). On the other hand, no difference in activation was observed in the right cerebellum between the UR and BM conditions ($UR=0.868\pm0.282$, $BM=1.274\pm0.240$; $F(1,12)=1.6$, $P=0.23$), or between the UR and BP conditions ($UR=0.868\pm0.282$, $BP=1.548\pm0.362$; $F(1,12)=3.365$, $P=0.091$) (Fig. 3, lower right). Thus the effect is specific to the non-dominant hand.

UL > BM

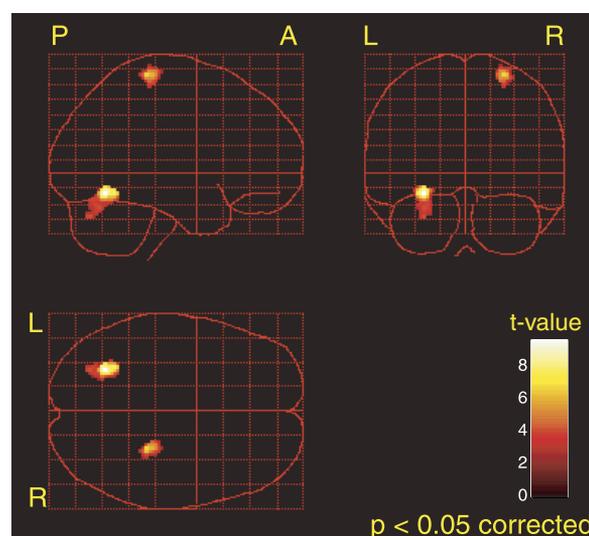


Fig. 2. More prominent activation during the UL than the BM condition as revealed by group analysis with the random effects model. The results shown are statistically significant at a level of $P<0.05$, corrected for multiple comparisons at the cluster level. The 3D information was collapsed into 2D sagittal, coronal, and transverse images (i.e. the maximum intensity projections viewed from the right, back, and top of the brain).

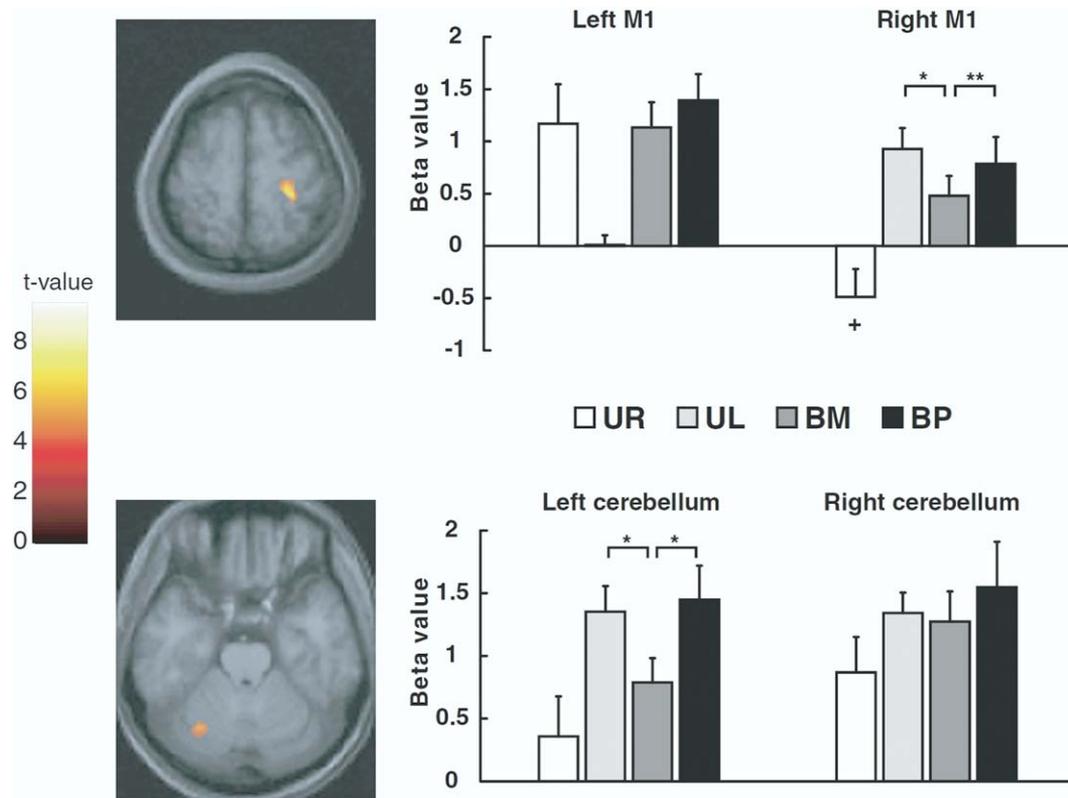


Fig. 3. More prominent activation during the UL than the BM condition superimposed on a transaxial high resolution MRI averaged across the 13 subjects of the present study, at the level of $z=68$ mm (upper left) and $z=-24$ (lower left). The color bar indicates the t -values. The signal intensity change (beta value) from the baseline in the right M1 ($-26, -34, 68$) (upper middle), the left M1 (upper right), the left cerebellum (lower left) and the right cerebellum (lower right) in each condition are plotted. The white, light gray, dark gray, and black bars correspond to the UR, UL, BM, and BP conditions, respectively. * $P<0.01$ (repeated measures ANOVA with predefined contrast), ** $P<0.05$ (repeated measures ANOVA with predefined contrast), + $P<0.05$ (one-sample t -test).

DISCUSSION

Previous neuroimaging studies of bimanual coordination aimed to depict the specific areas involved in bimanual coordination by looking at activation patterns during different modes of coordination (Sadato et al., 1997; Stephan et al., 1999a,b; Ullen et al., 2003; Debaere et al., 2004) or by making a comparison between bi- and single-limb coordination (bimanual vs. unimanual) (Koeneke et al., 2004). The candidate areas for the control of bimanual coordination are the supplementary motor area (SMA), primary sensorimotor area (SM1), premotor cortex, cingulate motor area, posterior parietal cortex, basal ganglia, and cerebellum. Thus, the control of bimanual coordination cannot be assigned to a single locus; rather, it seems to involve a distributed network in which interactive processes take place between many neural assemblies to ensure efferent organization and sensory integration (Swinnen, 2002). Thus, the delineation of the neural interactions between distributed areas is an important issue to be solved. Recently, Aramaki et al. (in press) showed that the phase transition from the bimanual parallel mode to the more stable mirror mode is related to the transient activation of the distributed networks upstream of the M1. The activation related to the phase transition was right-lateralized, and hence the transitional effect may work from the left to the right hemisphere. In the present study, we tried to identify the

neural interaction which makes the mirror mode stable. Because our hypothesis was that the asymmetric interhemispheric interaction during the mirror mode occurs in the right M1, we specifically compared left unimanual movement with bimanual mirror movement.

It is well known that the phase transition from the parallel to the mirror mode is frequency-dependent: the faster the movement, the earlier the phase transition occurs (Kelso, 1984). Hence it is conceivable that the crosstalk effect would be larger at a higher frequency of movement. Our previous study showed that, at 3.8 Hz, participants could only maintain the parallel mode for about 10 s (Aramaki et al., in press). Therefore, to maintain the parallel mode for 30 s while maximizing the effect of crosstalk, we used a frequency of 3 Hz.

The performance of subjects in terms of the variability of the ITI did not differ significantly across the conditions. In contrast, previous studies have reported a "bimanual advantage": the variability of tapping behavior becomes smaller during synchronous bimanual tapping than during unimanual tapping (Helmuth and Ivry, 1996; Ivry and Richardson, 2002). This difference may be because previous studies utilized self-paced movement, whereas the present study adopted auditory-cued movements, which might have masked the bimanual advantage.

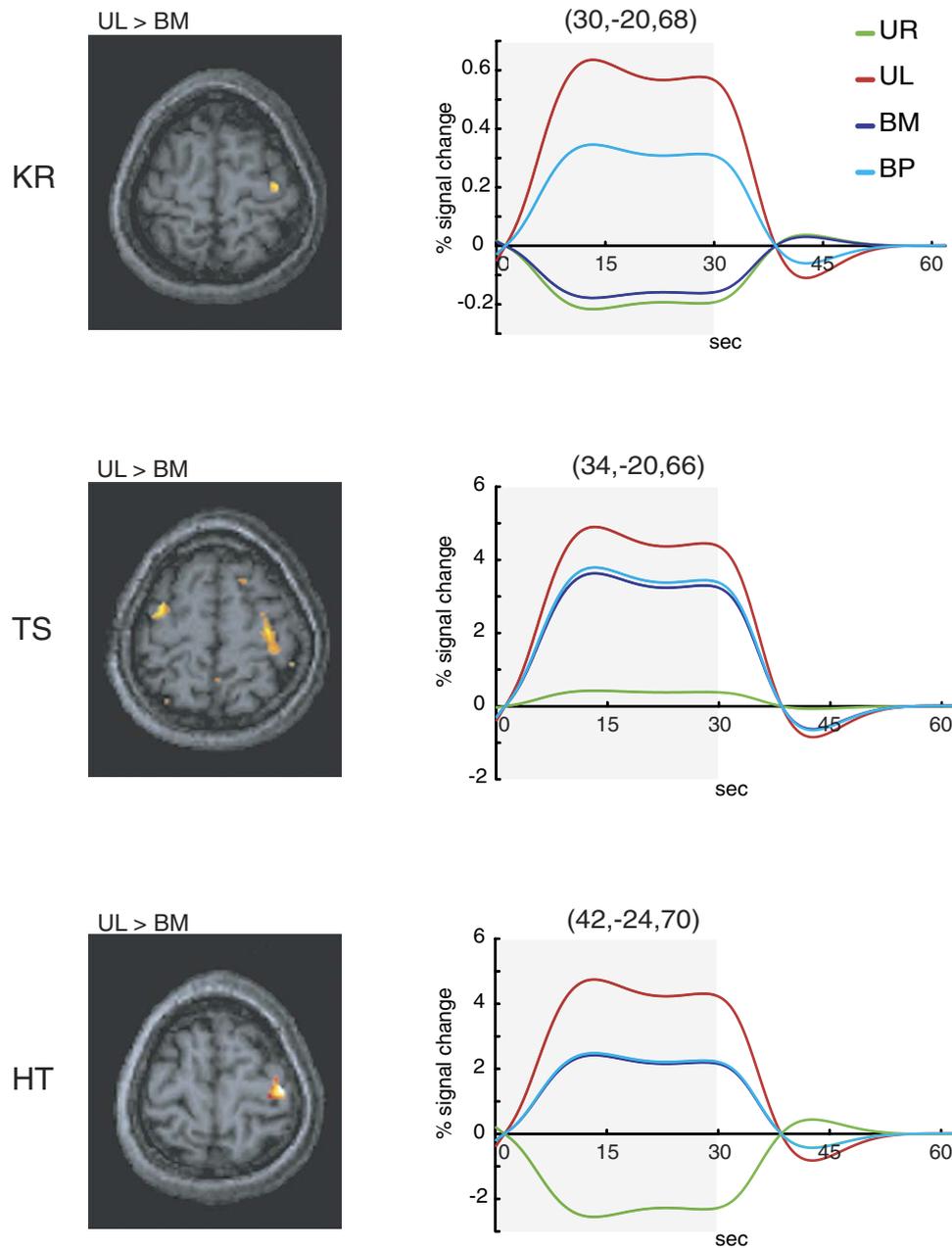


Fig. 4. Plot of the fitted hemodynamic response in the right M1 in each condition for the three individual subjects. The green, red, dark blue, and light blue lines correspond to the UR, UL, BM, and BP conditions, respectively. The light gray zone represents the task period.

The right M1 revealed a task-related decrease in the blood oxygen level–dependent (BOLD) signal during the UR condition whereas the left M1 did not show a similar decrease during the UL condition. Assuming that inhibitory control is expressed as a decrease in the BOLD signal (Allison et al., 2000; Waldvogel et al., 2000; Hamzei et al., 2002; Stefanovic et al., 2004; Newton et al., 2005), this is consistent with the idea that the (dominant) left M1 of a right-handed person inhibits the right M1 more effectively than vice versa (Netz et al., 1995). This asymmetric interhemispheric interaction during unimanual movement is likely to be modified during biman-

ual coordination. Our hypothesis was that the high-level cortico-cortical interaction specific to mirror movements is exerted on the neural substrates of unimanual movements, in particular M1, which specifies the hand-specific movement parameters.

As expected, the right M1 was less prominently activated during bimanual mirror movements compared with contralateral unimanual movements, but the left M1 was not. If, during mirror movement, a fraction of any force command is sent through the ipsilateral pathway from the left M1, the “demand” for the force command from the right M1 decreases such that the same perfor-

mance is achieved. Although the neuronal mechanism underlying the “demand” for the force command from the right M1 remains speculative, there are some pertinent electrophysiological findings. Using TMS, Ziemann and Hallett (2001) found asymmetric ipsilateral innervation of M1. They showed that finger movements resulted in an increase in the amplitude of the motor evoked potential (MEP) for the hand not performing the task. This increase was significantly less when the right rather than the left hand was used. This difference was seen only in muscles homologous to the primary task muscles. They interpreted this finding as evidence of more prominent ipsilateral innervation of the left M1 than the right M1. As the asymmetry could not be explained by changes in excitability at the level of the spinal motoneuron (F-wave measurements), they concluded that the asymmetric ipsilateral innervation and the effective transcallosal inhibitory control of M1 are closely intertwined, representing one property of motor dominance (Ziemann and Hallett, 2001). This notion is relevant for bimanual coordination in light of a recent study by Kennerley et al. (2002) reporting that callosotomy patients cannot perform even in-phase bimanual circle drawing. In these patients, phase transitions were observed from anti- to in-phase and vice versa, whereas controls made the transition only from anti- to in-phase. Therefore, in normal subjects, the interaction of the bilateral hemispheres through the corpus callosum is important for the enhanced stability of in-phase symmetrical movements.

Less prominent activity in the right M1 during BM compared with UL was shown to be mirror-specific, because parallel movements did not show such a reduction in activity. This might be explained by the previous electrophysiological finding that the interhemispheric suppression during unimanual movement is specific to the homologous muscles (Ziemann and Hallett, 2001). During the mirror movement, the homologous muscles are activated simultaneously; hence the effect of the interhemispheric suppression from both right-to-left and left-to-right may be weighted to cause net asymmetric interhemispheric inhibition, represented by the decreased activity of the right M1 while left M1 activity remained unchanged (Fig. 3). During parallel movement, non-homologous muscles were activated simultaneously and therefore suppression did not occur. This hypothetical transcallosal interaction during mirror movements might represent the balance between the ipsilateral force command from the left M1 and the “demand” of the right M1.

Similar to M1, the reduction of activation in the cerebellum is mirror-specific: unlike M1, the cerebellar reduction is left-side specific. Considering the closed loop between the M1 and the cerebellum (Kelly and Strick, 2003) and the fact that the M1 controls the contralateral side of the body while the cerebellum controls the ipsilateral side of the body, this correlated reduction in the left cerebellum may be caused by the reduction in activation of the right M1.

CONCLUSION

In conclusion, during mirror movements, the movement parameters of homologous muscles are specified in the left M1 and derived through the ipsilateral corticospinal pathway while the right M1 is suppressed transcallosally. As a result, during symmetrical bimanual movement the non-dominant motor system seems to entrust a part of the control of the non-dominant hand to the dominant motor system via the uncrossed efferent pathway.

Acknowledgments—This study was supported by a Grant-in-Aid for Scientific Research S#1710003 (N.S.) from the Japan Society for the Promotion of Science, and by Special Coordination Funds for Promoting Science and Technology 018#17021045 (N.S.) from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government, and by Sasakawa Grants for Science Fellows, the Japan Science Society (Y.A.).

REFERENCES

- Allison JD, Meador KJ, Loring DW, Figueroa RE, Wright JC (2000) Functional MRI cerebral activation and deactivation during finger movement. *Neurology* 54:135–142.
- Aramaki Y, Honda M, Okada T, Sadato N. Neural correlates of the spontaneous phase transition during bimanual coordination. *Cereb Cortex*, in press.
- Cattaert D, Semjen A, Summers JJ (1999) Simulating a neural cross-talk model for between-hand interference during bimanual circle drawing. *Biol Cybern* 81:343–358.
- Chen R, Gerloff C, Hallett M, Cohen LG (1997) Involvement of the ipsilateral motor cortex in finger movements of different complexities. *Ann Neurol* 41:247–254.
- Debaere F, Wenderoth N, Snaert S, Van Hecke P, Swinnen SP (2004) Cerebellar and premotor function in bimanual coordination: parametric neural responses to spatiotemporal complexity and cycling frequency. *Neuroimage* 21:1416–1427.
- Di Lazzaro V, Oliviero A, Profice P, Saturno E, Pilato F, Insola A, Mazzone P, Tonali P, Rothwell JC (1998) Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. *Electroencephalogr Clin Neurophysiol* 109:397–401.
- Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. *J Physiol* 453:525–546.
- Friston KJ, Ashburner J, Poline JB, Frith CD, Heather JD, Frackowiak RSJ (1995a) Spatial registration and normalization of images. *Hum Brain Mapp* 2:165–189.
- Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ (1995b) Statistical parametric maps in functional imaging: A general linear approach. *Hum Brain Mapp* 2:189–210.
- Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD (1996) Detecting activations in PET and fMRI: levels of inference and power. *Neuroimage* 4:223–235.
- Friston KJ, Holmes AP, Worsley KJ (1999) How many subjects constitute a study? *Neuroimage* 10:1–5.
- Haaland KY, Harrington DL (1994) Limb-sequencing deficits after left but not right hemisphere damage. *Brain Cogn* 24:104–122.
- Haaland KY, Harrington DL, Yeo R (1987) The effects of task complexity on motor performance in left and right CVA patients. *Neuropsychologia* 25:783–794.
- Hamzei F, Dettmers C, Rzanny R, Liepert J, Buchel C, Weiller C (2002) Reduction of excitability (“inhibition”) in the ipsilateral primary motor cortex is mirrored by fMRI signal decreases. *Neuroimage* 17:490–496.

- Helmuth LL, Ivry RB (1996) When two hands are better than one: Reduced timing variability during bimanual movements. *J Exp Psychol Hum Percept Perform* 22:278–293.
- Ivry RB, Richardson TC (2002) Temporal control and coordination: The multiple timer model. *Brain Cogn* 48:117–132.
- Kelly RM, Strick PL (2003) Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *J Neurosci* 23:8432–8444.
- Kelso JA (1984) Phase transitions and critical behavior in human bimanual coordination. *Am J Physiol* 246:R1000–R1004.
- Kennerley SW, Diedrichsen J, Hazeltine E, Semjen A, Ivry RB (2002) Callosotomy patients exhibit temporal uncoupling during continuous bimanual movements. *Nat Neurosci* 5:376–381.
- Kimura D (1977) Acquisition of a motor skill after left-hemisphere damage. *Brain* 100:527–542.
- Koeneke S, Lutz K, Wustenberg T, Jancke L (2004) Bimanual versus unimanual coordination: what makes the difference? *Neuroimage* 22:1336–1350.
- Marteniuk RG, MacKenzie CL (1980) Information processing in movement organization and execution. In: *Attention and performance VIII* (Nickerson R, ed), pp 29–57. Hillsdale: Erlbaum.
- Mechsner F, Kerzel D, Knoblich G, Prinz W (2001) Perceptual basis of bimanual coordination. *Nature* 414:69–73.
- Netz J, Ziemann U, Homberg V (1995) Hemispheric asymmetry of transcallosal inhibition in man. *Exp Brain Res* 104:527–533.
- Newton JM, Sunderland A, Gowland PA (2005) fMRI signal decreases in ipsilateral primary motor cortex during unilateral hand movements are related to duration and side of movement. *Neuroimage* 24:1080–1087.
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97–113.
- Sadato N, Yonekura Y, Waki A, Yamada H, Ishii Y (1997) Role of the supplementary motor area and the right premotor cortex in coordination of bimanual movements. *J Neurosci* 17:9667–9674.
- Stefanovic B, Warnking JM, Pike GB (2004) Hemodynamic and metabolic responses to neuronal inhibition. *Neuroimage* 22:771–778.
- Stephan KM, Binkofski F, Posse S, Seitz RJ, Freund HJ (1999a) Cerebral midline structures in bimanual coordination. *Exp Brain Res* 128:243–249.
- Stephan KM, Binkofski F, Halsband U, Dohle C, Wunderlich G, Schnitzler A, Tass P, Posse S, Herzog H, Sturm V, Zilles K, Seitz RJ, Freund HJ (1999b) The role of ventral medial wall motor areas in bimanual co-ordination. A combined lesion and activation study. *Brain* 122 (Pt 2):351–368.
- Swinnen SP (2002) Intermanual coordination: from behavioural principles to neural-network interactions. *Nat Rev Neurosci* 3:348–359.
- Swinnen SP, Jardin K, Meulenbroek R, Dounskaia N, Hofkens-van den Brandt M (1997) Egocentric and allocentric constraints in the expression of patterns of interlimb coordination. *J Cogn Neurosci* 9:348–377.
- Ugawa Y, Hanajima R, Kanazawa I (1993) Interhemispheric facilitation of the hand area of the human motor cortex. *Neurosci Lett* 160:153–155.
- Ullen F, Forssberg H, Ehrsson HH (2003) Neural networks for the coordination of the hands in time. *J Neurophysiol* 89:1126–1135.
- Waldvogel D, van Gelderen P, Muellbacher W, Ziemann U, Immisch I, Hallett M (2000) The relative metabolic demand of inhibition and excitation. *Nature* 406:995–998.
- Wyke M (1971) The effects of brain lesions on the performance of bilateral arm movements. *Neuropsychologia* 9:33–42.
- Ziemann U, Hallett M (2001) Hemispheric asymmetry of ipsilateral motor cortex activation during unimanual motor tasks: further evidence for motor dominance. *Clin Neurophysiol* 112:107–113.

APPENDIX

Supplementary data associated with this article can be found, in the online version, at doi: [10.1016/j.neuroscience.2006.05.030](https://doi.org/10.1016/j.neuroscience.2006.05.030).

(Accepted 12 May 2006)
(Available online 21 June 2006)