

Memory Formation in the Motor Cortex Ipsilateral to a Training Hand

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Cortical reorganization within the primary motor cortex (M1) contralateral to a practicing hand has been extensively investigated. The extent to which the ipsilateral M1 participates in these plastic changes is not known. Here, we evaluated the influence of unilateral hand practice on the organization of the M1 ipsilateral and contralateral to the practicing hand in healthy human subjects. Index finger movements elicited by single-pulse transcranial magnetic stimulation (TMS) delivered to each M1 were evaluated before and after practice of unilateral voluntary index finger abduction motions. Practice increased the proportion and acceleration of TMS-evoked movements in the trained direction and the amplitude of motor-evoked potentials (MEPs) in the abduction agonist first dorsal interosseous (FDI) muscle in the practicing hand and decreased the proportion and acceleration of TMS-evoked abduction movements and MEP amplitudes in the abduction agonist FDI in the opposite resting hand. Our findings indicate that unilateral hand practice specifically weakened the representation of the practiced movement in the ipsilateral M1 to an extent proportional to the strengthening effect in the contralateral M1, a result that varied with the practicing hand's position. These results suggest a more prominent involvement of interacting bilateral motor networks in motor memory formation and probably acquisition of unimanual motor skills than previously thought.

Keywords: inhibition, ipsilateral M1, motor learning, plasticity, TMS, training

Introduction

Skill acquisition is accomplished through repetition, which in turn leads to performance improvements (Shadmehr and Mussa-Ivaldi 1994; Nudo, Milliken, et al. 1996; Bays and Wolpert 2007). Encoding of motor memories in the primary motor cortex (M1) may represent one of the steps preliminary to the acquisition of a motor skill (Donchin et al. 2002; Krakauer and Shadmehr 2006). For example, practice of finger movements in a particular direction leaves a short-lasting memory trace in the contralateral M1, as evidenced by an increased probability, at the end of the training period, that transcranial magnetic stimulation (TMS) applied over M1 will elicit movements in the practiced direction (Classen et al. 1998). This cortical reorganization associated with practice (Nudo, Wise, et al. 1996; Classen et al. 1998) is thought to engage long-term potentiation-like mechanisms (Butefisch et al. 2000) that could support learning and memory processes (Rioullet-Pedotti et al. 1998; Sawaki et al. 2002).

In addition to changes in the M1 contralateral to a practicing hand, it has been reported that the M1 ipsilateral to a hand performing a novel motor task is active to various degrees (Kawashima et al. 1994; Chen et al. 1997) and that this activity decreases progressively as the task becomes overlearned (Daselaar et al. 2003; Rossini et al. 2003; Bischoff-Grethe et al. 2004). This activation has been interpreted, depending on the context, as a possible epiphenomenon of task complexity (Chen et al. 1997; Hummel et al. 2003; Rossini et al. 2003; Verstynen et al. 2005), as erroneous localization of a predominantly dorsal premotor activation (Hanakawa et al. 2005), or as an active contribution to the learning effort (Grafton et al. 2002).

Besides, previous studies evaluated changes in corticomotor excitability of the ipsilateral M1 during performance of a unilateral motor task by means of TMS and reported both inhibitory (Leocani et al. 2000; Duque, Mazzocchio, et al. 2005; Koch et al. 2006) and facilitatory (Muellbacher et al. 2000; Hortobagyi et al. 2003) effects. A possible explanation for these conflicting results during task performance is that the relative net effect of performing a unilateral hand movement on corticomotor excitability of the other hand varies from inhibitory to facilitatory depending on the behavioral set (Liepert et al. 2001; Sohn et al. 2003; Perez et al. 2007; Perez et al. forthcoming). It remains to be determined whether changes in the organization of M1 ipsilateral to a moving hand, so far identified during unilateral movements, persist after the end of a training period. In other words, it would be useful to determine if unilateral hand training, in addition to encoding a memory trace in the contralateral M1 (Classen et al. 1998), elicits reorganizational changes in the ipsilateral M1 and if so the characteristics or specificity of this form of use-dependent plasticity. Understanding these characteristics could potentially strengthen the design of emerging neurorehabilitative interventions in the clinical arena (Whitall et al. 2000; Wolf et al. 2006).

In summary, the functional details of reorganizational changes in the ipsilateral M1 after motor training are incompletely understood. To address this issue, we utilized an experimental protocol that permits the evaluation of movement kinematics and motor-evoked responses elicited by single-pulse TMS applied over the human M1 (Classen et al. 1998). Our main findings were that unilateral motor practice encodes reciprocal memory traces in both M1s, characterized by strengthening of the representation of the practiced movement in the M1 contralateral to the practicing hand and by reduction of the mirror movement representation in the opposite M1, an effect that varied in magnitude with the practicing hand's position.

Materials and Methods

Subjects

Fifteen healthy volunteers (9 women and 6 men; 33.3 ± 2.2 years) participated in Session 1, 9 of whom were also involved in Sessions 2 and/or 3 ($n = 8$ in each session) provided that 1) TMS applied over M1 elicited isolated and consistent contralateral abductions of the nondominant index finger and 2) they were able to perform brisk voluntary abduction movements of the dominant index finger. All participants gave written informed consent, and the Institutional Review Board of the National Institute of Neurological Disorders and Stroke approved the study protocol. Two individuals (no. 9 and no. 11 in Tables 1–3) were left-handed according to the Edinburgh handedness inventory (Oldfield 1971).

Subjects sat comfortably with both forearms supported on an armrest adapted for each individual. The practice of the dominant index finger was performed with the hand positioned palm down (Session 1) or turned at 90° thumb up (Sessions 2 and 3), and the nondominant nonpracticing hand was always placed palm down at rest (Fig. 1*a*). The 3 sessions were performed on separate days. The index fingers were kept completely unrestrained, and the 3 last fingers of each hand were attached to the armrest with tape.

Motor Practice

Preceding practice, the optimal scalp positions for induction of contralateral index finger movements with the lowest stimulus intensity were determined and marked on the scalp to ensure identical placement of the coil throughout the experiment. This technique has proven reliable in the past to ensure stable positioning of the coil location in experimental designs requiring several TMS testing blocks (Gilio et al. 2003; Duque, Vandermeeren, et al. 2005; Pal et al. 2005). Applied in this way, TMS induced abduction movements in the nondominant index finger of all subjects (inclusion criteria, see above). In Session 1, we tested the hypothesis that TMS-evoked abduction movements in the nondominant index finger could be altered by practice of the dominant index finger consisting of repetition of index finger abductions (mirroring the direction of TMS-evoked abduction movements in the nondominant hand), as shown in Figure 1*a*, Session 1. In 2 additional experiments performed on 2 separate days in a randomized order (4 subjects performed Session 3 before Session 2, whereas the others performed Session 2 before Session 3), the

practicing hand was turned at 90° thumb up to investigate the effect of the same abduction movements performed in a direction different from that in Session 1 (Fig. 1*a*, Session 2) or of flexion movements performed toward the midline (mirroring the direction of TMS-evoked abduction movements in the nondominant hand as in Session 1, Fig. 1*a*, Session 3). The practiced movements were paced at 1 Hz, and each practice session lasted for 30 min, a duration sufficient to encode a memory trace that reflects the kinematic details of the trained motions in the cortical representation of the practicing finger (Classen et al. 1998). Accuracy and consistency of practiced movements were monitored online by the investigators, and, if necessary, instructions were repeated to the subject. Additional measurements were obtained all along experimental sessions to calculate offline the strength (length of the acceleration vector) and accuracy (dispersion and angular deviation from the instructed practice direction) of the training movements (see Table 1 for individual data on practice kinematics).

Transcranial Magnetic Stimulation

The effect of practice was investigated with the subjects at rest by applying TMS to both M1s before and after practice with the 2 hands palm down (Fig. 1*b*). This hand position was used for testing pre- and posttraining TMS-evoked index finger movement directions and motor responses in all 3 sessions, even when practice was performed with the hand turned at 90° thumb up in Sessions 2 and 3. TMS was applied by means of a figure-of-8 magnetic coil (diameter of wings 70 mm) connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The coil was placed tangentially on the scalp with the handle pointing backward and laterally at a 45° angle away from the midline, approximately perpendicular to the central sulcus (Werhahn et al. 1994). The hot spot was defined for both M1s as the optimal position for eliciting an isolated and consistent contralateral index finger movement. The resting motor threshold (rMT) was defined, at the hot spot, as the minimal TMS intensity needed to elicit motor-evoked potentials (MEPs) larger than $50 \mu\text{V}$ peak-to-peak in the relaxed first dorsal interosseous (FDI) in 5 out of 10 consecutive trials. The TMS intensity was then adjusted to elicit mild index finger movements in all trials in each of the 2 hands. Same intensities (% output) were used during pre- and postdeterminations in all 3 sessions (see Table 2). Sixty TMS pulses were delivered to each M1 at 0.2 Hz before and after each practice session to determine TMS-evoked finger movement directions and MEP amplitudes in both hands according to a well-established protocol (Classen et al. 1998).

Table 1

Individual practice movement kinematics

Subjects	Motor practice								
	Dispersion ($^\circ$)			Deviation ($^\circ$)			Acceleration vector length		
	Session 1 ($n = 15$)	Session 2 ($n = 8$)	Session 3 ($n = 8$)	Session 1 ($n = 15$)	Session 2 ($n = 8$)	Session 3 ($n = 8$)	Session 1 ($n = 15$)	Session 2 ($n = 8$)	Session 3 ($n = 8$)
1	12.54	16.62	15.65	10.34	14.17	38.64	36.21	29.94	50.62
2	9.12	14.55	19.88	24.01	3.03	46.49	52.15	45.73	43.40
3	9.38	—	13.08	2.04	—	24.24	13.45	—	40.16
4	9.53	14.99	17.06	29.15	25.41	3.75	33.27	24.73	34.73
5	11.58	7.80	5.99	2.63	21.31	43.45	53.65	47.64	80.59
6	15.48	—	—	13.99	—	—	51.51	—	—
7	44.14	15.25	17.10	38.87	68.43	30.46	34.65	39.81	34.21
8	11.61	10.66	13.49	34.92	62.29	61.34	16.47	46.52	72.95
9	24.60	—	—	65.69	—	—	55.18	—	—
10	25.12	6.15	—	42.87	70.27	—	55.29	59.64	—
11	17.54	—	—	10.97	—	—	64.11	—	—
12	18.50	—	—	14.50	—	—	42.49	—	—
13	28.07	—	—	40.14	—	—	35.81	—	—
14	12.65	—	—	28.37	—	—	36.73	—	—
15	10.55	10.62	14.60	3.61	5.51	68.75	46.50	58.72	65.48
Mean (SE)	17.4 (2.5)	12.1 (1.4)	14.6 (1.5)	24.1 (4.7)	33.8 (10.1)	39.6 (7.3)	41.8 (3.7)	44.1 (4.4)	52.8 (6.4)

Note: Practice movement kinematics of all individuals in the 3 practice sessions. The dispersion of the trained movements around the instructed direction, the angular deviation of trained movements from the optimal practice direction, and the length of the acceleration vector were computed to assess the accuracy and strength of the motor practice in the 3 sessions (see Materials and Methods for detail). Fifteen subjects participated in Session 1. Nine of them participated in Sessions 2 and/or 3. Em dash indicates subjects who did not participate in Sessions 2 and/or 3.

Table 2
rMT and TMS intensity

	Nonpracticing hand						Practicing hand					
	rMT (% output)			TMS intensity (% output)			rMT (% output)			TMS intensity (% output)		
	Session 1 (n = 15)	Session 2 (n = 8)	Session 3 (n = 8)	Session 1 (n = 15)	Session 2 (n = 8)	Session 3 (n = 8)	Session 1 (n = 15)	Session 2 (n = 8)	Session 3 (n = 8)	Session 1 (n = 15)	Session 2 (n = 8)	Session 3 (n = 8)
Pre	46 ± 2.2	41 ± 1.9	43 ± 3.5	58 ± 2.8	50 ± 3.4	53 ± 4.3	44 ± 2.1	42 ± 3.6	42 ± 3.5	55 ± 2.5	54 ± 4.0	53 ± 3.8
Post	47 ± 2.1	41 ± 1.9	44 ± 3.4	58 ± 2.8	50 ± 3.4	53 ± 4.3	43 ± 1.9	41 ± 3.1	41 ± 3.0	55 ± 2.5	54 ± 4.0	53 ± 3.8

Note: rMT and TMS intensity used for stimulation of the cortical representation of the practicing and nonpracticing index fingers before and after motor practice in the 3 sessions.

Electromyography and Kinematic Recording Procedures

Electromyography (EMG) activity and MEPs were recorded bilaterally from surface electrodes placed over the FDI (MEP_{FDI}), acting as abduction (and to a lesser extent flexion) agonist, and from the first palmar interosseous (FPI, MEP_{FPI}), acting as abduction antagonist (illustrated in Fig. 1*a,b*). During practice, there was no EMG activity or movements detectable in the nonpracticing hand as reflected by EMG and accelerometric monitoring. Movements of each index finger were recorded by means of 3-dimensional accelerometers (Kistler Instrument, Amherst, NY) mounted on the distal phalanx of the index fingers. The direction of TMS-evoked and voluntary index finger movements was calculated from the direction of vectors constructed from the first peak acceleration in the 2 orthogonal axes of the principal movement plane (abduction-adduction and flexion-extension) (Classen et al. 1998). The acceleration along the horizontal movement axis (abduction-adduction) was also quantified separately. Arbitrarily, abduction was always assigned positive values, whereas the opposite direction (adduction) was assigned negative values. EMG and acceleration signals were digitized at 5 kHz using a data collection-analysis program written in LabView (National Instruments, Austin, TX). Please note that what is described as M1 plasticity in the present study refers to plastic changes in the corticospinal system.

Measurements

The effect of the 3 separate practice sessions was examined by evaluating TMS-evoked movement directions and MEP amplitudes before and after motor practice in both the practicing and nonpracticing hands positioned palm down at rest regardless of the position held during the practice period (Fig. 1*a*). That is, the nonpracticing hand remained at rest in all 3 sessions.

Practice Zones

Practice zones (PZs) were defined in all sessions as ±45° quadrants centered on the index finger practiced movement (PZ_M; abduction, flexion) and on the index finger practiced direction (PZ_D, inward, upward, see Fig. 1*b*). A different measure, PZ_{ALL}, defined as PZ_M + PZ_D reflected the combined effect of muscle activity and direction during the practice period. In Session 1, PZ_M (abduction) and PZ_D (inward) coincided, expressed as PZ = PZ_{ALL} in Figure 1*b*. In Sessions 2 and 3, because of the different practice hand position (Fig. 1*a*), PZ_M and PZ_D diverged (Fig. 1*b*). In Session 2, subjects practiced index finger abductions in an upward direction (Fig. 1*a*). Therefore, PZs (defined with the hand palm down) corresponded to a PZ_M in abduction and a PZ_D upward (Fig. 1*b*). In Session 3, subjects practiced index finger flexions in an inward direction (Fig. 1*a*). Therefore, PZs were defined with PZ_M in flexion and PZ_D inward (note again the divergence of PZ_M and PZ_D, Fig. 1*b*). The rationale for defining separately the 2 PZs was to capture the effects of muscle activity, PZ_M, and direction of movement, PZ_D, during the practice period. We evaluated the changes in the proportion of TMS-evoked movements falling within the PZs as a function of practice. For the nonpracticing hand, we defined a mirror practice zone (P_{MZ}), which was centered on abduction in all sessions and was therefore the mirror image of PZ (in Session 1, PZ_M and PZ_D were the same, Fig. 1*b*), PZ_M (in Session 2), or of PZ_D (in Session 3, see above and Fig. 1*b*). We also defined a parallel practice zone (P_{PZ}), which was the parallel image of PZ, PZ_M, or PZ_D (in Sessions 1, 2, and 3,

Table 3

Session 1. Individual TMS-evoked movements (n = 15)

Subjects	Nonpracticing hand				Practicing hand	
	P _{MZ}		P _{PZ}		PZ	
	Pre	Post	Pre	Post	Pre	Post
1	0.98	0.00	0.00	0.95	0.50	0.94
2	0.93	0.36	0.00	0.25	0.98	1.00
3	0.84	0.47	0.05	0.35	0.19	0.63
4	0.65	0.05	0.22	0.84	0.85	0.97
5	0.80	0.50	0.07	0.36	0.81	0.95
6	0.35	0.02	0.09	0.06	0.00	0.11
7	0.70	0.37	0.19	0.44	0.17	0.23
8	0.72	0.04	0.02	0.02	0.05	0.32
9	0.87	0.75	0.00	0.00	0.73	0.62
10	0.24	0.20	0.08	0.15	0.29	0.35
11	0.67	0.24	0.04	0.09	—	—
12	0.78	0.46	0.00	0.23	0.27	0.37
13	0.72	0.72	0.12	0.07	0.72	0.92
14	0.84	0.40	0.05	0.49	0.13	0.43
15	0.82	0.75	0.03	0.10	0.28	0.43
Mean (SE)	0.73 (0.05)	0.36 (0.07)	0.06 (0.02)	0.29 (0.07)	0.43 (0.09)	0.59 (0.08)

Note: Individual data showing the proportion of TMS-evoked index finger movements falling into the PZ for the practicing hand and in the P_{MZ} and P_{PZ} for the nonpracticing hand, before (pre) and after (post) practice, for each of the 15 subjects. Data for the practicing hand could not be acquired in one subject (—, no. 11).

respectively) and other nonspecific intermediate locations (P_IZ). We then calculated changes in the proportion of TMS-evoked movements that fell within the P_{MZ}, P_{PZ}, and in P_IZ in the nonpracticing hand after each of the 3 practice sessions, once both hands were at complete rest (see Fig. 1*b*). These 3 PZs in the nonpracticing hand were defined to distinguish how practice in one hand altered the cortical representation of the mirror or parallel movements in the nonpracticing hand (Fig. 1*b*).

MEP Amplitudes

MEP_{FDI} and MEP_{FPI} amplitudes were measured in each hand and compared before and after practice.

Data Analysis

All data are expressed as mean ± standard error. Distribution normality was tested by the Kolmogorov-Smirnov tests for each variable. First, in order to test whether training kinematics were comparable across the 3 different practice sessions, the length of the acceleration vector, the dispersion, and the angular deviation of the trained movements were analyzed by means of one-way repeated measure analysis of variance (ANOVA_{RM}) with SESSION_(Session1/Session2/Session3) as factor. Second, for each session and for each hand, we tested the effect of practice on the rMT, MEP amplitudes, and motor kinematics of TMS-evoked movements (horizontal acceleration and proportion of TMS-evoked movements in PZ_{ALL}, PZ_M, PZ_D, P_{MZ}, P_{PZ}, and P_IZ) by means of one-way ANOVA_{RM} with PRACTICE_(pre/post) as factor. In addition, we used one-way ANOVA_{RM} with factor SESSION_(Session1/Session2/Session3) to study the relative influence of the 3 different practice sessions on MEP amplitudes and

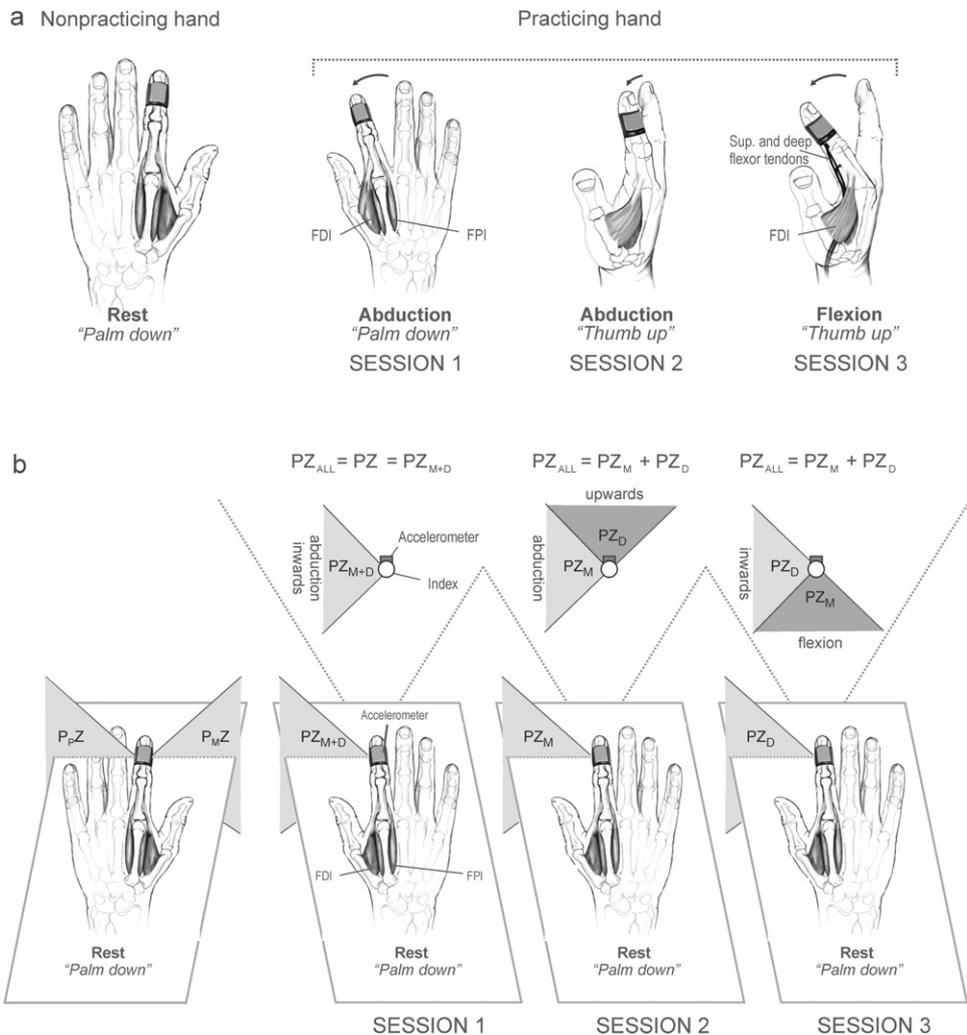


Figure 1. (a) Motor practice. In separate sessions on different days, subjects practiced moving their dominant index finger with the hand positioned palm down (Session 1, index finger abduction) or turned at 90° thumb up (Session 2, index finger abduction and Session 3, index finger flexion), whereas the nondominant, nonpracticing hand was always positioned palm down. Sup, superficial. (b) Measurement of practice effects in the 3 sessions. Practice effects were investigated at rest with both hands palm down. In the practicing hand in Session 1, we measured changes in the proportion of TMS-evoked movements falling in the PZ, defined as a $\pm 45^\circ$ quadrant centered on the mean practiced index finger abduction movements. In Session 2 or 3, the PZ was centered either on the practiced movement (PZ_M , index finger abduction) or on the practiced direction (PZ_D , toward the midline), respectively. In addition, $PZ_{ALL} = (PZ_M + PZ_D)$ was introduced to assess the overall practice effect despite the hand position change, including the representation of both the practiced muscle and movement direction. In the nonpracticing hand, we measured changes in the proportion of TMS-evoked movements falling in the P_mZ (a $\pm 45^\circ$ quadrant centered on abduction and therefore mirror to PZ, PZ_M , or PZ_D in Sessions 1, 2, or 3, respectively) and in the P_pZ (a $\pm 45^\circ$ quadrant parallel to PZ, PZ_M , or PZ_D in Sessions 2 or 3, respectively). The FDI is an index finger abductor agonist muscle, and the FPI is an abductor antagonist muscle.

TMS-evoked movements in the nonpracticing hand (post/pre). Paired *t*-tests corrected for multiple comparisons were used for post hoc analysis when appropriate. Finally, we determined correlations by means of the Pearson and Spearman tests when adequate.

Results

Motor Training Kinematics

Motor training kinematics including the length of the acceleration vector of the practiced movements and the dispersion and angular deviation of the training motions from the instructed practice direction revealed no differences across the 3 training sessions (see Table 1 for group and single subjects performance), despite the different movement directions and muscles involved across sessions.

rMT before and after Practice

rMTs were comparable in the practicing and nonpracticing hands at baseline in all 3 sessions (Table 2, ANOVA_{RM}, not significant [ns]). Training did not result in significant changes in rMT in neither hand in any of the 3 sessions (Table 2, ANOVA_{RM}, ns). Before practice, the proportion of TMS-evoked movements in the practicing hand falling in the PZ in Session 1, PZ_M in Session 2, and PZ_D in Session 3 was comparable: 0.43 ± 0.09 , 0.46 ± 0.12 , and 0.36 ± 0.11 for Sessions 1, 2, and 3, respectively. Similarly, the proportion of TMS-evoked movements in the P_mZ for the nonpracticing hand was also comparable in the 3 sessions: 0.73 ± 0.05 , 0.59 ± 0.10 , and 0.61 ± 0.08 for Sessions 1, 2, and 3, respectively, indicating that each practice session did not influence baseline determinations in the following sessions.

Effect of Different Forms of Right-Hand Motor Practice

Session 1

Training in this session involved index finger abduction movements performed inward with the hand palm down.

Effects on the practicing hand

ANOVA_{RM} revealed that practicing abduction index finger movements with the palm down (Fig. 1*a*, Session 1) induced a significant increase in the proportion of TMS-evoked movements falling in PZ (a $\pm 45^\circ$ quadrant centered on the mean practiced index finger abduction movements, $F = 15.82$, $P = 0.002$, Table 3 shows all individual subjects' data), in the acceleration peak of TMS-evoked abduction movements ($F = 5.34$, $P = 0.04$) and on the amplitude of MEPs recorded from the agonist muscle (MEP_{FDI}, $F = 4.48$, $P = 0.05$) but not from the antagonist muscle (MEP_{FPI}, $F = 1.48$, $P = 0.25$, all individual subjects' data are shown in Table 4). These findings are consistent with previous reports indicating that training strengthens the representation of the practiced finger movement in the M1 contralateral to the practicing hand (Classen et al. 1998). Figures 2 and 3*a* show results from a single subject and group data, respectively, whereas Tables 3 and 4 show all single subject data.

Effects on the nonpracticing hand

More importantly, we found that the proportion of TMS-evoked movements decreased in the mirror P_MZ (from 0.73 ± 0.05 to 0.36 ± 0.07 , $F = 29.56$, $P < 0.001$) but increased in the parallel P_PZ zone (from 0.06 ± 0.02 to 0.29 ± 0.07 , $F = 10.43$, $P = 0.006$, Fig. 3*a, b*) and in the intermediate P_IZ zone (from 0.21 ± 0.05 to 0.35 ± 0.08 , $F = 7.25$, $P = 0.017$). It is noteworthy that the increase in the proportion of TMS-evoked movements in the P_PZ of the nonpracticing hand was similar to that in the P_IZ (paired *t*-test, $t = 0.85$, $P = 0.41$, see Fig. 3*b*), suggesting that practice did not specifically enhance representation of that particular (practiced) movement *direction* (toward the left) in the nonpracticing hand. In addition, practice induced an overall decrease in the horizontal acceleration (reduced abduction

component) of TMS-evoked movements ($F = 21.82$, $P < 0.001$, see Fig. 3*a*) and the amplitude of MEP_{FDI} ($F = 9.33$, $P = 0.009$, Figs 2 and 3, and Tables 3 and 4) in the nonpracticing hand. The decreased horizontal acceleration of TMS-evoked movements in the nonpracticing hand correlated with the increase in the proportion of movements evoked in PZ in the practicing hand ($r = -0.06$, $P = 0.02$). The amplitude of MEPs in the nonpracticing FPI, an index finger adductor muscle, was not influenced by training ($F = 1.38$, $P = 0.26$).

Session 2

Training in this session involved index finger abduction movements performed upward with the hand turned at 90° thumb up (Fig. 1*a*).

Effects on the practicing hand

As mentioned above, the length of the acceleration vector of the practiced finger abduction movements and the dispersion and angular deviation of the training movements from the instructed practice direction were comparable in Sessions 1 and 2, despite the different postures (Fig. 1*a*, Table 1).

Despite this homogeneity in motor training kinematics, practice in Session 2 did not demonstrate an increase in the proportion of TMS-evoked movements in PZ_{ALL} in the practicing hand (from 0.88 ± 0.17 to 0.98 ± 0.04 , $F = 2.8$, $P = 0.14$, $n = 8$, see circular histograms in Fig. 4*a*, left), possibly due to a ceiling effect, because at baseline most subjects already showed a maximum proportion of TMS-evoked movements in PZ_{ALL}. Consistent with this hypothesis, all subjects who had lower baseline proportion of TMS-evoked movements in PZ_{ALL} in the practicing hand showed a strong increase (ranging from 0.76 ± 0.17 to 0.96 ± 0.04 , $n = 4$). We found no evidence for a preferential enhancement of PZ_M or PZ_D in the practicing hand performing this task.

Effects on the nonpracticing hand

Following this form of practice, we found no quantifiable training-related changes in the direction of TMS-evoked movements in the nonpracticing hand (ANOVA_{RM}, ns, Fig. 4*a, b*, left).

Table 4

Session 1. Individual FDI and FPI MEP amplitudes ($n = 15$)

Subjects	Nonpracticing hand				Practicing hand			
	FDI		FPI		FDI		FPI	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	1.07	0.64	0.46	0.89	1.93	2.13	0.53	0.33
2	2.87	1.69	0.48	0.52	4.90	7.17	1.21	1.23
3	2.84	1.57	0.85	0.53	2.69	2.74	0.77	0.82
4	1.33	0.47	0.53	0.40	0.48	2.09	0.41	0.69
5	1.07	1.15	0.45	0.46	2.41	2.67	0.94	1.23
6	1.29	0.73	0.43	0.46	0.55	0.73	0.30	0.50
7	1.11	1.76	1.00	1.24	1.87	2.76	0.22	0.21
8	3.74	1.02	1.52	0.75	1.64	2.52	1.82	2.64
9	1.13	0.92	0.56	0.51	3.64	2.84	0.97	0.62
10	0.92	0.66	0.34	0.16	0.92	0.69	0.34	0.20
11	1.52	1.11	0.71	0.52	—	—	—	—
12	1.93	0.84	1.27	0.57	4.58	4.98	1.39	1.46
13	2.75	1.61	0.56	0.26	4.88	8.17	0.87	1.06
14	0.71	0.77	0.41	0.53	2.27	1.78	0.55	0.43
15	2.63	2.53	0.78	1.04	2.20	2.29	0.81	0.99
Mean (SE)	1.80 (0.24)	1.16 (0.14)	0.69 (0.09)	0.59 (0.07)	2.49 (0.40)	3.11 (0.59)	0.80 (0.12)	0.89 (0.17)

Note: MEP amplitudes in the FDI and the FPI for the practicing and nonpracticing hands, before (pre) and after (post) practice, in the 15 subjects. Data for the practicing hand could not be acquired in one subject (—, no. 11).

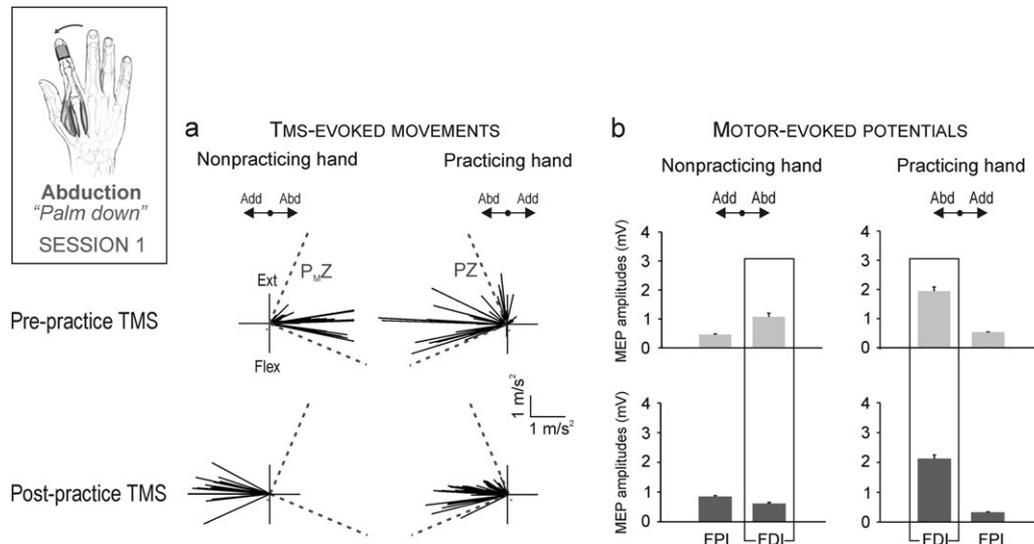


Figure 2. Session 1. Data from a single subject depicting (a, left) the direction of all individual TMS-evoked finger movements (each individual TMS-evoked movement is represented by 1 vector) and (b, right) MEPs in the nonpracticing and practicing hands before and after training in abduction with the practicing hand positioned palm down (Session 1). For the practicing hand, the proportion of TMS-evoked movements falling within the PZ increased ($P < 0.001$), whereas for the nonpracticing hand, the proportion of TMS-evoked movements falling within the P_{MZ} strongly decreased ($P < 0.001$), mostly switching from abduction (Abd) to adduction (Add) in this subject. Consistently, the amplitude of MEP_{FDI} increased in the practicing hand (from light to dark gray columns in right inset, before to after practice), whereas it decreased in the nonpracticing hand (left inset, $P < 0.001$). PZ, practice zone in the practicing hand; a $\pm 45^\circ$ quadrant centered around abduction; P_{MZ} , practice mirror zone in the nonpracticing hand; a $\pm 45^\circ$ quadrant mirror to the PZ. Ext, extension; Flex, flexion. Add, adduction; Abd, abduction (please, see all individual and group data in Tables).

Session 3

Training in this session involved index finger flexion movements performed inward with the hand at 90° thumb up (Fig. 1a).

Effects on the practicing hand

The length of the acceleration vector of the practiced finger movements and the dispersion and angular deviation of the training movements from the instructed practice direction were comparable in Sessions 1 and 3, despite the different motions involved (Table 1). However, similar to Session 2, practice did not show training-related increases in the proportion of TMS-evoked movements in PZ_{ALL} (from 0.49 ± 0.36 to 0.68 ± 0.32 ; $F = 2.1$, $P = 0.19$, $n = 8$, Fig. 4a, right) or any convincing evidence for a preferential enhancement of PZ_M or PZ_D (ANOVA_{RM}, ns, see Fig. 4a).

Effects on the nonpracticing hand

Training flexion index finger movements into the same direction in space as in Session 1 (inward) led to a significant reduction in TMS-evoked movements in the mirror P_{MZ} (ANOVA_{RM}, $F = 5.46$, $P = 0.05$, Fig. 4a,b, right), and the acceleration of TMS-evoked movements tended to decrease ($F = 4.71$, $P = 0.067$). Consistently, ANOVA_{RM} revealed a significant effect of the factor SESSION on practice-related changes (post/pre) in the proportion of TMS-evoked movements falling in P_{MZ} ($F = 11.84$, $P = 0.002$, Fig. 5), on the acceleration peak of TMS-evoked abduction movements in the nonpracticing hand ($F = 10.70$, $P = 0.009$), and in MEP_{FDI} amplitudes ($F = 5.50$, $P = 0.025$). The reduction of TMS-evoked movements in P_{MZ} for the nonpracticing hand correlated with the increase in the proportion of TMS-evoked abduction movements in PZ_D for the practicing hand ($r = -0.83$; $P = 0.005$).

Discussion

Motor practice results in cortical reorganization within the M1 contralateral to the practicing hand (Kleim et al. 1998; Nudo

2003; Stefan et al. 2005). Understanding the degree to which the M1 ipsilateral to a practicing hand reorganizes and the characteristics of this reorganization following unimanual hand practice were the goals of this investigation.

The Paradigm

Using our paradigm, it has been shown that repetitive practice of finger movements in a particular direction leaves a short-lasting memory trace in the contralateral M1, as evidenced by an increased probability, at the end of the training period that TMS applied over M1 will elicit movements in the practiced direction (Classen et al. 1998). The effects of this type of training on the organization of the ipsilateral M1 outlasting the training period are not known. In this investigation, we addressed this question by studying TMS-induced kinematic and EMG responses from muscles agonistic and antagonistic to the practiced movement in both hands, providing information on cortical organization of both finger motor representations (Stefan et al. 2005).

Effects of Motor Training on the Organization of the Ipsilateral M1

The main result of this study was that practice of unilateral index finger abduction movements inward decreased the proportion of TMS-evoked index finger abduction movements in the nonpracticing resting hand to an extent proportional to the increase in the practicing hand. Corticospinal excitability changes were consistent with these kinematic observations, showing a decreased excitability of the index finger abduction agonist FDI in the nonpracticing hand. Corticospinal excitability of the index finger adductor muscle (FPI, abduction antagonist) in the nonpracticing hand was not influenced by training, indicating that practicing right index finger abduction to the left did not result in a facilitation of the muscle controlling index finger movements in the same direction

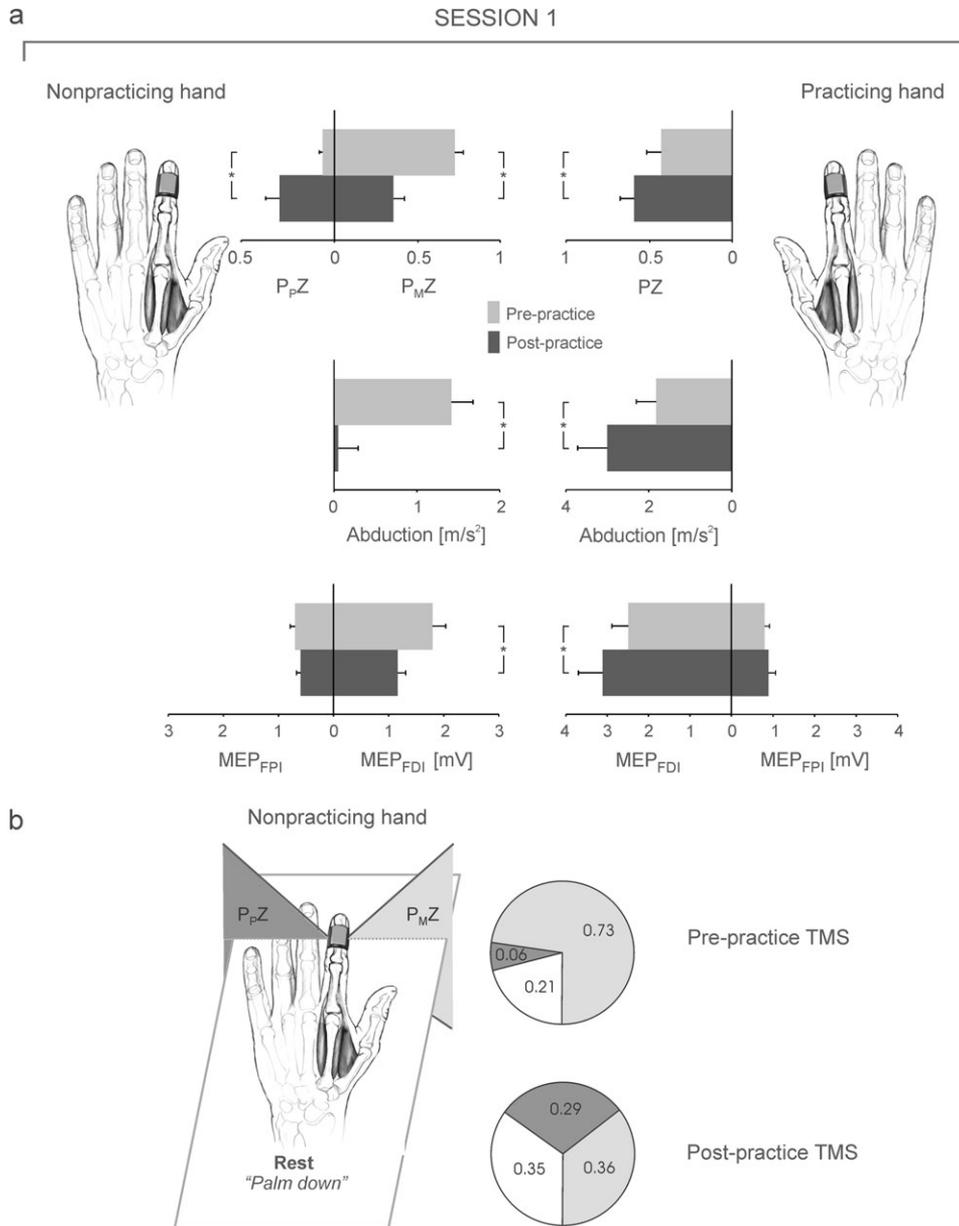


Figure 3. (a) Session 1. Group data (hands palm down, $n = 15$). The hand drawings depict the practicing hand (in this case, the right-hand) and the nonpracticing hand. Light and dark gray columns show values before and after practice, respectively. Note the reciprocal practice-dependent changes in the proportion of TMS-evoked movements (upper graph, increased in the PZ of the practicing hand but decreased in the P_{MZ} of the nonpracticing hand), in the horizontal acceleration of abduction movements (middle graph, increased for the practicing hand and decreased for the nonpracticing hand), and in the MEP_{FDI} amplitude, mediating index finger abduction motions (lower graph, similarly increased in the practicing hand and decreased in the nonpracticing hand). MEP amplitudes in the FPI (abduction antagonist) did not undergo significant changes. Similar effects were observed in right- and left-handers. Data are expressed as mean \pm standard error. See all individual subjects' data in Tables 3 and 4. (b) Session 1. The circular histogram shows the average proportion of TMS-evoked movements falling in P_{MZ} (light gray), P_{pZ} (dark gray), and in intermediate areas (PZ, white) in the nonpracticing hand in all subjects. Note that before practice most TMS-evoked index movements in the nonpracticing hand fell in the P_{MZ} and only very few fell in the P_{pZ} and PZ zones. Practice changed radically this proportion increasing the TMS-evoked movements in the P_{pZ} and PZ and decreasing them in the P_{MZ}. Please, see Table 3 for all individual subjects' data.

(toward the left) in the nonpracticing hand. These results indicate that unimanual hand practice, as implemented in Session 1, induced reciprocal plastic changes in mirror movement representations in both M1s. These changes were characterized by strengthening of the representation of the practiced movement in the contralateral M1 and a proportional weakening of the mirror movement representation in the ipsilateral M1.

In Sessions 2 and 3, we tested the effects of practicing the same index finger movement in another direction in space

(abduction upward, Session 2) and another index finger movement (flexion) but in the same direction in space (inward, Session 3) relative to Session 1. The proportion of TMS-evoked index finger abduction movements in the nonpracticing hand decreased only when practice movements mirrored the direction of abduction movements in the nonpracticing hand (abduction inward in Session 1, flexion inward in Session 3) but not when practice movements were performed upward even if they were also abduction (Session 2). Corticospinal excitability

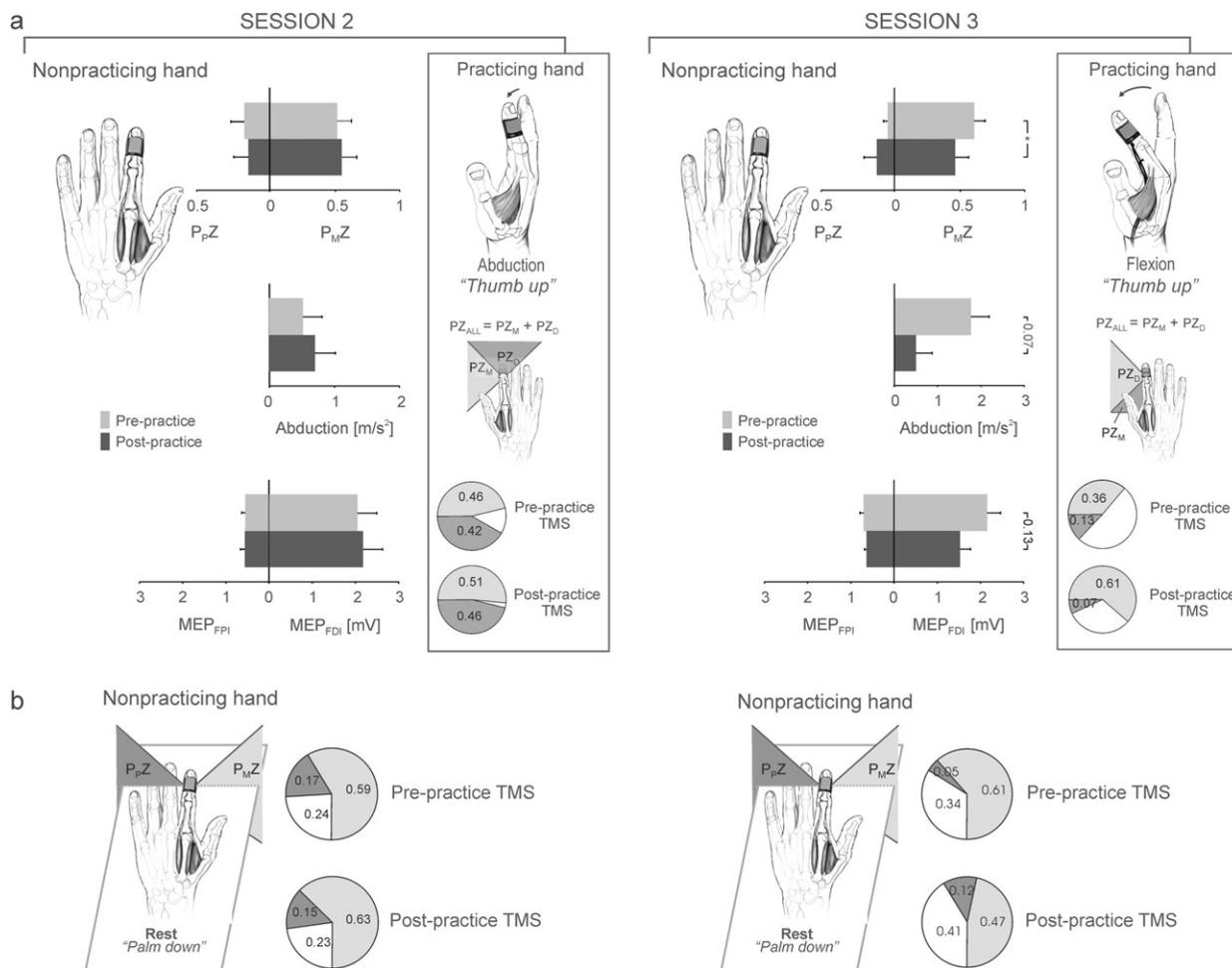


Figure 4. (a) Sessions 2 and 3 (left and right, respectively). Group data (practicing hand 90° thumb up, $n = 9, 8$ in each session). The hand drawings depict the nonpracticing hand (left) for practice in Session 2 (abduction upward) and Session 3 (flexion inward) (right). Light and dark gray columns show values before and after practice, respectively. Note the practice-dependent decrease in the proportion of TMS-evoked movements in the P_{M,Z} in Session 3 but not in Session 2. The horizontal acceleration of abduction movements (middle graph, $P = 0.067$) and MEP_{FDI} amplitudes, mediating index finger abduction motions (lower graph, $P = 0.13$), also tended to be reduced following practice in Session 3 but not 2. Data are expressed as mean \pm standard error. See all individual subjects' data in Table 5. Insets represent the practiced position and movements in Session 2 and 3. Circular histograms show the average proportion of TMS-evoked movements falling in PZ_M and PZ_D for the practicing hand. (b) Sessions 2 and 3 (left and right, respectively). The circular histograms show the average proportion of TMS-evoked movements falling in P_{M,Z} (light gray), P_{P,Z} (dark gray), and in intermediate areas (P_Z, white) in the nonpracticing hand in all subjects before and after motor practice in Sessions 2 and 3. Note that practice in Session 3 (flexion inward) decreased the proportion of the TMS-evoked movements falling in the P_{M,Z} in the nonpracticing hand, whereas practice in Session 2 (abduction upward) did not. Please, see Table 5 for all individual subjects' data.

changes were consistent with these kinematic observations, showing a decreased excitability of the index finger abduction agonist FDI in the nonpracticing hand only following practice movements that mirrored its action, that is inward (abduction in Session 1, flexion in Session 3) but not following practice of abduction movements toward a different direction in space as in Session 2. Therefore, despite comparable motor training kinematics, stable baseline primary endpoint measures of plasticity in the nonpracticing hand, and comparable training effects on plasticity in the M1 controlling the practicing hand, training in Sessions 2 and 3 elicited fundamentally different changes in the organization of the M1 controlling the nonpracticing hand. Our results on differential plastic changes in the organization of M1 controlling the nonpracticing hand as a function of the 3 practice sessions, cannot be explained then by differential effects of training on M1 plasticity controlling the practicing hand in Sessions 2 and 3.

This is to our knowledge the first report of use-dependent changes in the cortical organization of an M1 that outlasts

a period of training of the ipsilateral hand. Of additional interest is the hint that this form of cortical reorganization may be influenced by the kinematic details of the movements practiced by the opposite hand (see Fig. 5). A full exploration of this hypothesis was, however, beyond the goals of our experiment.

Effects of Motor Training on the Organization of the Contralateral M1

We found that practicing abduction index finger movements with the palm down (Session 1) induced an increase in the proportion of TMS-evoked movements falling in the PZ (PZ = PZ_{ALL}), in the acceleration peak of TMS-evoked abduction movements, and in the amplitude of MEPs recorded from the agonist (MEP_{FDI}), but not from the antagonist (MEP_{FPI}) muscles, consistent with previous reports (Classen et al. 1998; Butefisch et al. 2000; Stefan et al. 2005). This finding is also in tune with our present understanding of the contribution of the contralateral M1 to motor learning and skill acquisition (Shadmehr and Brashers-Krug 1997; Lu and Ashe 2005; Ashe et al. 2006;

Matsuzaka et al. 2007). We did not find convincing evidence for specific or differential increases in the proportion of TMS-evoked movements in PZ_M , PZ_D , or in $PZ_{ALL} = (PZ_M + PZ_D)$ of the practicing hand in Sessions 2 and 3. Therefore, training as implemented in Sessions 1 and 3, which induced comparable plasticity in the organization of M1 controlling the non-practicing hand, had substantially different effects on the organization of the M1 controlling the practicing hand. Possible reasons for the lack of changes in the proportion of TMS-evoked movements in PZ_M , PZ_D , or PZ_{ALL} of the practicing hand in Sessions 2 and 3 may include 1) most TMS-evoked movements already fell in the PZs before practice, reducing the sensitivity of this measure to detect additional increases after training in the practicing hand (ceiling effect), 2) training as implemented in these 2 sessions did not influence the proportion of TMS-evoked movements in PZ_M or PZ_D of the practicing hand, and 3) the change in hand position from

practice “thumb up” (Fig. 1a) to TMS testing “palm down” (Fig. 1b) in Sessions 2 and 3 may have affected the sensitivity of our kinematic and EMG measures. We accepted these limitations because the experiment was designed primarily to secure consistency of motor training kinematics across sessions, a goal that was successfully accomplished (see Table 1), and to assess changes in TMS-evoked responses in the nonpracticing hand, which remained always in the same hand position (palm down, Fig. 1a,b).

Mechanisms of Reorganizational Changes in the M1 Ipsilateral to a Training Hand

Transcallosal interactions between motor regions in the 2 hemispheres do exist (Ferbart et al. 1992; Mochizuki et al. 2004). They link supplementary, primary, and premotor areas between themselves (Gould et al. 1986; Rouiller et al. 1994; Liu et al. 2002; Marconi et al. 2003) and are predominantly (but not exclusively) inhibitory. These interhemispheric connections operate in the process of generation of voluntary movements (Duque, Hummel, et al. 2005; Koch et al. 2006; Duque et al. 2007) and contribute to motor learning as well as to inter-manual transfer of acquired motor skills (Perez et al. 2007; Perez et al. forthcoming). Differential excitability changes in both M1s have been suggested before when noted that 1-Hz repetitive TMS applied to one M1, which decreases motor cortical excitability under the stimulating TMS coil, results in a relative increase in excitability in the opposite unstimulated M1 (Gilio et al. 2003; Schambra et al. 2003; Pal et al. 2005). These effects reported in the past suggested that excitability of homologous movement representations in the 2 hemispheres might be to some extent interdependent and that each of them could be affected by excitability or activity-dependent changes in the other (Gilio et al. 2003). Our results now indicate that reciprocal plastic changes in the organization of the 2 M1s occur after unimanual motor training and that some of these changes are kinematically specific, influenced predominantly by the direction of the practiced movement rather than by the muscles involved, a finding consistent with the known role of M1 in motor control and aspects of spatial processing (Shen and Alexander 1997a; Kakei et al. 1999, 2003; Duque, Mazzocchio, et al. 2005).

On the other hand, it is also possible that interhemispheric interactions targeting the M1 ipsilateral to the practicing hand originated from non-M1s like premotor areas, where direction of movements are strongly represented (Shen and Alexander

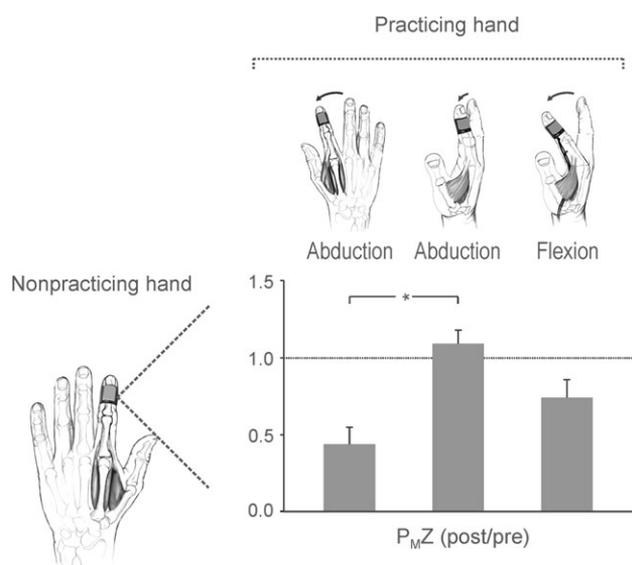


Figure 5. Relative influence of the 3 practice sessions on direction of TMS-evoked movements in the nonpracticing hand (post/pre). Note the decrease in TMS-evoked movements falling in the region mirror to the practiced movement directions (P_{MZ}) in Sessions 1 and 3, in the absence of changes in Session 2, when practice movements were identical to those in Session 1 but in a different direction in space. Data are expressed as mean \pm standard error.

Table 5

Sessions 2–3. Individual TMS-evoked movements in P_{MZ} and P_{PZ} of nonpracticing hand ($n = 9$)

Subjects	Session 2 (abduction upward)				Session 3 (flexion inward)			
	P_{MZ}		P_{PZ}		P_{MZ}		P_{PZ}	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	0.63	0.75	0.12	0.00	0.59	0.05	0.00	0.73
2	0.87	0.77	0.06	0.02	0.41	0.16	0.00	0.00
3	—	—	—	—	0.84	0.75	0.00	0.03
4	0.70	0.76	0.02	0.05	0.92	0.79	0.00	0.04
5	0.36	0.56	0.02	0.02	0.53	0.48	0.11	0.04
7	0.93	1.00	0.00	0.00	0.88	0.82	0.02	0.02
8	0.20	0.15	0.78	0.80	0.40	0.33	0.02	0.00
10	0.21	0.26	0.29	0.28	—	—	—	—
15	0.78	0.75	0.10	0.00	0.34	0.36	0.22	0.10
Mean (SE)	0.59 (0.10)	0.63 (0.10)	0.17 (0.09)	0.15 (0.10)	0.61 (0.08)	0.47 (0.10)	0.05 (0.03)	0.12 (0.09)

Note: Em dash indicates subjects who did not participate in Sessions 2 or 3.

1997b; Kakei et al. 2001, 2003). The premotor cortex exerts inhibitory influences on the contralateral M1 (Mochizuki et al. 2004) and is a major contributor to hand selection processes during unimanual movements in health (Schluter et al. 1998; Hoshi and Tanji 2000; Rushworth et al. 2003; Cisek and Kalaska 2005; Koch et al. 2006) and disease (Johansen-Berg et al. 2002; Fridman et al. 2004). Note that, despite previous data pointing to the contrary (Classen et al. 1998), we cannot rule out completely that spinal mechanisms, in which symmetry around the midline axis dominates, could have partially contributed to our results. Finally, one methodological consideration in this study is that our subjects were instructed to watch the motor practicing hand to enhance the effects of physical training alone, as commonly done in neurorehabilitative treatments (Stefan et al. 2005; Celnik et al. 2006).

Possible Role of Reciprocal Bibemispheric Plasticity after Unimanual Training

What could be the role of this form of bihemispheric plasticity after unimanual practice? In the healthy central nervous system, it is possible that reciprocal changes in the organization of the motor cortices contralateral and ipsilateral to a practicing hand may facilitate accuracy in learning of skilled unimanual finger movements or of bimanual movements that require differential contributions of the 2 hands (Johansson et al. 2006; Koch et al. 2006) and contribute to optimize movement focality (Davare et al. 2007) or to a more accurate control of newly learned lateralized distal hand motor skills (Swinnen 2002; Serrien et al. 2006), possibly through surround inhibition mechanisms (Sohn and Hallett 2004). From a clinical point of view, our findings may provide some insight into the mechanisms underlying the beneficial effects of newly developed rehabilitative interventions that appear to improve motor function in the paretic hand after brain lesions like stroke. Constraint-induced movement therapy is a rehabilitative treatment that focuses on intensive training of the paretic hand and restraint of movement in the intact hand (Rossini et al. 2003; Wolf et al. 2006). Noninvasive cortical stimulation with TMS or transcranial direct current stimulation (tDCS) that upregulates cortical excitability in the ipsilesional M1 (Hummel et al. 2005; Khedr et al. 2005; Kim et al. 2006) or that downregulates excitability in the contralesional M1 (Mansur et al. 2005; Takeuchi et al. 2005; Hummel and Cohen 2006) also appears to exert beneficial effects. On the other hand, we do not yet know the extent to which this form of reciprocal M1 plasticity after unimanual hand training is task specific. Is it for example as operational when more proximal or less focal arm motor training is implemented (e.g., during bilateral arm training [Whitall et al. 2000]) as when training precise focal distal hand movements (present study)? More work is required to sort out these questions.

In summary, we found that unilateral hand motor practice encodes reciprocal memory traces in both motor cortices, characterized by strengthening of the representation of the practiced movement in the M1 contralateral to the practicing hand and by reduction of the mirror movement representation in the opposite M1. These results highlight the role of interacting bilateral motor networks in motor memory formation and skill acquisition, an issue of relevance in motor control and neurorehabilitation.

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