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Effects of intermanual transfer induced by repetitive precision grip on input-output properties of untrained contralateral limb muscles

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RESEARCH　ARTICLE

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Abstract Although there were many reports relating to intermanual transfer of behavioral motor tasks in humans, it is still not well-known whether the transfer phenomenon between the trained and untrained hand is accompanied by corresponding changes in motor system. In the present study we applied transcranial magnetic stimulation to investigate the practice effects of unilateral fingertip precision grip on corticospinal excitability, regarding both the trained and untrained hand muscles. The results showed that after practice fingertip grip force became steady and safety margin dramatically decreased not only in the trained hand, but also in the untrained hand. Regarding MEP and background EMG (B.EMG) activities, the regression slope of MEP/B.EMG ratio in the first dorsal interosseous (FDI) muscle became significantly steeper after practice in both hands, but in the thenar (TH) muscle there were no clear modulations. These results indicated that through practice qualitative or functional changes of corticospinal systems related to the reorganization for a fingertip precision grip prominently reflect only on FDI muscle which plays a dominant role in the task. More importantly, such effects were simultaneously seen in the untrained hand correspondent to the trained hand, i.e., changes of input-output property in M1 occur not only in the trained hand, but also in the untrained hand. Based on the present results, we suggest that training-induced neural adaptations of the central nervous system may include improvement of its predicting fingertip grip force for self-lifting of the object in the untrained hand.

Keywords Fingertip precision grip・Intermanual transfer・Input-output property・Motor evoked potential (MEP)・Transcranial magnetic stimulation (TMS)

Introduction

Motor learning may alter rapidly the functional organization of human primary motor cortex (M1) (Classen et al. 1998; Liepert et al. 1999; Muellbacher et al. 2001, 2002; Pascual-Leone et al. 1995). For example, the precision grip using the tips of thumb and index finger when lifting small objects has been investigated extensively, and rapid associative learning is thought to generate internal representations that link object identification with the scaling forces required to lift them. That is, when manipulating a grasped object, sufficient fingertip grip force must be generated to prevent slip due to load force exerted by the object. The predictive control mechanisms can be efficiently explained and fingertip grip force is accurately scaled to the object's weight in such a way that it is always slightly higher than the minimum required to prevent it slipping (safety margin; Johansson and Westling 1984, 1988; see also Cole and Rotella 2002).

On the other hand, fingertip grip force is also modulated in parallel with lifting the object of constant weight and surface friction. That is, immediate sensorimotor memory obtained from previous lifts is a powerful factor influencing predictive fingertip grip force control, indicating that motor prediction reduced safety margin to be efficiently exploited and then there is a memory process that influences fingertip grip forces according to the previous lift (Johansson 1996). These training effects were found not only in the trained hand but also in the untrained hand (Gordon et al. 1994; Schulze et al. 2002). Such a phenomenon which is called ‘‘intermanual transfer’’, reflects that unilateral hand practice affects performance of the other hand. There were many reports relating to motor learning and intermanual transfer of human motor behaviors, and it is a general consensus that the central nervous system (CNS) is capable of generalizing motor skills from one hand to the other hand (Calford and Tweedale 1990; Gordon et al. 1994; Sainburg and Wang 2002; Criscimagna-Hemminger et al. 2003). Although the CNS is capable of adapting fingertip grip forces to a wide range of object shapes, weights and frictional properties in order to provide optimal and secure handling in a variety of objects, it is still not well-known that whether the intermanual transfer is accompanied by corresponding changes in motor output system after unilateral motor practice. In particular, it is not clear whether the stimulus-response properties of the corticospinal system, namely input-output properties of which different intensities of stimulation are applied, are modulated in the untrained hand. It is well-known that the corpus callosum is the major neural pathway that connects cortical areas on either hemisphere, including the prefrontal, motor, somatosensory, parietal, and occipital areas (Bloom and Hynd 2005). Since the effect of intermaunal transfer is absent in the patient with split brain (Levin et al. 1993) or with callosal agenesis (Gordon et al. 1994), we can assume that corpus callosum integrates information across the hemispheres and thus serves a function in interhemispheric communication. It is supported by multiple lines of evidence that M1 play a more active role in both acquisition and retention of motor skills, and it may be a site of storage for the internal representation of skilled movement (Muellbacher et al. 2001, 2002). In particular, anatomical, physiological and behavioral evidences suggest that M1 is crucial to precise and dexterous object handling (Johansson 1996; see also Porter and Lemon 1993). As described-above, through skillful learning of a motor task reorganization of M1 would be occurred contralateral to the trained hand. Through the interhemispheric neural pathway and/or projections from other brain regions that at a higher hierarchical level, therefore, it seems possible that reorganization of the M1 contralateral to the untrained hand occurs similarly to the M1 contralateral to the trained hand. In the present study, we used transcranial magnetic stimulation (TMS) technique to address this possibility.

Investigating the excitability of M1, motor evoked potentials (MEPs) to TMS have been used extensively. The changes of MEP depend on excitability changes of M1, which determine the amplitude and number of I-waves that are recruited, and on excitability changes of the spinal motoneuron pool, which determine how many motoneurons are recruited by a given descending input. In many single pulse TMS studies of M1, the size and threshold of MEPs are measured before and after practice. Any changes of MEP could be due to excitability changes at either cortical or spinal level related to input-output properties. In the present study, therefore, we applied the stimulus-response curves of targeted muscles which could provide information about the cortical excitability as similar as cortical mapping (Ridding and Rothwell 1997), and focused on the excitability changes in the bilateral corticospinal systems through unilateral practice of fingertip precision grips. We addressed the following questions; 1) how motor behavioral modulations occur in the trained hand after repetitive fingertip precision grip, 2) how changes in the corticospinal excitability occur in the trained hand accompanying motor behavioral changes and 3) how these behavioral and corticospinal excitability changes in the trained hand could be similarly observed in the untrained hand?

Materials and methods

Subjects

Seven healthy volunteers (five males and two females, age range 22-34 years) participated in the present study after giving their informed consent. There was no participant who has attained proficiency in especially bilateral hand motor tasks, and all of them were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). The experiment was performed in accordance with the Declaration of Helsinki and with the approval of the Local Ethics Committee of Hiroshima University.

Experimental procedures

A hand-made object (loaded force about 0.1N, see Fig. 1A) with a built-in force sensor was used in the present study. All subjects were asked to raise the object horizontally using thumb and index finger (fingertip precision grip), and were also instructed to perform by self-paced and to hold the object several seconds (Fig. 1A). Fingertip precision grips were repeated as follows; 1) Before practice of task by the right hand, 10 trials in the left hand were done under the same condition as the right hand without TMS. Then, 15-20 trials in the left hand were done with TMS. 2) Fingertip precision grips by the right hand were done in 15-20 trials with TMS. Then five sessions included 50 trials (10 trials per session) were repeated in the right hand without TMS (practice session). During practice, subjects were instructed to perform the same task with a strong emphasis on the efficiency. They could get visual feedback of the grip force which was presented by an oscilloscope in front of them. After practice, again 15-20 trials in the right hand were done with TMS. 3) Performances by the left hand were done again under the above-mentioned condition as before practice, i.e., 10 trials were done without TMS and 15-20 trials were done with TMS, respectively. TMS pulse was always applied during the holding phase when subject steadily hold the object without oscillations.

Grip force, EMG and MEP recordings

During fingertip precision grips by the left or right hand, we simultaneously recorded grip forces and EMG activities from the first dorsal interosseous (FDI) and thenar (TH) muscles (Fig. 1B). The surface EMGs were recorded from both FDI and TH muscles with pairs of surface Ag-AgCl cup electrodes (outer diameter 1.0 cm) in a berry-tendon montage. EMG signals were amplified at a bandwidth of 5 Hz to 3 kHz (model AB-621G, Nihonkohden, Tokyo, Japan), sampled at 5 kHz and fed to a computer for off-line analysis. Maximal *df/dt* (*df/dt* max) of grip force and holding force were measured and background EMG (B.EMG) activities of a 100-ms window prior to the TMS application during holding force phase were also measured (see Fig. 1B).

TMS was given through a figure-of-eight shaped coil, external diameter of wings 9 cm (Magstim

Company, Whitland, UK). The coil was placed tangentially to the scalp with the handle positioning backward and rotated appropriately 30° away from the mid-sagittal line. At the beginning of experiment, optimal positions of the coil were systematically adjusted on each (left and right) scalp over the motor cortex for activating both areas correspondent to the target muscles. As described-above, we elicited 15-20 MEPs in holding force phase from both muscles in each hand at before and after practice sessions, respectively. In the present study, since we should avoid any implicit practice effects before practice as much as possible, we did not measure the active motor threshold of the FDI and TH muscles by which a great deal of repetition of the task would be carried out. Intensities of TMS were adjusted from 25% to 50% maximal output, and 2-3 trials were done with each intensity. In such a range of TMS intensity, we could clearly identify the MEPs in both muscles apart from the B.EMG activities. The inter-stimulus interval was about 15-20 seconds.

Data and statistical analyses

To evaluate practice effects on fingertip precision grip, we calculated means of *df/dt* max and holding force before and after practice. Then, we determined the effects of practice by using Student’s paired *t*-test. We have already shown that mean values of tonic EMG activities obtained from a 100-ms window is the optimal estimation of B.EMG activities (Hasegawa et al. 2001; Kasai and Yahagi 1999; Yahagi et al. 2003) and MEP/B.EMG ratio reflects on the occurrence of reorganization of input-output properties in corticospinal systems for an efficient performance as a function of motor learning (Yahagi et al. 2005). To determine the effects of the repetitive fingertip precision grip on corticospinal systems, therefore, we calculated the MEP/B.EMG ratio in each trial and in each muscle. Then, we calculated Spearman’s rank-order correlations and regression coefficients (TMS intensities cross MEP/B.EMG ratio) at before and after practice sessions in both muscles, respectively. Regarding the regression slope of all subjects, the differences in FDI and TH muscles of each hand between before and after practice sessions were compared by a paired *t*-test with Holm's sequential Bonferroni correction (Holm 1979). The statistical significant level was determined as $P<0.05$. The data are expressed as means±SD.

Results

Fig. 2A shows superimposed grip force curves (ten trials) of the trained (right) hand before (left traces) and after (right traces) practice obtained from a single subject. These results showed that after practice grip force curves became steady and the force required to lift and hold the object dramatically decreased. Fig. 2B shows means and standard deviations of *df/dt* max (left) and holding force (right) of all subjects before and after practice. Both *df/dt* max and holding force significantly decreased after practice in comparison with those before practice ($P<0.05$, respectively), suggesting that through practice the subject could minimize the grip force and then bring it close to the minimal force that is required for preventing slip, namely decrease the safety margin.

Fig. 2C shows superimposed MEP specimen recordings (three trials) of FDI (left traces) and TH (right traces) muscles before and after practice at three different TMS intensities (30%, 40% and 50% maximal output, respectively) obtained from the single subject as shown in Fig. 2A. Regarding B.EMG, statistical analyses (n=7) showed that in FDI muscle it was tended to be decreased after practice in comparison with that before practice ($P=0.056$), while that of TH muscle showed no change ($P=0.27$). Then, we calculated MEP/B.EMG ratio of both muscles in all TMS intensities before and after practice. Fig. 2D shows representative examples of MEP/B.EMG ratio dependent on TMS intensities obtained from the single subject. The results showed that in FDI muscle (left) the regression slope of MEP/B.EMG ratio after practice (squares and thick line) became steeper than that before practice (circles and thin line), but in TH muscle (right) there was no clear modulation. Then, regression slopes of FDI (upper left) and TH (lower left) muscles of all subjects before and after practice are shown in Fig. 4 (left). In FDI muscle mean regression slope after practice was significantly larger than that before practice (*P*<0.01), but in TH muscle there were no clear changes. These results indicated that during performing fingertip precision grip the index finger plays a dominant role and the training effects might reflect only on functions of the prime mover (FDI) muscle of the index finger.

Fig. 3A, B, C, and D show results of the untrained (left) hand as similar representations as Fig. 2. The representative examples of grip force curves (Fig. 3A), MEP recordings (Fig. 3C) and MEP/B.EMG ratio (Fig. 3D) were obtained from the identical subject as shown in the Fig. 2A, C and D. Surprisingly, there is a great resemblance in the results of the trained hand. Statistical analysis (n=7) showed that, after practice *df/dt* max and holding force dramatically decreased and amount of these decreases were statistically significant (*P*<0.05, respectively). Regarding B.EMG, in FDI muscle it was tended to be decreased after practice in comparison with that before practice (*P*=0.052), although in TH muscle there was no change (*P*=0.12). The results of MEP/B.EMG ratio showed that the regression slope in FDI muscle after practice became also steeper than that before practice (*P*<0.05), but there were no clear changes in TH muscle. The results of all subjects are shown in Fig. 4 (right) as similar presentations as the trained hand.

Discussion

It is common knowledge that when people practice in order to become skillful at a motor task, remarkable improvements of performance can be obtained as shown in the present study. For example, in sports activities, many complex skills require humans to coordinate intralimb and interlimb joints in a variety of rhythmic patterns, e.g., running, throwing, jumping, dancing, etc. In general through these sports activities, it is found that not only the trained limb but also the untrained limb shows improvements of performance in the same task. Thus, highly flexible motor behavioral mechanisms might play an important role for these improvements. Based on behavioral data of the present results, irrespective of training decreases of *df/dt* max in the initial holding phase of the object occurred and in holding phase the amount of grip force decreased to be only slightly greater than the minimum needed to prevent slip, providing a safety margin. These results indicated that the CNS adapted predicting grip forces for self-lifting of the object not only in the trained hand but also in the untrained hand. That is, predictive motor learning in the trained hand might be generalized and its dynamic properties could be also altered in the untrained hand by a trial-by-trial bias (Wolpert and Flanagan 2001).

Effects of repetitive precision grip on the trained hand

Peripherally recorded MEPs to TMS represent the sum of intracortical, subcortical and spinal effects. The effects of TMS do not remain restricted to the stimulated region, but might influence other regions with which the targeted cortical area has functional connections (Valero-Cabre et al. 2001). Although the exact contribution of each of these elements is not well understood, the present resulting MEP/B.EMG ratio as similar to stimulus-response gradient (Boroojerdi et al. 2001; Carroll et al. 2001; Devanne et al. 1997; Ridding and Rothwell 1997), functional demand (Ni et al. 2006a) and different voluntary drives (Ni et al. 2006b) is a sensitive reflection of the functional integrity of the corticospinal system. Additionally, it is suggested by our recent report that modulations of MEP/B.EMG ratio reflect the pattern of neural recruitment, the number of descending volleys, and the density of excitable motoneurons (Yahagi et al. 2005). In other words, variations of the MEP/B.EMG ratio indicate changes in the corticospinal excitability and reflect strategic changes intended to perform a fingertip precision grip efficiently.

Regarding trained hand in the present study, regression line of MEP/B.EMG ratio after practice became steeper in FDI muscle but not in TH muscle (Fig. 2D; Fig. 4 left). These phenomena reveal that training effects might reflect only on FDI muscle which plays a dominant role in the task of fingertip precision grip. The reason why the changes were not simultaneously observed in these two muscles is that, the index finger is especially engaged in the precise control and plays the role of force calibration for efficient precision grip; whereas the thumb is devoted to a more postural or sustaining function. The present results allowed the identification of one finger as being selectively engaged in the precise force control and revealed that the control strategy through practice as in the case of thumb-index grip control (Bonnard et al. 2007). Additionally, although Bonnard et al. (2007) suggested that MEP changes did not concern the same muscle in all of the subjects and this evidence is probably due to individual strategies, in the present study the results of MEP/B.EMG ratio of each muscle were presented similarly through practice in all subjects. It is therefore suggested that finger functions relating to both muscles might be selected and separated for efficient fingertip precision grip through practice.

There are two possible explanations of the above-mentioned modulations of MEP/B.EMG ratio in FDI muscle as being selectively engaged in the precise force control. One relies on changes in excitability of subliminal fringe of M1, and the other on changes in response of motoneuron pool to a given descending input. The former presents a possibility that, although the excitabilities of pyramidal tract neuron might be decreased for decreasing output force in order to perform the task more efficiently through practice, the increased excitabilities of subliminal fringe of M1 might also be recruited to fire by TMS and be additionally reflected in MEPs. In other words, the more increased excitability the subliminal fringe, the more increased the MEP amplitude to increasing intensity of TMS. On the other hand, the latter indicates a possibility that although B.EMG of FDI muscle tended to be decreased through practice in the present study, the sensibility of motoneuron pool to a given descending input could be increased. In this scenario, even if the descending volleys evoked by TMS were constant through practice, the increased gain might provide additionally firing motoneurons and it would be reflected in MEPs. Thus, changes of the MEP/B.EMG ratio of FDI muscle in the present study could be according to excitability changes at either cortical or/and spinal levels. In other words, it might indicate qualitative or functional changes of corticospinal systems related to the reorganization for a fingertip precision grip induced by practice.

Effects of intermanual transfer on input-output properties in the untrained hand

The phenomenon of increased motor skill in the untrained contralateral limb is called ‘intermanual transfer effect’, and positive transfer effects of motor learning between both hands have been reported frequently (Imamizu and Shimojo 1995; Sathian and Zangaladze 1998; Temprado and Swinnen 2005; Thut et al. 1996, 1997, 1999). These studies have focused on the adaptation to novel task conditions, i.e., transfer was reflected by anticipation of the novel conditions during subsequent opposite arm performance. Once the task is practiced at a level that it can be performed automatically, it was proposed that the movement could be stored as muscle specific codes (Karni et al. 1998; Kleim et al. 2004). The present observation therefore indicates that the information of consolidation of muscle specific codes may be transferred via the corpus callosum, based on the evidence that through practice deficit in intermanual transfer could be observed in patients with disease in corpus callosum (Levin et al. 1993; Gordon et al. 1994).

Concerning finger movement, it is known that independent finger movement during manipulation and precision grip is controlled by the contralateral M1 via the corticospinal system (Porter and Lemon 1993) and a well-ordered within-limb somatotopic organization in M1 (Shieber 2001). In addition, the previous study has shown that practice of a novel activity with unilateral limb affects subsequent performance with the other limb (Sainburg and Wang 2002). That is, when the dominant right limb is used in learning dynamics, the information could be represented in the left hemisphere with neural elements tuned to both right and left limbs (Criscimagna- Hemminger et al. 2003). The previous reports have been emphasized factors like hand dominance and task complexity/difficulty as playing a role in determining the involvement of the ispilateral hemisphere during unimanual movements (Caramia et al. 2000; Chen et al. 1997; Cramer et al. 1999; Huang et al. 2004; Kawashima et al. 1998; Kobayashi et al. 2003; Koeneke et al. 2006a,b; Sadato et al. 1996; Verstynen et al. 2005). It is also known that the dominant M1 has a greater ability to reorganize with learning than that of the subdominant M1 (Hammond and Vallence 2006; Koeneke et al. 2006b). In line with these previous studies, our results suggest that ipsilateral M1 (right hemisphere) activation induced by practiced (right) hand may play a crucial role for the intermanual transfer from the dominant (right) to the subdominant (left) hand. The dominant (left) M1 is involved in learning with the right hand and the subdominant (right) M1 is also involved during learning with the dominant hand. Most importantly, in the present study the modulations of MEP/B.EMG ratio are observed not only in the trained hand but also in the untrained hand. As described-above, changes in MEP/B.EMG ratio indicate functional changes of corticospinal systems related to the reorganization. Thus, it is most likely that intermanual transfer of sequential motor tasks in the present study is at least in part related to the functional changes of the corticospinal system. In an intrinsic hand muscle such as FDI (the prime mover) muscle for performing sequential fingertip precision grip, therefore, input-output properties dependent on changes of functional demands most probably reflects qualitative changes of recruitment comprising the corticospinal system, perhaps via the corpus callosum (Schulze et al. 2002).

Relationship to predictive control mechanisms

Since adaptation to dynamic transformation is mediated by distinct neural mechanisms (Wang and Sainburg 2004), the present evidence indicates that both forward (for prediction) and inverse (for control) internal models also contribute to positive transfer phenomenon as similar to voluntary movement as suggested by Kawato (1999). That is, an internal forward model can be trained and updated by comparing the predicted and actual outcome of a motor command. Well established computational learning rules can be used to translate predictive errors into changes in synaptic weights which will improve future predictions of the forward model (Wolpert and Ghaharamani 2000). In concrete, when holding the object with fingertip precision grip in the present study, predictive control mechanisms can be effectively exploited after practice and behavior towards the object exhibit stable and efficient properties. Such predictive control is essential for the rapid movements observed in dexterous human behavior (Wolpert and Flanagan 2001). Recently, the cerebellum has been suggested as a critical site for constructing and manipulating forward internal models based on functional imaging study in humans (Imamizu et al. 2000). Thus, the present result suggests that improvement of these internal models by practice might also contribute to the mechanism of positive transfer phenomenon.

Conclusion

Training-induced neural adaptations may include improvements in muscle coordination and reductions in the activity when performing the task efficiently as shown in the present study, and the reorganization also simultaneously occur in the untrained hand correspondent to the trained hand. This transfer has already described for the motor system (Bonato et al. 1996; Zanette et al. 1995) and its functional significance might be to maintain balance or integration between corresponding cortical fields during practice (Calford and Tweedale 1990). Thus, the present results of post-practiced MEP behavior in the untrained hand muscles suggest that common mechanism is involved in the reversible modulation of M1 excitability for both hemispheres. This crossed modulation might represent an interhemispheric transfer of information between homologous cortical areas on either hemisphere via the neural pathway of the corpus callosum, and/or as a result of improved internal models that might be also contributory to the interhemispheric transfer through practice.

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Figure legends

Fig. 1 **A** Illustration of the fingertip precision grip task by the thumb and index finger. **B** Traces of EMG activities and precision grip force obtained from a single trial. Upper two traces show EMG activities of the first dorsal interosseous (FDI; upper trace) and the thenar (TH; lower trace) muscles, respectively. The bottom shows the precision grip force curve, and *df/dt* max and holding force were measured as shown by arrows.

Fig. 2 Results of the trained (right) hand obtained from a single subject. **A** Ten superimposed recordings of force curves before (left traces) and after (right traces) practice. **B** Means and standard deviations of *df/dt* max (left) and holding force (right) obtained from all subjects (n=7) before and after practice. **C** Three superimposed recordings of MEPs in the FDI (left traces) and TH (right traces) muscles at different TMS intensities before and after practice. **D** Regression lines of MEP/B.EMG ratio of the FDI (left) and TH (right) muscles in different TMS intensities before (circles, thin line) and after (squares, thick line) practice. *P<0.05

Fig. 3 Results obtained from the untrained (left) hand as the same presentation as shown in Fig 2. The representative examples of Fig 3. **A**, **C** and **D** are obtained from the identical subject as shown in Fig 2. **A**, **C** and **D**. Note that the results are similar to those in Fig 2. *P<0.05

Fig. 4 Means and standard deviations of regression slope (thick lines) of FDI (upper) and TH (lower) muscles obtained from all subjects (n=7) in the trained and untrained hands before and after practice. *P<0.05, **P<0.01

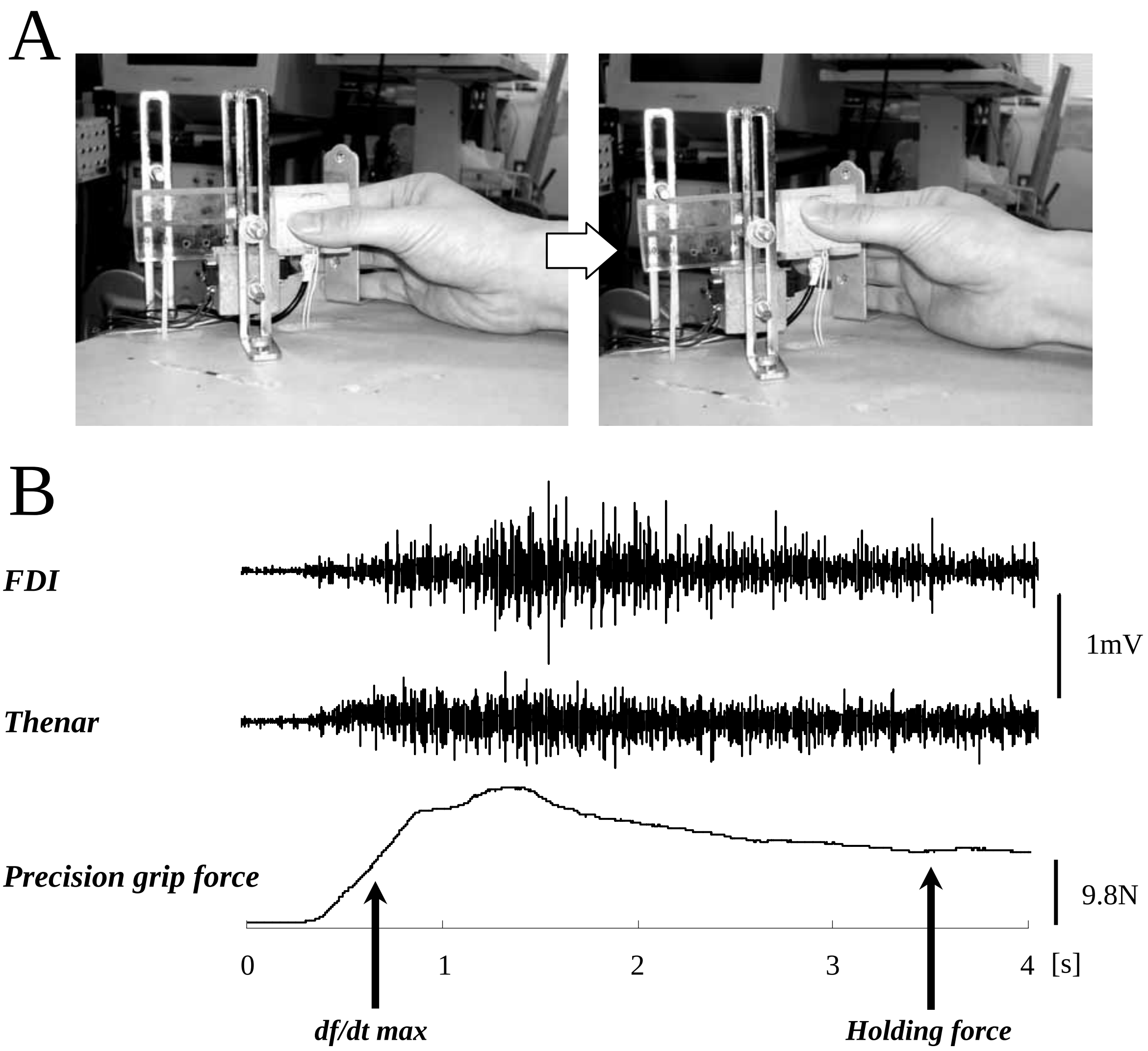
A
B
FDI
1mV
Thenar
Precision grip force
9.8N
0
1
2
3
4
[s]
df/dt max
Holding force

Fig. 1

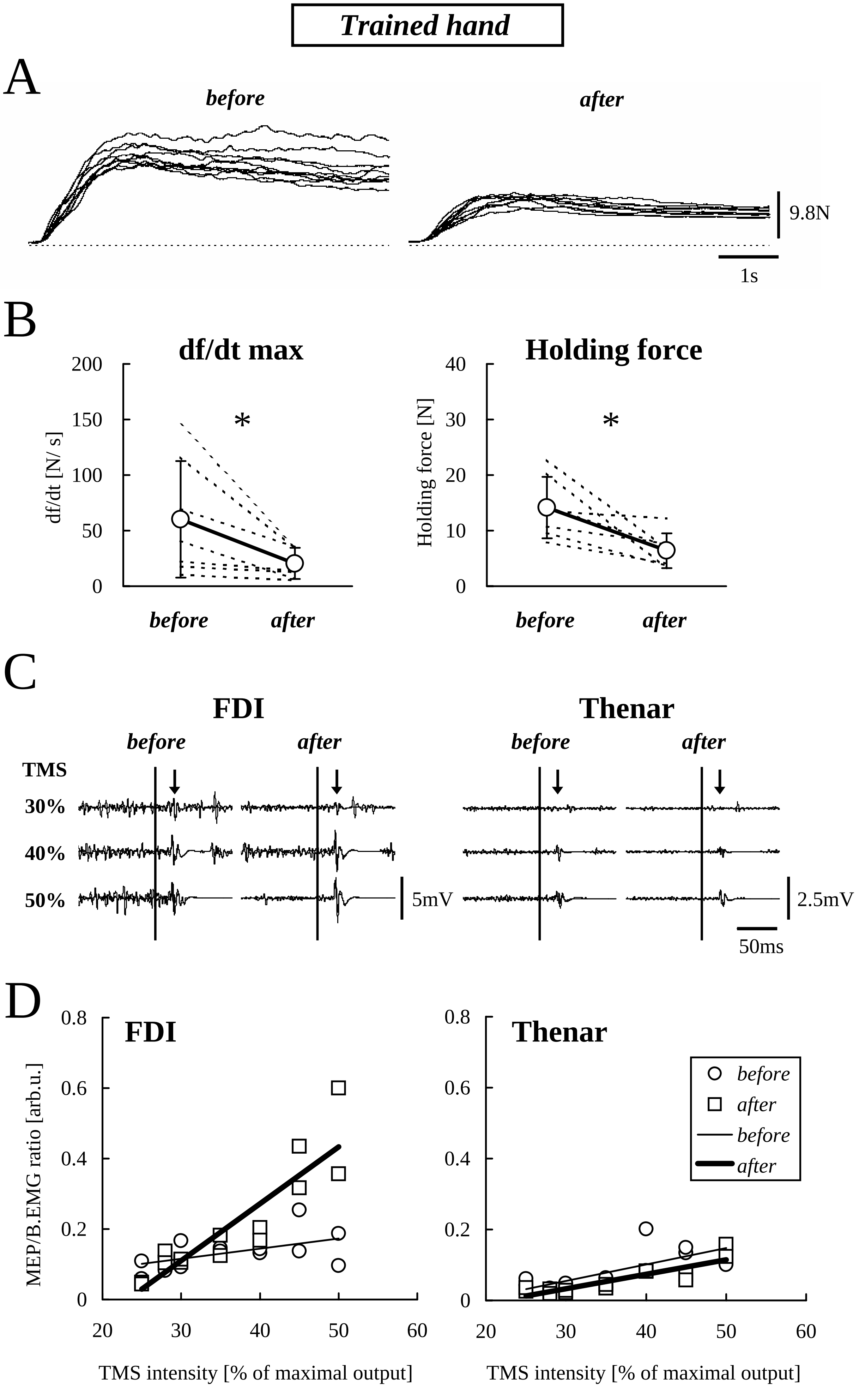
Trained hand
A
before
after
9.8N
1s
B
df/dt max
200
150
100
50
0
df/dt [N/ s]
*
before
after
Holding force
40
30
20
10
0
Holding force [N]
*
before
after
C
FDI
before
after
TMS
30%
40%
50%
5mV
Thenar
before
after
2.5mV
50ms
D
FDI
0.8
0.6
0.4
0.2
0
MEP/B.EMG ratio [arb.u.]
20
30
40
50
60
TMS intensity [% of maximal output]
Thenar
0.8
0.6
0.4
0.2
0
○ before
□ after
— before
▬ after
20
30
40
50
60
TMS intensity [% of maximal output]

Fig. 2

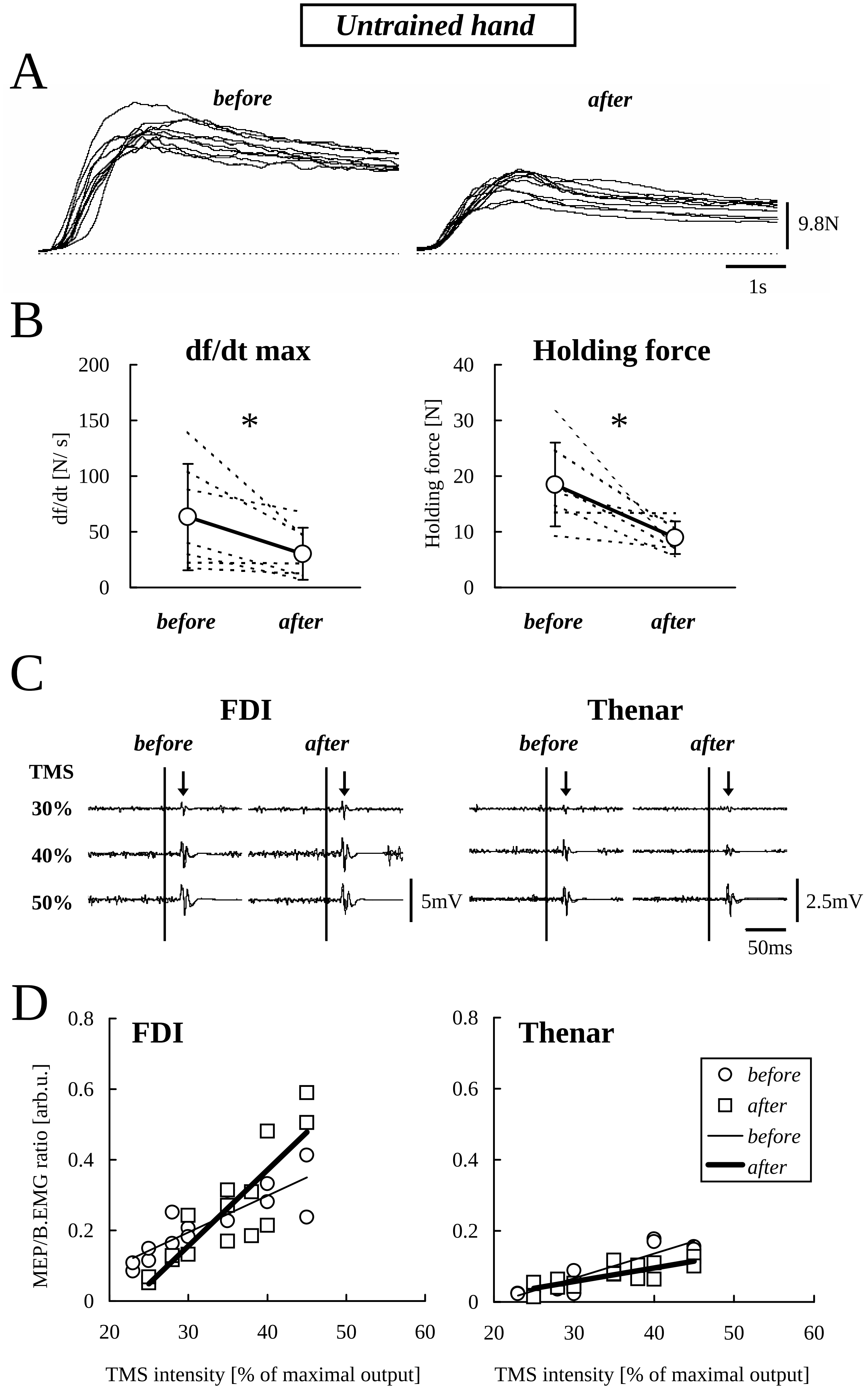
Untrained hand
A
before
after
9.8N
1s
B
df/dt max
200
150
100
50
0
df/dt [N/ s]
*
before
after
Holding force
40
30
20
10
0
Holding force [N]
*
before
after
C
FDI
before
after
TMS
30%
40%
50%
5mV
Thenar
before
after
2.5mV
50ms
D
0.8
0.6
0.4
0.2
0
MEP/B.EMG ratio [arb.u.]
FDI
20
30
40
50
60
TMS intensity [% of maximal output]
0.8
0.6
0.4
0.2
0
Thenar
○ before
□ after
before
after
20
30
40
50
60
TMS intensity [% of maximal output]

Fig. 3

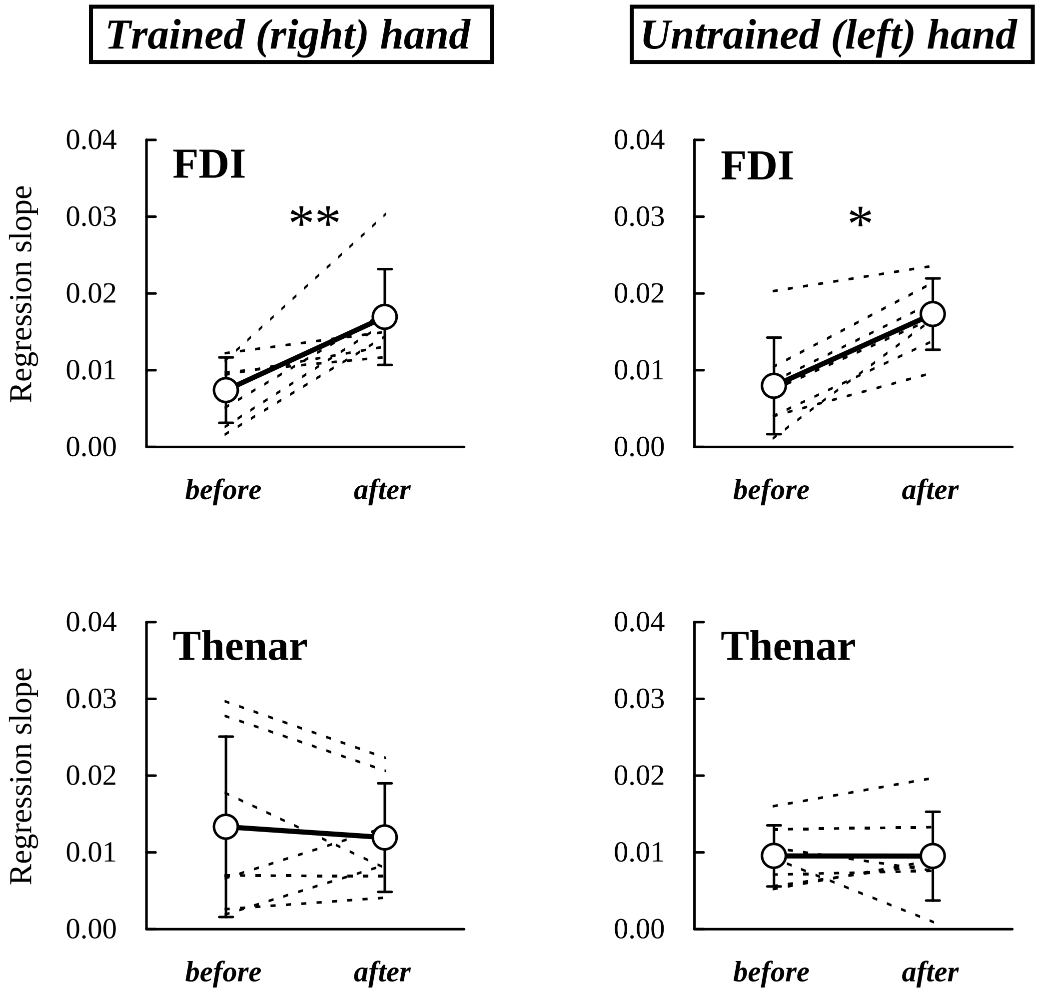
Trained (right) hand
Untrained (left) hand
FDI
FDI
Thenar
Thenar
**
*
Regression slope
Regression slope
0.04
0.03
0.02
0.01
0.00
before
after

Fig. 4