J Neurophysiol 98: 3230–3241, 2007.
First published October 17, 2007; doi:10.1152/jn.00750.2007.

Motor Cortical Measures of Use-Dependent Plasticity Are Graded From Distal to Proximal in the Human Upper Limb

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Submitted 6 July 2007; accepted in final form 13 October 2007

Krutky MA, Perreault EJ. Motor cortical measures of use-dependent plasticity are graded from distal to proximal in the human upper limb. *J Neurophysiol* 98: 3230–3241, 2007. First published October 17, 2007; doi:10.1152/jn.00750.2007. In humans, it is well established that practicing simple, repetitive movements with the distal upper limb induces short-term plasticity in the neural pathways that control training. It is unknown how the neural response to similar training at more proximal joints differs. The purpose of this study was to quantify how ballistic training at proximal and distal upper limb joints influences measures of corticomotor plasticity. To accomplish this goal, we had subjects repetitively practice simple movements for 30 min using the index finger, wrist, or elbow. Before and after training, transcranial magnetic stimulation (TMS) was used to activate the corticomotor pathways innervating the trained joint. We assessed the effect of training by quantifying changes in TMS-elicited joint movements and motor-evoked potentials in the training agonists and antagonists. These measures of training-induced neural plasticity were graded from distal to proximal in the upper limb. Training had the greatest immediate effect on the pathways controlling the index finger and this effect decreased for more proximal joints. Our results suggest that the relative sizes and properties of the cortical areas controlling the proximal and distal upper limb influence the effect of training on the corticomotor pathways. These results have implications for how training influences the neural pathways controlling movement in the proximal and distal portions of the human upper limb and the degree to which these effects can be quantified using TMS.

INTRODUCTION

The neural pathways that control human movement are continually reorganized according to daily use; this gives us the ability to learn novel motor skills and to modify existing motor behaviors through practice. Even a single session of repetitive motor practice induces short-term, use-dependent changes in the neural structures that control training (Classen et al. 1998). For example, 30 min of repetitive, ballistic thumb flexion training rapidly increases the excitability of the corticomotor pathways controlling a thumb flexor, a training agonist, relative to that of the pathways controlling a thumb extensor, a training antagonist (Butefisch et al. 2000; Classen et al. 1998). Similarly, using the fingers to learn to play a sequence of keys on the piano (Pascual-Leone et al. 1995) or to read Braille (Pascual-Leone et al. 1993) is accompanied by increased excitability in the motor pathways used in those tasks. These corticomotor excitability (CE) shifts may transiently store the neural traces of training before they become permanent motor memories (Muellbacher et al. 2002), and they may be linked to the cortical plasticity that accompanies motor recovery after a neurological insult such as stroke (Liepert et al. 1998). To date, short-term, use-dependent plasticity has been studied extensively in the pathways controlling the distal upper limb yet only sparingly in pathways innervating more proximal muscles (Ziemann et al. 2001) that contribute to limb posture and placement of the hand in space.

Numerous studies have suggested that use-dependent plasticity occurs within motor cortex, by excitability shifts in facilitatory and inhibitory motor cortical interneurons (Lotze et al. 2003; Muellbacher et al. 2001; Stefan et al. 2006; Ziemann et al. 2004). Furthermore, the extensive interneuronal architecture within motor cortex seems to provide the structure by which use-dependent plasticity may alter the functional topography of cortical representations (Hess and Donoghue 1994; Hess et al. 1996). However, it is unknown whether the effect of repetitive training on plasticity within motor cortex is influenced by the structural differences between the representations controlling proximal and distal upper limb muscles. The rationale for studying this is that there are fewer monosynaptic projections from motor cortex to the proximal upper limb than there are to the distal upper limb (Palmer and Ashby 1992), and these projections arise from a smaller area of cortical tissue (Penfield and Boldrey 1937; Wassermann et al. 1992). Therefore comparing use-dependent plasticity in proximal and distal representations of the upper limb may allow us to compare the relative motor cortical contributions to learning in the pathways that control tasks such as whole limb reaching movements, hand grasping and releasing, and finger manipulation. No studies to date have compared training-induced excitability changes in pathways controlling the proximal and distal upper limb joints.

The purpose of this work was to quantify the degree with which repetitive motor training induces immediate CE shifts in the pathways controlling proximal and distal upper limb joints in humans. Direct descending pathways from motor cortex project to muscles throughout the upper limb (Colebatch et al. 1990; de Noordhout et al. 1999); therefore we hypothesized that motor training would result in increased excitability in agonist pathways, relative to antagonist pathways, used in training of the elbow, wrist, and finger joints. To test this hypothesis, we had subjects conduct simple, repetitive movements for 30 min using the target joint. Transcranial magnetic stimulation (TMS) was used to assess the influence of these training paradigms on CE.

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METHODS

Subjects

Seventeen subjects (15 right- and 2 left-handed), 21 to 31 yr of age (8 males and 9 females), participated in this study. No subject had a history of neurological impairment, orthopedic limitations of the upper limb, or contraindications to TMS. Subjects gave written, informed consent and were free to withdraw at any time. This protocol was approved by the Institutional Review Board of Northwestern's Office for the Protection of Research Subjects.

Three sets of primary experiments were conducted to investigate the influence of repetitive training movements at the index finger, wrist, and elbow on the pathways controlling these joints. Each of the three sets of primary experiments was completed by 10 of the 17 total subjects. In each of the three primary experiments 9 of 10 subjects were right-handed. Three of the 17 subjects participated in all experiments, 7 participated in two experiments, and 7 participated in only a single experiment. Subjects participating in more than one experiment had a minimum of 1 wk between successive sessions. For those subjects the order in which target joints were chosen for training was randomized.

Equipment

Subjects sat with the trunk secured to an immobile chair (Biodex, Shirley, NY) and the right upper arm was supported in a plastic trough. The initial position for all training protocols was with the right upper limb fixed at about 80° shoulder abduction, 45° shoulder flexion, 90° elbow flexion, and full forearm pronation (palm down). All joints proximal to the training joint were secured to the experimental frame with Velcro straps to prevent movement. Movements of the target joint, during training and CE assessment, were measured using a two-dimensional accelerometer (ADXL202; Analog Devices, Norwood, MA) mounted to the limb segment immediately distal to the joint of interest. In index finger experiments the accelerometer was mounted to the distal phalange to monitor flexion/extension and abduction/adduction movements. In experiments involving the wrist joint the accelerometer was mounted collinear to the third metacarpal on the dorsal surface of the hand to assess wrist flexion/extension and adduction/abduction. In experiments involving the elbow joint the accelerometer was mounted on the dorsal surface of the wrist to monitor elbow flexion/extension in the horizontal plane.

TMS was used to assess CE before and after training. A Magstim 200 stimulator (Magstim, Dyfed, UK) delivered stimuli by two types of stimulating coils. A figure-of-eight coil (70-mm windings), which produces focal cortical microcurrents (Cohen et al. 1990) below the coil's center, was used to selectively activate musculature in the index finger and wrist training experiments. A round coil (90 mm), which produces cortical current along the coil's entire outer edge, was used to generate more widespread, higher-intensity current (Cohen et al. 1990) and to activate the higher-threshold proximal muscles monitored in the elbow experiments. This coil has been used in many studies of the proximal upper limb (Colebatch et al. 1990; de Noordhout et al. 1999; Palmer and Ashby 1992).

Electromyographic (EMG) data were recorded from a single agonist and antagonist muscle at each target joint during training and during CE assessment. In index finger experiments, flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC) were monitored. In wrist experiments, extensor carpi radialis (ECR) and flexor carpi radialis (FCR) were monitored. In elbow experiments, brachioradialis (BRD) and triceps lateral head (TriLat) were monitored. These muscles are not the sole contributors to movements about these joints, but they are major contributors and can be monitored reliably with surface EMG. Standard skin preparation techniques were performed before applying disposable dual electrodes (Noraxon USA, Scottsdale, AZ) to the skin. EMG signals were amplified with a Bortec AMT-16 EMG measurement system (Bortec Biomedical, Calgary, AB, Canada) with high- and low-pass cutoff frequencies of 10 and 1,000 Hz, respectively.

Both EMG and acceleration signals were antialias filtered with custom fifth-order low-pass Bessel filters with a cutoff frequency of 500 Hz. These data were then sampled at 5 kHz (PCI-DAS 1602/16; Measurement Computing, Middleboro, MA) using custom software.

Corticomotor excitability

TMS was applied before and after training to assess changes in CE. Specifically, the effect of right upper limb training on left motor cortex was tested in right- and left-handed subjects. This had no influence on results because the dominant and nondominant cortex exhibit the same capacity for use-dependent plasticity (Ridding and Flavel 2006). Procedures were similar to those used by Classen et al. (1998). Assessments were made before training, immediately after training, and at subsequent 5-min intervals until 30 min after training, or until training-induced changes in TMS-evoked movements of the target joint were no longer evident. Each assessment involved recording 20 motor-evoked potentials (MEPs) at 0.2 Hz.

TMS was applied at the optimal scalp location for producing isolated movements of the target joint. Resting threshold (R_{TH}) and movement threshold (M_{TH}) were evaluated at this position. For the experiments involving the index finger and wrist, the TMS coil was held in this position with the handle pointing backward and oriented at 45° to the midline. R_{TH} was defined as the lowest TMS intensity that produced at least five MEPs >50 μV amplitude in both target muscles, in response to ten consecutive stimuli (Rossini et al. 1994). M_{TH} was the lowest TMS intensity that produced at least five of ten just-detectable movements (accelerations >0.5 m/s^2). TMS intensity during the experiment was set to the lowest intensity above M_{TH} that induced consistent, isolated movements of the target joint, as assessed visually by the experimenters. If consistent responses were not observed at about 150% of M_{TH} the experiment was aborted. Stimulation at such intensities and higher has been shown to saturate MEPs, making it possible that training-induced CE shifts could be masked (Carroll et al. 2001; Devanne et al. 1997).

Training protocols

Training involved rapid, ballistic movements of the target joint in the direction (either flexion or extension) closest to the opposite direction of TMS-induced movements recorded before training. For instance, if pretraining TMS caused movements with components of flexion and abduction, training movements were only in extension. Each training period lasted for 30 min and was paced by a metronome. Index finger and wrist training involved 1-Hz flexion or extension. This training rate has been shown to effectively induce short-term plasticity (Butefisch et al. 2000; Classen et al. 1998). Finger and wrist extension movements were performed with the forearm fully pronated (as described earlier), but flexion training was performed with the shoulder fully adducted and the forearm fully supinated (palm up). These upper limb configurations ensured that training movements were against gravity, and that the finger or wrist was returned to its neutral position without activation of the antagonist.

Elbow training was conducted in the horizontal plane at 0.5 Hz. During elbow training, the forearm rested on a low-friction rolling platform attached to an elastic spring (Thera-Band; Hygenic, Akron, OH). The purpose of the spring was to passively return the elbow to its starting position. The purpose for training at 0.5 Hz was to give subjects ample time to conduct unidirectional elbow movements and to let the elbow passively return to the starting position. This resulted in fewer elbow movements than were performed with the finger and wrist, but pilot data demonstrated that increasing the training time to 60 min does not significantly alter the results. This was determined in a preliminary study in which subjects ($n = 7$) performed ballistic, unidirectional elbow movements in the horizontal plane at 0.5 Hz.

TMS-evoked MEPs obtained from training agonists and antagonists were unchanged after 30 min of training ($t = 1.02$; $P = 0.348$), and they remained unaffected with an additional 30 min of training ($t = 1.38$; $P = 0.215$). Therefore elbow training in the present study was restricted to 30 min.

All subjects were given the following training instructions: *1*) Make ballistic motions in the training direction using only the agonist. *2*) Time movements to the metronome and rest between subsequent movements. *3*) Let the joint passively return to the starting position. *4*) If training feels fatiguing, continue to make movements quickly, yet less vigorously. Compliance with these instructions was monitored in real time using the recorded EMG and acceleration signals. To double-check that no subjects fatigued significantly during training, we also examined EMG-based measures of training during data analysis (see following text).

Control experiments

In addition to the primary experiments examining the influence of finger, wrist, and elbow training, several control experiments were performed. First, to observe whether CE changed over time in the absence of training, the wrist ($n = 5$) and elbow ($n = 5$) experiments were repeated with subjects who did not perform any training movements. Also, the wrist experiment was repeated ($n = 5$) with the round TMS coil, which was used in the primary elbow experiments, to determine whether differences in coil geometry could influence the observed results. All other aspects of these control studies were matched to the primary experiments.

Data processing and analysis

QUANTIFYING CHANGES IN CORTICOMOTOR EXCITABILITY. During CE assessment, TMS-evoked agonist and antagonist MEPs were recorded as EMG-based measures of CE. Figure 1*A* displays an example of MEPs recorded from the index finger muscles. Individual MEPs collected in each pre- and posttraining evaluation period were rectified and averaged before further processing. MEP magnitude was quantified as the average rectified EMG value within the 30-ms period after MEP onset. Trials in which muscles were activated before TMS were discarded before analysis. The average posttraining MEPs were normalized by the average pretraining values. This was done separately for the agonist ($nMEP_{ag}$) and antagonist ($nMEP_{ant}$) muscles of each subject. The ratio of the normalized agonist and antagonist responses ($nMEP_{ag}/nMEP_{ant}$) was used as a net measure of excitability about the joint. A similar ratio has been used previously to quantify the strength of the use-dependent encoding of directional information in corticomotor pathways (Butefisch et al. 2000; Kaelin-Lang et al. 2005).

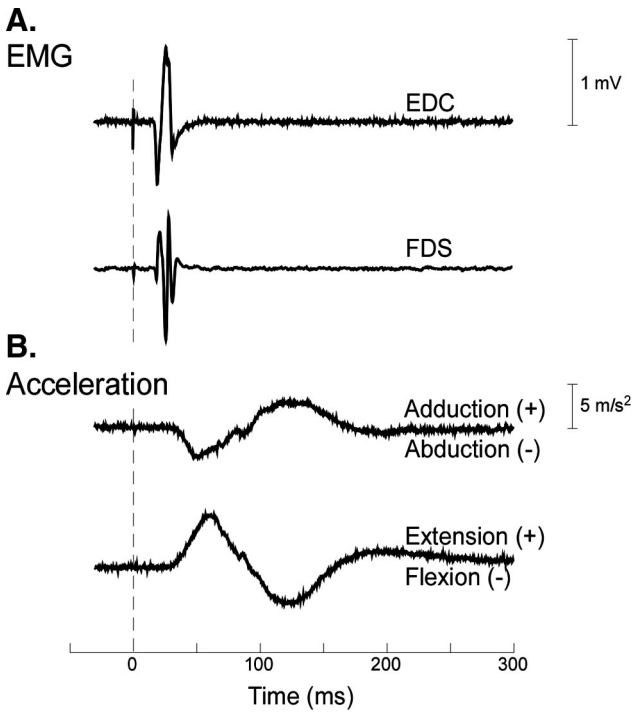

FIG. 1. Example of raw electromyographic (EMG) and acceleration data. Transcranial magnetic stimulation (TMS) pulse is denoted by the dashed line. *A*: motor-evoked potentials (MEPs) from extensor digitorum communis (EDC) and flexor digitorum superficialis (FDS), extrinsic index finger extensors and flexors. *B*: acceleration traces as recorded with the bidirectional accelerometer.

Each TMS pulse also elicited movement-based measures of CE. TMS-elicited motions of each target joint were quantified by the acceleration in the plane of movement. This was a plane defined by the flexion/extension and abduction/adduction directions for the index finger and wrist experiments. For elbow experiments elbow flexion/extension was monitored in the horizontal plane. A single acceleration vector was used to quantify the movement elicited in each trial. This vector corresponded to that measured at the time when the acceleration magnitude reached its first peak after the TMS pulse (Classen et al. 1998). Figure 1*B* displays finger acceleration data, recorded along the two monitored axes, from the single index finger trial. The maximum two-dimensional vector constructed from two components that were the maximum first-peak acceleration obtained from each of the two monitored axes, was used to determine the magnitude and direction of the joint acceleration after each application of TMS. The acceleration vectors from the pretraining trials were averaged for each subject. Deviations from this average pretraining vector were quantified by the magnitude of the angle between the vector from each individual trial and the average pretraining vector. This was done for both pre- and posttraining assessments.

EQUIVALENCE OF MOVEMENT- AND EMG-BASED MEASURES OF PLASTICITY. To examine whether TMS-evoked accelerations and MEPs were correlated on a trial-by-trial basis, we used logistic regression to predict the direction of TMS-evoked movements based on $nMEP_{ag}$ and $nMEP_{ant}$ values during each pre- and posttraining trial. Acceleration vectors that were within ±45° of the training direction and larger than the median acceleration vector for each subject were assigned a value of 1 and designated "training." Movements were assigned a 0 value (and designated "pretraining") if they were within ±45° of the average pretraining acceleration vector and larger than the median acceleration for that subject. Only data meeting these criteria were included to remove movements that may have been influenced by nonmonitored muscles, although additional magnitude thresholds also were tested to ensure that the selected values did not significantly bias our results. MEPs associated with included trials were normalized to the average pretraining MEP, and the ratio of each normalized agonist MEP to each normalized antagonist MEP [$nMEP(i)_{ag}/nMEP(i)_{ant}$] was calculated. The model was used to predict the probability of observing a TMS-evoked movement in the training direction at each empirical $nMEP(i)_{ag}/nMEP(i)_{ant}$ value.

MOVEMENT- AND EMG-BASED MEASURES OF TRAINING. To ensure that plasticity measures were not influenced by joint-dependent differences in training kinematics we evaluated the quality of training for each joint. Kinematic- and EMG-based measures of training movements were recorded approximately every 5 min throughout the course of each training session. Data from about 60 total training movements per subject were recorded for the finger and wrist during training. About 30 total movements per subject were recorded for the elbow. The angular deviation of the acceleration of training motions, relative to the average pretraining TMS-evoked endpoint acceleration, was used to quantify training direction. The circular dispersion (Fisher 1993) of training acceleration vectors about the mean training direc-

tion was used to quantify training variability, as demonstrated previously (Butefisch et al. 2000, 2004). Dispersion, ranging from 0 to 1, is defined as the magnitude of the resultant of all training movement acceleration vectors divided by the sum of the magnitude of the acceleration vectors recorded from all training movements. A value of 1 indicates that all training movements were in an identical direction, whereas a value of 0 indicates that training movements were directionally inconsistent.

We also examined fatigue during training by quantifying the EMG associated with training movements for each joint. The first ten movements from the 1st min of training were compared with the last ten movements from the 30th min of training by testing the average, root-mean-square EMG (RMS-EMG) from the training agonist. Any subject demonstrating a significant change in the agonist RMS-EMG during the 30th min of training would have been excluded from analysis.

Statistical models

The dependent variables ($nMEP_{ag}$, $nMEP_{ant}$, $nMEP_{ag}/nMEP_{ant}$, and angular deviation) for each joint were analyzed using general linear models. In these models, the independent variables were time after training and the joint being tested. Time was treated as a continuous variable, linearly related to each dependent variable, and subjects were treated as random factors to account for the fact that repeated measures were made within and across joints. Offsets of these general linear models were tested to determine the effect of training; slopes of the general linear models were tested for the effect of time after training.

In most cases normal error distributions were used to fit the kinematic data and gamma distributions closely fit our EMG-based plasticity measures. Gamma distributions typically are used to fit nonnegative, random, continuous variables (Hogg and Craig 1995). A two-sample Kolmogorov–Smirnov test was used to determine which distribution was most appropriate for inclusion in the general linear model. The choice of these distributions was verified by comparing the empirical cumulative distribution function (ECDF) to that of normal and gamma distributions fit to the same data. All P values were 0.57 ± 0.19 (mean ± SD), indicating that there was no statistically significant difference between our data and the chosen distribution.

For all statistical comparisons, a significance level of $P < 0.05$ was adopted. All post hoc comparisons were corrected for multiple comparisons. All statistical analyses were conducted using the R software package, version 2.2.1 (R Development Core Team, Vienna, Austria).

RESULTS

Equivalence of motor training between joints

The performance quality of motor training was equivalent for the primary experiments involving the index finger, wrist, and elbow. As indicated by the angular deviation values displayed in Table 1, the direction of training movements, relative to the direction of pretraining TMS-evoked movements, was nearly identical for the three target joints (one-way ANOVA; $F = 0.04$; $P = 0.963$). Additionally, training movements were remarkably consistent because dispersion values (Table 1) for all joints were nearly 1 and were statistically indistinguishable (one-way ANOVA; $F = 0.59$; $P = 0.563$). Finally, no subject exhibited significant fatigue during training. RMS-EMG values obtained from the training agonist during the 1st and 30th min of index finger (IF), wrist (W), and elbow (E) training were statistically indistinguishable (paired t-test; $t_{IF} = 0.18$; $P_{IF} = 0.858$; $t_W = 0.07$; $P_W = 0.943$; $t_E = 0.18$; $P_E = 0.862$).

TABLE 1. *Kinematic measures of training quality*

Experiment	Angular Deviation Degrees	Dispersion, r
Index finger (p)	144.0 ± 11.15	0.98 ± 0.01
Wrist (p)	147.0 ± 6.42	0.96 ± 0.01
Elbow (p)	145.3 ± 3.20	0.97 ± 0.02
Wrist (c)	153.9 ± 10.92	0.99 ± 0.00
Wrist (c-nt)	N/A	N/A
Elbow (c-nt)	N/A	N/A

Values are means ± SE. "Experiment" column denotes the joint tested. p, primary experiment; c, control experiment; nt, no training was performed.

Training-induced changes in TMS-evoked movements

Index finger training caused TMS-evoked finger motions to shift toward the direction of training. These results are consistent with those previously reported for the thumb (Classen et al. 1998). Figure 2*A* displays pre- and posttraining index finger acceleration vectors for a single subject. Before training, TMS-evoked finger accelerations were in flexion, but immediately after extension training TMS-evoked accelerations were in finger extension. After training, TMS-evoked motions systematically transitioned from extension to flexion. Finger movements had returned to the direction of pretraining within 30 min.

Statistically significant training effects on TMS-elicited movements were observed in the group data for all joints, although these were much more pronounced for the finger and wrist. Angular deviation data from the index finger experiment are presented in the first column of Fig. 2*B*. Training caused a significant increase in the angular deviation of posttraining finger motions, as indicated by the intercept of the general linear model of deviation data relative to pretraining (119°; $t = 8.19$; $P < 0.001$). Angular deviation values decreased as the training effect diminished with time, as indicated by the significant negative slope of the model (−2°/min; $t = -5.80$; $P < 0.001$). Within 30 min after training, group deviation values for the index finger were not significantly different from pretraining values ($P > 0.05$).

Repetitive wrist training also caused a significant change in the direction of TMS-evoked movements of the wrist, but the training effect was more variable between subjects, as indicated by the larger error bounds in Fig. 2*B* (*second column*). In some subjects posttraining TMS-evoked movements were initially in the training direction and then recovered. In some subjects posttraining TMS-evoked motions persisted in the training direction. In other subjects training had little effect. Overall, wrist training caused group angular deviation values to increase immediately after training (92°; $t = 4.71$; $P < 0.001$), then to decrease during the course of posttraining (−0.6°/min; $t = -3.35$; $P = 0.001$). Within 25 min posttraining, the orientation of the TMS-evoked wrist accelerations was not significantly different from pretraining values ($P > 0.05$).

For the elbow, repetitive training did not change the direction of TMS-evoked movements. In all ten subjects pretraining TMS produced elbow flexion, training was in elbow extension, and posttraining TMS-evoked movements were in flexion. As seen in Fig. 2*B* (*third column*), angular deviation values were not significantly different from pretraining values at any of the measured time points ($P > 0.05$). However, there was a statistically significant decrease in the deviation values mea-

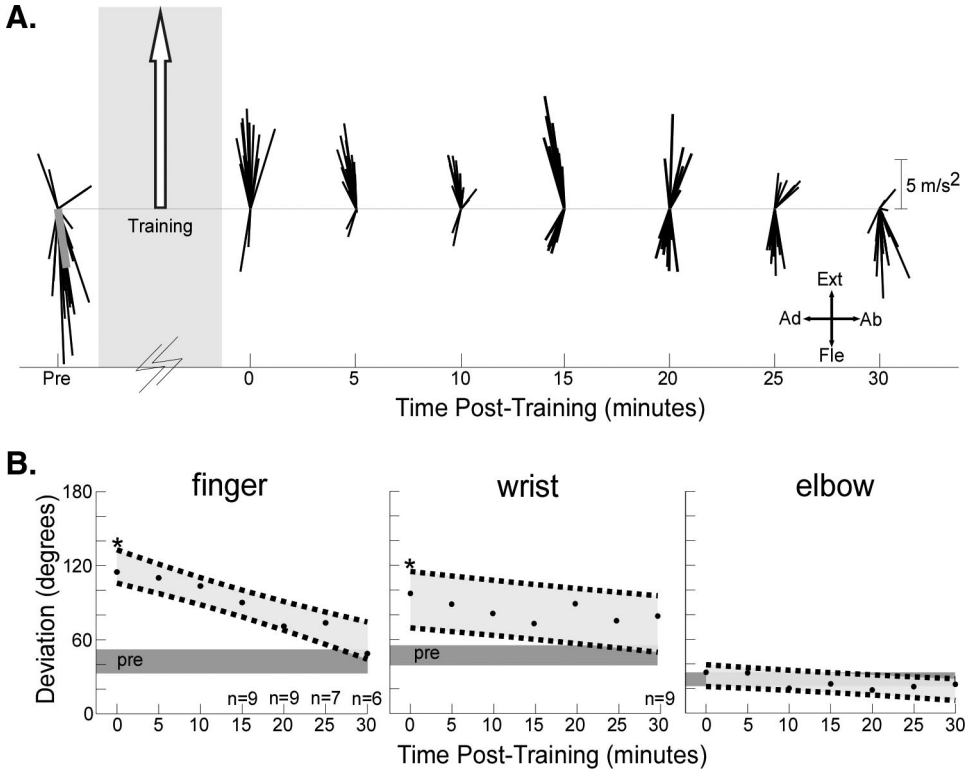

FIG. 2. TMS-evoked endpoint acceleration vectors from a single subject in the index finger experiment, and group angular deviation values from all experiments. *A*: each thin black line represents a single TMS-evoked acceleration. Thick gray line indicates the averaged pretraining acceleration. Gray box represents the training session. Thick white arrow, outlined in black, indicates the average magnitude and direction of the acceleration of training movements. *B*: group angular deviation data. Black circles are means, and black dashed lines depict 95% confidence intervals. Dark gray shaded block (pre) indicates 95% confidence intervals of values calculated before training. Pretraining angular deviation values were not calculated after training, but are displayed for comparison to posttraining values. Black stars (*) indicate a significant effect of training ($P < 0.05$).

sured throughout this posttraining period (−0.4°/min; t = −4.01; $P < 0.001$), suggesting that a small training effect was present.

Training-induced changes in agonist and antagonist MEPs

Changes in TMS-evoked movements of the tested joints were associated with selective training-induced changes in agonist and antagonist MEPs. Figure 3*A* displays an example of the immediate effect of finger training on averaged, surface EMG traces of FDS and EDC from one subject. Before training, TMS generated MEPs in FDS that were larger than those in EDC, and pretraining finger motions were in flexion. Immediately after extension training, EDC MEPs increased and FDS MEPs decreased, suggesting that the training-induced changes in the TMS-evoked movement direction were due to corresponding changes in agonist and antagonist CEs.

Similar changes in agonist and antagonist CEs were observed in the finger and wrist data for all subjects; a consistent time-dependent change in the MEPs of the training antagonist was observed at all three joints (Fig. 3, *B* and *C*). Agonist MEPs for the finger were significantly increased and antagonist MEPs were significantly decreased immediately after training, as seen in the *first column* of Fig. 3, *B* and *C* ($nMEP_{ag} = 1.68$; $t_{ag} = 2.12$; $P_{ag} = 0.039$; $nMEP_{ant} = 0.70$; $t_{ant} = -1.87$; $P_{ant} = 0.047$). The agonist MEP increase was persistent and did not depend on time (t = 1.02; $P = 0.312$). Antagonist MEPs for the finger, which initially decreased, were not significantly different from pretraining values within 5 min posttraining and were significantly greater ($P < 0.05$) than pretraining values by 30 min posttraining. Therefore antagonist MEPs for the index finger increased significantly over time (0.02/min; t = 4.74; $P < 0.001$). Wrist training had similar effects, demonstrating a significant increase in agonist MEPs (1.66; t = 2.70; $P = 0.009$) that was persistent and did not depend on time (t = 1.12; $P = 0.268$). Although wrist antagonist MEPs never differed significantly from pretraining values ($P > 0.05$), they did increase significantly in the posttraining period (0.01/min; t = 2.75; $P = 0.008$). The only significant change observed after elbow training was a time-dependent increase in the size of the antagonist MEPs (0.01/min; t = 2.54; $P = 0.014$).

Equivalence of movement- and EMG-based measures of plasticity

There was a direct correspondence between the movement-based and MEP-based measures of CE used in this study. Figure 4 illustrates how the direction of TMS-evoked motions could be predicted from $nMEP_{ag}/nMEP_{ant}$ data using a logistic regression model. It displays the model's predictive probability as a function of the MEP data from a single subject. Black circles above the dashed line and white circles below the dashed line are movements predicted correctly. The prediction accuracy for these data was 91.0%. Across all subjects 85.2 ± 9.5% of the elicited finger movement directions and 82.9 ± 7.9% of the elicited wrist movement directions were accurately predicted from the measured MEPs. These results demonstrate that our two measures of plasticity were correlated on a trial-by-trial basis, within each joint. This analysis was not performed for the elbow because the effect of elbow training was minimal (Fig. 2*B*, *third column*). Because there was no variation in the direction of TMS-elicited elbow movements before or after training, modeling would have been a trivial exercise.

Additionally, to ensure that this analysis did not bias our results toward equivalence, we performed a similar analysis on acceleration vectors larger than the 25th, 10th, and 0th percentile acceleration vectors. The size of the acceleration vectors

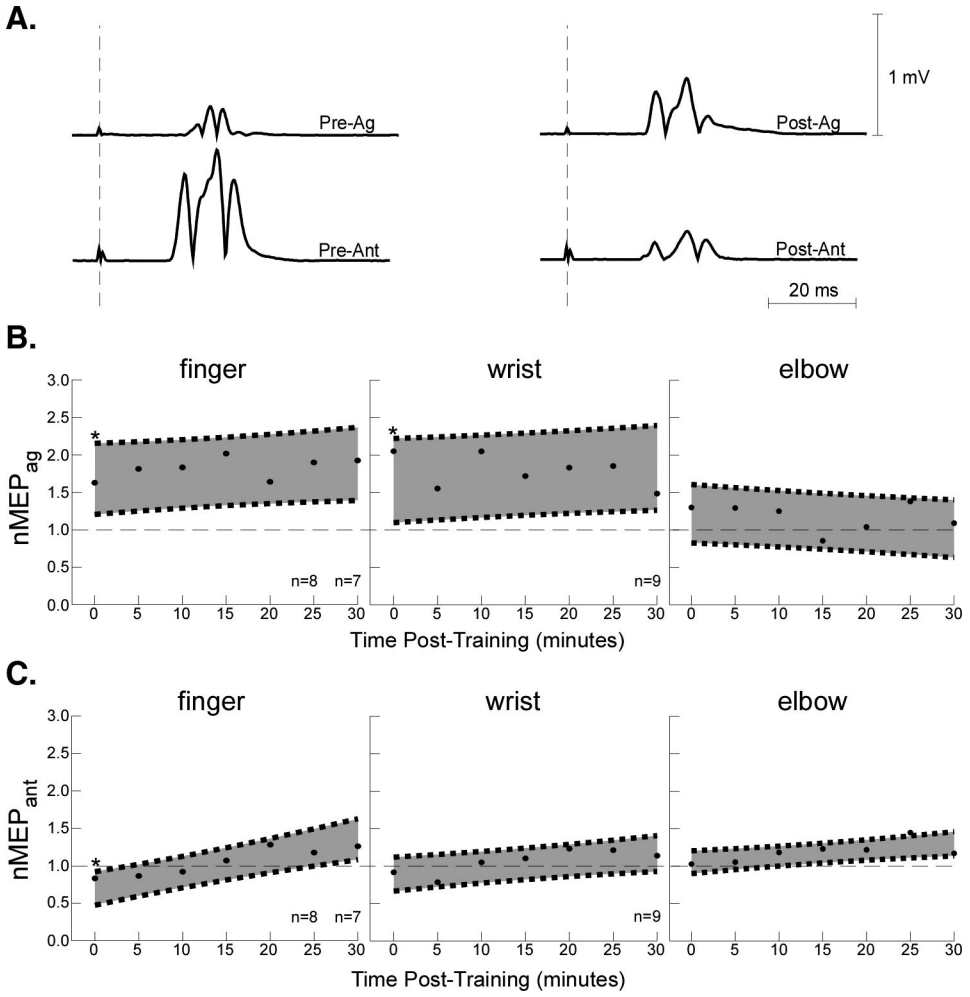

FIG. 3. Averaged, rectified MEPs from a single subject in the index finger experiment, and a summary of normalized MEP values in agonists and antagonists. *A*, *left column*: recorded before training. *Right column*: recorded at 0 min posttraining. *1st row*: recorded from EDS (Ag). *2nd row*: recorded from flexor digitorum communis (FDC, Ant). Dashed lines indicate TMS application. *B*: averaged agonist MEP values. Black circles are means. Thick black dashed lines are 95% confidence intervals. Thin dashed line denotes no change from pretraining. Black stars (*) denote a significant effect of training ($P < 0.05$). *C*: normalized MEP values of the antagonist. Conventions are the same as for *B*.

included in our analysis did not have a significant effect on the prediction accuracy of the logistic regression model for finger or wrist data (one-way ANOVA; $F_{IF} = 2.20$; $P_{IF} = 0.105$; $F_W = 0.61$; $P_W = 0.613$).

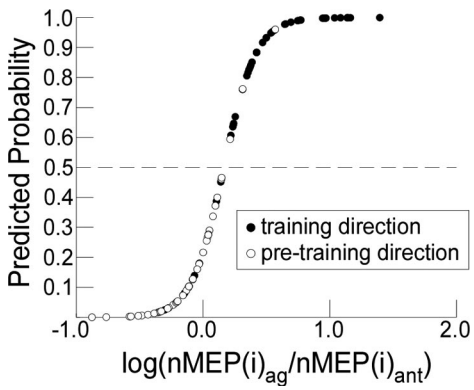

FIG. 4. Predicted probability of observing a TMS-evoked movement in the direction of training, based on EMG responses. Representative subject in the index finger experiment. Probability values >0.5 predict movements in the training direction, whereas values <0.5 predict movements in the pretraining direction. Black/white circles indicate the actual direction of TMS-evoked movements in either the training/pretraining direction. The log of $nMEP_{ag}/nMEP_{ant}$ values was taken to condense the range of high ratio values and expand the range of low ratio values for this figure. This had no effect on the model's predictions.

Between-joint comparison of plasticity

Statistical comparisons between joints were made solely on the basis of MEP data because, unlike movement-based measures, MEP-based measures are not influenced by the inertial differences of the limb segments distal to each of the target joints. Specifically, we compared the training-induced changes in CE across joints using the $nMEP_{ag}/nMEP_{ant}$ ratio, shown to be strongly correlated with the movement directions at an individual joint (Fig. 4).

We observed that repetitive training had a greater influence on these TMS-based measures of CE in distal muscles than in proximal muscles. Figure 5*A* displays group $nMEP_{ag}/nMEP_{ant}$ data after training at the index finger, wrist, and elbow joints. Index finger training caused a significant increase in this ratio immediately posttraining (2.93; $t = 5.51$; $P < 0.001$). During the 30 min after training, the agonist/antagonist MEP ratio for the finger endured a time-dependent recovery toward baseline, consistent with the recovery of finger movements toward the pretraining direction (−0.05/min; $t_{finger} = -3.45$; $P_{finger} = 0.001$). For the wrist, repetitive training also significantly increased the $nMEP_{ag}/nMEP_{ant}$ ratio immediately after training (2.01, $t = 3.68$; $P = 0.001$), and this increase decayed with time after training (−0.02/min; $t_{wrist} = -2.11$; $P_{wrist} = 0.039$). These EMG data were also consistent with the time-dependent recovery of TMS-elicited motions of the wrist. Finally, elbow

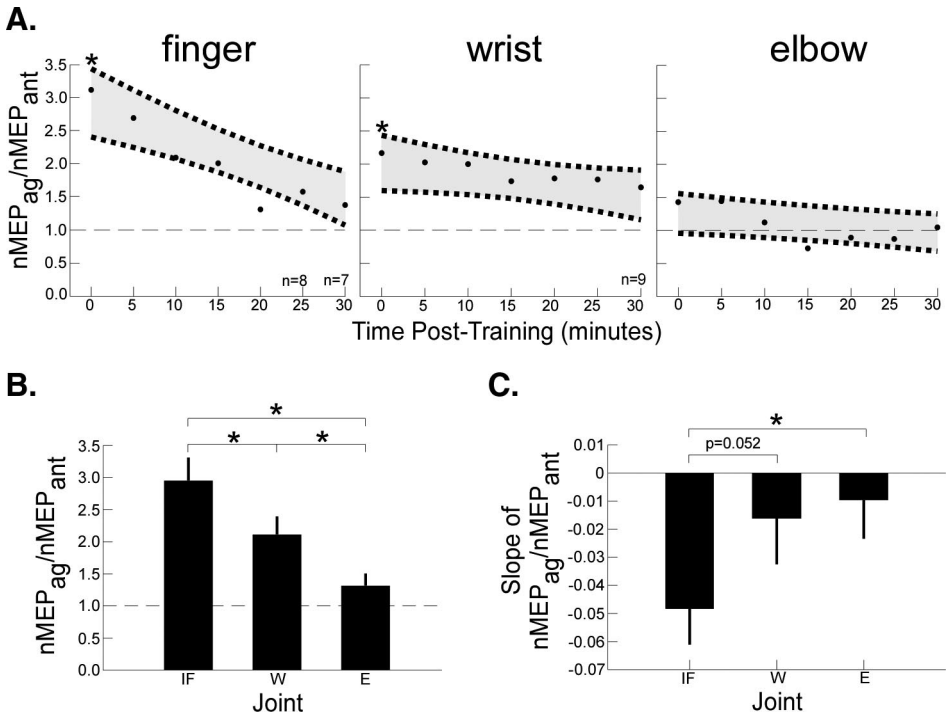

FIG. 5. Summary of $nMEP_{ag}/nMEP_{ant}$ values. *A*: black circles are means and thick black dashed lines are 95% confidence intervals. Thin dashed lines denote no change from pretraining. Black stars (*) indicate a significant effect of training ($P < 0.05$). *B*: magnitude of $nMEP_{ag}/nMEP_{ant}$ values obtained immediately after training. *C*: loss of training-induced increases in $nMEP_{ag}/nMEP_{ant}$ values. Bars are mean ± SE. Black stars (*) indicate significance between joints after corrections for multiple comparisons.

training had no significant effect on $nMEP_{ag}/nMEP_{ant}$ values at any point after training ($P > 0.05$), but the effect of time after training was significant (−0.01/min; $t_{elbow} = -2.48$; $P_{elbow} = 0.016$). Immediately after training (Fig. 5*B*), the $nMEP_{ag}/nMEP_{ant}$ ratio for the index finger was greater than that for the wrist (post hoc; $t = -2.60$; $P = 0.010$) and the elbow (post hoc; $t = -5.22$; $P < 0.001$). Additionally, the training-induced increase in $nMEP_{ag}/nMEP_{ant}$ data for the wrist was greater than that for the elbow ($t = -2.81$; $P = 0.005$). The time-dependent decrease in the $nMEP_{ag}/nMEP_{ant}$ ratio after training (Fig. 5*C*) was significantly greater in the finger than that in the elbow (post hoc; $t = 2.80$; $P = 0.006$). Statistical significance was not reached for the finger-to-wrist comparison (post hoc; $t = 1.96$; $P = 0.052$) or the wrist-to-elbow comparison (post hoc; $P > 0.05$).

Control studies without motor training

Changes comparable to those observed after training were not observed in subjects who did not perform any training movements. This was assessed in a subset of subjects from the primary experiments by replacing the training period with an equivalent rest period. TMS pulses applied before the rest period are considered the "pretraining" set and those after the rest period are considered the "posttraining" set. In the control wrist experiment ($n = 5$) both CE measures, angular deviation and $nMEP_{ag}/nMEP_{ant}$, remained at the pretraining magnitudes ($t_{angle} = -0.30$; $P_{angle} = 0.764$; $t_{ratio} = -0.07$; $P_{ratio} = 0.945$) and were not dependent on time ($t_{angle} = 0.06$; $P_{angle} = 0.949$; $t_{ratio} = 0.17$; $P_{ratio} = 0.868$).

Additionally, to verify that training was the cause of the time-dependent angular deviation and $nMEP_{ag}/nMEP_{ant}$ values after elbow experiments (Figs. 2*A* and 5*A*), we performed a similar no-training elbow experiment ($n = 5$). In this experiment time had no effect on angular deviation or $nMEP_{ag}/nMEP_{ant}$ data ($t_{angle} = 0.03$; $P_{angle} = 0.974$; $t_{ratio} = -0.68$; $P_{ratio} = 0.502$), and neither was significantly different from the pretraining values ($t_{angle} = 0.74$; $P_{angle} = 0.467$; $t_{ratio} = 0.26$; $P_{ratio} = 0.791$). These results verify that the corticomotor plasticity observed in the training studies was due to the effects of training and not the assessment protocol. These results also verify that repetitive, low-frequency (0.2 Hz) TMS does not cause shifts in excitability in the corticomotor pathways controlling the wrist and elbow, consistent with previous results reported for the untrained thumb (Classen et al. 1998), and a study that reported that 0.1-Hz repetitive TMS had no effect on the CE of abductor pollicis brevis (APB) (Chen et al. 1997).

Influence of stimulation intensity

Due to the different motor thresholds of the muscles tested in this study, there were variations in the TMS intensity used to assess CE at each joint (one-way ANOVA; $F = 7.78$; $P = 0.002$; Fig. 6*A*). TMS intensities relative to resting threshold in each primary experiment are shown in Fig. 6. Absolute stimulator intensities, R_{TH} values, M_{TH} values, and raw peak-to-peak pretraining agonist and antagonist MEPs from all experiments are reported for completeness in Table 2. To determine whether relative TMS intensity influenced the observed joint-dependent changes in CE, we examined whether the normalized MEP responses at each joint were intensity dependent. Figure 6, *B–D* shows how $nMEP_{ag}/nMEP_{ant}$ values varied with stimulation intensity relative to R_{TH} within our subject population. Each circle in the figure corresponds to the average $nMEP_{ag}/nMEP_{ant}$ ratio from each subject at 0 min posttraining. Lines in the figures are linear regressions of TMS intensity onto $nMEP_{ag}/nMEP_{ant}$. If the decreased plasticity observed in proximal muscles was related to increased TMS intensities we would expect to observe decreasing $nMEP_{ag}/nMEP_{ant}$ ratios with increasing intensity, which was not observed. There was no significant relationship between TMS intensity and $nMEP_{ag}/nMEP_{ant}$ for the muscles crossing the finger, wrist, or

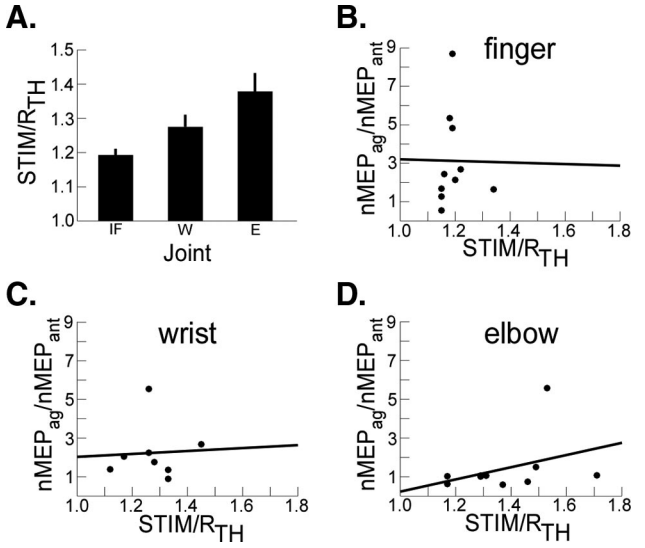

FIG. 6. TMS intensities used in all experiments, and $nMEP_{ag}/nMEP_{ant}$ values obtained at these intensities immediately after training. *A*: bars are mean + SE of TMS intensities relative to resting threshold (R_{TH}). *B*, *C*, and *D*: each circle represents the $nMEP_{ag}/nMEP_{ant}$ values obtained at 0 min posttraining from each subject. Lines are simple linear regression of TMS intensity data onto MEP data.

elbow because the slopes of the models presented in Fig. 6 were not significant ($t_{IF} = 0.03$; $P_{IF} = 0.979$; $t_W = 0.13$; $P_W = 0.900$; $t_E = 1.09$; $P_E = 0.306$).

Influence of coil geometry

A figure-of-eight TMS coil was used to improve muscle selectivity when stimulating finger and wrist muscles, but a circular coil, which has a less focal area of stimulation (Di Lazzaro et al. 2002), was needed to consistently activate elbow muscles. To ensure that the difference in plasticity measures across joints was not related to coil selection we repeated the wrist training experiment using the round coil ($n = 5$). The quality of training movements in this experiment was the same as that in the primary wrist experiment (Table 1; $t_{deviation} = 0.59$; $P_{deviation} = 0.566$; $t_{dispersion} = 1.65$; $P_{dispersion} = 0.124$). Wrist training caused a significant increase in $nMEP_{ag}/nMEP_{ant}$ data obtained with the round coil ($t_{ratio} = 5.45$; $P < 0.001$), as indicated by the leftmost light gray bar in Fig. 7 and as previously observed for the figure-of-eight coil (Fig. 7, leftmost dark gray bar). There was also a significant directional change in TMS-evoked wrist movements obtained with the round coil ($t = 6.18$; $P < 0.001$). These results suggest that the lack of CE modulation observed in the elbow experiment was not related to coil selection.

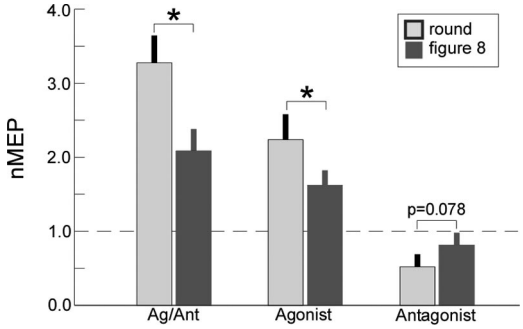

FIG. 7. Comparison of EMG-based plasticity measures obtained with the round coil and the figure-of-eight shaped coil, immediately after wrist training. Ratio of agonist to antagonist MEP values, agonist MEP values, and antagonist MEP values are displayed. Bars are mean + SEs. Black stars (*) indicate a significant effect of coil ($P < 0.05$).

Interestingly, the observed training-related changes in both plasticity measures immediately after training were larger when assessed with the round coil than with the figure-of-eight coil (Fig. 7, first pair of bars; $t_{ratio} = 4.00$; $P_{ratio} < 0.001$; $t_{angle} = 2.49$; $P_{angle} = 0.014$). These increased plasticity measures were caused by posttraining agonist MEPs that were significantly larger and antagonist MEPs that appeared smaller (antagonist MEPs did not reach statistical significance), compared with those obtained with the figure-of-eight coil (Fig. 7; $t_{ag} = 3.05$; $P_{ag} = 0.003$; $t_{ant} = -1.78$; $P_{ant} = 0.078$). Additionally, antagonist MEPs increased during posttraining, whereas agonist MEPs did not depend on time after training as observed in all experiments ($t_{ant} = 4.95$; $P_{ant} < 0.001$; $t_{ag} = 0.15$; $P_{ag} = 0.883$).

DISCUSSION

This study quantified changes in CE induced by repetitive movements of the index finger, wrist, and elbow. To our knowledge this study was the first to directly compare use-dependent excitability changes in the motor pathways innervating proximal and distal joints of the upper limb. Changes in TMS-evoked muscle activity and joint movements were taken as evidence of short-term corticomotor plasticity, and changes in TMS-evoked MEPs were used to compare this plasticity between joints. Based on these measures, we observed the largest training effects in the corticomotor pathways innervating distal muscles. This effect decreased in the pathways innervating more proximal muscles of the upper limb. Differences in the training effect across joints could not be attributed to inconsistencies in the quality of motor training across joints because kinematic measures of motor training were equivalent

TABLE 2. *Pretraining measures of corticomotor excitability and TMS parameters*

Experiment	Coil	$MEP_{agonist}$, mV	$MEP_{antagonist}$, mV	R_{TH}, % max.	M_{TH}, % max.	TMS Intensity % max.
Index finger (p)	F8	0.59 ± 0.19	0.79 ± 0.16	36.1 ± 1.5	39.3 ± 1.6	43.2 ± 1.9
Wrist (p)	F8	0.50 ± 0.14	0.77 ± 0.12	36.3 ± 1.9	41.6 ± 2.8	47.0 ± 3.0
Elbow (p)	R	0.20 ± 0.02	0.49 ± 0.11	40.4 ± 1.1	48.0 ± 1.6	55.6 ± 2.5
Wrist (c)	R	0.65 ± 0.15	0.66 ± 0.08	36.8 ± 1.7	40.6 ± 2.0	46.2 ± 2.4
Wrist (c-nt)	F8	0.42 ± 0.12	0.67 ± 0.09	38.2 ± 1.9	41.8 ± 2.2	47.6 ± 2.6
Elbow (c-nt)	R	0.10 ± 0.02	0.29 ± 0.05	44.2 ± 2.5	50.4 ± 2.6	60.6 ± 3.8

Values are means ± SE. "Experiment" column denotes the joint tested. p, primary experiment; c, control experiment; nt, no training was performed. Data obtained from both figure-of-eight (F8) and round (R) TMS coils are included. R_{TH}, M_{TH}, and TMS intensity values used in experiments are reported as a percentage of the stimulator's maximal output.

(Table 1). In addition, the differences in the training effect across joints were not due to differences in limb inertia, stimulus intensity, or coil geometry. Rather, our results suggest a fundamental difference in the motor cortical contributions to short-term motor plasticity in the pathways controlling proximal and distal joints in the human upper limb. These results have implications for how motor learning occurs in proximal and distal muscles in the human upper limb and the utility of using motor cortical TMS to quantify the effects of that learning.

Equivalence of movement- and EMG-based measures of plasticity

We used an EMG-based measure of CE to compare the training effects across joints. Previous studies have used both kinematic and EMG measures to quantify CE at individual joints. We chose to use only an EMG-based comparison so that our results would not be biased by the inertial differences at the finger, wrist, and elbow. Nevertheless, we were able to demonstrate a trial-by-trial equivalence of the EMG and kinematic measures at the finger and wrist. Not all previous studies have reported such an equivalency. For example, some studies of simple thumb training have demonstrated training-induced MEP changes that persisted beyond the observed recovery of kinematic effects (Butefisch et al. 2002, 2004). These differences may have resulted from unrecorded muscles contributing to the thumb movements. The equivalency demonstrated in this study suggests that we were able to record from muscles that were the prime contributors to the observed movements, or at least close synergists to the prime contributors.

Distal-to-proximal gradation of plasticity

The measure of use-dependent plasticity used in this study was greatest in the pathways controlling the most distal joint tested, the index finger. Finger training caused TMS-evoked index finger motions to move toward the direction of training then to recover toward the pretraining direction. These results are consistent with movement data presented previously for the thumb (Classen et al. 1998). Changes in TMS-evoked finger motions were the result of temporary excitability increases in agonist pathways relative to antagonist pathways, as summarized by MEP responses normalized to pretraining values (Fig. 5). Posttraining $nMEP_{ag}/nMEP_{ant}$ values for the finger, which were larger than those for the wrist or the elbow immediately posttraining, decreased as use-dependent excitability changes gradually diminished. The increased $nMEP_{ag}/nMEP_{ant}$ values immediately posttraining are consistent with raw agonist and antagonist MEP values recorded in previous studies of the thumb (Butefisch et al. 2000; Celnik et al. 2005; Kaelin-Lang et al. 2005; Stefan et al. 2005). The rate of decrease in $nMEP_{ag}/nMEP_{ant}$ values appeared to occur more quickly for the finger than for the wrist (significance was not reached) and occurred most slowly for the elbow (Fig. 5*C*). These differences between joints appear to be mediated predominantly by changes in magnitude of the antagonist MEPs, which had joint-specific differences, rather than those of the agonist MEPs.

EMG data obtained from the wrist experiment exhibited trends consistent with those observed after finger training. The increased $nMEP_{ag}/nMEP_{ant}$ values for the wrist, which were smaller than those from the index finger, were caused by changes in agonist and antagonist MEPs that mirrored those observed in the finger (Fig. 4). These changes were not present in the absence of training. Few studies have investigated corticomotor plasticity after wrist training, but our data are consistent with a report of increased agonist MEPs relative to antagonist MEPs after unidirectional wrist training (Wolters et al. 2001). Our data are also consistent with a study that examined bidirectional wrist training and reported increased activity in excitatory interneurons within the cortical representation of ECR (Lotze et al. 2003), a muscle that contributed to antigravity movements in our study and this previous work.

The smallest amount of use-dependent plasticity was measured in the pathways controlling the elbow. Training did not induce a significant change in the direction of TMS-elicited elbow movements nor in the associated MEP responses. Nevertheless, there was a significant time-dependent change in the $nMEP_{ag}/nMEP_{ant}$ ratio after training that was not observed in the absence of training. This suggests that our training paradigm did induce changes in the motor cortical pathways controlling the elbow, but that the measured changes were small. One previous study has assessed the influence of elbow training on CE and found results consistent with ours; repetitive elbow flexion causes only small increases in biceps MEPs (Ziemann et al. 2001). Interestingly, these authors demonstrated large changes in biceps MEPs after repetitive training combined with ischemic nerve block; ischemic nerve block may have decreased the excitability of inhibitory interneurons, thus enhancing the effect of training. Alternative methods for enhancing training-induced plasticity have also been explored at more distal joints. These include TMS applied during training (Butefisch et al. 2004) and pharmacologic agents given before training (Butefisch et al. 2002; Floel et al. 2005; Sawaki et al. 2002). Such techniques may also enhance the effect of repetitive training at the elbow on changes in CE.

Similarity of motor training across joints

It is well known that ballistic motor training induces changes in CE that are strongly influenced by kinematic features of the performed movements (Classen et al. 1998; Muellbacher et al. 2001). This makes it possible that any differences in the quality of the training across joints could have contributed to our results. To minimize this possibility, we ensured that the kinematic features of the training were similar at each joint. This was verified using previously reported measures of angular deviation and dispersion (Fisher 1993), as previously used to quantify movement quality in studies of repetitive thumb training (Butefisch et al. 2000, 2004). These measures did not differ significantly across the tested joints, suggesting that the observed changes in CE did not result from differences in the quality of movement training across joints.

Influence of coil shape on plasticity measures

It is possible that the use of the nonfocal round coil may have masked CE changes in proximal muscles by activating surrounding inhibitory interneuronal networks (Chen et al. 1998), or by directly activating corticospinal projections (Di Lazzaro et al. 2002). However, plasticity measurements ob-

tained with the circular coil were larger than those obtained with the figure-of-eight coil after similar sessions of wrist training (Table 1; Fig. 7), indicating that use of this coil did not compromise the ability to detect training-dependent CE changes at the wrist. Thus we would expect to observe use-dependent CE changes after elbow training had they occurred, regardless of coil shape.

Influence of absolute TMS intensity on plasticity measures

It has been demonstrated that as absolute TMS intensity is increased corticospinal projections are stimulated more directly (Kaneko et al. 1996). Thus it is possible that the higher TMS intensities used for the elbow study (Table 2) may have directly activated pyramidal cell bodies, producing motor responses that were uninfluenced by use-dependent changes in intracortical excitability (Rothwell 1997). Although the present data cannot directly rule out this possibility, we believe that this is an unlikely contributor to our results. First, there was no significant relationship between our EMG-based plasticity measures and TMS intensity relative to resting threshold (Fig. 6, Table 2). Second, the activation of direct projections with a round TMS coil occurs at an average of about 80% of maximal stimulator output (Kaneko et al. 1996), >24% higher than the average intensity used in our experiments. Finally, the possibility of direct corticospinal activation can be assessed by examining decreases in MEP latency with increases in TMS intensity because direct stimulation of corticospinal pathways result in MEPs with a 1- to 2-ms shorter latency than that of MEPs activated by transynaptic pathways (Werhahn et al. 1994). In a single subject, we determined that this latency shift occurred only at TMS intensities >22% more than the highest intensity used for any subject (>94% maximal stimulator output). This test was not continued because such high intensities caused marked discomfort. Nevertheless, these results are consistent with previously reported values (Kaneko et al. 1996).

It is also conceivable that the high-intensity TMS used in the elbow experiment induced current spread beyond the center of stimulation, activating surrounding inhibitory cortical interneurons. Such neurons, similar to those studied in humans (Chen et al. 1998) and animals (Krnjevic et al. 1966), could have masked excitability increases in pathways to the target muscles. However, if surround inhibition influenced our results, we would have expected decreased plasticity measures in the wrist experiment performed with the round coil, relative to those obtained from the figure-of-eight coil; TMS from the round coil is more likely to activate cortical tissue surrounding the target (Di Lazzaro et al. 2002). Instead, plasticity measures obtained from the wrist experiment performed with the round TMS coil were larger, making it unlikely that surrounding inhibitory interneurons influenced our results.

Mechanisms underlying the measured differences in proximal versus distal motor learning

Differences in the organization and function of motor cortical areas controlling proximal and distal muscles likely contribute to the joint-specific differences in plasticity observed in this work. First, large topographical areas of motor cortex are associated with the distal upper limb, whereas the proximal upper limb has smaller cortical representations (Penfield and Boldrey 1937; Wassermann et al. 1992). Second, the number of direct projections from motor cortex to upper limb motor neurons is greater for distal muscles than for proximal muscles (Palmer and Ashby 1992). Third, monosynaptic projections may play a relatively larger role in the control of the hand than in more proximal muscles (Turton and Lemon 1999). Finally, motor cortical plasticity may also differ in the regions controlling proximal and distal muscles. This is supported by studies in which inhibition induced by theta burst stimulation (Martin et al. 2006) and use-dependent interhemispheric inhibition (Sohn et al. 2003) were shown to be more effective in distal representations than in proximal representations.

Our results do not imply that motor learning cannot occur in the neural structures controlling the proximal musculature. In fact, long-term, highly skilled training leads to long-term enlargement in the cortical representation of the medial deltoid, as observed in elite volleyball players but not in recreational athletes (Tyc et al. 2005). Additionally, numerous previous studies have demonstrated the adaptability of proximal muscle control during whole limb force-field adaptation tasks, over a timescale similar to that studied in our experiments (Shadmehr and Mussa-Ivaldi 1994). The results presented herein only imply that any immediate effects of ballistic training that may have occurred, beyond the small motor cortical effect reported here, were not readily observable with the TMS techniques used in this work.

Other pathways may play a larger role in the neural adaptation that accompanies changes in proximal muscle control. A potential region, which has been shown to be involved in early proximal motor skill acquisition, is prefrontal cortex (Shadmehr and Holcomb 1997). There are also a number of indirect, ipsilateral descending pathways that are known to preferentially contribute to the control of proximal muscles, but any use-dependent changes in these pathways, had they occurred, would not have been observed in this study. It has been suggested that motor responses to ipsilateral TMS may be evoked from these pathways; thus it is conceivable that ipsilateral TMS may have revealed use-dependent changes, had they occurred. Such potential pathways include: small-diameter corticospinal pathways (Colebatch et al. 1990), corticobulbospinal pathways (Colebatch et al. 1990), and corticoreticulospinal pathways (Ziemann et al. 1999).

An alternative explanation is that the short-term training paradigm used in this study simply did not induce a comparable degree of plasticity in the aggregate pathways controlling the elbow comparable to that measured in the corticomotor pathways innervating the wrist and finger. Although it has been suggested that motor learning by repetitive, "feedforward" movements induces neural changes within motor cortex (Baraduc et al. 2004), these authors examined movements of the index finger only. It is possible that similar short-term neural processes may not occur when similar training is conducted with the proximal upper limb.

Role of agonist and antagonist CE in repetitive motor learning

Ballistic, single-joint training generated selective excitability changes that were similar in the pathways leading to agonists and antagonists of the finger and wrist. Additionally,

in all three tested joints antagonist MEPs increased over time, as they were significantly dependent on time. Interestingly, MEPs obtained with the figure-of-eight TMS coil may have restricted our view of the cumulative training-induced changes in both agonist and antagonist CEs. This is because the figure-of-eight coil, compared to the round coil, induces focal cortical currents (Cohen et al. 1990). Therefore in the finger and wrist experiment a scalp location was chosen by positioning the figure-of-eight coil at a location that produced consistent joint movements. By definition in our protocol, the muscles stimulated most directly by this positioning became the training antagonists. Consequently, CE data obtained with the figure-of-eight coil may have been dominated by changes in antagonist excitability. This is supported by the fact that the time-dependent changes in antagonist MEPs more closely matched the time-dependent changes in endpoint accelerations than did the persistent changes in the agonist.

The wrist experiment performed with the round TMS coil suggests that motor memories may be closely linked to the encoding of CE changes in pathways innervating both agonists and antagonists. The round coil stimulates a larger area of cortical tissue, thereby directly activating a broader group of muscles than primarily the training antagonist (Di Lazzaro et al. 2002). This increased activation likely caused our observation that, immediately after wrist training, agonist MEPs were larger and antagonist MEPs appeared smaller when elicited with the round coil (Fig. 7). This led to assessments of CE changes that were significantly larger than those in the original wrist experiment. These results suggest that the use of a round stimulating coil may provide a more complete view of the pathways altered by movement training.

In conclusion, this study directly compared training-induced plasticity in distal and proximal upper limb corticomotor pathways using TMS of the motor cortical areas. According to our measures, the motor cortical plasticity induced by single-joint, repetitive upper limb training was graded from proximal to distal, with the greatest changes observed in distal muscles. The relative sizes, structures, and roles of the motor cortical areas controlling the proximal and distal upper limb may be associated with the relative degree with which plasticity occurred in proximal and distal pathways. Subsequently, primary motor cortex may have a larger role in the short-term neural adaptation driven by repetitive ballistic training at the distal joints of the human upper limb, relative to that at more proximal joints.

ACKNOWLEDGMENTS

We thank Dr. Leah Welty for statistical consultation and Drs. William Z. Rymer, Colum MacKinnon, and Ferdinando Mussa-Ivaldi for insightful comments and spirited discussions.

GRANTS

This work was supported by American Heart Association Predoctoral Fellowship 0615573Z, National Institute of Child Health and Human Development Grant K25 HD-044720, and the Falk Family Trust.

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