Hemispheric Differences in the Relationship Between Corticomotor Excitability Changes Following a Fine-Motor Task and Motor Learning

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Garry, Michael I., Gary Kamen, and Michael A. Nordstrom. Hemispheric differences in the relationship between corticomotor excitability changes following a fine-motor task and motor learning. J Neurophysiol 91: 1570–1578, 2004. First published November 19, 2003; 10.1152/jn.00595.2003. Motor practice induces a postexercise increase in corticomotor excitability that may be associated with motor learning. We investigated whether there are hemispheric differences in the extent and/or time course of changes in corticomotor excitability following a manipulation task (Purdue pegboard) and their relationship with motor performance. Single- and paired-pulse (3 ms) transcranial magnetic stimulation (TMS) was used to assess task-induced facilitation of the muscle evoked potential (MEP) and intracortical inhibition (ICI) for three intrinsic hand muscles acting on digits 1, 2, and 5. Fifteen right-handed subjects performed three 30-s pegboard trials with left or right hand in separate sessions. TMS was applied to contralateral motor cortex before and after performance. Number of pegs placed was higher with the right hand, and performance improved (motor learning) with both hands over the three trials. MEP facilitation following performance was short-lasting (<15 min), selective for muscles engaged in gripping the pegs, and of similar magnitude in left and right hands. ICI was reduced immediately following performance with the right hand, but not the left. The extent of MEP facilitation was positively correlated with motor learning for the right hand only. We conclude that the pegboard task induces a selective, short-lasting change in excitability of corticospinal neurons controlling intrinsic hand muscles engaged in the task. Only left hemisphere changes were related to motor learning. This asymmetry may reflect different behavioral strategies for performance improvement with left and right upper limb in this task or hemispheric differences in the control of skilled hand movements.

INTRODUCTION

Motor practice induces plastic changes in primary motor cortex (M1) which can be studied with transcranial magnetic stimulation (TMS). These changes include an expansion of motor representations (Karni et al. 1995; Nudo et al. 1996; Pascual-Leone et al. 1994, 1995), changes in the kinematics of movements evoked by TMS (Büttetsch et al. 2000; Classen et al. 1998), and facilitation of the muscle evoked potential (MEP) in task muscles tested at rest for ≤60 min after the practice session (Büttetsch et al. 2000; Caramia et al. 2000; Classen et al. 1998; Hauptmann et al. 1997; Mullerbacher et al. 2001; Pascual-Leone et al. 1995; Rossi et al. 1999; Samii et al. 1998; Ziemann et al. 2001). The latter phenomenon has been termed postexercise facilitation in some studies, however, we will use the term task-induced MEP facilitation in the present study, as it can be induced by motor imagery of a complex task in the absence of muscle activation (Pascual-Leone et al. 1995) and is not seen following nonfatiguing muscle contraction evoked by peripheral nerve stimulation (Ziemann et al. 2001). There is increasing evidence that task-induced changes in M1 are important for motor learning (Donoghue and Sanes 1994; Karni et al. 1998; Sanes and Donoghue 2000). Several studies have shown that task-induced MEP facilitation is positively correlated with improvements in performance (Pascual-Leone et al. 1995; Mullerbacher et al. 2001; Ziemann et al. 2001), and it has recently been suggested that task-induced MEP facilitation may reflect the early consolidation stage of motor skill acquisition in M1 (Mullerbacher et al. 2002).

None of the previous studies have addressed whether there are hemispheric differences in the extent or time course of task-induced MEP facilitation or whether the relationships between the changes in corticomotor excitability and task performance or motor learning differ when using the preferred or nonpreferred hand. The representation of hand muscles and synaptic interconnectivity in primary motor cortex is larger in the dominant (left) hemisphere than the nondominant (right) hemisphere (Hammond 2002). In addition, activation of contralateral M1 is not symmetrical for unimanual tasks performed with left or right hand (Brouwer et al. 2001; Semmler and Nordstrom 1998; Volkmann et al. 1998), so there is reason to suspect that the extent of task-induced MEP facilitation may differ for performance with left and right hands. Another possible source of asymmetry is that the ipsilateral sensorimotor cortex plays a greater role in finger movements of the left hand than the right (Chen et al. 1997; Kim et al. 1993; Ziemann and Hallett 2001). If task-induced MEP facilitation reflects corticofugal plasticity related to motor learning, as has been proposed, hemispheric differences in these processes may contribute to asymmetries in hand preference for skilled motor tasks. In the present study we have begun to address this question by comparing task-induced MEP facilitation and performance on a fine manipulation task (Purdue pegboard) (Tiffen 1968) for both hands of right-handed subjects. To provide information about the specificity of the changes in each hemisphere, we studied two muscles used to manipulate the pegs, first dorsal interosseous (FDI) and abductor pollicis brevis (APB), and the abductor digiti minimi (ADM) muscle, which was commonly active during the task but did not contribute directly to performance.

Finally, task-induced MEP facilitation is influenced by...
GABAergic intracortical inhibition (ICI) (Ziemann et al. 2001). Disinhibition may play an important role in motor learning by unmasking excitatory connections to corticospinal neurons in M1 and/or promoting plastic changes at synapses by facilitating long-term potentiation (Hess and Donoghue 1994; Hess et al. 1996; Jones 1993). Hemispheric differences in ICI might contribute to differences in motor skill between hands, but a relationship between ICI and skilled motor performance of left and right hands has not been assessed in previous studies. To explore the role and specificity of ICI in task-induced MEP facilitation and motor learning with preferred and nonpreferred hands we used a paired-pulse TMS paradigm (Kujirai et al. 1993) to assess ICI for the three muscles before and after pegboard performance with each hand.

METHODS

Fifteen healthy adult volunteers (10 male, 5 female), including two of the authors, ranging in age from 18 to 44 yr gave informed written consent for participation in the experiment. Subjects were right-hand dominant according to the Edinburgh Handedness Inventory (Oldfield 1971) with a median Laterality Quotient (LQ) of 0.80 (range 0.55–1.00). Nine of the 15 subjects had an LQ > 0.80. The experimental procedures conformed with the declaration of Helsinki, and the protocol was approved by the Human Research Ethics Committee of the University of Adelaide.

Apparatus

Subjects were seated in a dental chair with their right or left arm resting comfortably on a Purdue pegboard (Lafayette Instruments model 32020, Lafayette, IN) that was firmly clamped to a table. The height of the chair and position of the pegboard were adjusted to allow unrestricted, comfortable movement of the arm over the entire surface of the pegboard. The surface electromyogram (EMG) was recorded from the left and right FDI, APB, and ADM muscles using bipolar Ag-AgCl electrodes. The signals were amplified (×200–2000), filtered (20 Hz to 1 kHz), and recorded on tape (Vetter model 400D; 22 kHz/ch). Peristimulus epochs of data were digitized (2 kHz/ch sampling rate) and averaged on-line (Labview). TMS was applied using two Magstim 200 (Magstim, Dyfed, UK) stimulators connected via a Bistim module to a single 90-mm circular coil. This allowed delivery of single- or paired-pulse [3-ms intersstimulus interval (ISI)] TMS to assess both test MEP size (single test pulse) and effectiveness of ICI by comparison of size of MEPS in conditioned (paired-pulse) and single-pulse trials (Kujirai et al. 1993). Two oscilloscopes positioned directly in front of the subject displayed EMG from FDI, APB, and ADM of the task hand. Subjects were instructed to monitor these signals to maintain electrical silence in all muscles during delivery of TMS. This was necessary for testing of ICI as it is known to be suppressed during muscle activation (Ridding et al. 1995). Surface electrodes attached over the ulnar and median nerves at the wrist were used with a Digitimer D180 electrical stimulator (Digitimer, UK) to deliver supramaximal stimulation (0.5 Hz, pulse duration 100 μs) of the nerves to elicit maximal M-waves in each muscle.

Protocol

The left and right hands were tested in separate sessions on the same day. The hand tested first was alternated across subjects. Maximal M-waves were recorded for each muscle prior to (Pre) and following (Post) TMS testing of each hand. The optimal location for TMS was identified by initially placing the circular coil at the vertex and then moving it in small steps until the site from which the largest MEPs in all three muscles was found using a moderately suprathreshold intensity. This location was marked on the scalp to allow consistent coil placement during the experiment. The current direction in the coil (viewed from above) was counterclockwise for right-side muscles (left motor cortex) and clockwise for left-side muscles (right motor cortex). These coil orientations induce current flow in the brain that traverses the central sulcus of the hemisphere contralateral to the test muscles in a posterior–anterior direction, which is optimal for production of a MEP at lowest threshold with TMS (Day et al. 1989). Resting motor threshold was defined as the weakest TMS intensity (2% increments) that yielded ≥3 of 5 MEPs > 50 μV in relaxed FDI. Active threshold (3/5 MEPs > 100 μV) was assessed with weak voluntary activation of FDI. Test TMS intensity was adjusted to produce an MEP of approximately 0.5 mV in relaxed FDI, and reliable responses in the other two muscles. ICI was assessed using a paired-pulse paradigm (Kujirai et al. 1993) with a 3-ms ISI. The intensity of the conditioning stimulus in the paired-pulse trials was below active motor threshold and adjusted to produce approximately 50% reduction of the FDI MEP at rest prior to the pegboard task. Subjects performed three 30-s trials of the Purdue pegboard in which they picked individual pegs from a well using the thumb and index finger and placed them in individual holes in the pegboard. Robust MEP facilitation is induced in FDI following performance of the pegboard task (Rosset et al. 1999). The intertrial interval was approximately 10–20 s. Subjects were encouraged to place as many pegs as possible and the number of pegs placed on each trial was recorded. No practice trials were provided. Prior to and following completion of the pegboard task, subjects were instructed to keep their hand muscles relaxed aided by visual feedback of EMG from the three muscles of interest. EMG from the three muscles was recorded on tape during task performance.

TMS was delivered with all muscles at rest at three times with respect to pegboard performance: prior to the first pegboard trial (Pre), immediately following the final pegboard trial (+0), and 15 min following the final trial (+15). Each block consisted of 24 trials in which single- or paired-pulse TMS (3-ms ISI) was delivered under computer control (randomized), with an intertrial interval of 5 s. Each block, therefore, took 2 min to complete.

After the final block of TMS, M-waves were assessed a second time to determine any peripheral neuromuscular effects of pegboard performance. After a rest period of approximately 10 min, the entire sequence was repeated with the other hand.

Analysis

Between-hemisphere differences for resting motor threshold and test TMS intensity were assessed using paired t-test. MEP and M-wave areas were calculated from the averaged rectified EMG. Effectiveness of ICI was quantified as the ratio of the conditioned and test MEP areas, expressed as a percentage. Performance of the pegboard task was quantified as the sum total of pegs placed over the three 30-s trials (Pegboard score). Within-session relative improvement of pegboard performance (Improvement score) was given by the equation (pegs placed in trial 3 – pegs placed in trial 1)/pegs placed in trial 1.

Statistical analyses of the effects of Hand (L, R), muscle (FDI, APB, ADM), and Time (Pre, +0, +15) on test MEP size and effectiveness of ICI were performed using repeated-measures ANOVA followed by pairwise posthoc comparisons using Tukey’s honestly significant difference multiple comparison procedure. Linear regression was used to analyze the relationship between changes in test MEP size and ICI immediately following the pegboard task (+0) and their relationship with task performance. For these comparisons, MEP data were normalized by using the ratio of the value obtained immediately following the pegboard task (+0) and the baseline period preceding the task (Pre). Data are reported as mean ± SE unless otherwise stated. All statistical tests were considered significant at P < 0.05.

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RESULTS

Performance measures

Performance in the pegboard task is summarized in Fig. 1A. Performance was better overall with the right hand \([F(1,14) = 6.56, P = 0.023]\). The mean number of pegs placed by the right hand for the three trials was 42.9 ± 1.4 while the left hand placed 40.7 ± 1.3. Performance improved monotonically across the three trials \([F(2,28) = 40.04, P < 0.0001]\) with scores on the second and third trials being significantly better than the preceding trial (Tukey’s test; \(P < 0.05\); 1st, 12.7 ± 0.4; 2nd, 14.2 ± 0.3; 3rd, 14.9 ± 0.3). The hand by trial interaction was not significant \([F(2,28) = 0.2, P = 0.813]\), indicating that the improvement in performance was similar for both the left and right hands.

Although there was a significant overall tendency for task performance to improve with successive trials, performance improvement varied over a large range in different subjects. Linear regression revealed a significant negative relationship between the Pegboard Score and Improvement Score from both hands of the 15 subjects (Fig. 1B: \(r = -0.40, P = 0.03\)). That is, those subjects with the greatest improvement over the three trials also tended to have the lowest overall score. This relationship was not significant \([F(2,28) = 0.2, P = 0.813]\), indicating that the improvement in performance was similar for both the left and right hands.

M-wave area was analyzed using separate two-way ANOVAs for each muscle with hand (left, right) and time (pre, post) as factors. The time factor was not significant for any muscle \((P > 0.05)\) nor was the main effect of hand or the interaction \((P > 0.05)\). Thus performance of the pegboard task had no significant effect on M-wave area.

TMS intensity

Mean resting motor thresholds (expressed as a percentage of maximum stimulator output) were 58 ± 3% for the left hand and 56 ± 2% for the right hand. This difference was not significant \((t_{14} = 1.22, P = 0.24)\). Test TMS intensities were 70 ± 3% for the left hand and 68 ± 3% for the right hand, a nonsignificant difference \((t_{14} = 0.76, P = 0.46)\). Relative to resting threshold, test TMS intensities were 121 ± 2% for the left hand and 121 ± 3% for the right hand. This difference was not significant \((t_{14} = 0.18, P = 0.86)\). Conditioning TMS intensities were 78 ± 2 and 80 ± 2% of active threshold for the left and right hands, respectively. This difference was not significant \((t_{14} = 0.96, P = 0.35)\). Thus corticomotor excitability and TMS intensities used for the experiments were equivalent for left and right hemispheres.

Changes in MEPs following the pegboard task

Figure 2A is an example of EMG activity in the three muscles of the right hand during performance of the pegboard task. Both FDI and APB show robust, phasic activity consistent with their role in peg retrieval and manipulation. By contrast, activity in ADM is substantially weaker and more persistent with their role in peg retrieval and manipulation. By contrast, activity in ADM is substantially weaker and more...
Muscles MEP size returned to baseline within 15 min (H11001) clear facilitation of the MEP in both FDI and APB. For both following performance of the pegboard task (B sustained. Figure 2B shows the MEPs obtained in the same three muscles at each of the three time points. Immediately following performance of the pegboard task (+0) there was a clear facilitation of the MEP in both FDI and APB. For both muscles MEP size returned to baseline within 15 min (+15). There was no facilitation of the ADM MEP following the pegboard task.

Figure 3 shows the mean MEP area in the three muscles of the left and right hands at each time point for the 15 subjects. As expected, mean MEP area increased significantly following performance of the pegboard task [F(2,28) = 6.93, P = 0.004], consistent with the findings of Rossi et al. (1999). MEPs immediately following the pegboard (+0: 5.01 ± 0.48 mV ms) were significantly larger than those obtained prior to performance (Pre: 3.83 ± 0.31 mV ms) and following 15 min rest (+15: 3.79 ± 0.32 mV ms). There was no significant difference between the Pre and +15 MEPs, indicating that task-induced MEP facilitation was relatively short lasting. However, as seen in Fig. 3, the three muscles were not equally affected by the pegboard task, an observation confirmed by a significant muscle by time interaction [F(4,56) = 3.00, P = 0.026].

Both muscles engaged in manipulation of the pegs, FDI and APB, showed significant task-induced MEP facilitation at +0. MEPs in FDI were 38% larger than prepegboard MEPs, while MEPs in APB increased by 39%. MEPs in both muscles returned to prepegboard size by +15 (change from prepegboard: FDI = −3%, APB = 1%). By contrast, pegboard performance had no significant effect on the ADM MEP at either +0 (+10%) or +15 (−1%), even though ADM was active during task performance. Thus MEP facilitation induced by pegboard performance appears to be selective for hand muscles engaged in manipulating the pegs and is relatively short lasting (<15 min).

There was no overall difference in the size of MEPs in the left and right hands [F(1,14) = 0.04, P = 0.84] nor were there any significant between-hand differences for the muscle by time interaction [F(4,56) = 0.52, P = 0.73].

ICI

The effectiveness of ICI was assessed from the ratio of the MEP size in conditioned and test-alone trials. The effects of pegboard performance on ICI are summarized in Fig. 4. Pegboard performance reduced the effectiveness of ICI [F(2,28) = 4.03, P = 0.029]. This effect was uniform for the three muscles [F(4,56) = 1.2, P = 0.34], but differed for left and right hands [F(2, 28) = 3.42, P = 0.047]. Posthoc tests revealed a significant reduction of ICI effectiveness for the right hand immediately following the pegboard task (+0: 0.66 ± 0.04) compared with the prepegboard trial (Pre: 0.50 ± 0.04). There was a tendency for reduced ICI effectiveness after the pegboard task for both hands at both time points, but the other changes were not significant (Tukey’s test; P > 0.05).

Relationship between task-induced changes in MEP size and ICI effectiveness

The relationship between the change in test MEP size and ICI immediately following the pegboard task (+0/Pre) was assessed with linear regression. For all muscles in both hands, these variables tended to be negatively related. However, none of the regressions were statistically significant (P > 0.05).

Relationship between task-induced MEP facilitation and task performance

Significant MEP facilitation was observed in FDI and APB immediately following pegboard performance (+0 in Fig. 3). To examine the relationship between pegboard performance and task-induced MEP facilitation we calculated the ratio of the MEP size at +0 and Pre for the three muscles of each subject, and performed linear regression analysis with the total

FIG. 3. Mean MEP area (±SE) for FDI, APB, and ADM of the left and right hand (n = 15). There was significant task-induced MEP facilitation immediately following the pegboard task (+0) in both FDI and APB, but not ADM. MEP area had returned to prepegboard size after 15 min (+15). The magnitude of MEP facilitation was similar in the left and right hands.

FIG. 4. Conditioned MEP size (±SE) at Pre, +0, and +15 for the left and right hands. Data are pooled for the 3 muscles. The effectiveness of conditioning TMS was significantly reduced at +0 for the right hand (P < 0.05).
Figure 5 shows the relationship between Pegboard Score (total number of pegs placed) and task-induced MEP facilitation for each muscle of both hands. A higher level of proficiency on the pegboard task, as indicated by more pegs placed, tended to be associated with low MEP facilitation. This relationship was only significant, however, for right FDI (Fig. 5).

Figure 6 shows the relationship between the within-session improvement in performance (Improvement Score) and task-induced MEP facilitation for each muscle of the right hand. Subjects with the largest gains in performance over the 3 trials had the largest MEP facilitation, but only in muscles of the right hand engaged in the task.
induced MEP facilitation. There was a significant positive relationship between these variables in FDI and APB, but only for the right hand. Subjects with a large improvement in performance tended to have greater MEP facilitation immediately following the task, but only for muscles of the right hand engaged in manipulation of the pegs. The coefficient of determination ($r^2$) indicates that the relative performance improvement accounted for 49% of the variance in the right FDI MEP facilitation and 28% for right APB.

The relationship between changes in effectiveness of ICI immediately after the practice session (+0/Pre) and performance was examined in the same manner as the Figs. 5 and 6 analyses. There was no significant relationship between the changes in ICI and Pegboard Score or Improvement Score for any hand or muscle.

**DISCUSSION**

The principal finding of the present study is a hemispheric asymmetry of the relationship between task-induced MEP facilitation following performance of a fine motor task and within-session improvement of performance (motor learning). Performance of the pegboard task with the contralateral hand induced an increase in corticomotor excitability that was similar in magnitude for the left and right hemispheres, however, only changes in the left M1 were related to performance. There was a strong positive relationship between the change in excitability of FDI and APB representation in the left hemisphere and within-session improvement in performance with the right (preferred) hand. Consistent with earlier findings (Muellbacher et al. 2001), the changes in excitability were specific for the corticomotor representation of hand muscles used for task performance (FDI and APB), as no change was seen for the ADM muscle, which was active during the task but did not contribute to performance. As rapid changes in M1 corticomotor excitability with motor practice has been found to be related to motor learning (Muellbacher et al. 2001, 2002), the present finding points to a different strategy for performance improvement with left and right hands in this task and/or a hemispheric asymmetry in the role of sensorimotor cortex in motor learning of hand skills.

**Mechanisms of task-induced MEP facilitation**

Practice of a variety of simple motor tasks induces a facilitation of the MEP in task muscles tested with TMS at rest immediately after the practice session, and this effect lasts for $\approx 60$ min. Examples include steady isometric contraction of wrist muscles (Rossi et al. 1999; Samii et al. 1998), ballistic elbow flexion movements (Ziemann et al. 2001), ballistic pinch grip (Muellbacher et al. 2001), and isolated thumb movements (Bütefisch et al. 2000; Classen et al. 1998). Performance of more complex tasks such as the Purdue pegboard (Rossi et al. 1999; present study) or sequential finger tapping (Pascual-Leone et al. 1995) also facilitates hand muscle MEPs. In the latter study, mental imagery without physical practice also induced MEP facilitation immediately after the training session. These facilitatory changes are believed to be cortically mediated, as training has little effect on the MEP produced by brain stem or cervical stimulation (Muellbacher et al. 2001). Further evidence comes from experiments showing that voluntary practice of thumb movements alters the direction of TMS-evoked movements of the thumb, but training in this way is less effective in altering the direction of thumb movements evoked by transcranial electrical stimulation (TES) (Classen et al. 1998). As TES preferentially activates corticospinal axons directly (Day et al. 1987), the TES results suggest that practice has few aftereffects on segmental excitability. In the present study there was no change in M-waves following the pegboard task, so the MEP facilitation was not due to a change in the peripheral neuromuscular apparatus. The selectivity of task-induced MEP facilitation, which was restricted to hand muscles used to grip the pegs (FDI and APB), excludes nonspecific processes such as arousal or attention, as these would also be expected to affect ADM as well. Active engagement of the motor cortex is necessary for task-induced MEP facilitation—it could not be induced by peripheral nerve stimulation or passive movement alone (Ziemann et al. 2001). While we did not directly assess segmental motor excitability with TES or H-reflexes, previous studies suggest that the changes in corticocortical excitability we observed reflect changes at the level of the cortex.

**Task-induced MEP facilitation and motor learning**

Currently, the mechanisms responsible for usage-dependent plasticity in the motor cortex are not well understood. However, the data are consistent with a usage-dependent modification of cortical synapses that has been proposed to underlie motor learning (Asanuma and Pavlides 1997; Sanes and Donoghue 2000). Synaptic plasticity in the cortex is influenced by N-methyl-d-aspartate (NMDA) receptor activation (Castro-Alamancos and Connors 1996) and GABAergic disinhibition (Hess and Donoghue 1994; Hess et al. 1996), and practice-induced changes in MEPs and movement kinematics in humans are blocked by dextromethorphan (an NMDA receptor blocker) and reduced by lorazepam (a GABA$_A$ agonist) (Bütefisch et al. 2000).

Motor learning can be defined as the acquisition of new patterns of muscle activation in time and space to improve performance of a motor task (Sanes and Donoghue 2000). Several TMS studies have demonstrated an association between task-induced MEP facilitation and improvements in performance (Muellbacher et al. 2001; Ziemann et al. 2001). It has recently been suggested that practice-induced changes in M1 excitability reflect the early stages of memory consolidation in M1 of the practiced movement related to motor learning (Muellbacher et al. 2002). This is supported by the finding that repetitive TMS (rTMS) of M1 immediately following motor practice abolishes gains in performance. The disruption of performance gains is not observed when rTMS is delivered following a 6-h consolidation period nor when it is given over cortical regions outside M1 (e.g., parietal cortex) (Muellbacher et al. 2002). Also consistent with this view is the finding that practice-dependent increases in M1 excitability are no longer present once a motor skill has been overlearned (Muellbacher et al. 2001).

**Hemispheric differences in task-induced MEP facilitation and its relation with motor learning**

In the present study subjects improved their performance of the pegboard task progressively over three trials (Fig. 1). That
is, motor learning occurred over trials 1–3, and performance improvement had not plateaued by trial 3. The improvement in performance was similar for left and right hands, although the strategy may have differed (see the first possible explanation below). Overall performance was better with the right hand, consistent with previous findings in right-handed subjects (Brouwer et al. 2001; Tiffen 1968).

The present study is the first to address the issue of whether task-induced plasticity of M1 differs in the left and right hemisphere and more specifically whether the relationships with motor learning show a hemispheric asymmetry. Task-induced MEP facilitation was similar in FDI and APB muscles of right and left hands and was not seen in ADM, which was active during the task but was not critical for task performance (Fig. 3). At first glance these results suggest no hemispheric asymmetry of task-induced MEP facilitation in the pegboard task and a similar relationship with motor learning since performance improvements were similar with each hand. However, regression analysis of data from individual subjects revealed a strong positive relationship between task-induced MEP facilitation in FDI and APB and performance improvement for the right hand only (Fig. 5). We consider several possible explanations for this difference between left and right hands.

First, the performance improvement of the two hands may be mediated by different behavioral strategies. The pegboard task requires coordinated control of the muscles of the entire arm, not just the index finger and thumb. A complete cycle of peg retrieval and placement consists of several phases, each differentially dependent on the behavior of arm or hand muscles. Retrieving and placing pegs is heavily reliant on manipulative control of the digits, while transport of the hand is governed largely by proximal muscles of the arm. Improvement in pegboard performance could be brought about through modifications of any, or all, of these phases.

As the peg retrieval and placement phases are both time consuming and critical to skilled performance of the pegboard task, it is likely that at least some of the performance improvement of both hands involved modifications of control of the digits in these phases. This could account for task-induced MEP facilitation observed in FDI and APB of both hands. However, modifications of the reaching phase are likely to be asymmetrical. Behavioral studies consistently report a right arm advantage for the control of intersegmental limb dynamics (Baguier and Sainburg 2002; Goodale 1988; Sainburg 2002) and a relative disadvantage for the left arm when “homing in” on the target (Roy et al. 1994). Thus the left arm is likely to complete aiming movements more slowly due to a relative difficulty in accurately terminating the movement. On the basis of these findings it seems possible that a greater proportion of left arm improvement could have come about through adjustments of the reaching component, which would ultimately mask the relationship between task-induced MEP facilitation in intrinsic hand muscles and improvement in the pegboard score. As we did not monitor the kinematics of pegboard performance in this study, or EMG of more proximal muscles, this possibility will need to be addressed in future investigations.

A second possible explanation for the asymmetry of the relationship between task-induced MEP facilitation and improvement in performance relates to the hemispheric control of goal-directed movements of the right and left hand. A substantial body of evidence indicates that, for right handed subjects, the left sensorimotor cortex contributes to the performance of both hands, whereas the right hemisphere is important for use of the left hand, but not the right. Performance of right hand movements is accompanied by activation primarily of the left (contralateral) sensorimotor cortex, whereas performance of left hand movements is associated with activation of both the right (contralateral) and left (ipsilateral) sensorimotor areas (Kawashima et al. 1993). Left M1 is involved in motor imagery of unilateral movements of either hand, whereas right M1 is only involved in imagery of left hand movement (Fadiga et al. 1999). Studies of stroke patients indicate this involvement of the left hemisphere is functionally important. Wyke (1968, 1971) found that unilateral stroke of the right hemisphere was accompanied by a performance deficit only of the contralateral left hand. By contrast, stroke affecting the left hemisphere was associated with performance deficits of both hands. Similarly, ideomotor apraxia, which is characterized by disturbances in the performance of goal-directed movements, results from damage to the left frontal and parietal areas (Haaland et al. 2000) and rarely from damage to the right hemisphere. In most people, inactivation of the left hemisphere with intracarotid injection of barbiturate (Wada test) impairs skilled movements of both hands, whereas right-sided injection impairs only left hand movements (Heilman 2000). Further evidence of the importance of the left M1 in left hand control is provided by TMS studies. Chen et al. (1997), using repetitive TMS, showed that stimulation of the left M1 during a key pressing task disrupted performance with the contralateral right hand as well as the ipsilateral left hand. Stimulation of the right M1 had a much weaker effect on performance with the right hand. Left M1 involvement in left hand movements increased with increasing complexity of the sequence of key presses.

For the pegboard task it seems reasonable to assume that skilled performance of the right hand was governed largely by the left (contralateral) hemisphere. Task-induced facilitation of the MEP in the right hand, reflecting plasticity in left M1, was strongly associated with motor learning. However, this relationship will not be as straightforward following left hand performance since at least some of the neural processes mediating skilled performance with the left hand are present in the left (ipsilateral) M1. The absence of a relationship between task-induced MEP facilitation and performance improvement following left hand use (Fig. 5) may be due to a contribution of the left hemisphere to motor learning of the left hand, which was not assessed with our protocol as TMS was applied only to the hemisphere contralateral to the task hand. This hypothesis could be addressed in future studies by testing corticomotor excitability of both hemispheres with TMS following unimanual performance.

**Hemispheric differences in ICI and its relation with motor learning**

It has recently been demonstrated that practice-dependent plasticity in M1 is influenced by GABAergic inhibition (Ziemann et al. 2001). MEP facilitation induced in biceps by practice of ballistic elbow flexion movements was increased in the presence of ischemic nerve block of the hand, which is known to suppress GABAergic inhibition (Ziemann et al. 1998). This was accompanied by a concomitant decrease in the
effectiveness of ICI circuitry assessed with paired-pulse TMS (Ziemann et al. 2001). By contrast task-induced MEP facilitation was completely blocked by the administration of lorazepam, a GABAA agonist, with an accompanying increase in ICI effectiveness. Thus the effect of practice on M1 excitability can be influenced by altering the effectiveness of ICI circuits. Reduced intracortical inhibition could contribute to task-induced MEP facilitation by unmasking existing excitatory connections to corticospinal neurons that are activated by TMS and/or by enhancing plastic changes in cortical synaptic connections during training by mechanisms such as long-term potentiation (Hess and Donoghue 1994; Hess et al. 1996; Jones 1993).

Ziemann et al. (2001) found that significant MEP facilitation was induced in left biceps by motor practice alone without any change in ICI effectiveness in right M1 evident following task performance. Similar results were observed for left hand muscles in the present study. Task-induced MEP facilitation is therefore not dependent on a concurrent GABAergic disinhibition and unmasking of latent excitatory synaptic connections in M1. ICI effects are suppressed during voluntary activation (Ridding et al. 1995), however, and this may help to fractionate hand muscle activity (Zoghi et al. 2003) as well as promote plastic changes in M1 that persist beyond task performance once ICI returns to baseline levels.

ICI does not differ between hemispheres at rest (Cicinelli et al. 2000; Civardi et al. 2000; Maeda et al. 2002), but this has not been assessed during or after voluntary activation of the muscles. When the right hand was used to perform the pegboard task, ICI effectiveness in left M1 was significantly reduced in the period immediately following the task (Fig. 4). No change in ICI effectiveness was observed in the right hemisphere, however, following left hand performance. Unlike the task-induced MEP facilitation, the task-induced suppression of ICI was not selective for the corticospinal neurons controlling FDI and APB muscles (i.e., the muscle by hand interaction was not significant) nor was its magnitude associated with task performance. The size of task-induced MEP facilitation was not related to the amount of suppression of ICI following pegboard performance. Our results indicate that motor practice is more effective in suppressing ICI circuits in left M1 than right M1 in the immediate postpractice period. At present the functional significance of this hemispheric difference in ICI for plasticity of corticomotor representations in M1 and motor learning remains unclear.

In summary, brief performance of a fine-motor manipulation task induces transient increases in excitability of the contralateral M1 regardless of whether the task is performed with the left or right hand. The task-induced changes observed with single TMS are similar in magnitude, duration, and selectivity in both hemispheres, although only changes in the left hemisphere were directly correlated with the within-session improvement in performance (motor learning). Intracortical inhibition was suppressed immediately following the task, but only in the left M1 and not selectively for the cortical representation of the task muscles. These asymmetries may reflect different behavioral strategies involving arm and hand muscles that mediate performance improvement with left and right upper limb or hemispheric differences in the control of skilled hand movements. Future studies in this area will need to take these asymmetries into account.

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