Corticospinal Facilitation Following Prolonged Proprioceptive Stimulation by Means of Passive Wrist Movement

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The purpose of this study was to evaluate the delayed effects of repetitive sensory stimulation with passive wrist movement on corticospinal excitability of the forearm and hand musculature. Motor evoked potential responses to single and double pulse transcranial magnetic stimulation were recorded from the flexor carpi radialis, extensor carpi radialis, and the first dorsal interosseous muscles of the right limb. Data were collected before and after a 1 hour session of passive wrist movement (intervention group, n = 11) or after a same period of rest (control group, n = 9). Motor evoked potential size and area were analyzed to evaluate corticospinal excitability and short interval intracortical inhibition and facilitation. Training with passive movement resulted in a prolonged increase in corticospinal excitability in the flexor carpi radialis and extensor carpi radialis (until at least 1 hour postintervention), but did not evoke significant changes in the levels of short interval intracortical inhibition and facilitation. No such effects were noted in the control group or first dorsal interosseous muscle. Prolonged proprioceptive stimulation with passive wrist movement induces a delayed increase in corticospinal excitability of the forearm muscles. Accordingly, this intervention may promote motor cortical reorganization in the targeted muscles. Results show induced effects from passive movement training that may prove useful for neurorehabilitation therapies.

Key Words: Passive movement, Transcranial magnetic stimulation, Corticospinal excitability, Intracortical inhibition and facilitation, Sensory-induced plasticity.

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Repetitive stimulation of the afferent pathways has been shown to generate persistent neuroplastic changes not only in sensory, but also in motor areas of the adult mammalian cortex (Deletis et al., 1992; Nudo et al., 1996; Sakamoto et al., 1987; Stefan et al., 2000, 2002; Zarzecki et al., 1978). These effects have recently been explored in humans with transcranial magnetic stimulation (TMS) during and/or after the application of electrical nerve stimulation (Chen et al., 1999; McKay et al., 2002), muscle tendon vibration (Rosenkranz and Rothwell, 2003; Steyvers et al., 2003a,b), and cyclical passive movement (Lewis and Byblow, 2004; Lewis et al., 2001). The aforementioned studies have been part of growing attempts to understand the role of sensory-driven plasticity in recovery of motor functions after stroke (Calautti and Baron, 2003; Conforto et al., 2002; Fraser et al., 2002; Matteis et al., 2003; Nelles et al., 1999a, 2001; Ridding et al., 2000, 2001). In addition to TMS, medical imaging techniques, e.g., functional magnetic resonance and positron emission tomography have occasionally been used to monitor modulations of regional cerebral blood flow during and/or following training with passive movement. Overall, these studies have indicated that, in addition to the primary sensory area, passive movement activates large parts of a motor network, such as supplementary motor area, inferior parietal cortex, and primary motor cortex (Carel et al., 2000; Lotze et al., 2003; Nelles et al., 1999b). The existence of widespread cortical activation as a result of repetitive sensory stimulation suggests that this intervention could play a role in restoration of motor functions after stroke (e.g., Nelles et al., 1999a).

Previous studies using TMS already showed that passive wrist movement evokes phasic modulations in the excitability of cortical circuits representing the wrist flexors and extensors in neurologically intact individuals (Lewis and Byblow, 2002; Lewis et al., 2001). However, no conclusive evidence for long-lasting facilitatory effects mediated by this type of intervention has been reported so far. For example, Lewis and Byblow (2004) reported an increase in size and area of motor evoked potential (MEP) responses of the wrist flexors and/or extensors immediately after 30 minutes training with passive movements but the general picture revealed inconsistency among subjects. Since they conducted their postintervention TMS sessions immediately after the end of the intervention, no long lasting (delayed) effects on motor cortex excitability could be established.

In a recent study, we showed that prolonged sensory stimulation with tendon vibration induced delayed corticospinal facilitation in the vibrated muscle that persisted more than 60 minutes after the end of the intervention (Steyvers et al., 2003a). A facilitatory effect with a progressively increasing cortical excitability over the course of 45 to 60 minutes was also observed following the application of selective muscle vibration (Rosenkranz and Rothwell, 2004), electrical peripheral nerve stimulation (Fraser et al., 2002; McKay et al., 2002; Ridding et al., 2001), and/or direct stimulation of sensorimotor cortical circuits with repetitive TMS (Huang et al., 2005). These similar time courses may reflect involvement of common neural substrates that promote delayed facilitation of M1 (e.g., Bestmann et al., 2004). Therefore, it is hypothesized that prolonged proprioceptive stimulation by means of passive wrist movement could elicit a delayed corticospinal facilitation both in the flexor and extensor muscles of the wrist that outlast the period of intervention. It is also hypothesized that sensory training with passive movement reaches larger portions of the motor cortex than selective (focal) afferent stimulation of individual muscles. The latter hypothesis is supported by observations suggesting that cyclical passive movement of the wrist induces phasic modulations of corticomotor excitability in both flexor and extensor muscles of the driven joint (e.g., Lewis and Byblow, 2002; Lewis et al., 2001).

In the present study, we explored whether application of passive wrist movement in neurologically-intact individuals induces delayed facilitation of corticospinal and corticocortical motor representations of the forearm and hand muscles of the driven limb. Five sets of TMS measurements were conducted: one before and four after a single 1 hour session of passive wrist flexion-extension movement. These four postintervention TMS measurements were conducted 0, 15, 30, and 45 minutes after the end of the intervention. To the best of our knowledge, it is the first time that the potential delayed effects of this intervention are monitored over a time period within which corticomotor facilitation is expected to emerge.

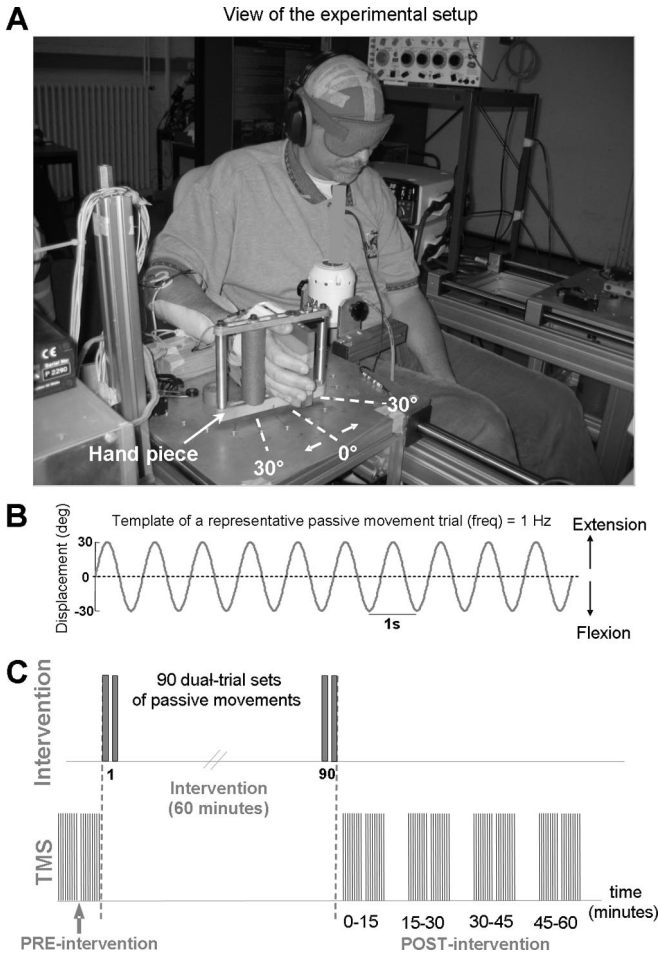

FIGURE 1. **A**, View of the experimental setup and (**B**) displacement data (wrist angle) of a passive movement trial. **C**, Graphical illustration of the intervention and TMS protocols used in the present study.

METHODS

Subjects

Twenty healthy volunteers participated in the experiment (12 men, 8 women; aged 21–29 years). All participants were right handed (assessed by the Edinburgh Handedness Inventory; Oldfield, 1971). The participants were naive about the purpose of the experiment and were screened for potential risk of adverse events during TMS stimulation. All participants provided written consent before participation. The experimental procedures were approved by the local Ethics Committee for Biomedical Research at the Katholieke Universiteit Leuven.

Manipulandum

Subjects were seated in front of a purpose-built manipulandum with their right shoulder in slight abduction (10°–20°), elbow at 90° and forearm supported and in a neutral prosupination position (Fig. 1A). The dominant (right) hand was inserted and secured in a hand piece while the nondominant (left) hand rested unrestrained. The proximal end of the hand-piece was mounted on a rotating shaft located coaxially with the wrist joint, enabling free rotation of the hand from −45° through to +45°. The 0° position was defined as the angle at which the forearm and the palmary surface of the hand were aligned; negative angles referring to wrist flexion. Motion of the wrist joint was induced by means of an AC servo motor (AMK DV764, Goedhard PMC, Helmond, NL) that was mounted underneath the unit and was coupled to the shaft of the manipulandum via a 10:1 reducer (Alpha Gearbox, Type LP120). The motor generated a sinusoidal motion of a programmable amplitude, frequency, and duration.

Electromyographic Recording

Electromyographic (EMG) signals of the flexor (FCR) and extensor (ECR) carpi radialis and first dorsal interosseous (FDI) of the right forearm and hand were recorded using disposable Ag-AgCl surface electrodes (Blue Sensor SP). The electrodes were placed 2 cm apart, over the middle

portion of the muscle belly, and aligned with the longitudinal axis of the muscles. The EMG signals were amplified (×1000, Noraxon Myosystem, 2000) and bandpass filtered (15–1,000 Hz). The amplified signals were sampled at 5,000 Hz (CED Power 1401, Cambridge Electronic Design, Cambridge, UK) and stored on a PC for off-line analysis.

Transcranial Magnetic Stimulation

Motor evoked potentials in the forearm and hand muscles of the right limb were elicited by TMS over the left motor cortex. A Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK) with a figure-of-8 coil (70-mm diameter standard double coil) was used to deliver the stimuli. The stimulation coil was positioned over the subjects' left hemisphere, tangentially to the scalp. The intersection of the two windings pointed backward and approximately 45° laterally away from the midsagittal line, such that the induced current flow was in a posterior-anterior direction at the optimal position for eliciting MEPs in the right FCR. Responses of the right ECR and FDI muscles were also evoked in this position. The test-stimulation intensity was set at 120% of the FCR rest motor threshold. The rest motor threshold was defined as the lowest stimulation intensity needed to evoke MEPs in the relaxed FCR of at least 50 μV of amplitude in 5 out of 10 consecutive stimuli (Rossini, 1994). Thresholds (FCR rest motor threshold) ranged from 42% to 65% maximal stimulator output (mean, 50.5 ± 8.2) for the intervention group and 40% to 66% maximal stimulator output for the control group (mean, 52.9 ± 8.2).

A paired pulse protocol (Kujirai et al., 1993) allows a more detailed investigation of intracortical excitatory and inhibitory interactions in the human motor cortex. This technique consists of a subthreshold conditioning pulse followed by a suprathreshold test pulse at different latencies. Depending on the interstimulus interval, the effect of the conditioning pulse might be either inhibitory or excitatory. Specifically, the interstimulus intervals were set at 2 milliseconds for short interval intracortical inhibition (SICI) and at 15 milliseconds for intracortical facilitation (ICF). The intensity of the conditioning pulse was set at 90% of the FCR active motor threshold and the test stimulus was set at 120% of the rest motor threshold. The active motor threshold was determined as the minimum intensity where 5 out of 10 stimuli evoked a discernable MEP (approximately 100 μV) peak-to-peak during isometric wrist flexion at 10% of the maximum voluntary contraction. Measurements of force during wrist flexion were conducted by means of a load cell (Tedea-Huntleigh, model 601), digitized (1,000 Hz) and were projected online on a PC monitor that was positioned in front of the subject. FCR active motor thresholds ranged from 33% to 48% maximal stimulator output (mean, 40.2 ± 4.6) for the intervention group and 29% to 44% maximal stimulator output for the control group (mean, 38.8 ± 5.2).

Protocol

Participants were randomly assigned into intervention (N = 11) and control (N = 9) groups. During the intervention, the subject's right wrist underwent a series of 90 dual-trial sets of rhythmic, passive flexion-extension movements of 60° amplitude at a mean frequency of 1 Hz (Fig. 1B). Subjects were instructed to relax their forearm and hand muscles at all times. EMG activity of FCR, ECR, and FDI muscles during passive movement was monitored in parallel with the displacement signal (digital shaft encoder, resolution = 0.088°) of the hand-piece, low-pass filtered (0–500 Hz) and sampled at 1,000 Hz. Each passive-movement set combined two successive trials of 10 cycles that were separated by a 5 to 8 seconds pause interval. All participants were blindfolded and wore ear plugs to obstruct any background noise. A total of 1,800 cycles (= 90 sets × 2 trials/set × 10 cycles/trial) of passive movement were applied over a time period of 60 minutes (Fig. 1C). In 90% of the sets, the frequency of the passive movement in the second trial was either faster or slower than that in the first trial (range: ±0.033 to ±0.233 Hz, distributed randomly). To increase and facilitate attention to the passive movement (Stefan et al., 2004), participants were instructed to indicate whether movement speed in the second trial was "faster," "slower," or "equal" to that presented in the first trial of each dual-trial set.

Five sets of TMS measurements were conducted in total; one before and four after the 60 minutes period of passive wrist movement (in the intervention group) or after 60 minutes rest (in the control group), at 0 to 15, 15 to 30, 30 to 45, and 45 to 60 minutes intervals (Fig. 1C). Each TMS measurement consisted of two 5-minute TMS runs separated by a minute, each run consisting of 15 single-pulse stimuli and 30 double pulse stimuli that were delivered every 6 to 8 seconds at random. The same intensity of stimulation was used in the pre- and postintervention trials. Triggering of EMG collection was initiated at 35 milliseconds before stimulus onset and continued across 150 milliseconds.

Data Reduction

Motor evoked potentials were analyzed off-line using Signal software (2.02 Version, Cambridge Electronic Design, Cambridge, UK). Those responses, in which the background EMG activity in one of the three muscles exceeded 20 μV peak-to-peak amplitude in the 20 milliseconds period before the MEP were discarded (mean background EMG at rest <10 μV peak-to-peak). All remaining responses (>80% of the total number of stimuli in each TMS session) were processed and the mean peak-to-peak amplitudes and areas were calculated for each MEP response in the three muscles of interest.

Corticospinal Excitability

Corticospinal excitability was assessed by measuring the peak-to-peak amplitude of MEPs in the right FCR, ECR, and FDI muscles. The two measures of MEP size (i.e., amplitude and area) were analyzed separately. The peak-to-peak amplitude and area of each response were normalized by the MEP parameters (i.e., peak-to-peak amplitude or area) of the maximum response recorded at baseline. Modulations in MEP excitability between the pre- and postconditions

($\Delta MEP_{post\text{-}pre}$) were expressed as percentage of baseline value according to the formula:

$$\Delta MEP_{post-pre} = 100 \times \frac{M_{post} - M_{pre}}{M_{pre}} \quad (1)$$

Data were obtained at the four postintervention/rest trials (0–15, 15–30, 30–45, and 45–60 minutes intervals) and were prepared for further statistical analysis as described next.

Intracortical Inhibition and Facilitation

For SICI and ICF, single trial peak-to-peak amplitudes were measured and averages were calculated for each stimulus condition. Intracortical inhibition and facilitation were then expressed as a percentage of the unconditioned MEP.

$$SICI = 100 \times \frac{MEP_{SICI}}{MEP_{Single}} \quad (2)$$

$$ICF = 100 \times \frac{MEP_{ICF}}{MEP_{Single}} \quad (3)$$

MEP_{Single} is the mean peak-to-peak amplitude of MEPs evoked during unconditioned TMS. MEP_{SICI} and MEP_{FCI} are the mean peak-to-peak amplitudes of MEPs evoked in the paired-pulse TMS at interstimulus interval = 2 milliseconds and interstimulus interval = 15 milliseconds, respectively. Data were averaged within each group (i.e., intervention and control) and each time condition (i.e., baseline and the four postintervals at 0–15, 15–30, 30–45, and 45–60 minutes) and were expressed as mean ± SEM.

Statistical Analysis

Advanced linear models applications (STATISTICA 6.0, StatSoft Inc.) were used for statistical analysis. Effects of intervention/rest on corticospinal excitability (MEP amplitude and area), SICI and ICF were compared using repeated measures analysis of variance (ANOVA) at two steps. It was first tested whether wrist muscles and FDI responded similarly to the stimulation by computing the differences between control and intervention groups in the postintervention conditions. As a clear difference was observed between these two groups of muscles, we decided to examine them separately. A 2 × 5 (GROUP × TIME) ANOVA was used to determine if the two groups of subjects differed from each other across time. It was then established whether the postintervention measurements were significantly higher than those measured before the intervention for each group separately using a one-way ANOVA with TIME (five levels) as the only factor. When significant effects were found, contrast analysis (Tukey HSD) was conducted to identify the source of the differences. Differences from 0 were also computed systematically to evaluate group and muscle differences. The root mean square (rms) amplitudes of EMG activity in the three muscles during the 60 minutes intervention were compared with their baseline levels using the paired Student's *t* test.

RESULTS

Modulations in Corticospinal Excitability

Overall, the intervention resulted in an increase of MEP size in the FCR and ECR while FDI remained unaffected. The three muscles (Fig. 2A) were compared by calculating the average of the four control group $\Delta MEP_{post\text{-}pre}$ scores at the 0 to 15, 15 to 30, 30 to 45 and 45 to 60 minutes postintervention intervals subtracted from their corresponding $\Delta MEP_{post\text{-}pre}$ scores in the intervention group. In this respect, the group data analysis (Figs. 2B and 2C) showed that 60 minutes of afferent stimulation resulted in a steady increase of MEP size over time in the two forearm muscles (FCR and ECR) that extended more than 60 minutes beyond cessation of the intervention. This intervention had no such effect on levels of MEP in the FDI.

Differences Between Muscles

The FCR and ECR muscles were modulated by the intervention while the FDI muscle was not. Comparing the three muscles (Fig. 2A) by calculating the average of the four control group postintervention scores (0–15 to 45–60) subtracted from their corresponding scores in the intervention group shows that both wrist muscles present a markedly increased response after stimulation (+30% to +36% for amplitude and +37% to +42% for area) whereas the FDI amplitude response remains largely unchanged (+0.2% for amplitude and −12% for area). Histogram distributions for these values were normal (K-S test was always >0.18 for amplitude and >0.30 for area) and a one-way ANOVA with muscle as the only factor revealed a significant effect of muscle on amplitude ($F = 44.9$, $P < 0.001$) and area ($F = 12.24$, $P < 0.01$). Contrast analysis showed that FCR and ECR were not different from each other ($P = 0.38$ for amplitude and $P = 0.90$ for area) but both differed from FDI ($P < 0.001$ for amplitude and $P < 0.05$ for area). These results enabled us to analyze both wrist muscles together, separately from FDI.

Motor Evoked Potential Amplitude

Across Group Effects

The effects of the 60 minutes intervention/rest period on corticospinal excitability as indicated by the MEP amplitude scores in the wrist muscles and FDI are shown in Figure 2B. In a 2 × 5 GROUP × TIME ANOVA, a significant interaction was observed for both wrist muscles ($F > 3.34$, $P < 0.05$) but not for the FDI ($F = 0.24$, $P > 0.90$, NS). A significant TIME main effect also occurred for the wrist muscles ($F > 4.23$, $P < 0.01$), and a marginally significant GROUP main effect ($F > 3.11$, $P = 0.08$). Tukey contrast analysis showed that for MEP facilitation in the wrist muscles, a significant difference was observed between baseline and the 15 to 30, 30 to 45, and 45 to 60 minutes intervals ($P < 0.01$).

Within Group Effects

One-way ANOVAs with TIME as the only factor revealed significant effects of TIME on MEP amplitude in the wrist muscles in the intervention group ($F = 6.02$, $P \leq$

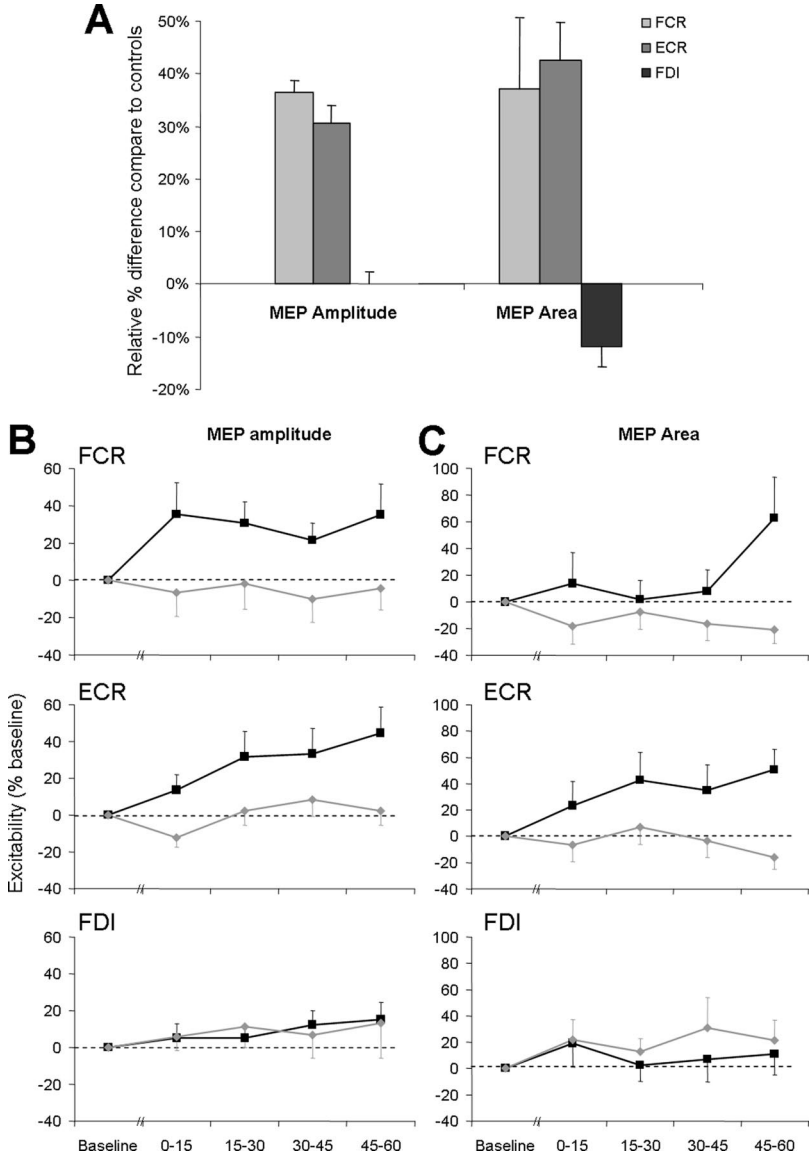

FIGURE 2. **A**, Mean relative percentage differences between intervention and control groups on the four postintervention measurements of MEP amplitude and area in FCR, ECR, and FDI muscles. **B** and **C**, Time courses of change in MEP amplitude and area in the same muscles with respect to their baseline levels at 0 to 15, 15 to 30, 30 to 45, and 45 to 60 minutes intervals following the end of a 60 minutes sensory stimulation with passive movement (black squares) or rest (gray diamonds). Data plotted as group mean ± SEM.

0.001). No such effects were observed in the FDI ($F = 1.55$, $P > 0.2$). Contrast analysis was used to reveal the conditions significantly different from baseline. For the wrist muscles, a sizeable increase with statistical significance with respect to baseline amplitude was observed at 15 to 30 minutes after the end of intervention (31% ±13 vs. baseline, $P < 0.01$) and also at the 30 to 45 (27% ±12 vs. baseline, $P < 0.05$) and 45 to 60 minutes (40% ±15 vs. baseline, $P < 0.001$) postinterventional interval. A marginally significant difference between wrist muscle excitability at baseline and immediately after intervention was also noticed (25% ±13 vs. baseline, $P < 0.05$). Subjects in the control group did not demonstrate consistent modulations in MEP amplitude following the end of the 60 minutes rest period. The TIME effect for MEP amplitude did not reach significance for any muscle in this group (wrist muscles and FDI: all $F \leq 1.06$, $P > 0.38$).

Comparison to 0

T-tests for single means showed that the wrist muscles amplitude significantly differs from 0 at all latencies in the intervention group (all $P < 0.05$). FDI is never different from 0 in the intervention group (all $P > 0.14$) and both wrist muscles and FDI are not different from 0 in the control group (all $P > 0.17$).

Motor Evoked Potential Area

Across Group Effects

The effects of the 60 minutes intervention/rest period on corticospinal excitability as indicated by the MEP area scores in the wrist muscles and FDI are shown in Figure 2C. The 2 × 5 ANOVA revealed a significant GROUP × TIME interaction for the wrist muscles ($F > 3.8$, $P \leq 0.01$). Contrast analysis revealed no significant differences between

groups regarding the four postintervention conditions ($P > 0.24$).

Within Group Effects

Our observations revealed tendencies that are similar to those observed for the amplitudes of MEPs. One-way ANOVAs with TIME as the only factor revealed a significant main effect of TIME for the wrist muscles ($F = 4.76$, $P < 0.01$) in the intervention group. A sizeable facilitation was observed only at the 45 to 60 minutes (57% ±23 vs. baseline) postinterventional interval, reaching statistical significance ($P < 0.001$). Again, no consistent change in MEP areas was observed for the wrist muscles in the control group (or for the FDI in both groups).

Comparison to 0

T-tests for single means showed that the wrist muscles area is significantly different from 0 at 45 to 60 minutes after intervention (all $P < 0.01$). FDI is never different from 0 in the intervention group (all $P > 0.18$) and both wrist muscles and FDI are not different from 0 in the control group (all $P > 0.12$).

The Effects of Intervention on Intracortical Excitability

In general, the 60 minutes period of repetitive afferent stimulation with passive movement did not significantly influence the levels of SICI and ICF.

Short Interval Intracortical Inhibition

One-way ANOVA with TIME as main factor revealed no significant difference in the levels of SICI as a result of the intervention (each muscle, $F < 1$). Scores (mean ± SD) for SICI were 53% ±17 (baseline) and 50% ±14 to 54% ±25 (postintervention) for the FCR; 52% ±13 (baseline) and 51% ±10 to 61% ±15 (post) for the ECR; 44% ±14 (baseline) and 44% ±12 to 48% ±10 (post) for the FDI. The 2 × 4 ANOVA revealed neither significant main GROUP effects, nor GROUP × TIME interactions (all: $F < 2.25$, $P > 0.10$); suggesting that no significant differences in the levels of SICI were noted between intervention and control.

Intracortical Facilitation

One-way ANOVA with TIME as main factor revealed no significant main effects (each muscle, $F < 1$). Scores (mean ± SD) for ICF were 115% ±26 (baseline) and 108% ±10 to 132% ±30 (post) for the FCR; 132% ±14 (baseline) and 121% ±22 to 131% ±29 (intervention) for the ECR; 116% ±15 (baseline) and 115% ±29 to 134% ±62 (post) for the FDI. Again, no differences in the levels of ICF between intervention and control were noticed (all: $F < 2.37$, $P > 0.10$).

Modulations in Electromyographic Activity During the Intervention

Rms scores (mean ± SD) for EMG activity during passive movement and at rest were respectively: 5.91 ± 1.94 and 2.62 ± 0.98 μV for the FCR ($P < 0.01$), 4.24 ± 0.99 and 2.92 ± 1.20 μV for the ECR ($P < 0.05$), and 7.31 ± 4.82 and 2.47 ± 0.55 μV for the FDI ($P < 0.05$). No significant differences between these mean rms amplitudes at the beginning and the end of the intervention period were observed for any of the three muscles (all, $P > 0.1$). It was apparent that during passive movements of the wrist there was a larger overall enhancement of EMG activity in the FCR (140% ±90 of rms level at rest) than in the ECR (62% ± 54 of rms level at rest, $P < 0.05$).

Although the level of EMG activity in the three muscles increased occasionally above the background (rest) level during the intervention, there was no evidence to link this increased activity with the postintervention effects. More specifically, we found no significant correlations between the amount of MEP facilitation at the 0 to 15 or 45 to 60 minutes postintervention intervals and the increase of EMG activity during the intervention. The Pearson R^2 correlation coefficients were 0.128 (0–15 minutes) and 0.343 (45–60 minutes) for the FCR, 0.103 (0–15 minutes) and 0.020 (45–60 minutes) for the ECR, 0.066 (0–15 minutes) and 0.172 (45–60 minutes) for the FDI (all, $R^2 > 0.1$).

DISCUSSION

The Effects of Passive Movement on Corticospinal Excitability

The present experiment shows for the first time that a lasting corticospinal facilitatory effect can be generated in the forearm muscles by repetitive passive movement of the wrist. Extending previous studies (e.g., Rosenkranz and Rothwell, 2003, 2004; Rosenkranz et al., 2003; Steyvers et al., 2003a,b), we used the activation of Ia muscle spindle afferents as the main source of somatosensory stimulation (even though other sensory receptors may also have been involved). In this respect, the application of 60 minutes of passive movement resulted in a progressively increasing corticospinal excitability until significant levels of facilitation were obtained over the course of 30 to 45 minutes postintervention. As such, the present findings indicate that repetitive proprioceptive stimulation through activation of Ia pathways is capable of producing persistent changes in corticospinal excitability.

It has been well established that phasic modulations in the excitability of corticomotor projections to forearm muscles during rhythmical passive movement are mainly mediated through alterations in firing rate of the muscle spindles (e.g., Burke et al., 1988; Lewis et al., 2001). These modulations may have contributed to the late facilitation build-up in the motor output of the target muscles as observed in our study. Furthermore, (1) the rapid decrease of H-reflex modulation in the order of seconds after cessation of passive movement intervention (Misiaszek et al., 1995; Voigt and Sinkjaer, 1998) and (2) the fact that brain-stem stimulation showed similar MEPs before and after intervention with electrical peripheral sensory stimulation (Kaelin-Lang et al., 2002), indicate that the effects of passive movements observed here were mainly of cortical origin (Huang et al., 2005; Siebner and Rothwell, 2003; Siebner et al., 2000; Tinazzi et al., 2005; Ziemann et al., 2002a,b).

Lewis et al. (2001) also demonstrated that in healthy human subjects, cyclical passive movements of the wrist

induce immediate phasic changes in SICI. However, the absence of an observable modulation in SICI or ICF in the present study does not rule out the supposed cortical origin of the excitatory effects that where observed with the single pulse TMS measurements. Specifically, this could be the case if the inhibitory circuits that regulate motor cortex excitability in response to afferent signals are influenced only during the intervention. As such, the delayed effect of the intervention on the cortical motor network would not be visible on SICIs and ICFs. Indeed, Kaelin-Lang et al. (2002) showed that ICF and inhibition were not changed after 2 hours of electrical sensory stimulation. Furthermore, the administration of Lorazepam (which facilitate $GABA_A$ receptor-mediated inhibition) suppressed the excitatory effects of an electrical sensory stimulation, indicating that these inhibitory circuits were actually involved in the regulation of motor cortex excitability during the intervention although they are not modulated anymore following the intervention.

An increase in amplitude and/or area of the evoked responses from the wrist muscles is argued to indicate recruitment of a larger number of descending motor pathways in response to cortical stimulation with TMS. In general, the MEP peak-to-peak amplitude indicates the peak of simultaneous excitement of the descending pathways, whereas MEP area reflects the total amount of excited motoneurons (e.g., Ikoma et al., 1996). As stimulus intensity was kept at the same level in both the pre- and postintervention sessions, we propose that the sustained increase in MEP amplitude and area could signify a gradual increase in the number of neurons recruited by TMS pulses after cessation of the intervention. This phenomenon may have been mediated by increasing the number of excitatory interactions within the cortical muscle representation without changing the inhibitory interactions (as no delayed effects of the intervention were observed for SICIs).

Training With Passive Movement as a Means to Promote Plasticity

Somatosensory stimulation by means of peripheral electrical nerve stimulation, tendon vibration, and/or passive movement and their potential to drive motor cortex reorganization in neurologically intact individuals and patients with brain injury have been underscored increasingly in the past years (e.g., Chen et al., 1999; Lewis and Byblow, 2004; McKay et al., 2002; Rosenkranz and Rothwell, 2004; Steyvers et al., 2003a; Tinazzi et al., 2005). In this respect, close similarities were observed between the time course of the increase in corticospinal excitability following our passive movement intervention and that obtained after comparable periods of continuous peripheral sensory intervention with electrical stimulation (Chen et al., 1999; Fraser et al., 2002; McKay et al., 2002; Pitcher et al., 2003; Ridding et al., 2001; Tinazzi et al., 2005) or after the application of low-intensity stimulation to the human motor cortex with repetitive TMS during short periods (Huang et al., 2005; Pascual-Leone et al., 1994). Consequently, an important future goal is to investigate to what extent excitability and/or reorganization changes in forearm muscle representations following somatosensory intervention with passive movement are associated with functional improvements in movement control.

The present intervention evoked a delayed MEP facilitation of both FCR and ECR muscles, indicating that sensory training through the application of passive movement enhanced the excitability of corticospinal pathways of both flexors and extensors. More specifically, we suggest that prolonged proprioceptive stimulation by means of passive wrist movement can access larger parts of the distributed neural network as compared with those accessed through the application of focal afferent stimulation by means of electrical peripheral nerve stimulation (Hamdy et al., 1998; Ridding et al., 2000, 2001) or muscle vibration (Rosenkranz and Rothwell, 2004). However, it seems that the intervention with proprioceptive training of the forearm muscles (ECR and FCR) did not propagate to the hand muscles (FDI). The latter observation is consistent with earlier work showing that afferent stimulation of specific musculature induces focal effects on corticospinal excitability in the targeted muscle(s) without changing the level of motor excitability in general (c.f., Rosenkranz and Rothwell, 2004).

Training with passive movements is often used in rehabilitation therapy whenever self-induced motion with a paretic limb is either too difficult or impossible. Mapping of regional cerebral blood flow in stroke patients has shown that longitudinal intervention with passive movements before clinical recovery elicits brain activation patterns in the sensorimotor cortex that are similar to those observed during active movements after substantial motor recovery (Nelles et al., 1999a,b). Correlations between increases in brain activation during passive movement intervention and degree of functional recovery in hemiplegic stroke patients following the intervention have been observed (Matteis et al., 2003; Ward et al., 2006). Those observations point clearly toward reorganization of sensory and motor neural substrates in the affected hemisphere. In this respect, it is appealing to conclude that the observed increase in the motor representations of the hand musculature in our study may have been an integral part of sensory-induced reorganization of the motor system. However, our results await confirmation with clinical groups.

To summarize, we have demonstrated that prolonged training with passive wrist movement, applied to neurologically-intact individuals, resulted in a delayed increase of motor output from the (targeted) forearm muscles for at least 1 hour after the end of the intervention. The present observations highlight the potential effect of sensory training with passive movement on increasing motor excitability in the human brain. The fact that the effects outlast the period of kinaesthetic stimulation by more than 45 minutes is encouraging for therapeutic manipulation of brain plasticity.

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