Human corticospinal excitability evaluated with transcranial magnetic stimulation during different reaction time paradigms

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Summary
The aim of this study was to evaluate corticospinal excitability of both hemispheres during the reaction time (RT) using transcranial magnetic stimulation (TMS). Nine right-handed subjects performed right and left thumb extensions in simple (SRT), choice (CRT) and go/no-go auditory RT paradigms. TMS, inducing motor-evoked potentials (MEPs) simultaneously in the extensor pollicis brevis muscles bilaterally, was applied at different latencies from the tone. For all paradigms, MEP amplitudes on the side of movement increased progressively in the 80–120 ms before EMG onset, while the resting side showed inhibition. The inhibition was significantly more pronounced for right than for left thumb movements. For the left SRT, significant facilitation occurred on the right after EMG onset. Initial bilateral facilitation occurred in SRT trials with slow RT. After no-go tones, bilateral inhibition occurred at a time corresponding to the mean RT to go tones. The timing of the corticospinal rise in excitability on the side of movement was independent of task difficulty and RT. This suggests that corticospinal activation is, to some extent, in series and not in parallel with stimulus processing and response selection. Corticospinal inhibition on the side not to be moved implies suppression of movement is an active process. This inhibition is more efficient for right- than for left-side movements in right-handed subjects, possibly because of left hemispheric dominance for movement.

Keywords: motor cortex; human; reaction time; transcranial magnetic stimulation

Abbreviations: CRT = choice reaction time; EPB = extensor pollicis brevis; fMRI = functional MRI; MEP = motor-evoked potential; RT = reaction time; SRT = simple reaction time; TMS = transcranial magnetic stimulation

Introduction
The activity of corticospinal tract neurons during movement preparation has been investigated in monkeys using intracortical recordings (Evarts, 1966, 1968, 1974, 1981; Fetz and Finocchio, 1972). The time course of the activation differs according to movement type (Evarts, 1974, 1981). When the movement is performed in response to an external stimulus, the same neuron may discharge hundreds of milliseconds before a slow and accurate movement of small amplitude, or only 60–100 ms before a ballistic movement (Evarts, 1974, 1981). In humans, facilitation of the efferent pathway to the agonist muscle during motor preparation has been demonstrated by changes in the amplitude of H reflexes (Hayes and Clark, 1978; Day et al., 1983; Eichenberger and Ruegg, 1984; Ruegg and Drews, 1991) and in reciprocal inhibition (Day et al., 1983). With electrical stimulation (Rossini et al., 1988; Starr et al., 1988) and transcranial magnetic stimulation (TMS) (Starr et al., 1988; Pascual-Leone et al., 1992) below resting threshold, the probability of evoking motor responses gradually increases in the agonist muscle, beginning ~100 ms before EMG onset. In the agonist muscle, a gradual increase has also been described in studies using TMS above the motor threshold (Hoshiyama et al., 1996, 1997). Effects on the contralateral homologous muscle at rest have not been studied extensively during

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the reaction time (RT). During steady, submaximal muscle contraction (Hess et al., 1986, 1987; Meyer et al., 1995), facilitation of the resting contralateral homologous muscle has been reported. On the other hand, corticocortical inhibition of the area of the motor cortex supplying the contralateral homologue has been described using TMS (Ferbert et al., 1992). During voluntary motor responses in an RT paradigm, occasional facilitatory effects on the contralateral homologous muscle have been observed (Rossini et al., 1988). Moreover, the effect of the side of movement (dominant versus non-dominant side) has not been investigated previously.

Another issue in the study of RT is whether preparation for the motor response occurs in series or in parallel with stimulus processing. For example, in a choice reaction time (CRT) task (Ortiz et al., 1993), where subjects had to move their right or left hand depending on the occurrence of one of two go-signals, premovement potentials occurred earliest contralateral to the hand that was required to move more frequently, even before movements of the other hand. The authors suggested that response selection and motor preparation could occur in parallel with sensory discrimination.

In order to evaluate whether the pattern changes in cortical excitability during motor preparation differ according to the type of sensory discrimination and response selection involved in the task, we compared different RT paradigms. We also investigated the timing of the changes in efferent excitability to homologous muscles on the two sides during unilateral movements and determined whether these effects are lateralized in right-handed subjects. As a collateral study, since it has been reported that transcranial electrical and magnetic stimulation may influence the RT (Day et al., 1989; Pascual-Leone et al., 1992; Taylor et al., 1995), we also tested the ability of TMS to affect the RT under the experimental conditions of this study.

Methods

Subjects and experimental conditions

Nine healthy volunteers (seven men, two women; mean age 30.7 years, range 21–64) participated in the experiments. Subjects were right-handed according to the Edinburgh scale defined as the minimum intensity evoking at least five MEPs (Oldfield, 1971). Subjects gave their informed consent to the study, which was approved by the NINDS Institutional Review Board. During the experiments, the subjects sat on a chair with the forearms pronated, semiflexed and supported by a pillow.

Auditory stimulation

Acoustic stimuli of frequency 500 or 2000 Hz were administered through a loudspeaker with an intensity of 95 dB above normal hearing level. The interstimulus interval was varied randomly between 6 and 8 s in order to avoid anticipation by the subject.

Simple reaction time (SRT)

Subjects had to extend their right or left thumb as soon as possible after the acoustic stimulus. A block of 100 trials was performed for each side. A 500 Hz tone signalled a movement on the right and a 2000 Hz tone a movement on the left.

Choice reaction time (CRT)

A block of 300 trials was performed. The tones were varied randomly between 500 and 2000 Hz, with 50% probability for each frequency. The subject had to extend the right thumb for the tone at 500 Hz and the left thumb for the tone at 2000 Hz.

Go/no-go reaction time

Two blocks of 300 trials each, one for each movement side, were performed. In the blocks involving the right side (go/no-go right), the tones were administered similarly to the CRT trial, but the subject had to extend the right thumb for the 500 Hz tone and abstain from responding to stimuli at 2000 Hz. In the other blocks (left go/no-go) the subject had to repeat the same movement on the left side to a tone of 2000 Hz but not to tones at 500 Hz.

Transcranial magnetic stimulation

TMS was performed using a monophasic stimulator (Cadwell Laboratories, Kennewich, Wash., USA). The 140-mm outer diameter round coil was placed near the vertex, with the handle oriented posteriorly, in the area of minimum threshold for evoking simultaneously motor potentials in the extensor pollicis brevis (EPB) muscle of the two sides. It is believed that such a method activates cells of the corticospinal tract mainly within the primary motor area via interneurons (Amassian et al., 1990). In positioning the coil, effort was made to obtain motor-evoked potentials (MEPs) simultaneously from the EPBs on the two sides, with equal threshold and similar amplitude at the intensity used during the experiment (2–5% above motor threshold). Motor threshold was defined as the minimum intensity evoking at least five MEPs out of 10 trials above 50 mV in both EPBs. Once the optimal position had been established, the coil was held on a pantograph arm and fixed to the head with an elastic bandage. Current flow direction in the coil was varied randomly in the different subjects.

Recording

The EMG of both EPBs was recorded simultaneously by surface electrodes. The signal was amplified (Counterpoint Electromyograph; Dantec, Skoveland, Denmark) and filtered (band-pass 10–1000 Hz) using a Dantec Counterpoint, visualized, and digitized with a sampling frequency of
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5000 Hz for further analysis. The absence of voluntary contraction was continuously verified visually and by auditory monitoring of the EMG signal.

**Experimental protocol**

After verbal instruction, the subject practised for a few minutes with visual and auditory feedback of the EMG activity (continuous feedback was given during practice only). The subject was specifically instructed to maintain both EPB muscles at rest in the intervals between the acoustic stimuli and to respond as quickly and accurately as possible only with the side required, with a brisk movement of short duration (100–200 ms). Before each block of trials, 10 MEPs with a 5-s interstimulus interval were obtained. The average peak-to-peak amplitude of the 10 MEPs was considered to be the basal value for each block. During the RT paradigms, magnetic stimuli were administered in 80% of the trials, at random delays between 20 and 400 ms after the acoustic signal in the choice and go/no-go trials, and 20–300 ms after the tone of the SRT trials. In 10 randomly interspaced trials of each RT block (catch trials), the magnetic stimulus was administered without the acoustic stimulus to evaluate MEP amplitude during auditory stimulus expectation. The EMG activity of both EPB muscles was recorded simultaneously between 100 ms before and 700 ms after each tone, allowing both the behavioural response and the MEP amplitude for each EPB to be evaluated.

**Data analysis**

The EMG recordings from all trials were inspected visually. Trials with gradual EMG onset or background EMG activity in either EPB before the motor response or to TMS were excluded. Particular attention was paid to trials with mirror EMG activity, which were also excluded. RTs greater than 700 ms were not recorded and were considered to be incorrect responses. The number of excluded trials (ranging from 8 to 11% of the total across tasks) did not differ substantially across tasks; the major reason for exclusion was failure in relaxation, which occurred with different frequencies across subjects but consistently across tasks. Catch trials followed by motor responses, which occurred frequently only in the SRT paradigm, were not excluded since the data of interest were MEP amplitudes in the absence of any acoustic stimulus. For each trial, the following parameters were evaluated: (i) RT, and (ii) peak-to-peak amplitude of the MEPs on both sides, expressed for each side and for each block as a percentage of the mean amplitude of the corresponding 10 MEPs previously recorded at rest. When MEPs occurred after the onset of a voluntary motor response, the amplitude was measured only on the resting side.

For each block, we evaluated MEP amplitudes with respect to their latency from voluntary EMG onset, and RTs in trials with and without magnetic stimulation. In no-go trials in which no movement occurred, we evaluated MEPs with respect to their latency from the acoustic tone. For displaying MEP changes, the percentage data obtained from all subjects at each data point were pooled. In order to test significance of MEP changes compared with rest and comparing the two sides, the Wilcoxon signed rank test was used on the percentage data averaged at each latency point within each subject. To evaluate the effects of the magnetic stimulus on the RT, we averaged data within subject for each TMS latency after the auditory stimulus, up to the time prior to the expected RT (i.e. 20 ms before the average RT in trials without stimulation). To avoid considering non-conditioned RTs, trials in which the MEP fell after EMG onset were excluded. The overall effects of TMS were evaluated using Kruskal–Wallis non-parametric analysis of variance. RTs preceded by TMS were compared with RTs without TMS using the Wilcoxon signed rank test.

**Results**

**Mirror EMG activity**

Mirror EMG activity of the homologous resting muscle occurred in eight of nine subjects. In most cases, this consisted of very slight muscle contraction with no visible movement. However, visible movements also occurred occasionally and these were frequently recognized by the subject. An example of mirror EMG activation is given in Fig. 1. In five of the subjects with mirroring, these occurred only when the left thumb was required to move and never during movements of the right thumb. In the other three subjects, mirroring was more frequent for left-handed movements. The greater occurrence of mirrors during voluntary movement of the left hand compared with the right was statistically significant ($P = 0.012$; Wilcoxon rank test).

![Fig. 1 Example of spontaneous mirror EMG activity (right EPB) during voluntary contraction of the left EPB in a single trial (left thumb, go).](image-url)
Fig. 2 RTs for the right hand at each TMS latency in the CRT task relative to the go signal. no TMS = RT with no TMS. Note the blank window caused by a lack of voluntary reactions from 15 to 40 ms after TMS.

Fig. 3 Distribution of RTs for the CRT (responses with the left hand) without (broken line) and with (continuous line) TMS. (A) TMS latency 180–200 ms. (B) TMS latency 240–260 ms.

**Effect of magnetic stimulation on reaction time**
RMs with and without TMS are reported in Fig. 2. The RTs were significantly shorter than CRTs and go RTs for both sides (P = 0.008). RTs were significantly faster when movements were performed with the left than with the right thumb in CRTs (P = 0.008). An example of the distribution of raw RTs at different TMS latencies for the CRT paradigm with left thumb movements is shown in Fig. 3. Here, magnetic stimulation created a 40-ms period of EMG silence, shown as an empty window in the RT distribution appearing for TMS latencies of >100 ms for the SRT and 140 ms for the CRT and go paradigms. The blank windows occur when the RT is ~20 ms longer than the latency of the magnetic stimulation (20 ms is approximately the MEP latency after delivery of the stimulus). This may be interpreted as a lack of voluntary motor responses in the 20 ms following the MEPs. Since Fig. 3 represents RTs measured during the voluntary EMG responses against different TMS latencies, it is implicit that in these trials movement actually occurred and was not suppressed by TMS. Considering that subjects had no cue for the forthcoming TMS, which was administered at random latency, it is very unlikely that the blank window results from anticipating the RT prior to TMS. Rather, it is more reasonable to suppose that TMS delays voluntary movement. Such data demonstrate the impossibility of voluntarily activating the EPB for 40 ms after the magnetic stimulus (or for 20 ms after an MEP), resulting in a delayed RT. This delay is also evident from the frequency distribution of RTs. For example, in Fig. 3 (left movement in CRT), a second peak in the distribution of the RTs is present after magnetic stimulation, as the voluntary responses accumulate immediately after the silent period due to the magnetic stimulus, thus creating a bimodal distribution and an increased average of RTs.

The mean RT differed according to the delay of the magnetic stimulus from the acoustic signal (Fig. 4). The latency of magnetic stimulation significantly influenced the RT (choice left, P = 0.001; choice right, P = 0.027; P < 0.0001 in all other tasks; Kruskal–Wallis test). RTs became significantly increased, compared with the non-stimulated condition, for later TMS latencies (for SRT, P < 0.2 starting at 100 ms for the right and at 120 ms for the left; for CRT, P < 0.04 starting at 160 ms for the left and P < 0.03 starting at 200 ms; for go starting at 200 ms, P < 0.03 for the left and P < 0.04 for the right). In addition to delaying the RTs, magnetic stimulation may also induce shortening of them. In fact, the RT appeared reduced compared with trials without magnetic stimulation when the magnetic stimuli were administered immediately after the acoustic signal (20 ms in the SRT trials and 40 ms in the trials in the CRT and go trials). This reduction was statistically significant only in the go trials (P = 0.021 for the left and P = 0.008 for the right).

**MEP amplitudes in different tasks**

**Simple reaction time**
Figures 5–8 show MEP amplitudes (in percentage of the amplitude at rest) according to their latency from voluntary EMG onset in the different tasks and for each side of movement. For statistical analysis, MEPs from both sides before EMG onset were compared with rest and with each other for latencies between ~180 ms and ~60 ms. Since not
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Fig. 4 RTs without TMS (time = 0) and at different TMS latencies from the tone. Data at each time point are the average of the average values within each subject. Open diamonds = choice left; filled diamonds = choice right; open squares = go left; filled squares = go right; open circles = simple left; filled circles = simple right.

Fig. 5 Data from the SRT task. (Top) Movement performed with the right side. (Bottom) Movement performed with the left side. Plots are of MEP amplitude, in percentage of rest, aligned on voluntary EMG onset. Numbers on the abscissa indicate the time from the magnetic stimulus to the voluntary EMG response. Negative values indicate that magnetic stimulation was administered before voluntary EMG onset. A zero value indicates magnetic stimuli occurring from −15 to 0 ms with respect to voluntary EMG onset.

all subjects in all tasks yielded data points closer to EMG onset than 60 ms, these data were pooled when present with the 60-ms time interval. For the SRT trials performed with right and left thumbs (Fig. 5), a first phase of bilateral facilitation of MEPs was observed when the magnetic stimuli preceded EMG onset by 200–140 ms (at −160 ms, $P = 0.028$...
Fig. 6 Data from the SRT task. Plots are of MEP amplitude (as a percentage of rest) aligned on the voluntary EMG onset. Numbers on the abscissa indicate the time from the magnetic stimulus to the voluntary EMG response. Negative values indicate that magnetic stimulation was administered before voluntary EMG onset. A zero value indicates magnetic stimuli occurring from –15 to 0 ms after voluntary EMG onset. (A and B) Right thumb movement. (C and D) Left thumb movement. (A and C) Trials with RT < 170 ms. (B and D) Trials with RT > 170 ms.

Fig. 7 Data from the CRT task. (Top) Movement performed with the right side. (Bottom) Movement performed with the left side. MEP amplitude (as a percentage of rest) aligned on voluntary EMG onset. Numbers on abscissa indicate the time from the magnetic stimulus to the voluntary EMG response. Negative values indicate that magnetic stimulation was administered before voluntary EMG onset. A zero value indicates magnetic stimuli occurring from –15 to 0 ms with respect to voluntary EMG onset.

for both EPBs in the SRT right; \( P = 0.05 \) for the left EPB in the SRT trials with the left thumb; Wilcoxon rank test). As the average RT was ~162 ms in the SRT trials, initial facilitation of MEPs would have occurred during motor responses with higher latency than the average. When the trials with shorter and longer RTs than the average were
examined separately (Fig. 6), bilateral facilitation was absent in the short RT trials, whereas it was present in the long RT trials.

After the first facilitatory peak and up to 100–80 ms before voluntary reaction, the MEPs were slightly facilitated bilaterally in both trials. Then, beginning at around –100 ms, MEPs gradually increased on the side of movement, becoming significantly higher than at rest at ~60 ms for the right side ($P = 0.012$) and at ~80 ms for the left ($P = 0.008$).

MEPs of the non-moving side decreased progressively but became significantly inhibited only for right-sided movement (at ~60 ms, $P = 0.036$).

Figures 5 and 6 show that MEPs from magnetic stimuli preceding movement by 40 ms were not recorded. This was due to the fact that the movement never began <40 ms after the magnetic stimulus (Figs 3 and 4). Therefore, the lack of magnetic stimuli in the 40-ms period preceding voluntary EMG instead represents a lack of motor responses in the 40 ms following the magnetic stimulus.

After voluntary EMG onset, only MEPs on the side at rest were measured, and statistical analysis was performed up to 100 ms after EMG onset. Considering that the shortest EMG responses lasted ~100 ms, TMS falling in this time period was delivered during EMG contraction. MEPs were modulated differently according to the movement side. In SRT trials using the right thumb, MEPs in the left EPB remained unchanged for the first 20–40 ms (Fig. 5) and became inhibited subsequently ($P = 0.008$ at 60 ms, $P = 0.015$ at 80 ms, $P = 0.008$ at 100 ms). When movement was performed with the left side, MEPs in the right EPB were facilitated in the first 100 ms and only later were they inhibited, but these changes were not significant. The difference between the MEPs on the two resting sides was statistically significant when the values at each interval were compared ($P = 0.02$ at 40 and 60 ms; $P = 0.038$ at 80 ms; $P = 0.008$ at 100 ms).

**Choice reaction time**

Because of the longer RT in this task, the time course of the change in MEP amplitude was longer compared with that seen in the SRT paradigm (Fig. 7). For magnetic stimuli preceding the voluntary EMG response by 400–140 ms, MEPs in the left EPB were unchanged or inhibited compared with those evoked at rest, whereas MEPs in the right EPB were slightly facilitated, regardless of the side of the following movement. This inter-side difference seemed to be intrinsic to the CRT paradigm, as it was also revealed in the catch trials ($P = 0.008$), in which the magnetic stimulus was administered without the acoustic stimulus. Before the side of movement was indicated, MEPs evoked in the right EPB were facilitated, while MEPs in the left side were inhibited. This shows that preferential activation of the left hemisphere together with inhibition of the right occurs in right-handed subjects in the period before the go signal.

Around 100 ms before movement of the right side and ~80 ms before movement of the left, MEPs increased
progressively on the movement side, with little effect on the resting side. The difference between MEPs on the movement and resting sides became significant beginning at –100 ms if the movement was performed on the right side (P = 0.028) and –60 ms if it was performed on the left (P = 0.008).

As in the SRT paradigm, MEPs evoked in the resting EPB after voluntary EMG onset were inhibited early for movement performed with the right side, while they were initially facilitated and only subsequently inhibited in left-sided movement, but this difference did not reach significance (P = 0.059 at 20 ms).

**Go/no-go reaction time: go trials**

For the go trials in the 400–140 ms before movement, MEPs from the two sides showed no significant change in amplitude (Fig. 8). For right-sided movement, there was non-significant, symmetrical facilitation and for left-sided movement there was a small facilitation of left MEPs. In the 120–100 ms preceding movement, similar to what was seen for the SRT and CRT, there was progressive facilitation on the movement side and inhibition on the opposite side. Only the facilitation on the moving side became significant (at –60 ms, P = 0.017 for the right and P = 0.011 for the left). The difference between the moving and the non-moving sides became significant at –100 ms for right movement (P = 0.038) and at –60 ms for left movement (P = 0.008). After voluntary EMG onset, there were slight oscillations between inhibition and facilitation on the resting side, followed by an inhibitory phase, which did not reach significance (P = 0.051 at 100 ms for the left EPB in the go right condition). The side-to-side difference after contralateral EMG onset was just below the limit of statistical significance (P = 0.051 at 60 ms).

**Go/no-go reaction time: no-go trials**

Figure 9 shows the percentage changes in MEP during no-go trials of the go/no-go tasks performed with the right and left thumbs. Since there was no movement in these trials, MEPs were aligned with respect to the latency of the magnetic stimulus from the acoustic no-go stimulus. In the no-go right condition, bilateral MEP facilitation was present 20–100 ms after the tone, while for no-go left this facilitation was evident only in the left EPB at 80 ms. Bilateral inhibition followed 220–240 ms after the tone for both the no-go right and no-go left conditions. This inhibition became significant for the right EPB at 300 ms in the no-go right (P = 0.028) and at 260 ms for the left EPB in the no-go left condition. Data aligned with respect to the TMS latency from the tone in the case of go stimuli are shown in Fig. 10, for comparison with the no-go data. While in the no-go trials there was bilateral inhibition, in the case of go tones the MEPs on the moving side became facilitated, together with inhibition of the non-moving side. The purpose of this type of alignment is only

![Fig. 9 Data from the go/no-go RT (no-go trials). (Top) Movement performed with the right side. (Bottom) Movement performed with the left side.](image-url)
Discussion

Effects of TMS on reaction time

As in previous reports (Pascual-Leone et al., 1992; Ziemann et al., 1997), we found that TMS may shorten RT if applied early after the imperative stimulus, while it delays RT if applied close to the expected voluntary response. We could not describe the time course of corticospinal excitability in the 40 ms prior to voluntary EMG onset, since voluntary responses were absent in the 40 ms following magnetic stimulation. This was because subjects were temporarily unable to respond after TMS. The delay of the RT by TMS, also reported in previous studies (Day et al., 1989; Pascual-Leone et al., 1992; Taylor et al., 1995; Ziemann et al., 1997), resembles the silent period observed in tonic voluntary EMG after motor cortex stimulation (Marsden et al., 1983; Rothwell et al., 1987). By studying the H reflex, Fuhr and colleagues demonstrated that the first part of the silent period is due to motor neuron inhibition, whereas during the second part spinal motor neuron excitability is not affected (Fuhr et al., 1991), suggesting a reduced descending corticospinal output.

Magnetic stimuli can also cause EMG silence at intensities subliminal for evoking MEPs (Davey et al., 1994). Moreover, the site of optimal stimulation for producing the silent period does not coincide with that for MEP generation (Wassermann et al., 1993). Therefore, discharge of spinal motor neurons after the magnetic stimulus is not necessary for the generation of the silent period, and the inhibition is not merely a consequence of corticospinal activation.

It should be noted that there are some discrepancies regarding the optimal stimulation site for inducing both a silent period and a delay in RT. In fact, while the silent period is also obtained from areas not inducing MEPs (Wassermann et al., 1993), Taylor and colleagues reported that the optimal site of stimulation to induce prolonged RTs coincides with that for evoking MEPs (Taylor et al., 1995). Since voluntary contraction did not appear for 20 ms after a MEP, we may consider MEPs preceding the voluntary reaction by 20 ms as almost coinciding with the cortical zero time for motor initiation. Ziemann and colleagues reported that RT delay was more effective if TMS was administered at a time close to the expected voluntary response (Ziemann et al., 1997). The shortening of RT by TMS administered early after the auditory signal, previously reported by Pascual-Leone and colleagues (Pascual-Leone et al., 1992) may be related to ‘intersensory facilitation’ (Bernstein et al., 1969; Nickerson, 1973), or to some direct effect of TMS on cortical processing, or both.

Corticospinal excitability prior to contralateral movement and effect of paradigm

For all paradigms, gradual facilitation of the agonist muscle began ~100–120 ms before movement. This finding is consistent with earlier studies which used intracortical recording in animals (Evarts, 1966, 1968, 1974, 1981; Fetz and Finocchio, 1972) and transcranial electrical (Rossini et al., 1988; Pascual-Leone et al., 1992) or magnetic (Rossini et al., 1988; Pascual-Leone et al., 1992; Chen et al., 1998) stimulation in humans. Increased amplitude of transcranially evoked responses may derive directly from facilitation of corticospinal cells or from the activation of the spinal motor neurons by descending corticospinal or subcortical projections. Two types of evidence favour spinal preactivation: one is the increased size of the H reflex preceding movement (Hayes and Clarke, 1978; Day et al., 1983; Eichenberger and Ruegg, 1984; Ruegg and Drews, 1991), and the other is the increased probability of evoking MEPs before movement using transcranial electrical stimulation (Rossini et al., 1988), which is thought to activate corticospinal cells primarily at the axonal level. On the other hand, intracortical recordings in freely moving animals (Evarts, 1966, 1968, 1974, 1981; Fetz and Finocchio, 1972) have shown increased frequency of pyramidal cell discharge beginning ~150 ms and peaking 50 ms before movement, and declining 20–30 ms after movement onset. Taken together, this evidence suggests that
both spinal and cortical mechanisms play a role in the premovement facilitation of MEPs observed in our study.

RT increased with task difficulty, being shorter in the SRT than in paradigms requiring two possible responses (go/no-go and CRT) (Luce, 1986). If movement preparation occurs in parallel with stimulus processing, one should expect a longer preparation phase for tasks requiring discrimination between two stimuli or the preparation of two possible responses (go/no-go and CRT) than for SRT. Nevertheless, corticospinal facilitation on the moving side occurred ~100 ms before movement in all paradigms, with differences of ~20 ms, while RT varied in the order of ~100 ms. This finding agrees with previous studies on the discharge of pyramidal cells preceding voluntary movement before and after cooling of the monkey cerebellar dentate nucleus (Meyer-Lohmann et al., 1977). Such cooling delayed the RT by ~100 ms, but did not change the delay between the increase of pyramidal discharge and the onset of movement. Therefore, we may hypothesize that in our experiment the increased efferent activity to the limb that must be moved occurs, at least partially, in series to discriminative–decisional processes, which require more or less time according to the paradigm.

A finding encountered only in long RTs in the SRTs was an initial bilateral facilitation of MEPs. This facilitation was bilaterally symmetrical and occurred long before the voluntary response. Therefore, this phenomenon appeared to be unrelated to movement and preparation because it was seen only in slow RTs, and may actually have been responsible for the slower responses. This increased corticospinal excitability may have been a startle-like response. The reduced response speed could have been caused by the startle per se, or both the slowness and the tendency to startle could have been produced by a third factor. Goodin and Aminoff reported that a bimodal distribution of RTs may also be observed within individual subjects, who may switch from one response type to the other in different blocks of trials (Goodin and Aminoff, 1990). We found different states of corticospinal excitability within the same blocks. Early bilateral facilitation did not occur in the CRT and go RT. The reason for this difference is unclear. Moreover, the catch trials during the SRT blocks were usually followed by an erroneous voluntary movement. However, this did not occur for the choice and go/no-go trials. Other evidence of some motor presetting is the finding of a higher MEP amplitude on the right side compared with the left, early in the CRT paradigm. This prevalence, which was also present in the catch trials, also suggests that some degree of predicting may occur in the motor system prior to external inputs.

In the no-go trials, MEPs were bilaterally inhibited ~200–300 ms after the acoustic signal, corresponding approximately to the mean RT found in the go trials. This suggests that, when the acoustic tone instructed the subject not to perform the movement, the consequence was not just a lack of efferent activation, but inhibition. Inhibition of the agonist muscle at similar latency has been reported previously (Hoshiyama et al., 1997). In that study, inhibition was not selective and was also present in an antagonist muscle of the same spinal segment. In our study, inhibition was not side-selective and was expressed both in the muscle involved in the task and in the homologous muscle. Reduced MEPs in no-go trials could result from inhibition of the corticospinal output by control centres such as the premotor area, or could be mediated by descending inhibitory pathways at the spinal level. In favour of the first hypothesis is the finding of a negative potential recorded in the monkey prefrontal area during no-go trials in a similar paradigm (Sasaki and Gemba, 1986). Stimulation of the same zone delayed or suppressed movement (Sasaki et al., 1989). Stimulation of an area corresponding to the SMA in humans has been shown to inhibit initiation or to stop performance of ongoing movements (Lüders et al., 1988). Nevertheless, it has not yet been demonstrated whether the stimulation disrupts the activity of a structure involved in motor programming and execution, or excites an inhibitory structure. In either case, the absence of movement is an active process.

Corticospinal excitability to ipsilateral movement and laterality effects

When the excitability in the cortical representation of the agonist muscle increases prior to movement, its homologous muscle at rest undergoes inhibition. While we did not observe particular left–right differences in the corticospinal changes to the agonist muscles in the 100 ms preceding movement, the effects on the resting homologous muscle varied according to the side of movement. Preparation and execution of dominant hand movements in right-handed subjects inhibited the non-dominant homologous muscle, even though the latter was not involved at all in the task. In the same subjects, prior to movements performed with the non-dominant hand, inhibition of the dominant side was small or even replaced by facilitation, as in the SRT trials. The finding of inhibition seems to conflict with a previous report by Rossini and colleagues in which the right hemisphere was stimulated at subthreshold intensity in a SRT paradigm (Rossini et al., 1988); MEPs were observed occasionally in the left opponens pollicis muscle during voluntary opposition of the right thumb. However, a direct comparison of the two studies is not feasible.

The MEP amplitude changes found in our study of the non-moving side could be generated at the cortical or spinal level. Cortical effects could derive from interhemispheric connections or originate from the premotor areas, which also modulate the activity of both primary motor areas during unilateral movements. Asanuma and Okuda evoked facilitatory responses in the corticospinal cells of the cat by stimulating the contralateral primary motor area. The area where stimulation evoked facilitation in the contralateral cortex was surrounded by a zone where stimulation evoked inhibition (Asanuma and Okuda, 1962). In humans, it has
been shown that the voluntary contraction of a muscle may facilitate contralateral MEPs (Hess et al., 1986, 1987; Meyer et al., 1995). This facilitatory effect, whose temporal course has not been evaluated, also occurs in patients with lesions or agenesis of the corpus callosum (Meyer et al., 1995). The authors of this study concluded that the contralateral facilitation observed in these patients could be mediated by spinal effects. Nevertheless, it is not possible to say whether the same is true for normal subjects. In normal humans, inhibition of magnetically evoked MEPs was found after a conditioning magnetic stimulus had been applied 15 ms earlier to the contralateral side (Ferbert et al., 1992; Kujirai et al., 1993; Meyer et al., 1995). This inhibition is markedly reduced in patients with lesions or agenesis of the corpus callosum (Rothwell et al., 1991; Meyer et al., 1995), and has been considered transcallosal because the conditioning stimulus did not affect the H reflex or MEPs to electrical stimulation (Ferbert et al., 1992; Kujirai et al., 1993). However, inhibition of electrical MEPs has also been found (Gerloff et al., 1998). Another finding showing that transcallosal connections mediate motor inhibition between homologous areas of the two hemispheres comes from the observation of mirror movements in patients with callosal lesions (Tanaka et al., 1990).

Our results suggest that voluntary movement of the dominant side leads to inhibition of the MEPs of the resting homologous muscle, while the opposite may occur in non-dominant movements. This could be due to the different predominance of the two mechanisms (transcallosal and/or spinal facilitation versus transcallosal inhibition). In a study of normal subjects at rest, Netz and colleagues found that inhibition of MEPs by a conditioning magnetic stimulus over the contralateral primary motor area was stronger when the conditioning stimulus was applied over the dominant hemisphere in right-handed subjects (Netz et al., 1995). Cortical lesions of the hand motor area of the left hemisphere or of its efferent fibres at the level of the internal capsule may cause, in addition to contralateral paralysis, dysfunction of ipsilateral movements, while lesions of the right hemisphere leave movement of the ipsilateral limb relatively unchanged (Wyke, 1971). Also, repetitive TMS delivered to the ipsilateral primary motor hand area during execution of a unilateral complex finger sequence induced more timing errors in the left hand than in the right hand (Chen et al., 1997).

Using functional MRI (fMRI), Kim and colleagues observed bilateral activation of the sensorimotor areas during movement of the left hand, whereas during right-hand movement activation was almost entirely contralateral (Kim et al., 1993). Nevertheless, fMRI does not provide information on the inhibitory or excitatory nature of the cortical activation. In fact, we found significantly more frequent mirroring during movement of the non-dominant hand in right-handed normal subjects. This finding suggests that future studies of cortical activation for unilateral movements should provide EMG recordings of ipsilateral muscles to exclude mirror muscle activation.

The asymmetrical occurrence of mirroring also parallels the asymmetrical MEP effects during true unilateral movements. It can be hypothesized that both inhibition (probably in part transcallosal) and facilitation (probably spinal, through a direct pathway) of homologous contralateral muscles occur to different degrees. During movement of the dominant hand in right-handed subjects, inhibition of the right motor cortex prevails. Inhibition appears to be less pronounced during left-hand movement; in this circumstance there is facilitation of the ipsilateral motor pathways, resulting in sporadic mirror movements, even in normal subjects, and in facilitation of MEPs. It is likely that both mechanisms are involved in both hemispheres, but with a different balance which may also be modulated according to the task. Task modulation may explain why we found that facilitation of the dominant hand at rest is maximal in the SRT, which requires less inhibitory control. It may also explain the discrepancy between the facilitation of the right MEPs during left-side movement in our findings and the bilateral, interhemispheric inhibition found by Netz and colleagues using bilateral magnetic stimulation (Netz et al., 1995). Task modulation of the inhibitory and excitatory effects between homologous muscles could be useful for shifting from independent movement to bilateral movements. During a motor task, the inhibition/excitation balance tends to favour the dominant and to depress the non-dominant hand. This imbalance may even precede the go stimulus, particularly when there is a need to choose between the two sides. The lesser effect of inhibitory circuitry during left-side movement in right-handed subjects could also explain the paradoxical faster responses of the non-dominant hand (Annett and Annett, 1979; Bradshaw et al., 1990) and of the left hand in right-handed subjects observed in our study and in previous literature (Rastatter and Gallaher, 1982; Ortiz et al., 1993). The concentration of resources on the better-performing side favours response accuracy at the expense of response speed.

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