

Role of the Ipsilateral Primary Motor Cortex in Controlling the Timing of Hand Muscle Recruitment

M. Davare¹, J. Duque¹, Y. Vandermeeren¹, J.-L. Thonnard²
and E. Olivier¹

¹Laboratory of Neurophysiology, Department of Physiology and ²Rehabilitation and Physical Medicine unit and Education Physique et de Réadaptation, School of Medicine, Université catholique de Louvain, Avenue Hippocrate 54, B-1200 Brussels, Belgium

The precise contribution of the ipsilateral primary motor cortex (iM1) to hand movements remains controversial. To address this issue, we elicited transient virtual lesions of iM1 by means of transcranial magnetic stimulation (TMS) in healthy subjects performing either a grip-lift task or a step-tracking task with their right dominant hand. We found that, irrespective of the task, a virtual lesion of iM1 altered the timing of the muscle recruitment. In the grip-lift task, this led to a less coordinated sequence of grip and lift movements and in the step-tracking task, to a perturbation of the movement trajectory. In the step-tracking task, we have demonstrated that disrupting iM1 activity may, depending on the TMS delay, either advance or delay the muscle recruitment. The present study suggests that iM1 plays a critical role in hand movements by contributing to the setting of the muscle recruitment timing, most likely through either inhibitory or facilitatory transcallosal influences onto the contralateral M1 (cM1). iM1 would therefore contribute to shape precisely the muscular command originating from cM1.

Keywords: agonist–antagonist muscles, corpus callosum, interhemispheric inhibition, motor cortex, TMS

Introduction

Distal upper limb muscles are predominantly under the control of crossed corticospinal (CS) projections originating from the contralateral motor areas (Porter and Lemon 1993). However, converging evidence supports the view that the ipsilateral primary motor cortex (iM1) also contributes to hand and finger movements. Indeed, electrophysiological experiments have shown that, in monkeys, the activity of iM1 neurons exhibits a task-related modulation during upper limb movements (Tanji and others 1988; Donchin and others 1998; Kazennikov and others 1999; Steinberg and others 2002; Cisek and others 2003). In humans, both transcranial magnetic stimulation (TMS) (Stedman and others 1998; Tinazzi and Zanette 1998) and functional imaging studies (Kim and others 1993; Cramer and others 1999) have also concluded that iM1 contributes significantly to hand and finger movements, particularly when a high dexterity is required (Sadato and others 1996; Catalan and others 1998; Hummel and others 2003; Verstynen and others 2005). Accordingly, disturbing the iM1 activity by means of TMS prolongs simple reaction times (RTs) (Foltys and others 2001) and increases the number of errors in subjects performing complex sequences of finger movements (Chen and others 1997). Finally, in stroke patients, unilateral lesions involving motor areas have been repeatedly shown to impair ipsilesional upper limb movements (Colebatch and Gandevia 1989; Desrosiers and others 1996; Hermsdorfer, Laimgruber,

and others 1999; Hermsdorfer, Ulrich, and others 1999; Yarosh and others 2004).

Although all those studies corroborate the view that iM1 participates somehow in the control of hand and finger movements, its precise involvement remains poorly understood. A recent study has proposed that iM1 may play a crucial role in sequencing the recruitment of hand muscles, as suggested by the deficits in hemiparetic stroke patients while performing step-tracking movements with the nonparetic hand (Yarosh and others 2004). However, because, in those patients, lesions also involved brain areas other than iM1 and because it is likely that cortical reorganization had occurred, it is difficult to extrapolate, from those results, the actual involvement of iM1 in hand movement control in healthy subjects.

The purpose of the present study was to investigate, in healthy individuals, the role of iM1 in 2 tasks requiring precise hand and finger movements, namely, a step-tracking task (Hoffman and Strick 1986a, 1986b) and a grip-lift task (Johansson and Westling 1984). The former is representative of goal-directed movements and the latter of the precision grip between the thumb and index finger. Both tasks have already been extensively studied in healthy subjects (Johansson and Westling 1988; Hoffman and Strick 1990, 1999; Flanagan and Wing 1997; Augurelle and others 2003), and therefore, they provide an ideal framework to investigate the role of iM1 in hand movement control. To address this issue, we used TMS to disturb transiently the activity in iM1; combined with a precise quantification of the motor deficits consequent to such virtual lesions, this approach allowed us to infer the contribution of iM1 to the investigated tasks (Walsh and Cowey 2000).

Methods

A total of 17 healthy volunteers (23.5 ± 2.1 years) participated in this study. All subjects were right-handed according to the Edinburgh handedness inventory (Oldfield 1971). Their vision was normal, or corrected to normal, and none of them had a neurological history. Subjects were screened for potential risks of adverse reactions to TMS by means of the TMS Adult Safety Screen (Keel and others 2001). All experimental procedures were approved by the Ethics Committee of the Université catholique de Louvain, and all subjects gave written informed consent.

Grip-Lift Task

Experimental Procedure

Ten subjects (24.3 ± 2.3 years) sat comfortably on a padded chair at a height adjusted so that their right elbow was approximately flexed at 135° on a table with the wrist positioned midway between pronation and supination. The subjects were asked to grasp, under visual control, a 575-g apparatus between the right index and thumb (Fig. 1A) and to lift it to a height of about 20 cm, as indicated by an elastic band. The apparatus consisted of 2 parallel vertical grip surfaces of smooth brass

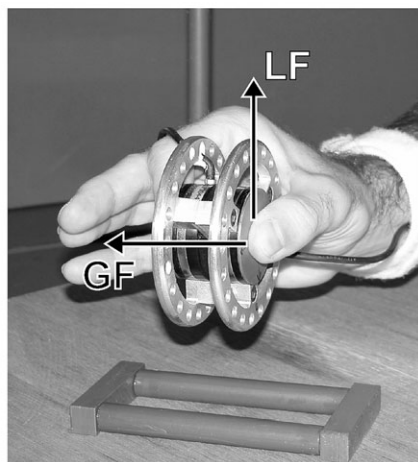
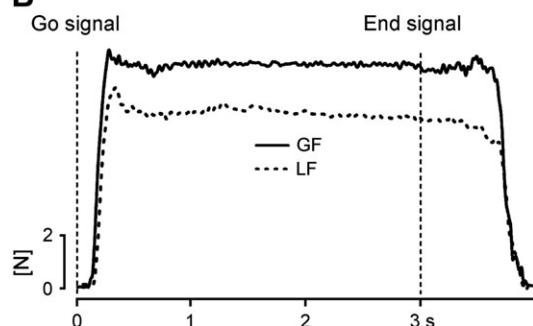
A**B**

Figure 1. (A) Apparatus used to measure forces during the grip-lift task. Only the thumb and index fingertips were in contact with the lateral surface of the apparatus. The GF and LF are illustrated for the thumb by horizontal and vertical vectors, respectively. (B) Representative control GF and LF traces. Following an auditory GO signal, the subject had to grasp and lift the apparatus. After about 3 s, another auditory signal indicated the end of the task.

(40 mm diameter, 30 mm apart; Fig. 1A). Two 3-dimensional force-torque sensors (Mini 40 F/T transducers, ATI industrial automation, Garner, NC) were used to measure the 3 orthogonal forces (F_x , F_y , F_z) applied to the grip surface. Sensing ranges for F_x , F_y , and F_z were ± 40 , ± 40 , and ± 120 N with a resolution of 0.02, 0.02, and 0.06 N, respectively. The force tangential to the grip surface (load force [LF]) was the result of the vectorial sum of F_x and F_y , and the force normal to the grip surface (grip force [GF]) was given by F_z . Subjects were instructed to grasp the object rapidly and to lift it by applying the minimum force required to avoid slips (Westling and Johansson 1984). An auditory GO signal was delivered at the beginning of the task and was followed, about 3 s later, by another beep indicating the end of the task (Fig. 1B).

The subjects began with 2 practice blocks of 12 trials without TMS to become acquainted with the task requirements. Then, the experimental session consisted of 6 blocks of 12 trials where repetitive transcranial magnetic stimulation (rTMS) was applied over iM1; half of the blocks consisted of sham stimulations (coil perpendicular to the scalp). Because no statistical difference was found between data gathered in the 3 sham blocks (all $F < 0.84$, all $P > 0.05$), results from these blocks were pooled together and used as control values. All blocks (3 sham and 3 experimental conditions) were counterbalanced among subjects.

Transcranial Magnetic Stimulation

rTMS was delivered using a Rapid Magstim model 200 stimulator (Magstim, Whitland, UK) through a 70-mm diameter figure-of-eight coil placed over the hand area of the right M1. The coil was held tangentially to the skull with the handle pointing laterally and orthogonally to the central sulcus. The coil location was adjusted to optimize the motor evoked potential (MEP) amplitude in the contralateral first dorsal

interosseous (1DI) muscle. Once the optimal coil position was found, the “hot spot” was marked on a closely fitting electroencephalography cap, and the motor threshold—defined as the lowest TMS intensity required to elicit 5 MEPs larger than 50 μ V in a series of 10 stimulations—was determined (Rossini and others 1994). The TMS intensity was set at 120% of the motor threshold. The rTMS train (10 Hz, 500 ms) was delivered synchronously with the GO signal. For safety reasons, rTMS trains were separated by at least 12 s (Wassermann 1998).

Data Acquisition and Analysis

The signals from the force transducers were digitized online at 1 kHz with a 12-bit 6071E analog-to-digital converter in a PXI chassis (National Instruments©, Austin, TX). After the analog-to-digital conversion, the signals were low-pass filtered (15 Hz) with a fourth-order, zero-phase-lag, Butterworth filter. The GF and LF onsets were determined automatically, when force values exceeded the mean + 2 standard deviations (SD) of the premovement resting value (Flanagan and Tresilian 1994).

Electromyographic (EMG) activity was recorded with surface electrodes (Neuroline, Medicotest, Denmark) from 2 intrinsic hand muscles, namely, the “abductor pollicis brevis” (APB) and 1DI and from 2 arm muscles, namely, the “brachio-radialis” (BrR) and the “triceps-brachialis” (TrB). EMG signals were amplified (gain 1K), band-pass filtered (10–500 Hz; Neurolog Digitimer Ltd, UK), and digitized online at 1 kHz using a personal computer. EMG signals were then rectified off-line and aligned with the GO signal. We calculated the EMG baseline by averaging the EMG activity that occurred during a 200-ms interval before the GO signal; then the onset of EMG was defined at a time when the EMG signal exceeded the baseline + 2SD. Because of the inconsistency of the TrB activity in this task, this muscle was not included in the subsequent analyses.

The following temporal parameters were measured (see Fig. 3A): 1) the RT, defined as the delay between the GO signal and the first EMG activity; 2) the preloading phase (T0–T1), that is, the delay between the mean contact time of the 2 fingers with the apparatus and the onset of LF; 3) the loading phase (T1–T2) during which both GF and LF increase progressively until LF equals the object’s weight; and 4) the onset time of the 1DI, APB, and BrR, with respect to the GO signal. The following parameters were also measured (see Fig. 3A): 1) the peak magnitude of the first derivative of GF (dGF/dt) and LF (dLF/dt), 2) its time of occurrence, 3) the maximum coefficient of correlation between dGF/dt and dLF/dt , and 4) the timeshift that gave the maximum cross-correlation. These 2 values were gathered for each individual trial by computing a cross-correlation function between dGF/dt and dLF/dt and were used to estimate the overall grip-lift synergy (Duque and others 2003). The maximum coefficient of correlation permits to quantify the similitude between GF and LF, and the timeshift provides a measure of the asynchrony between GF and LF; a positive value of timeshift indicating that GF leads LF.

Statistical Analysis

The effects of iM1 stimulation on temporal and dynamic parameters were analyzed by means of one-way repeated measure analysis of variance (ANOVA_{RM}) with TMS (sham or rTMS) as factor. In order to compute correlations (Pearson procedure), the influence of TMS on movement parameters was expressed as a percentage of control values (TMS/Sham $\times$ 100).

Step-Tracking Movements

Experimental Procedure

Ten subjects (22.7 ± 2.3 years) sat comfortably in front of a computer screen at a distance of 65 cm; their right forearm was fastened midway between pronation and supination on a padded armrest. The subjects used their right hand to grasp the handle of a lightweight manipulandum (Hoffman and Strick 1986a, 1986b) that allowed us to measure the wrist displacements in the horizontal (flexion-extension [FE]) and vertical (radial-ulnar deviation [RU]) axes (see Fig. 2A).

A feedback of the manipulandum position was continuously displayed on the computer screen as a yellow circle (diameter 4 mm). Each trial started with the wrist in a neutral position, indicated by a square

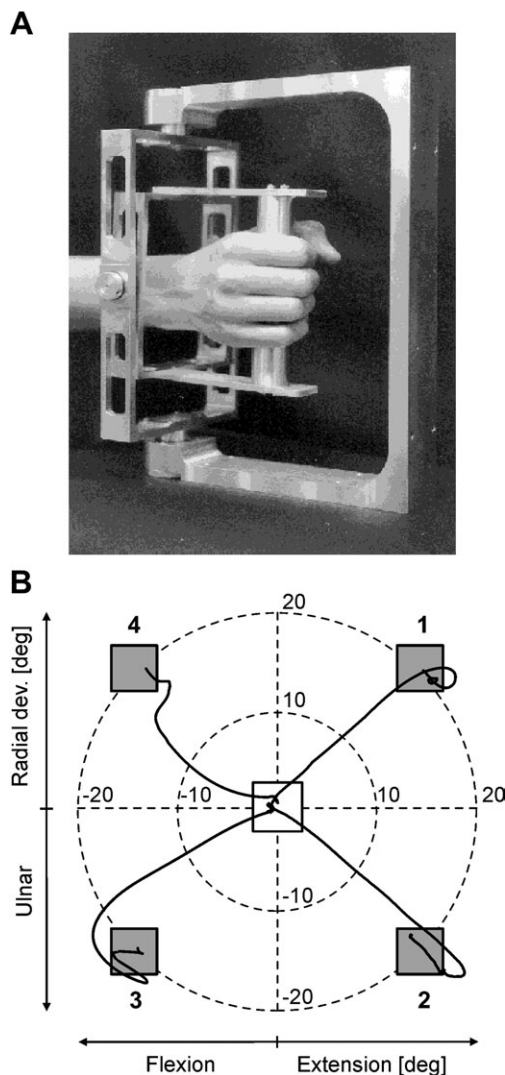


Figure 2. (A) Manipulandum used to study step-tracking wrist movements. Two potentiometers were coupled to this device to measure the wrist displacements in the horizontal (FE) and vertical (RU) axes. The subject's wrist was positioned carefully so that the rotation center of the handle matched that of the wrist. (B) Schematic view of the computer display, as viewed by the subject, showing the central square, the 4 peripheral targets (light gray), and 4 illustrative trajectories of control step-tracking movements. Only one peripheral target was presented at once. The path length of the wrist necessary to reach the target was 20 degrees. Flexion/extension movements of the wrist are represented along the x axis and radial/ulnar displacements along the y axis. Positive values on the x and y axes represent, respectively, an extension and a radial displacement.

displayed on the screen center for 700 ms. Then, the central square was turned off, and one peripheral target was displayed simultaneously. Targets were 17 mm squares (1.6 degrees) presented randomly at an eccentricity of 7 degrees in 1 of the 4 corners of the screen; the amplitude of the wrist movements required to move the yellow circle on the target was 20 degrees (Fig. 2B). Subjects were instructed to reach the target as rapidly and as accurately as possible and to keep the yellow circle stable on the target for at least 700 ms. The target was then turned off, and the subject had to move the manipulandum back to its neutral position.

We used single-pulse TMS applied over iM1 to disrupt its normal activity during movement preparation (see below). Before the experimental session, the subjects practiced the task without TMS (2 blocks of 60 trials). Then, TMS was applied over iM1 while subjects performed the step-tracking task (4 blocks of 40 trials). TMS was triggered randomly either 100 or 200 ms after target presentation; half of the

blocks were shammed (coil perpendicular to the scalp). Because no statistical difference was found between data gathered during the sham blocks (all $F < 0.29$, all $P > 0.05$), all results were pooled together and used as control values. All blocks (2 sham and 2 experimental conditions) were counterbalanced across subjects.

In order to examine more precisely the time course of iM1 contribution to hand movement control, we measured, a posteriori, the actual delay between TMS and agonist muscle onset for each individual trial. Then, all trials were sorted into 13 bins of 20 ms width, ranging between 220 ms before and 40 ms after the EMG onset. This analysis was performed for each subject, and for each bin, a mean value was calculated provided it contained at least 3 data points. Then, the values gathered for each subjects were averaged.

Transcranial Magnetic Stimulation

The right, ipsilateral, M1 was stimulated with a 70-mm diameter figure-of-eight coil connected to a Magstim 200 stimulator (Magstim, Whitland, UK) and placed in the same orientation. We determined the location of the coil that required the lowest stimulation intensity to produce a visible movement of the contralateral wrist. The motor threshold was defined as the TMS intensity that elicited a visible wrist movement in 5 out of 10 trials. Then, the TMS intensity was set at 120% of the motor threshold.

Data Acquisition and Analysis

The signals from the 2 potentiometers of the manipulandum were amplified (gain = 5), digitized (sampling rate: 1 kHz; PCI-6023E, National Instruments®, Austin, TX), and stored on a personal computer for off-line analysis. Signals were low-pass filtered off-line (16 Hz) with a fourth-order, zero-phase-lag, Butterworth filter. EMG activity was recorded from 4 forearm muscles, namely, the extensor carpi radialis longus (ECRL), extensor carpi ulnaris, flexor carpi radialis, and flexor carpi ulnaris (FCU). These muscles were selected because they are exclusively dedicated to wrist movements and because each of them has a pulling vector directed predominantly toward 1 of the 4 target directions (Hoffman and Strick 1999; Bawa and others 2000). EMG signals were recorded from surface electrodes (Neuroline, Medicotest, Denmark) separated by 20 mm. The raw EMG signal was amplified and filtered online (gain: 1K, band-pass filter: 10–500 Hz; Neurolog NL-824, Digitimer, UK), digitized at 1 kHz (PCI-6023E, National Instruments®, Austin, TX), and stored on a personal computer for off-line analysis. EMG data was then rectified and aligned on the target appearance. We calculated the EMG baseline during the 200-ms interval before the target presentation. The onset of EMG was defined as the time when EMG signal exceeded the baseline + 2SD.

The following temporal parameters were measured (Fig. 4A): 1) the RT, defined as the delay between the target appearance and the onset of the first voluntary EMG activity, 2) the movement time (MT), defined as the period of time between the voluntary EMG onset and the entry of the cursor into the target provided that it remained on the target at least for 700 ms, and 3) the onset time of the agonist, antagonist, and the mean onset time of the 2 stabilizer muscles (Hoffman and Strick 1999).

Additionally, we also measured the following kinematic parameters: 1) the total distance traveled by the wrist during MT and computed as follows:

$$\text{Distance} = \sum_{i=1}^{MT} \sqrt{(\text{FE}_i - \text{FE}_{i-1})^2 + (\text{RU}_i - \text{RU}_{i-1})^2}$$

where FE and RU were, respectively, the wrist positions along the FE and RU axes; 20 degrees being the shortest distance between the screen center and any peripheral target. 2) The peak velocity of wrist movements and 3) its time of occurrence. 4) An index of trajectory linearity, named the displacement ratio (DR), estimated by computing the ratio between the actual wrist path length and the shortest distance between the starting and movement end point; a straight wrist displacement, without overshooting, would give a unitary DR value. 5) The initial movement direction was determined by computing the direction of the velocity vector at the acceleration peak, which occurred about 80 ms (78.4 ± 18.2 ms, mean $\pm$ SD) after movement onset, before any visual feedback could take place (Prablanc and Martin 1992). 6) The error in

the initial movement direction relative to the target, defined as the absolute value of the difference between the initial movement direction and the target direction.

Statistical Analysis

Three-way ANOVAs_{RM} were performed on each movement parameter with TMS (sham or TMS) DELAY (100 or 200 ms), and TARGET location as within-subject factors. One-way ANOVAs_{RM} with BIN as within-subject factor were also performed to determine the time course of iM1 contribution to step-tracking movements. Post hoc tests were performed when required and corrected for multiple comparisons (Bonferroni). Data were considered significantly different for corrected *P* values < 0.05. In order to compute correlations (Pearson procedure), the influence of TMS on movement parameters was expressed as a percentage of control values (TMS/Sham × 100).

Results

Effect of iM1 Virtual Lesion on Grip-Lift Movements

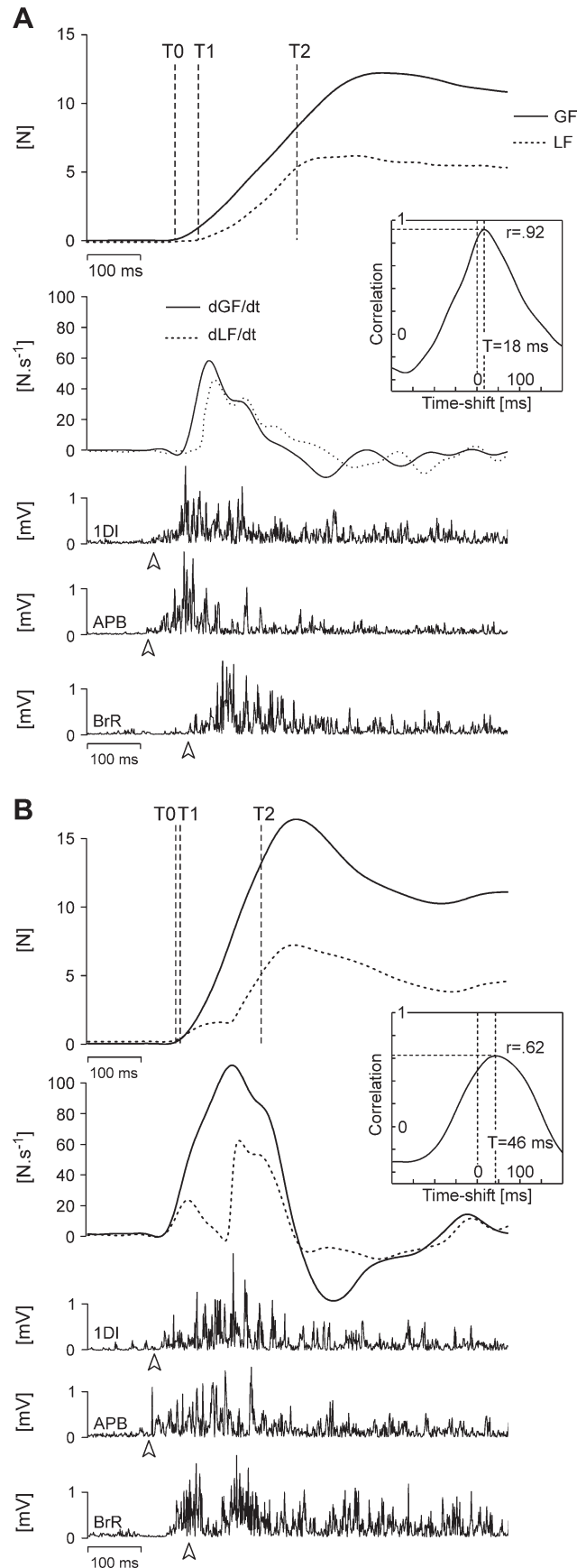
All control values of grip-lift movements are given in Table 1, and a typical example is shown in Figure 3A. It is well known that a parallel increase in both GF and LF is critical when performing grip-lift movements, leading to a tight synergy between the grip and lift phases (Johansson and Westling 1984). This synergy is evidenced by a high correlation coefficient between dGF/dt and dLF/dt, that unveils the similarity between GF and LF, and a minimal timeshift, which indicates a tight temporal coupling between GF and LF (Duque and others 2003). Disrupting the activity of iM1 altered dramatically grip-lift movements, as shown in Figure 3B (see also Table 1). Indeed, a virtual lesion of iM1 led to a significant decrease in both the preloading and loading phase durations (ANOVAs_{RM}, all *F* > 6.24, all *P* < 0.02) and to a higher peak value for both dGF/dt and dLF/dt (all *F* > 4.54, all *P* < 0.03). In addition, following TMS

Table 1
Effect of iM1 virtual lesion on grip-lift movements

	Control	iM1 TMS	<i>P</i>
RT (ms)	187.6 ± 37.4	192.1 ± 29.5	>0.05
Preloading phase (ms)	32.3 ± 16.1	21.6 ± 9.3	0.021*
Loading phase (ms)	187.2 ± 28.5	157.4 ± 28.3	0.004*
Peak value of dGF/dt (N s ⁻¹)	47.6 ± 6.2	65.8 ± 9.5	0.012*
Peak value of dLF/dt (N s ⁻¹)	43.7 ± 7.2	58.3 ± 7.1	0.032*
Time to peak dGF/dt (ms)	85.4 ± 14.8	79.5 ± 17.3	>0.05
Time to peak dLF/dt (ms)	92.7 ± 21.3	119.4 ± 25.7	0.002*
Cross-correlation coefficient	0.84 ± 0.09	0.55 ± 0.15	<0.001*
Timeshift (ms)	20.5 ± 8.8	57.2 ± 19.1	0.021*
APB-1DI interval (ms)	11.9 ± 5.5	13.2 ± 5.8	>0.05
1DI-BrR interval (ms)	33.5 ± 9.3	18.7 ± 10.4	0.002*

Note: Values are mean ± SD (*n* = 10). dGF/dt, GF rate; dLF/dt, LF rate; **P* < 0.05.

Figure 3. (A) Control recordings of different grip-lift task parameters, namely (from top to bottom), GF and LF, their first derivatives (dGF/dt and dLF/dt) and the EMG activity of the 1DI, the APB, and the BrR. T0-T1 and T1-T2 cursors delimit the preloading and loading phases, respectively. The white arrowheads indicate the EMG onset for each muscle in this particular trial. All traces were aligned on the GO signal. The inset shows the cross-correlation function computed between dGF/dt and dLF/dt (see Methods); *T* is the timeshift and *r* the cross-correlation coefficient. (B) Effect of TMS applied over iM1 on a grip-lift movement. Same conventions as in (A). White arrowheads show the EMG onset times of the above control trial. TMS of iM1 yielded a decrease of the preloading and loading phase durations together with a reduced 1DI-BrR recruitment delay, whereas the time to peak dLF/dt and the timeshift increased. This resulted in a smaller cross-correlation coefficient.



of iM1, we found that the peak of dLF/dt occurred later when compared with controls ($F = 5.21$, $P = 0.002$), whereas the time to peak of dGF/dt was unchanged ($F < 1$). It is noteworthy, however, that this later dLF/dt peak was systematically preceded by a smaller peak in dLF/dt (Fig. 3B). As further indicated by a lower correlation between dGF/dt and dLF/dt ($F = 10.56$, $P < 0.001$, see Fig. 3B) and a much longer timeshift ($F = 4.52$, $P = 0.021$) than in controls, we can conclude that a virtual lesion of iM1 altered the overall grip-lift synergy.

Additionally, a precise temporal recruitment of distal and proximal muscles is crucial to perform smooth grip-lift movements because it determines the appropriate duration of the preloading and loading phases (Johansson and Westling 1988). A virtual lesion of iM1 modified the delay between the recruitment of hand and forearm muscles (see Table 1). Indeed, the delay between the 1DI and BrR contraction decreased from 33.5 ± 9.3 ms in controls to 18.7 ± 10.4 ms following a virtual iM1 lesion ($F = 8.25$, $P = 0.002$); the delay between the intrinsic hand muscles was unchanged. The shortening of the interval between distal and proximal muscle recruitment correlated well with movement deficits, as evidenced by a significant correlation between the 1DI-BrR delay and both the preloading phase duration (Pearson correlation, $r = 0.87$, $P = 0.001$) and the cross-correlation coefficient between dGF/dt and dLF/dt (Pearson correlation, $r = 0.82$, $P = 0.001$).

Effect of iM1 Virtual Lesion on Step-Tracking Movements

All control values gathered for step-tracking movements are given in Table 2, and a typical movement is illustrated in Figure 4A. Step-tracking movements are typically characterized by a rapid and nearly rectilinear, overshooting, component followed by small corrective movements. The muscle recruitment pattern underlying such movements has been already extensively investigated in healthy subjects (Hoffman and Strick 1990, 1999).

As shown in Figure 4B,C, for both TMS delays, a virtual lesion of iM1 altered dramatically the trajectory of step-tracking movements and the muscle recruitment. ANOVAs_{RM} showed a significant TMS $\times$ DELAY interaction for the onset time of both the agonist ($F = 23.10$; $P = 0.001$) and antagonist muscles ($F = 8.45$, $P = 0.008$), for the agonist-antagonist delay, and for the agonist-stabilizer delay (all $F > 10.42$; all $P < 0.001$). We also found a significant TMS $\times$ DELAY interaction for MT ($F = 7.28$;

$P = 0.004$), DR ($F = 14.46$; $P = 0.004$), and the error in the initial movement direction ($F = 5.42$, $P = 0.012$). In contrast, the peak velocity, the time to peak, and the initial movement direction of step-tracking movements were unaltered following iM1 TMS (all $F < 1$; Table 2).

When TMS was applied over iM1 100 ms after target presentation (Fig. 4B), the recruitment time of the agonist muscle, which was used to determine the RT in the present experiment, occurred earlier than in controls ($t = 8.23$, $P < 0.001$; Table 2); the antagonist and stabilizer onset times remained unaffected. As a consequence, the agonist-antagonist and agonist-stabilizer delays increased in the 100-ms delay condition (all $t > 5.15$, all $P < 0.018$; Fig. 4B and Table 2). In contrast, TMS applied 200 ms after target presentation (Fig. 4C) significantly delayed the recruitment time of the agonist muscle ($t = 3.87$, $P = 0.004$); it also advanced the antagonist onset time ($t = 4.94$, $P = 0.003$) but left the stabilizer recruitment time unchanged when compared with controls. Therefore, this yielded a shorter agonist-antagonist delay and a shorter agonist-stabilizer delay (all $t > 6.55$, all $P < 0.001$; Fig. 4C). A virtual lesion of iM1 induced 200 ms after target presentation also led to a larger DR ($t = 7.43$, $P < 0.001$) and MT ($t = 4.21$, $P = 0.007$) and a larger error in the initial movement direction ($t = 4.47$, $P = 0.021$). Although TMS of iM1 failed to induce a systematic change in the mean initial movement direction of step-tracking movements (absence of main effect of TMS, ANOVA_{RM}, $F < 1$), the larger errors in the initial movement direction indicate that the initial direction was actually much more variable after iM1 virtual lesions.

For those 2 TMS DELAYS (100 or 200 ms), all the aforementioned effects were found irrespective of the movement direction, as shown by an absence of TARGET main effect (all $F < 1$).

Time Course of iM1 Contribution to Step-Tracking Movements

A more detailed analysis allowed us to determine precisely the time course of iM1 contribution to step-tracking movements (see Methods); ANOVAs_{RM} showed a significant effect of BIN on the muscle recruitment (all $F > 3.24$, all $P < 0.025$). As shown in Figure 5A, when TMS fell between 120 and 80 ms before the agonist onset, the agonist-antagonist delay increased significantly (all $P < 0.05$). Because, within that time window, the antagonist onset time was unchanged, it can be concluded that

Table 2
Effect of iM1 virtual lesion on step-tracking movements

	Control	iM1 TMS ₁₀₀	<i>P</i>	iM1 TMS ₂₀₀	<i>P</i>
RT (agonist onset time) (ms)	225.7 $\pm$ 16.1	189.2 $\pm$ 24.5	<0.001*	243.7 $\pm$ 26.7	0.004*
MT (ms)	403.2 $\pm$ 85.5	466.2 $\pm$ 93.6	>0.05	520.9 $\pm$ 109.3	0.007*
Peak velocity magnitude (degrees s ⁻¹)	338.7 $\pm$ 103.3	315.7 $\pm$ 118.1	>0.05	307.8 $\pm$ 126.6	>0.05
Time to peak velocity (ms)	101.5 $\pm$ 14.3	115.9 $\pm$ 16.1	>0.05	105.3 $\pm$ 12.8	>0.05
DR	2.02 $\pm$ 0.51	2.12 $\pm$ 0.28	>0.05	2.50 $\pm$ 0.54	<0.001*
Initial movement direction (degrees)					
Target 1 (45 degrees)	41.3 $\pm$ 6.8	40.5 $\pm$ 6.1	>0.05	42.7 $\pm$ 11.4	>0.05
Target 2 (135 degrees)	139.2 $\pm$ 7.1	141.4 $\pm$ 6.5	>0.05	137.3 $\pm$ 12.1	>0.05
Target 3 (225 degrees)	220.6 $\pm$ 6.3	221.3 $\pm$ 7.2	>0.05	219.1 $\pm$ 10.7	>0.05
Target 4 (315 degrees)	322.4 $\pm$ 7.9	319.6 $\pm$ 7.3	>0.05	317.5 $\pm$ 13.6	>0.05
Error in initial movement direction (degrees)	7.2 $\pm$ 2.9	7.1 $\pm$ 3.2	>0.05	14.3 $\pm$ 4.6	0.021*
Antagonist muscle onset (ms)	302.7 $\pm$ 18.5	305.6 $\pm$ 23.3	>0.05	263.7 $\pm$ 15.1	0.003*
Agonist-antagonist interval (ms)	72.3 $\pm$ 9.1	115.5 $\pm$ 22.7	0.018*	25.2 $\pm$ 12.4	<0.001*
Stabilizer muscle onset (ms)	257.4 $\pm$ 13.3	251.5 $\pm$ 15.4	>0.05	254.6 $\pm$ 21.6	>0.05
Agonist-stabilizer interval (ms)	29.8 $\pm$ 8.4	58.4 $\pm$ 11.7	0.001*	11.4 $\pm$ 8.2	<0.001*

Note: Values are mean $\pm$ SD ($n = 10$). TMS₁₀₀ or TMS₂₀₀, experimental conditions where TMS was delivered 100 or 200 ms after target presentation, respectively; * $P < 0.05$.

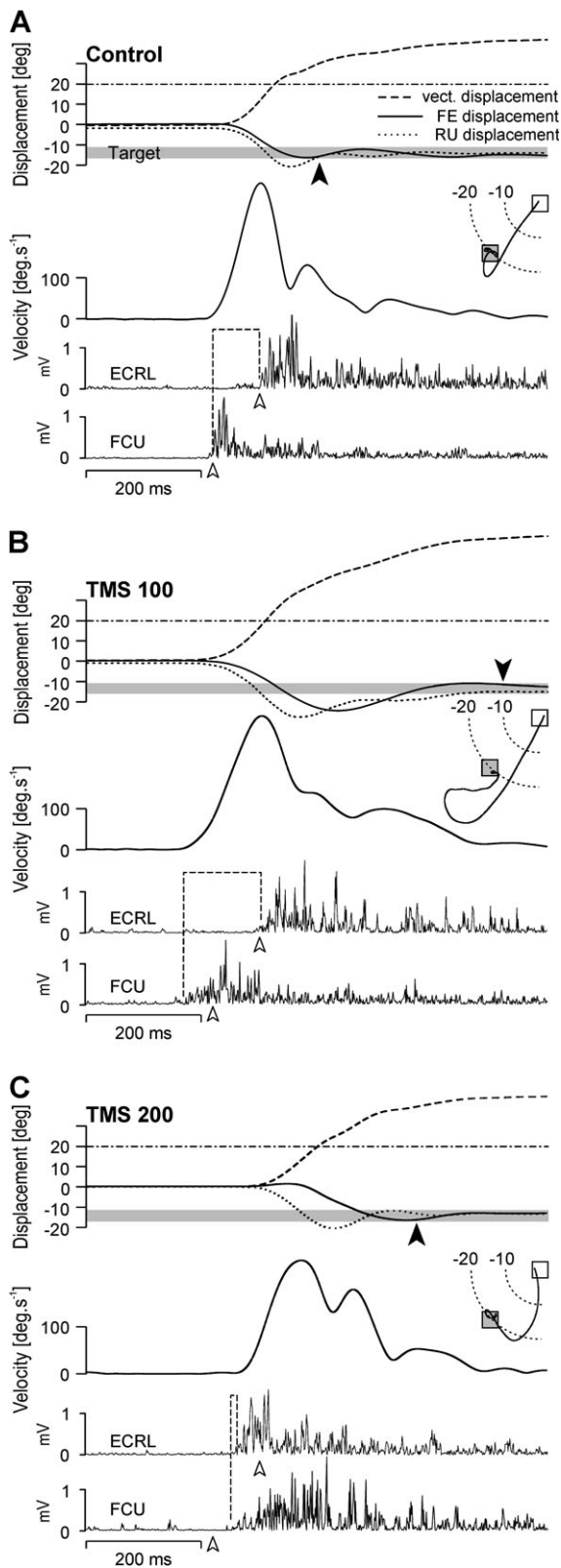


Figure 4. (A) Control recordings of the different step-tracking task parameters for a movement directed toward the bottom-left target (see inset). This figure shows, from top to bottom, the wrist displacement (FE, RU, and the path length), its vectorial velocity, and the EMG activity of the agonist (FCU) and antagonist (ECRL) muscles. All traces were aligned on target presentation. The shaded gray area in the displacement traces symbolizes the target location and its size (5 degrees); the black arrowhead indicates the end of the movement (see Methods). The dash-dotted line shows the

this increase in the agonist-antagonist delay was due to an early recruitment of the agonist. In contrast, when TMS was applied later, between 60 and 0 ms before the agonist onset, the agonist-antagonist delay was considerably shortened, along with a decrease in the antagonist onset time (all $P < 0.05$); this suggests that at those delays (60–0 ms), TMS of iM1 advanced the antagonist recruitment and/or delayed that of the agonist.

Comparable results were obtained for the stabilizer muscles. As illustrated in Figure 5B, when TMS occurred 120–80 ms before the agonist onset, the agonist-stabilizer delay increased as a consequence of an earlier agonist onset. In the 80- to 60-ms time window, TMS led to a shorter agonist-stabilizer delay because of an advanced stabilizer onset. It is noteworthy that, because the stabilizer recruitment occurred on average 29.8 ± 8.4 ms after that of the agonist, TMS applied in the 80- to 60-ms time window occurred actually 110–90 ms before stabilizers are normally recruited. Finally, we found an increased agonist-stabilizer delay when TMS fell 0–20 ms after the agonist onset (i.e., 30–10 ms before the stabilizer recruitment) consequent to a delayed stabilizer muscle contraction (ANOVAS_{RM}, all $F > 4.65$, all $P < 0.05$). In summary, these results suggest that a virtual iM1 lesion induced around 100 ms before the normal recruitment of a given muscle advances its contraction time, whereas it delays it when occurring about 30 ms before its contraction.

Those changes in muscle delays correlated tightly with the TMS-induced deficits observed in step-tracking movements. Indeed, the larger the changes in the agonist-antagonist delay, the longer the movement trajectories. This was true regardless of a decrease ($r = -0.89$, $P < 0.001$; left part of Fig. 5C) or an increase ($r = 0.9$, $P < 0.001$; right part of Fig. 5C) in the agonist-antagonist delay. However, it is noteworthy that step-tracking movements were more susceptible to a decrease, than to an increase, in the agonist-antagonist delay: a rather small decrease in the agonist-antagonist delay already affected the movement trajectory, whereas it was altered only for much larger increases in the agonist-antagonist delay. Comparable correlations between DR and the agonist-stabilizer delay were observed, both when the delay decreased ($r = -0.82$, $P = 0.003$) and when it increased ($r = 0.68$, $P = 0.03$). Finally, the MT and the error in initial movement direction were also significantly correlated with changes in both the agonist-antagonist and the agonist-stabilizer delays.

Discussion

The aim of the present study was to investigate the contribution of iM1 to hand movement control. Although previous studies have already pointed out the significant involvement of iM1 in tasks requiring a very precise control of forces (Ehrsson and others 2000, 2001) or accurate timings (Chen and others 1997; Hummel and others 2003; Verstynen and others 2005), the exact nature of its contribution remains unclear. To our knowledge, the present study is the first attempt to quantify

smallest path length (20 degrees) necessary to reach the target without any overshoot. White arrowheads show the EMG onset times, and the dotted lines indicate the agonist-antagonist delay in this particular trial. (B, C) Effect of TMS applied over iM1 either 100 ms (B) or 200 ms (C) after target presentation. White arrowheads show the EMG onset times of the above control trial. Same conventions as in (A). TMS of iM1 yielded either an increase (B) or a decrease (C) in the agonist-antagonist delay; both resulting in an increased DR and MT.

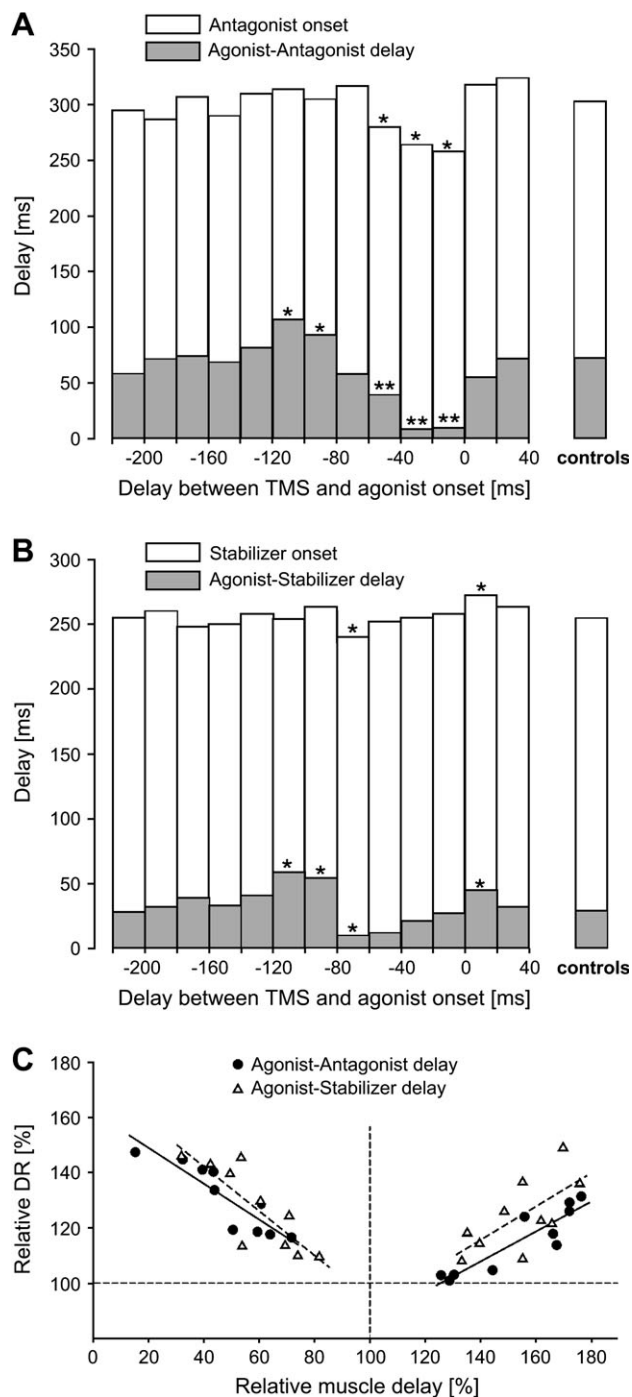


Figure 5. (A) Time course of the consequences of TMS of iM1 on the antagonist onset (white histograms) and on the agonist-antagonist muscle delay (gray histogram) with respect to the onset of the agonist muscle contraction. When TMS was applied 120–80 ms before the agonist onset, it increased the agonist-antagonist delay without affecting the antagonist contraction time. TMS applied in a 60- to 0-ms time window before movement onset, decreased both the agonist-antagonist delay and the antagonist contraction time. Controls are the mean values gathered in the sham condition: $**P < 0.001$ and $*P < 0.05$ obtained after Bonferroni *t*-tests. Bin width 20 ms. (B) Time course of the consequences of TMS of iM1 on the stabilizer onset (white histograms) and on the agonist-stabilizer delay (gray histogram) with respect to the onset of the agonist muscle contraction. When TMS was applied 120–80 ms before the agonist onset, it increased the agonist-stabilizer delay without affecting the stabilizer contraction time. TMS applied in an 80- to 60-ms time window decreased both the agonist-stabilizer delay and the stabilizer recruitment time and, finally, when applied in a 0- to 20-ms time window, it increased both the agonist-stabilizer delay and the stabilizer recruitment time. Same conventions as in (A). (C) Correlations

motor deficits induced by iM1 virtual lesions in 2 standard tasks, which have in common to rely critically on cortical control as evidenced by their susceptibility to CS lesions (Hoffman and Strick 1995; Forssberg and others 1999; Duque and others 2003; Hermisdorfer and others 2003; Yarosh and others 2004). Such an approach in healthy subjects permits to get round difficulties in interpreting results from stroke patient studies. The present study suggests that iM1 may play a crucial role in shaping the motor commands to hand muscles, most likely through transcallosal influences onto the cM1.

The main finding of the present study is that a virtual lesion of iM1 altered the timing of muscle recruitment, leading to significant motor deficits in both tasks. In the grip-lift task, the contraction of the BrR, the muscle involved in the lifting phase, occurred too early following TMS of iM1, yielding a shorter preloading phase. However, TMS of iM1 also delayed the dLF/dt peak leading to a longer timeshift between dGF/dt and dLF/dt than in controls. Those apparently contradictory results can be explained by the fact that the earlier BrR burst, which accounts for the preloading phase shortening, was inadequate to insure a proper lift of the object and was then followed by a second, postponed, BrR contraction, responsible for the delayed dLF/dt peak. Altogether, those alterations in movement parameters led to a less optimal grip-lift synergy, as evidenced by the results of the cross-correlation analysis.

A virtual lesion of iM1 also affected the muscle recruitment timing in the step-tracking task: when a virtual lesion of iM1 was induced about 100 ms before a muscle normally becomes active, it led to its earlier recruitment, and when TMS occurred closer to the normal contraction time of a given muscle, it delayed its recruitment. It is noteworthy that these changes in muscle recruitment delays led to noticeable deficits in step-tracking movements, highlighting the importance of a precise temporal muscle pattern for performing such a task accurately. In addition, we found that the motor deficits in step-tracking movements were more pronounced when TMS of iM1 induced a decrease than when it yielded an increase in muscle delays, confirming the deleterious consequences of muscle cocontractions on precise movements (Hoffman and Strick 1990, 1995; Yarosh and others 2004).

There is substantial evidence that, via the corpus callosum, each M1 exerts reciprocal influences on homonymous body part representations in the opposite motor cortex (Jenny 1979; Gould and others 1986; Ferbert and others 1992; Meyer and others 1995; Boroojerdi and others 1996; Di Lazzaro and others 1999). In healthy individuals, these interactions are known to be modulated during motor preparation. The transcallosal influence arising from iM1 and targeting cM1 is initially inhibitory and is maximal about 100 ms before the muscle recruitment; the inhibition then decreases progressively and converts to

between TMS-induced changes in DR and in muscle delays (agonist-antagonist and agonist-stabilizer) computed using the Pearson correlation procedure. Changes in both DR and muscle delays are expressed as a percentage of control values (TMS/Sham $\times$ 100); control values are therefore at the intersection of the 2 dotted lines. Both a decrease and an increase in muscle delays led to a longer trajectory of step-tracking movements. Correlations were computed only for the muscle delays significantly different from control values (see Fig. A,B). Solid lines indicate the regression computed between the agonist-antagonist delays and DR (left: $r = -0.89$, $P < 0.001$; right: $r = 0.9$, $P < 0.001$); dashed lines show the regression calculated between the agonist-stabilizer delays and DR (left: $r = -0.82$, $P = 0.003$; right: $r = 0.68$, $P = 0.03$). Black dots: agonist-antagonist delay, open triangles: agonist-stabilizer delays.

facilitation just before the muscle becomes active (Murase and others 2004). In stroke patients, an abnormal persistence of this transcallosal inhibitory influence may contribute to the paretic hand impairment (Murase and others 2004; Duque, Hummel, and others 2005).

In the present study, TMS of iM1 most likely interfered with these transcallosal influences during movement preparation, highlighting their critical contribution to movement control. Indeed, by producing a virtual lesion of iM1 100 ms before the contraction of a given muscle, we probably impeded the transcallosal inhibitory influence normally exerted by iM1 on the opposite hemisphere, leading to an early release of the transcallosal inhibition exerted on cM1, and therefore advancing that muscle recruitment. In contrast, by disrupting iM1 activity later, about 30 ms before the muscle contraction, when the transcallosal influence is facilitatory (Murase and others 2004; Duque, Hummel, and others 2005), we possibly hampered this facilitation and delayed the muscle recruitment. This hypothesis is illustrated in Figure 6 which shows the putative time course of iM1 influences exerted on the cM1 representa-

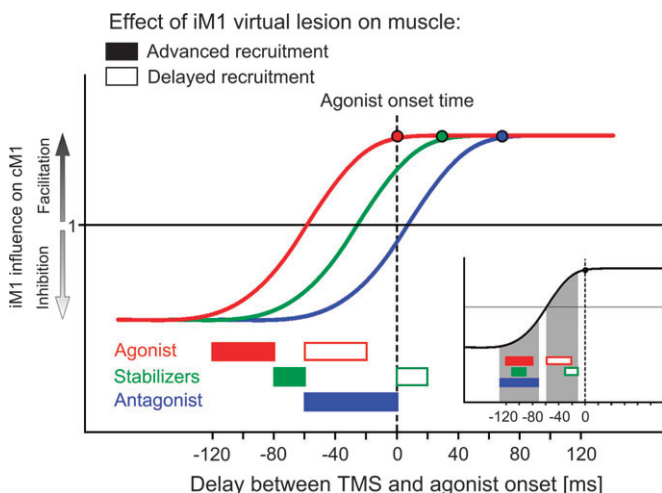


Figure 6. Schematic view of our hypothesis about the differential effects of iM1 virtual lesions on muscle contraction times. Our hypothesis is based on the results of a study by Murase and others (2004) showing that, at an early stage of movement preparation, the inhibition influence from iM1 to cM1 is maximal about 100 ms before the muscle recruitment; then it diminishes progressively and converts to facilitation just before the muscle becomes active. The time course of the transcallosal influence during movement preparation is represented by one sigmoid for each muscle group recruited sequentially in the step-tracking task (red: agonist, green: stabilizers, blue: antagonist); the 3 sigmoids were aligned with respect to the contraction time of the agonist (0 ms on the x axis). The color dots on each sigmoid indicate the approximate contraction time for each muscle as measured in control trials. The time windows during which TMS led either to an advanced or to a delayed recruitment of these 3 muscles are indicated by horizontal rectangles (see Fig. 5A,B for details). Filled rectangles indicate time windows when TMS advanced the muscle contraction and open rectangles when it delayed it. Color codes are the same as before: red, agonist; green, stabilizers; blue, antagonist. Because, in the present study, TMS was delivered a long way from the antagonist recruitment time, iM1 virtual lesions failed to delay its recruitment. The inset illustrates the same differential effects of TMS on muscle recruitment times but after shifting the 3 sigmoids in such a way that the contraction time of each muscle was realigned. This shows more clearly that the effects of iM1 virtual lesion on the muscle recruitment are the same for each muscle and only depend on the timing of TMS application. By inducing a virtual lesion of iM1 around 120–80 ms before the contraction of a given muscle, TMS advanced its recruitment, probably by impeding the transcallosal inhibitory influence normally exerted by iM1 on the opposite hemisphere. In contrast, by disrupting iM1 activity later, about 30 ms before the muscle contraction, when the transcallosal influence is facilitatory, we delayed the muscle recruitment, possibly by interfering with this facilitatory transcallosal influence.

tions of the 3 muscle groups involved sequentially in the step-tracking task. Each sigmoid symbolizes the time course of the transcallosal influence between iM1 and cM1 during movement preparation for each muscle involved sequentially in the step-tracking task, namely, the agonist (red), stabilizers (green), and antagonist (blue). The time windows during which TMS led either to an advanced or to a delayed recruitment of these 3 muscles are indicated by horizontal rectangles (see Legend of Fig. 6 for details). Consistently with our hypothesis, a recent study has reported impaired step-tracking movements in stroke patients when performing the task with their nonparetic hand because of a too early recruitment of the antagonist muscle (Yarosh and others 2004). This deficit was interpreted as the consequence of a constantly lower inhibitory influence from the lesioned hemisphere to the intact M1 (Liepert and others 2000; Shimizu and others 2002).

Inhibitory mechanisms involving interhemispheric (Ferber and others 1992; Murase and others 2004; Duque, Hummel, and others 2005; Duque, Mazzocchio, and others 2005), and also intracortical processes (Liepert and others 1998; Reynolds and Ashby 1999; Stinear and Byblow 2003), are thought to play a crucial role in motor control by ensuring the recruitment of a given set of muscles at the right timing (Hallett 2003, 2004; Murase and others 2004; Sohn and Hallett 2004a). This view is supported by many clinical studies on dystonia showing that an inappropriate inhibition is the main pathophysiological mechanism in those patients (Sohn and Hallett 2004b; Butefisch and others 2005). In healthy subjects, inhibitory mechanisms are likely to be of particular importance in tasks that require an accurate temporal control (Chen and others 1997; Hummel and others 2003; Verstynen and others 2005), a high-muscle selectivity (Verstynen and others 2005), or a very fine force production (Ehrsson and others 2000, 2001). It is therefore sensible to hypothesize that the more precise and selective a muscle sequence has to be during a given movement, the more critical the iM1 contribution is. In agreement with this view, functional imaging studies have shown that all these tasks lead consistently to a significant activation of iM1 (Kim and others 1993; Cramer and others 1999; Ehrsson and others 2000, 2001; Hummel and others 2003; Verstynen and others 2005).

Because the CS system is known to have a small contingent of uncrossed projections to the spinal cord (Nathan and others 1990; Galea and Darian-Smith 1997), it has been frequently suggested that iM1 could influence hand movements through these ipsilateral projections (Yarosh and others 2004; Verstynen and others 2005). However, in the present study this hypothesis appears unlikely. First, these projections mainly innervate proximal muscles of the upper limbs (Brinkman and Kuypers 1973; Lacroix and others 2004) but very few innervate hand muscles. Second, it has been shown that the optimal site to elicit ipsilateral MEPs is located lateral and ventral with respect to the site we stimulated (Wassermann and others 1994; Ziemann and others 1999). It is therefore unlikely that we have elicited ipsilateral descending volleys, as further suggested by the absence of ipsilateral MEPs in hand muscles. Finally, most studies that have investigated the M1 inhibitory influence on the excitability of ipsilateral hand muscles have shown that it mainly relies on transcallosal connections (Ferber and others 1992; Di Lazzaro and others 1999).

Besides, one might argue that the effects found in the present study were caused, at least partly, by a spread of induced current to premotor cortical areas, known to be activated during

ipsilateral hand movements (Cramer and others 1999; Ziemann and others 1999; Huang and others 2004; Hanakawa and others 2005; Verstynen and others 2005). However, it is unlikely that such a spread could be responsible for the effects reported here. Indeed, several studies have shown that TMS applied over M1 and to premotor cortex leads to differential deficits in hand movements (Schluter and others 1999; Johansen-Berg and others 2002; Davare and others 2006).

Finally, the distinct consequence of iM1 virtual lesions, depending on the TMS delays, allows us to rule out the hypothesis that the deficits in step-tracking movement were due to unspecific effects of TMS, such as the twitch induced in the contralateral hand. In addition, it has been shown that magnetically evoked hand muscle twitches fail to affect the movement performance of the opposite hand (Chen and others 1997).

In conclusion, the present study suggests that iM1 plays a significant role in shaping the muscular command generated by the cM1 by allowing the muscle recruitment at the appropriate timing, through either transcallosal inhibitory or facilitatory influences onto the cM1. However, because some asymmetries have been suggested in the activation of the dominant and nondominant M1 in the control of ipsilateral hand movements (Kim and others 1993; Cramer and others 1999; Haaland and others 2004; Verstynen and others 2005), the question arises as to whether the effect of virtual lesion of the dominant iM1 would lead to comparable deficits in the nondominant hand. Because the dominant M1 is thought to exert a greater control on ipsilateral hand movements than the nondominant M1 (Verstynen and others 2005), we would expect even greater deficits following a virtual lesion of the dominant iM1.

Notes

The authors are grateful to P.L. Strick for his help with the manipulation design and also to M. Penta and O. White for their help with data acquisition. MD is a research assistant supported by a grant from the Université catholique de Louvain (FSR, Belgium). JD is a research assistant at the National Funds for Scientific Research (FNRS, Belgium). This project was supported by grants from the Fonds de la Recherche Scientifique Médicale (FRSM, Belgium) and the Fondation Médicale Reine Elisabeth (FMRE, Belgium). *Conflict of Interest:* None declared.

Address correspondence to E. Olivier, Laboratory of Neurophysiology, Université catholique de Louvain, 54, Avenue Hippocrate, B-1200 Brussels, Belgium. Email: olivier@nefy.ucl.ac.be.

References

Augurelle AS, Smith AM, Lejeune T, Thonnard JL. 2003. Importance of cutaneous feedback in maintaining a secure grip during manipulation of hand-held objects. *J Neurophysiol* 89:665–671.

Bawa P, Chalmers GR, Jones KE, Sogaard K, Walsh ML. 2000. Control of the wrist joint in humans. *Eur J Appl Physiol* 83:116–127.

Boroojerdi B, Diefenbach K, Ferbert A. 1996. Transcallosal inhibition in cortical and subcortical cerebral vascular lesions. *J Neurol Sci* 144:160–170.

Brinkman J, Kuypers HG. 1973. Cerebral control of contralateral and ipsilateral arm, hand and finger movements in the split-brain rhesus monkey. *Brain* 96:653–674.

Butefisch CM, Boroojerdi B, Chen R, Battaglia F, Hallett M. 2005. Task-dependent intracortical inhibition is impaired in focal hand dystonia. *Mov Disord* 20:545–551.

Catalan MJ, Honda M, Weeks RA, Cohen LG, Hallett M. 1998. The functional neuroanatomy of simple and complex sequential finger movements: a PET study. *Brain* 121(Pt 2):253–264.

Chen R, Gerloff C, Hallett M, Cohen LG. 1997. Involvement of the ipsilateral motor cortex in finger movements of different complexities. *Ann Neurol* 41:247–254.

Cisek P, Crammond DJ, Kalaska JF. 2003. Neural activity in primary motor and dorsal premotor cortex in reaching tasks with the contralateral versus ipsilateral arm. *J Neurophysiol* 89:922–942.

Colebatch JG, Gandevia SC. 1989. The distribution of muscular weakness in upper motor neuron lesions affecting the arm. *Brain* 112(Pt 3):749–763.

Cramer SC, Finklestein SP, Schaechter JD, Bush G, Rosen BR. 1999. Activation of distinct motor cortex regions during ipsilateral and contralateral finger movements. *J Neurophysiol* 81:383–387.

Davare M, Andres M, Cosnard G, Thonnard JL, Olivier E. 2006. Dissociating the role of ventral and dorsal premotor cortex in precision grasping. *J Neurosci* 26:2260–2268.

Desrosiers J, Bourbonnais D, Bravo G, Roy PM, Guay M. 1996. Performance of the 'unaffected' upper extremity of elderly stroke patients. *Stroke* 27:1564–1570.

Di Lazzaro V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali P, Rothwell JC. 1999. Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. *Exp Brain Res* 124:520–524.

Donchin O, Gribova A, Steinberg O, Bergman H, Vaadia E. 1998. Primary motor cortex is involved in bimanual coordination. *Nature* 395:274–278.

Duque J, Hummel F, Celnik P, Murase N, Mazzocchio R, Cohen LG. 2005. Transcallosal inhibition in chronic subcortical stroke. *Neuroimage* 28:940–946.

Duque J, Mazzocchio R, Dambrosia J, Murase N, Olivier E, Cohen LG. 2005. Kinematically specific interhemispheric inhibition operating in the process of generation of a voluntary movement. *Cereb Cortex* 15:588–593.

Duque J, Thonnard JL, Vandermeeren Y, Sebire G, Cosnard G, Olivier E. 2003. Correlation between impaired dexterity and corticospinal tract dysgenesis in congenital hemiplegia. *Brain* 126:732–747.

Ehrsson HH, Fagergren E, Forssberg H. 2001. Differential fronto-parietal activation depending on force used in a precision grip task: an fMRI study. *J Neurophysiol* 85:2613–2623.

Ehrsson HH, Fagergren A, Jonsson T, Westling G, Johansson RS, Forssberg H. 2000. Cortical activity in precision- versus power-grip tasks: an fMRI study. *J Neurophysiol* 83:528–536.

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. 1992. Interhemispheric inhibition of the human motor cortex. *J Physiol* 453:525–546.

Flanagan JR, Tresilian JR. 1994. Grip-load force coupling: a general control strategy for transporting objects. *J Exp Psychol Hum Percept Perform* 20:944–957.

Flanagan JR, Wing AM. 1997. The role of internal models in motion planning and control: evidence from grip force adjustments during movements of hand-held loads. *J Neurosci* 17:1519–1528.

Foltys H, Sparing R, Boroojerdi B, Krings T, Meister IG, Mottaghy FM, Topper R. 2001. Motor control in simple bimanual movements: a transcranial magnetic stimulation and reaction time study. *Clin Neurophysiol* 112:265–274.

Forssberg H, Eliasson AC, Redon-Zouitenn C, Mercuri E, Dubowitz L. 1999. Impaired grip-lift synergy in children with unilateral brain lesions. *Brain* 122(Pt 6):1157–1168.

Galea MP, Darian-Smith I. 1997. Corticospinal projection patterns following unilateral section of the cervical spinal cord in the newborn and juvenile macaque monkey. *J Comp Neurol* 381:282–306.

Gould HJ III, Cusick CG, Pons TP, Kaas JH. 1986. The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. *J Comp Neurol* 247:297–325.

Haaland KY, Elsinger CL, Mayer AR, Durgarian S, Rao SM. 2004. Motor sequence complexity and performing hand produce differential patterns of hemispheric lateralization. *J Cogn Neurosci* 16:621–636.

Hallett M. 2003. Surround inhibition. *Suppl Clin Neurophysiol* 56:153–159.

Hallett M. 2004. Dystonia: abnormal movements result from loss of inhibition. *Adv Neurol* 94:1–9.

- Hanakawa T, Parikh S, Bruno MK, Hallett M. 2005. Finger and face representations in the ipsilateral precentral motor areas in humans. *J Neurophysiol* 93:2950-2958.
- Hermesdorfer J, Hagl E, Nowak DA, Marquardt C. 2003. Grip force control during object manipulation in cerebral stroke. *Clin Neurophysiol* 114:915-929.
- Hermesdorfer J, Laimgruber K, Kerkhoff G, Mai N, Goldenberg G. 1999. Effects of unilateral brain damage on grip selection, coordination, and kinematics of ipsilesional prehension. *Exp Brain Res* 128:41-51.
- Hermesdorfer J, Ulrich S, Marquardt C, Goldenberg G, Mai N. 1999. Prehension with the ipsilesional hand after unilateral brain damage. *Cortex* 35:139-161.
- Hoffman DS, Strick PL. 1986a. Activity of wrist muscles during step-tracking movements in different directions. *Brain Res* 367:287-291.
- Hoffman DS, Strick PL. 1986b. Step-tracking movements of the wrist in humans. I. Kinematic analysis. *J Neurosci* 6:3309-3318.
- Hoffman DS, Strick PL. 1990. Step-tracking movements of the wrist in humans. II. EMG analysis. *J Neurosci* 10:142-152.
- Hoffman DS, Strick PL. 1995. Effects of a primary motor cortex lesion on step-tracking movements of the wrist. *J Neurophysiol* 73:891-895.
- Hoffman DS, Strick PL. 1999. Step-tracking movements of the wrist. IV. Muscle activity associated with movements in different directions. *J Neurophysiol* 81:319-333.
- Huang MX, Harrington DL, Paulson KM, Weisend MP, Lee RR. 2004. Temporal dynamics of ipsilateral and contralateral motor activity during voluntary finger movement. *Hum Brain Mapp* 23:26-39.
- Hummel F, Kirsammer R, Gerloff C. 2003. Ipsilateral cortical activation during finger sequences of increasing complexity: representation of movement difficulty or memory load? *Clin Neurophysiol* 114:605-613.
- Jenny AB. 1979. Commissural projections of the cortical hand motor area in monkeys. *J Comp Neurol* 188:137-145.
- Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. 2002. The role of ipsilateral premotor cortex in hand movement after stroke. *Proc Natl Acad Sci USA* 99:14518-14523.
- Johansson RS, Westling G. 1984. Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. *Exp Brain Res* 56:550-564.
- Johansson RS, Westling G. 1988. Coordinated isometric muscle commands adequately and erroneously programmed for the weight during lifting task with precision grip. *Exp Brain Res* 71:59-71.
- Kazennikov O, Hyland B, Corboz M, Babalian A, Rouiller EM, Wiesendanger M. 1999. Neural activity of supplementary and primary motor areas in monkeys and its relation to bimanual and unimanual movement sequences. *Neuroscience* 89:661-674.
- Keel JC, Smith MJ, Wassermann EM. 2001. A safety screening questionnaire for transcranial magnetic stimulation. *Clin Neurophysiol* 112:720.
- Kim SG, Ashe J, Hendrich K, Ellermann JM, Merkle H, Ugurbil K, Georgopoulos AP. 1993. Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. *Science* 261:615-617.
- Lacroix S, Havton LA, McKay H, Yang H, Brant A, Roberts J, Tuszyński MH. 2004. Bilateral corticospinal projections arise from each motor cortex in the macaque monkey: a quantitative study. *J Comp Neurol* 473:147-161.
- Liepert J, Bauder H, Wolfgang HR, Miltner WH, Taub E, Weiller C. 2000. Treatment-induced cortical reorganization after stroke in humans. *Stroke* 31:1210-1216.
- Liepert J, Classen J, Cohen LG, Hallett M. 1998. Task-dependent changes of intracortical inhibition. *Exp Brain Res* 118:421-426.
- Meyer BU, Roricht S, Graf von Einsiedel H, Kruggel F, Weindl A. 1995. Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain* 118(Pt 2):429-440.
- Murase N, Duque J, Mazzocchio R, Cohen LG. 2004. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* 55:400-409.
- Nathan PW, Smith MC, Deacon P. 1990. The corticospinal tracts in man. Course and location of fibres at different segmental levels. *Brain* 113(Pt 2):303-324.
- Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97-113.
- Porter R, Lemon RN. 1993. Corticospinal function and voluntary movement. New York: Oxford University Press, 448 p.
- Prablanc C, Martin O. 1992. Automatic control during hand reaching at undetected two-dimensional target displacements. *J Neurophysiol* 67:455-469.
- Reynolds C, Ashby P. 1999. Inhibition in the human motor cortex is reduced just before a voluntary contraction. *Neurology* 53:730-735.
- Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH, Maertens de Noordhout AL, Marsden CD, Murray NMF, Rothwell JC, Swash M, Tomberg C. 1994. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol* 91:79-92.
- Sadato N, Campbell G, Ibanez V, Deiber M, Hallett M. 1996. Complexity affects regional cerebral blood flow change during sequential finger movements. *J Neurosci* 16:2691-2700.
- Schluter ND, Rushworth MF, Mills KR, Passingham RE. 1999. Signal-, set-, and movement-related activity in the human premotor cortex. *Neuropsychologia* 37:233-243.
- Shimizu T, Hosaki A, Hino T, Sato M, Komori T, Hirai S, Rossini PM. 2002. Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke. *Brain* 125:1896-1907.
- Sohn YH, Hallett M. 2004a. Disturbed surround inhibition in focal hand dystonia. *Ann Neurol* 56:595-599.
- Sohn YH, Hallett M. 2004b. Surround inhibition in human motor system. *Exp Brain Res* 158:397-404.
- Stedman A, Davey NJ, Ellaway PH. 1998. Facilitation of human first dorsal interosseous muscle responses to transcranial magnetic stimulation during voluntary contraction of the contralateral homonymous muscle. *Muscle Nerve* 21:1033-1039.
- Steinberg O, Donchin O, Gribova A, Cardoso de Oliveira S, Bergman H, Vaadia E. 2002. Neuronal populations in primary motor cortex encode bimanual arm movements. *Eur J Neurosci* 15:1371-1380.
- Stinear CM, Byblow WD. 2003. Role of intracortical inhibition in selective hand muscle activation. *J Neurophysiol* 89:2014-2020.
- Tanji J, Okano K, Sato KC. 1988. Neuronal activity in cortical motor areas related to ipsilateral, contralateral, and bilateral digit movements of the monkey. *J Neurophysiol* 60:325-343.
- Tinazzi M, Zanette G. 1998. Modulation of ipsilateral motor cortex in man during unimanual finger movements of different complexities. *Neurosci Lett* 244:121-124.
- Verstynen T, Diedrichsen J, Albert N, Aparicio P, Ivry RB. 2005. Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. *J Neurophysiol* 93:1209-1222.
- Walsh V, Cowey A. 2000. Transcranial magnetic stimulation and cognitive neuroscience. *Nat Rev Neurosci* 1:73-79.
- Wassermann EM. 1998. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol* 108:1-16.
- Wassermann EM, Pascual-Leone A, Hallett M. 1994. Cortical motor representation of the ipsilateral hand and arm. *Exp Brain Res* 100:121-132.
- Westling G, Johansson RS. 1984. Factors influencing the force control during precision grip. *Exp Brain Res* 53:277-284.
- Yarosh CA, Hoffman DS, Strick PL. 2004. Deficits in movements of the wrist ipsilateral to a stroke in hemiparetic subjects. *J Neurophysiol* 92:3276-3285.
- Ziemann U, Ishii K, Borgheresi A, Yaseen Z, Battaglia F, Hallett M, Cincotta M, Wassermann EM. 1999. Dissociation of the pathways mediating ipsilateral and contralateral motor-evoked potentials in human hand and arm muscles. *J Physiol* 518(Pt 3):895-906.