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Corticomotor excitability during a choice-hand reaction time task

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Abstract Fourteen neurologically healthy, right-handed subjects performed a choice-hand reaction time (RT) task, which involved wrist flexion or extension of either the left or right hand to one of three fixed target locations corresponding to 45° flexion, 20° flexion, or 20° extension from the starting position. In each trial, a pre-cue provided information regarding the forthcoming target location. The hand was specified by the imperative signal. Focal transcranial magnetic stimulation (TMS) was delivered over the hand motor area of either the right or left hemisphere at set times during the foreperiod, and at random intervals during the RT interval defined by electromyography onset. As expected, an increase in corticomotor excitability was observed in the agonist of the responding hand over the RT interval. When the cue appeared at a location that required flexion with either hand, an increase in excitability was observed following stimulation over the hemisphere ipsilateral to the responding hand, indicating activation of the homologous muscle. However, when the cue appeared at a location at which the response would require flexion with one hand and extension with the other, the modulation of excitability was also based on the direction of the response. This direction-specific effect was only observed for TMS delivered to the left hemisphere during the left-hand movement, and suggested goal-based preparation in the left hemisphere independent of whether the actual movement is made with the right or left hand. These results indicate

that both the homologous-muscle and the directional-specific constraints affect the corticomotor excitability of the non-responding hand.

Keywords Corticospinal excitability · Reaction time · Human · Movement · Motor-evoked potential

Introduction

A large body of literature has shown that the excitability of corticospinal projections innervating responding agonist muscles increases preceding voluntary movement (Rossini et al. 1988; Starr et al. 1988; Pascual-Leone et al. 1992a; Tomberg 1995; Hoshiyama et al. 1996; Chen et al. 1998; Leocani et al. 2000; Burle et al. 2002; McMillan et al. 2004). The increase in excitability likely represents the change in the activity of the corticospinal pathway from a resting level to that required for the discharge of spinal motor neurons and movement (Starr et al. 1988). Hoshiyama et al. (1996) reported a decrease in excitability of the responding antagonist during reaction time (RT). Other researchers, (Mackinnon and Rothwell 2000), however, have not observed modulation of corticospinal excitability in the antagonist prior to movement onset.

It is reasonable to assume that action goals may be established prior to the specification of actual movements. For example, the goal to pick up the coffee cup can become activated, with subsequent processes determining the hand that will be used to achieve this goal. The modulation of excitability of corticomotor pathways during movement preparation of the hand that is not used for the subsequent response, has received less attention. This question is the focus of the current study.

Leocani et al. (2000) used a circular transcranial magnetic stimulation (TMS) coil, positioned over the vertex, to stimulate both the left and the right motor cortices simultaneously, at random intervals during various unimanual RT finger tasks. They showed that while there was an increase in corticomotor excitability

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in the responding agonist preceding movement, responses in the non-responding homologous muscles of the contralateral hand were inhibited. They suggested that this may have been a compensatory mechanism to prevent the non-responding hand from moving in synchrony. Likewise, Hasbroucq et al. (2000) showed a decrease in H-reflexes in the wrist flexors of the non-responding limb during RT. However, Hasbroucq et al. (1999) showed a modulation of corticospinal excitability during the foreperiod of an RT task, i.e. prior to the selection of the responding hand, in which case we would expect that, at least during the early stages of RT, there would be a similar modulation of excitability in both limbs. Indeed, Burle et al. (2002) demonstrated increases in corticomotor excitability of homologous (non-responding) thenar muscles during the RT interval in a two-choice RT task in which a flexion response was required by either hand.

During muscular activation, there is an increase in corticomotor excitability of homologous muscles in the relaxed, contralateral limb. This has been shown with both tonic contraction (Hess et al. 1986; Stedman et al. 1998; Muellbacher et al. 2000; Stinear et al. 2001) and during complex movements (Tinazzi and Zanette 1998; Ziemann and Hallett 2001). It is possible that either neural pathways linking the two motor cortices (via the corpus callosum) (Muellbacher et al. 2000; Warbrooke and Byblow 2004) or bilaterally descending corticospinal projections (Ziemann et al. 1999), invariably link the two limbs, resulting in synchronous activation of homologous muscle groups.

Movements during which the homologous muscles of both limbs are activated synchronously are more stable and more easily performed, than movements involving asynchronous activation of homologous muscles (Kelso 1981; Riek et al. 1992; Swinnen et al. 1997, 1998; Carson et al. 2000; Temprado et al. 2003). However, movement direction in extrinsic space has also been shown to constrain bimanual movements. Behavioural studies have shown that bimanual movements performed isodirectionally in space, even if they involve non-homologous muscles, are generally more stable than movements performed by the two limbs in differing directions (Swinnen et al. 1997, 1998, 2003; Temprado et al. 2003).

In the present study, TMS was delivered over the hemisphere contralateral to either the responding or the non-responding hand at random intervals during a task in which the hand and direction of the movement were both varied. We were primarily interested in the modulation of corticomotor excitability related to the non-responding hand, as the subject prepared to move. Three hypotheses seemed plausible. First, selection of one hand for the response might result in a decrease in excitability of the non-responding hand to prevent the hand from performing the response (Leocani et al. 2000). Second, due to neural coupling between the two hemispheres, corticomotor excitability may be modulated in a similar way in both hemispheres, with the non-responding hand mimicking that of the homologous

muscles in the responding hand (Burle et al. 2002). Third, the modulation of excitability observed in the responding and non-responding hands may be dependent upon the direction of the upcoming response. At least in the early stages of response planning, the excitability of the non-responding hand may reflect directional tuning of that hand should it have been selected to make the response.

Methods

Subjects

Fourteen neurologically healthy volunteers (seven females and seven males) participated in the study for monetary compensation. Participation was limited to right-handed subjects who had moderate to strong scores on the Edinburgh Handedness Inventory (Oldfield 1971). The median Laterality Quotient across the 14 subjects was +81.8% with a range from +57.1 to +100%. All subjects had normal or corrected-to-normal visual acuity. The median age of the subjects was 24 years, with a range from 22 to 27 years. All subjects provided their written informed consent to participate in the study and were evaluated for suitability for TMS using a questionnaire. The study was approved by the University of Auckland Human Subjects Ethics Committee in accordance with the Declaration of Helsinki.

Experimental set-up

The subject was seated in a dark room in front of a specially designed apparatus. The subject's hands were placed in a semi-supinated position with the palms facing inwards against two aluminium hand-plates. Two adjustable posts were fitted against the dorsal surface of each hand (Fig. 1). The hand-plates were mounted on vertical spindles, which rotated in the transverse plane. The hands were positioned such that the wrist joints sat directly above the axes of rotation. The unit was fitted with rests for the forearms, each incorporating two adjustable stabilising posts mounted on either side of the forearm. This arrangement constrained movement of the wrist joint.

The spindles were connected to potentiometers which provided angular displacement signals via a 16-bit A/D converter (PCI-MIO-16XE-50, National Instruments, TX, USA). Holes in the table's aluminium top-plate accurately specified the angle of the hand-plates with respect to the midline of the subject's forearm. Steel pins were inserted into the holes, forming physical limits for calibration of the equipment. Seat height, forearm-locating posts, and hand-fixing posts were individually adjusted for subject's comfort and stability.

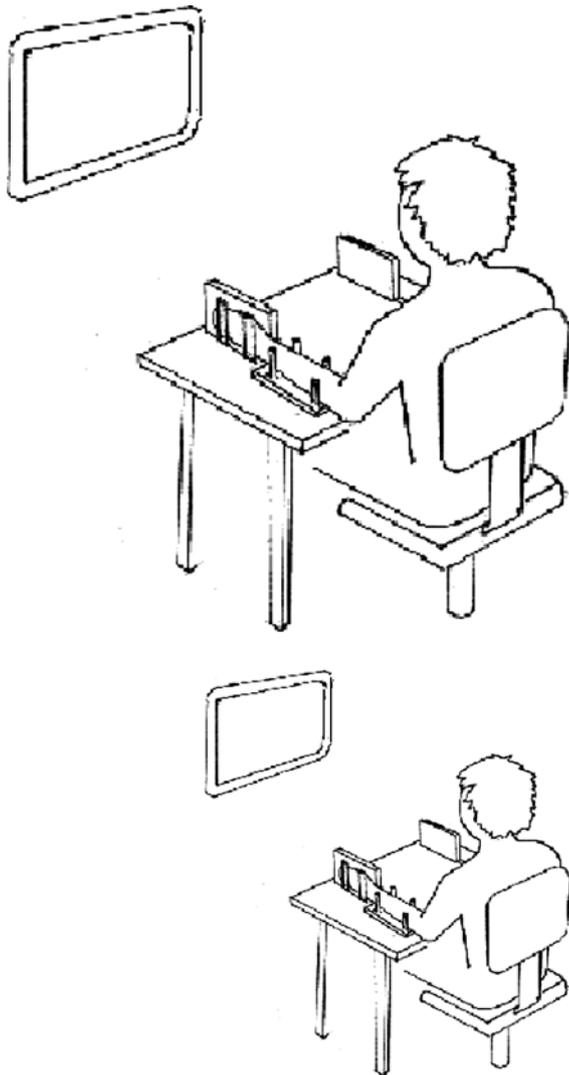


Fig. 1 Experimental setup

Data collection

Electromyography (EMG) signals were collected using 10-mm diameter Hydropot Ag–AgCl surface electrodes (Physiometrix Inc., MA, USA), fixed with tape over the belly of the right and left *flexor carpi radialis* (FCR) and *extensor carpi radialis* (ECR) muscles following standard skin preparation. EMG signals were amplified (Grass P511AC EMG amplifiers, Grass Instrument Division, RI, USA), band-pass filtered between 30 Hz and 1 kHz (–6 dB cut-off points), sampled at 2 kHz by a 16-bit A/D acquisition system (National Instruments, TX, USA), and displayed on-line using LabView 5.1 (National Instruments, TX, USA). Data were stored in disk for off-line analysis. The sampling duration of each trial was 1.5 s, beginning 500 ms prior to the time of TMS. When recordings were made during non-stimulated trials, EMG data were collected for 1.5 s, beginning 500 ms prior to the imperative signal. Signals from the two

potentiometers were sampled at 2,000 Hz simultaneously with the EMG data.

Maximal voluntary contraction (MVC) was determined from the EMG data for each muscle by making the subject perform maximal isometric contraction at the beginning of each experimental session.

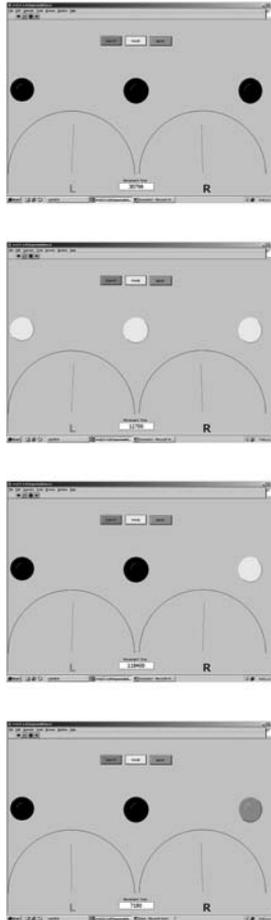
Experimental task

Subjects performed a two-choice RT task from the factorial combination of right or left wrist movements to one of three target locations which were pre-cued in advance of the imperative signal. With respect to the starting position, the three locations required $40^\circ (\pm 10^\circ)$ flexion (far-flexion, FF), $20^\circ (\pm 10^\circ)$ flexion (near flexion, NF), or $20^\circ (\pm 10^\circ)$ extension (EX). Target locations and visual wrist displacement feedback was provided on a 23 in computer monitor positioned approximately 1.5 m in front of the subject (Fig. 2). A trial would begin with a ‘warning signal’, during which all three horizontally aligned, circular targets (each 3 cm diameter) would change colour from black to yellow for a period of 400 ms. This would be followed by a location cue in which the circle at one location would remain yellow while the other two targets reverted to black. This cue specified the location for the forthcoming response, and thus indicated that the response would require one of the two possible movements (since the response hand was not yet specified). After 400 ms, the yellow circle would turn either blue (for a left-hand response) or red (for a right-hand response). This colour change specified the required response and served as the imperative signal. Subjects were instructed to move as quickly and accurately as possible, attempting to stop with the cursor directly in line with the target. On-line feedback concerning the position of the limbs was provided by the angular movement of two green cursors (10 cm long) on the computer screen. On reaching the target, a message appeared on the screen instructing the subject to ‘return to home position’. Home position was defined as the position in which the hands were at $0^\circ (\pm 2.5^\circ)$ with respect to the subjects’ forearms, with the cursors pointed vertically. Subjects were instructed to maintain their non-responding hand in a relaxed state at the home position throughout the trial. The program was designed such that the trial could not be completed unless the non-responding hand was at the home position. Trials in which the non-responding hand incorrectly responded to the imperative or drifted out of the home position were discarded from the main analysis.

Transcranial magnetic stimulation

The experiment was conducted over two sessions, separated by 24–48 h. The site of stimulation (motor cortex of right or left hemisphere) was varied between sessions.

Fig. 2 Experimental task



1. The three target locations are indicated by the black circles. The positions of the subject's hands are represented by two green cursors. The trial began when the subject's hands were in the "home" position (0 deg).

2 The start of the trial was signalled when the colour of the target circles changed to yellow (lightly shaded).

3. 400 ms later, two of the target circles changed back to black. The remaining yellow circle indicated the target position for that trial.

4. At 800 ms, the target circle turned blue or red, providing the imperative signal for either a left or right hand movement, respectively

The order of the two sessions was counterbalanced between subjects.

Stimulation was delivered using a Magstim 200 (Magstim Company, Dyfed, UK) via a figure-of-eight magnetic coil (70 mm coil diameter). The coil was held tangential to the scalp, with the handle positioned posterior and orthogonal to the assumed plane of the central sulcus. The subject wore a tight-fitting cotton cap with pre-marked coordinates in a 1-cm grid pattern. Motor-evoked potentials (MEPs) were collected from the FCR and ECR contralateral to the tested hemisphere for each coordinate of the 1-cm grid pattern surrounding a position 3 cm lateral to the vertex. Trials were examined online to determine the optimal coil position to elicit MEPs with the greatest amplitude for a given stimulus intensity in the contralateral FCR. The coil was held in this optimal position for all subsequent stimulations. Though the parameter setting procedures were prioritised for FCR, ECR parameters were assumed to be satisfactorily similar, due to the overlapping representations of forearm flexors and extensors (Scheiber 1990), and the lower threshold of the forearm extensor muscles.

Active threshold (ATh) was determined at the beginning of the experimental session. ATh was defined

as the lowest stimulus intensity sufficient to elicit an MEP $\approx 100 \mu\text{V}$ peak-to-peak in the contralateral FCR following at least five out of ten stimuli (Rossini et al. 1994) while the subject maintained an isotonic contraction of the contralateral FCR between 2.5 and 7.5% MVC.

Stimulus intensity was set at the intensity necessary to elicit MEPs with a peak-to-peak amplitude equal to half the maximum amplitude that could be elicited in the FCR at rest. To determine this, TMS pulses were delivered over a range of stimulation intensities and the EMG activity was observed online to determine the intensity at which the MEP amplitude was at maximum. Ten MEPs were recorded at this intensity while the subject remained at rest with their hands positioned at 0° , and the average peak-to-peak MEP amplitude was determined. Stimulation intensity was then reduced until an intensity was found at which the average peak-to-peak amplitude of ten sequential MEP responses was half that of the average maximum value. This stimulation level was then used throughout the remainder of the experimental session. The intensity of stimulation ranged from 133 to 210% of ATh, with an average intensity of 166% ATh in the right hemisphere and 167% ATh in the left hemisphere. Using this procedure, subjects were

examined at comparable regions of their individual TMS stimulus–response curve (Devanne et al. 1997).

Practice and incentive

The subjects were provided with online feedback regarding their movement time (MT) for each trial. MT was considered as the duration from the onset of the imperative signal to the time at which the “return to home position” cue appeared. In addition, a running average of their MT for the current block of trials was also displayed.

In order to familiarise the subjects with the task, each subject was provided with a practice block prior to beginning the experiment. This consisted of 48 trials, presented in a pseudo-randomised order, without magnetic stimulation (eight trials for each of the six responses). The subject’s average MT for the practice block was recorded. The subject was then provided with a second 48-trial practice block during which EMG was recorded. Prior to the start of this block, the subject was informed that he or she would receive a \$1 bonus if his or her average MT was faster than on the previous block. Almost all the subjects were able to earn this bonus. The faster of the average MT values from these practice blocks then served as the bonus criterion for all subsequent blocks. Subjects were paid a bonus of \$1 for each test block for which their average MT was below this criterion. This scheme was intended to maintain the subjects’ motivation across the test blocks. Pilot work indicated that the MT did not vary significantly between experimental sessions. Thus, the criterion determined during the first experimental session also served as the criterion for the subsequent session.

Experimental procedure

For each subject, the EMG activity collected during the second practice block was analysed to estimate their average RT. RT was defined as the duration between the onset of the imperative signal and the onset of EMG activity in the agonist muscle of the responding hand.

During the test blocks, a single TMS pulse was applied on each trial at a random interval. Each experimental session consisted of a total of 420 trials, divided into 12 blocks of 35 trials each. The timing of the TMS pulse was varied to encompass 0–120% of the RT range, using steps of 2%. Each of these 60 intervals was tested once for each of the six response conditions (two hands \times three target locations). In addition, the time of the TMS pulse was set at 200% of the average RT in six trials for each condition to provide baseline measures of excitability during activation, and at 100, 400, and 700 ms prior to the imperative signal in one trial for each condition to assess excitability during the foreperiod. For each subject, the order of presentation of

stimuli used in the first experimental session was maintained for the second session also.

Data processing and analysis

All trials were visually inspected to ensure that the correct response was made. Trials in which an overt response was made by the incorrect hand, or by the correct hand but in the wrong direction, were discarded. To ensure that the subject was at rest prior to TMS, the root-mean-square (RMS) of the EMG activity over a 100-ms interval immediately prior to the time of TMS was calculated. If the RMS for this window was greater than 2 SD above the average resting value in any of the four muscles, the trial was discarded. Trials in which TMS occurred during the EMG activity associated with the response (determined visually) were grouped (post-RT) and analysed with respect to the trials in which stimulation occurred during the RT epoch. Trials in which the TMS pulse was delivered after the response was completed, were excluded from the analysis. In all, approximately $30 \pm 9\%$ (mean \pm SD) of the trials were discarded from each experimental session, for the various reasons specified above.

Reaction time was defined as the duration between the presentation of the imperative signal and the onset of voluntary muscle activation. The RMS of the EMG activity of the responding agonist was determined for a window of time while the muscle was at rest, between the end of the MEP and the response onset. The point in time following this window, at which the RMS of the EMG activity increased by greater than 3 SD above rest was considered as the onset of voluntary muscle activation.

The time of the TMS pulse is presented differently for trials in which the stimulation was contralateral or ipsilateral to the response hand. For the contralateral trials, the stimulation time is reported relative to the average non-simulated RT determined during the second practice block. For the ipsilateral trials, the stimulation time is reported relative to the actual RT for the individual stimulated trial. We adopted these different criteria because RT was found to be delayed by contralateral stimulation, and not by the ipsilateral stimulation (see Results).

Our primary measure of corticomotor excitability was peak-to-peak MEP amplitude for the FCR and ECR muscles contralateral to the magnetic stimulation. The amplitude of each MEP was normalised as a percentage of the average MEP amplitude obtained when the target muscle was active as an agonist (%active). Our second dependent measure related to directional bias. This was the stimulus-evoked velocity (SEV), which we defined as the angular velocity of the wrist at the time of peak acceleration immediately following TMS. TMS over a given stimulus intensity, elicits an involuntary movement of the target limb. While TMS elicits MEPs in both agonists and antagonists of the

forearm simultaneously, SEV provides a measure of the net excitability for the entire forearm. Modulation of SEV suggests selectivity of a particular muscle group, in preparation to move the arm in a given direction (e.g. Sommer et al. 2001). In the present study, the SEV was obtained for only 9 of the 14 subjects, due to technical limitations. For each trial, displacement data from the test hand-plate potentiometer was examined for a 150-ms window of time starting from the onset of the magnetic stimulus. These data were filtered at 5 Hz using a dual-pass Butterworth filter, and differentiated to estimate velocity. The data were then filtered with a 10-Hz dual-pass Butterworth filter, and differentiated again to determine acceleration. The velocity ($^{\circ}/s$) at the time of peak acceleration within this window was determined using custom software. Ten MEPs were collected with the subject at rest and in the home position, immediately before and after the experimental session. The average SEV from the ten MEPs collected at the beginning of the experiment was subtracted from the SEV determined for each experimental trial, in order to remove resting bias.

Statistical analysis

Resting MEP amplitude data were analysed using a three-way repeated-measures analysis of variance (RM-ANOVA). Factors included *stimulated hemisphere* (left or right), *muscle* (FCR or ECR), and *time* (at the beginning or end of the experimental session).

Reaction times from the block of trials presented without TMS at the beginning of the first experimental session were analysed using a 2×3 RM-ANOVA considering the main effects of *hand* and *target*.

For the responding hand data, trials in which TMS was delivered during the RT interval were pooled into three arbitrary time bins defined by the timing of the TMS pulses: early (0–33%), middle (33–66%), or late (66–100%) within the individual subjects average non-stimulated RT for the hand involved. A fourth time bin (post-RT) consisted of trials in which TMS was presented following the onset of EMG burst associated with the response. Likewise, for the non-responding hand data, trials were pooled into four time bins based on the onset time of the TMS pulse. However, as reported in Results, we found that stimulation ipsilateral to the responding hand did not confound the measurement of RT during the stimulated trial. Therefore, for the non-responding hand data, we could relate the timing of the TMS pulse to the RT for each individual trial, rather than the average non-stimulated RT.

The 2×3×4 RM-ANOVAs, of *hemisphere stimulated* (left and right), *target* (EX, NF, and FF), and *time of stimulation* (early, middle, late, and post-RT), were performed on the dependent measures: FCR and ECR MEP amplitude, and SEV for the responding hand and non-responding hand data separately. For each ANOVA, planned contrasts were performed to determine whether there was a significant modulation in the

dependent measure during RT (indicated by a significant difference between early and late RT responses), and whether there was a significant modulation in the dependent measure following movement onset (indicated by a significant difference between late and post-RT responses).

The foreperiod was considered as the interval between the onset of the cue and the onset of the imperative signal. The cue informed subjects of the direction of the upcoming response, however, prior to the onset of the imperative signal there was an equal probability that either hand would be signalled to respond, and we assumed that subjects would be equally prepared to move either hand. Foreperiod trials from all subjects were pooled and analysed using 2×3×3 RM-ANOVAs for each of the dependent measures. These ANOVAs considered the main effects of *hemisphere stimulated* (left and right), *target* (left, middle, and right), and *time of stimulation* (700, 400, and 100 ms prior to the imperative signal). Planned contrasts compared the values of the dependent variables at 700 ms prior to the imperative signal with those collected at 100 ms prior, in order to determine any modulation over the foreperiod interval.

Results

MEP amplitude at rest

Table 1 shows the raw MEP amplitudes at rest from the beginning and the end of each experimental session for both the FCR and the ECR. Analysis of the normalised MEP amplitude revealed that the responses from ECR were significantly larger than those from the FCR ($F_{1, 8} = 22.4$, $p < 0.005$). There were no other main effects or interactions (all $p > 0.1$).

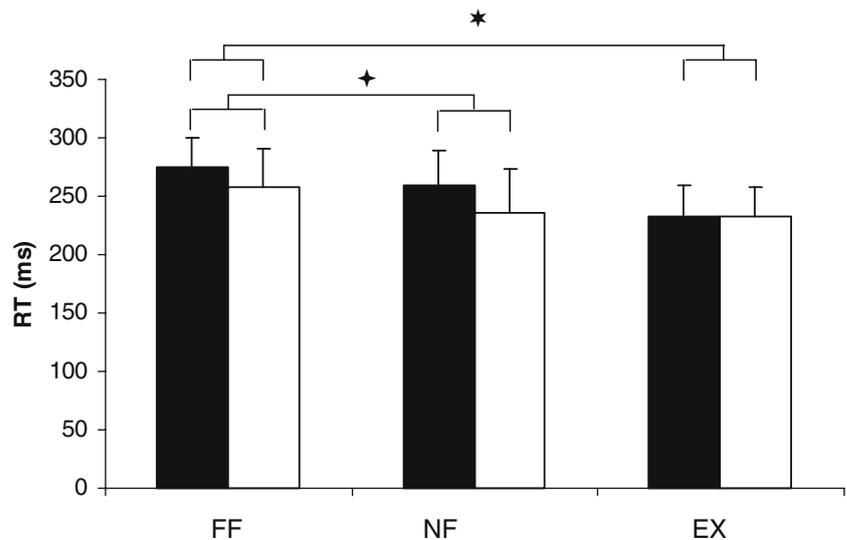
Reaction times without TMS

Reaction time for right-hand responses was significantly shorter than for left-hand responses ($F_{1, 13} = 10.6$, $p < 0.01$). The mean RT in the right hand was 242 ± 5.4 ms, compared to 256 ± 5.1 ms in the left hand (Fig. 3). There was also a significant main effect of *target* ($F_{2, 26} = 9.5$, $p < 0.01$), with planned contrasts showing

Table 1 Resting MEP amplitudes (mV) for FCR and ECR when stimulation was presented over either the left or right hemisphere at the beginning (pre) or end (post) of the experimental session

	FCR (mean \pm SEM)		ECR (mean \pm SEM)	
	Pre (mV)	Post (mV)	Pre (mV)	Post (mV)
Left	0.78 \pm 0.14	0.78 \pm 0.20	2.92 \pm 0.59	2.66 \pm 0.56
Right	0.53 \pm 0.98	0.69 \pm 0.18	1.99 \pm 0.42	1.86 \pm 0.43

Fig. 3 Mean reaction times in trials without TMS for left-hand (*filled bars*) and right-hand (*open bars*) responses for the three different target conditions. The effect of hand was significant ($p < 0.01$). *FF* flexion to the far target; *NF* flexion to the near target; *EX* extension. *Error bars* represent SEMs (*four-point star* $p < 0.05$, *six-point star* $p < 0.001$)



that RT for the FF condition was significantly longer than RT for the NF condition ($t_{13} = 2.00$, $p < 0.05$) and the EX condition ($t_{13} = 4.24$, $p < 0.001$). The difference in RT between the NF and the EX conditions did not reach significance ($t_{13} = 1.74$, $p < 0.10$). There was no significant *target* \times *hand* interaction ($F_{2, 26} = 2.45$, $p > 0.1$).

Reaction times with TMS

The relationship between the time of contralateral TMS and RT has been well established: the later the TMS is presented during RT, the greater the delay in movement onset (Day et al. 1989; Rothwell et al. 1989; Pascual-Leone et al. 1992a, b; Taylor et al. 1995; Romaguere et al. 1997; Schluter et al. 1999; Leocani et al. 2000; Meyer and Voss 2000; Burle et al. 2002; McMillan et al. 2004). Linear regression analyses confirmed this relationship in the present study. Data from all the subjects were pooled for the left and right hemisphere separately. The time of TMS (t) was expressed as a percentage of each individual subject's average non-stimulated RT specific to the hand involved in the upcoming movement, i.e. the hand contralateral to TMS. For left hemisphere TMS, the relationship between the time of TMS and RT (ms) was explained by the equation: $RT = 1.57t + 184.8$ ($R^2 = 0.59$). For right hemisphere TMS, the relationship was explained by the equation: $RT = 1.59t + 196.4$ ($R^2 = 0.54$).

Similar linear regressions were performed to determine if there is a correlation between ipsilateral TMS (as a percentage of the RT for other hand in each individual trial) and RT (ms). No relationship was observed between ipsilateral TMS and RT (R^2 values of 0.062 and 0.082 for left and right hemispheres, respectively). Quadratic regressions (Meyer and Voss 2000) were performed and provided a better fit than the linear regression for the left hemisphere ($F_{1, 1,651} = 9.37$, $p < 0.05$), but not the right ($F_{1, 1,657} = 2.95$, $p > 0.05$), but the variance explained was still very low ($R^2 = 0.0092$).

Responding hand

Figure 4a depicts a typical trial when the TMS pulse was delivered to the hemisphere contralateral to the response hand. In this example, the left hemisphere is stimulated in a trial in which the right hand flexes to the far target.

FCR MEP amplitude

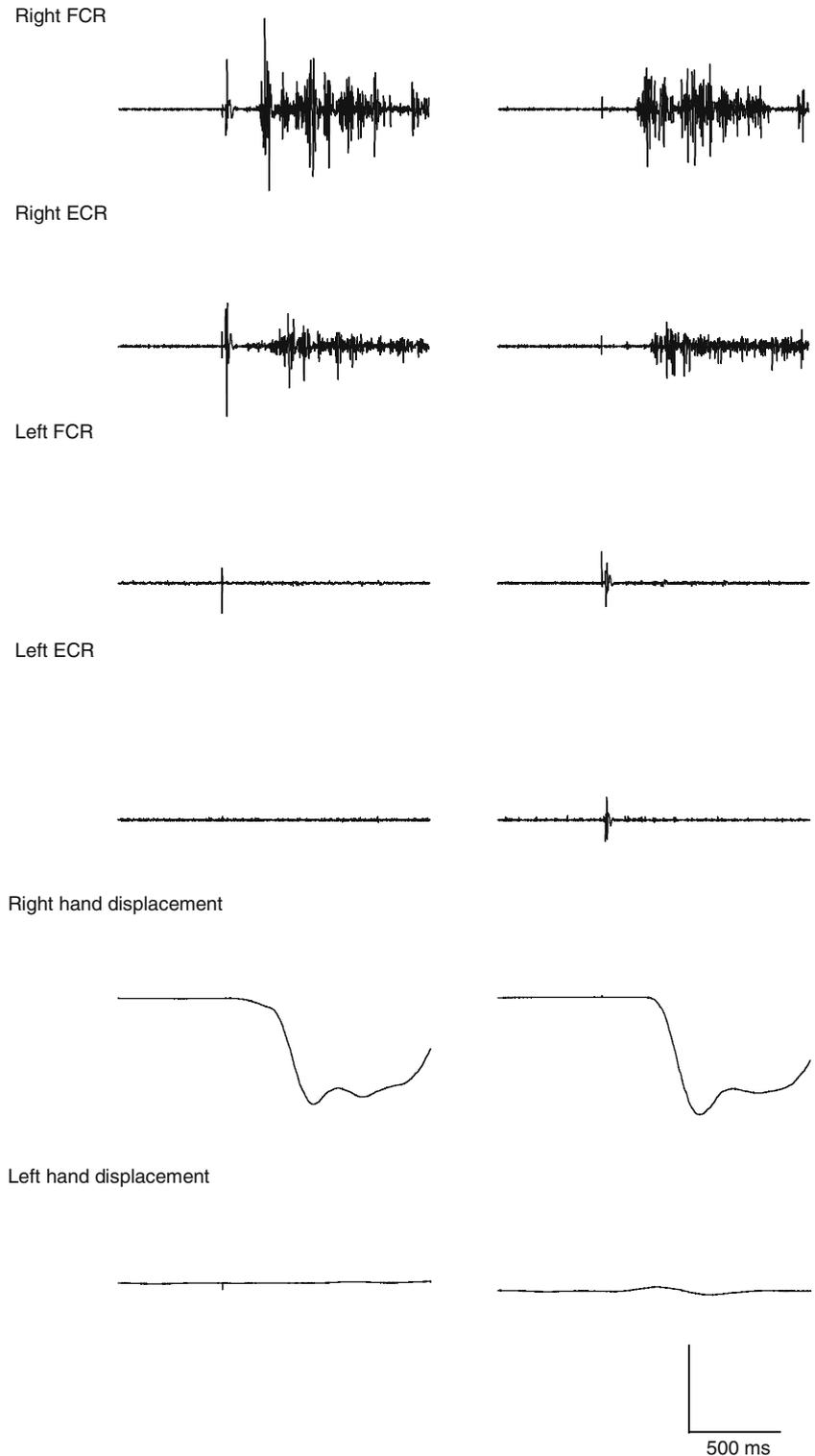
Figure 5a shows the modulation of responding hand FCR MEP amplitude following the onset of the imperative signal in the three different target conditions. There was a significant main effect of *target* ($F_{2, 26} = 102.9$, $p < 0.01$), and of *time* ($F_{3, 39} = 195.8$, $p < 0.01$), but no main effect of *hemisphere* ($F_{1, 13} < 1$). The *hemisphere* \times *target* interaction did not reach conventional levels of significance ($F_{2, 26} = 3.08$, $p = 0.06$), but there was a significant *hemisphere* \times *target* \times *time* interaction ($F_{6, 78} = 2.67$, $p < 0.05$) which did not decompose meaningfully in the contrasts. In the flexion conditions, FCR is the agonist for the forthcoming movement. For both FF and NF, there was a significant increase in FCR MEP amplitude during RT, following stimulation over either hemisphere ($t_{13} = 4.01$, $p < 0.01$; and $t_{13} = 5.25$, $p < 0.001$, for the left and right hemisphere stimulation respectively, in the FF condition, and $t_{13} = 3.75$, $p < 0.01$; and $t_{13} = 5.15$, $p < 0.001$, for the left and right hemisphere stimulation, respectively, in the NF condition). In both the conditions, there was a further increase in FCR MEP amplitude following movement onset ($t_{13} = 7.50$, $p < 0.0001$; and $t_{13} = 12.4$, $p < 0.0001$, for the left and right hemisphere stimulation, respectively, in the FF condition, and $t_{13} = 6.83$, $p < 0.0001$; and $t_{13} = 14.34$, $p < 0.0001$, for the left and right hemisphere stimulation, respectively, in the NF condition). In the EX condition, (where the FCR is the upcoming antagonist), there was no significant modulation of FCR MEP amplitude during

RT ($t < 1$), for either left or right hemisphere stimulation. However, there was an increase in MEP amplitude following movement onset which was significant with right hemisphere stimulation and neared significance with left hemisphere stimulation ($t_{13} = 3.31$, $p < 0.01$; and $t_{13} = 2.11$, $p = 0.05$, for the right and left hemisphere stimulation, respectively).

ECR MEP amplitude

For the ECR MEP amplitude, there was a significant effect of *target* ($F_{2, 26} = 36.5$, $p < 0.01$), a significant effect of *time* ($F_{3, 39} = 14.1$, $p < 0.01$), and a significant *target* \times *time* interaction ($F_{6, 78} = 31.1$, $p < 0.01$). There was

Fig. 4 Raw electromyography activity and hand potentiometer angular displacement during representative trials in which the subject was required to flex the right hand towards the far left target. **a** TMS was delivered over the left hemisphere, contralateral to the responding hand. **b** TMS was delivered over the right hemisphere, contralateral to the non-responding hand. Scale bars represent $200 \mu\text{V}$ EMG activity/ 30° potentiometer displacement (y -axis) and 500 ms (x -axis)



no significant effect of *hemisphere* ($F_{1, 13} < 1$) and none of the other interactions were significant.

Figure 5b shows ECR MEP amplitude of the responding hand following the onset of the imperative signal, in the three different target conditions. In the EX condition (where the ECR is the agonist in the upcoming movement), there was a significant increase in ECR MEP amplitude during RT when stimulation was delivered over either hemisphere ($t_{13} = 2.99, p < 0.05$; and $t_{13} = 2.82, p < 0.01$, for the left and right hemisphere stimulations, respectively) and a further significant increase following movement onset ($t_{13} = 5.87, p < 0.0001$; and $t_{13} = 9.00, p < 0.0001$, for the left and right hemisphere stimulation, respectively). In the flexion conditions, the ECR acts as an antagonist. No contrasts were significant in either flexion condition.

Stimulus-evoked velocity

There was a significant main effect of *target* ($F_{2, 26} = 145.9, p < 0.01$), and a main effect of *time* ($F_{3, 24} = 183.1, p < 0.01$), but no main effect of *hemisphere* ($F_{1, 8} = 1.62,$

$p > 0.1$). There was a significant *target* \times *time* interaction ($F_{6, 48} = 194.1, p < 0.0001$). The *hemisphere* \times *time* interaction neared significance ($F_{3, 24} = 2.85, p = 0.06$).

Figure 5c shows that during RT, the responding hand SEV increased significantly in the direction of the upcoming movement in all the three target conditions when stimulation was delivered over the left hemisphere ($t_8 = 3.29, p < 0.05$; $t_8 = 2.95, p < 0.05$; and $t_8 = 2.82, p < 0.05$, for FF, NF, and EX, respectively) and over the right hemisphere ($t_8 = 2.58, p < 0.05$; $t_8 = 4.90, p < 0.01$; and $t_8 = 4.62, p < 0.01$, for FF, NF, and EX, respectively). This was followed by a further increase in SEV following movement onset with stimulation over left hemisphere ($t_8 = 9.10, p < 0.0001$; $t_8 = 15.92, p < 0.0001$; and $t_8 = 14.35, p < 0.0001$) and with stimulation over the right hemisphere ($t_8 = 6.96, p < 0.001$; $t_8 = 15.9, p < 0.0001$; and $t_8 = 5.54, p < 0.001$) for FF, NF, and EX, respectively.

Non-responding hand

Figure 4b depicts a typical trial when TMS was delivered to the hemisphere ipsilateral to the responding

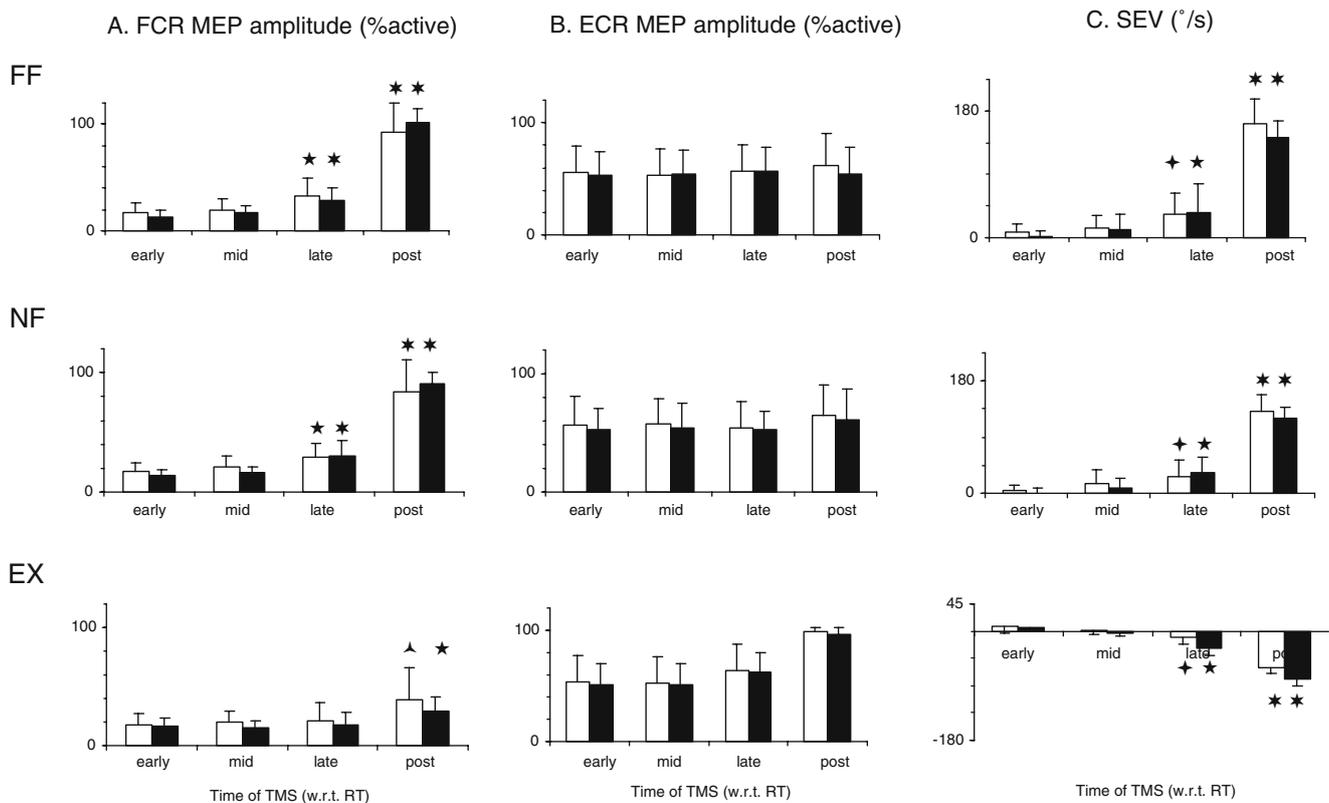


Fig. 5 a and b Responding hand MEP amplitudes (%active) in the FCR and ECR muscles, respectively. c Responding hand stimulus-evoked velocity (SEV) ($^{\circ}/s$). Positive SEV values indicate flexion; negative SEV values indicate extension. Right-hand responses (open bars). Left-hand responses (filled bars). The x-axis depicts the time of TMS when presented early; middle; or late within the RT interval; or following electromyography onset (post). FF flexion to the far target; NF flexion to the near target; EX extension. Symbols

over the late condition depict a significant difference between the early and the late phases of movement preparation for the respective hand. Symbols over the post condition depict a significant difference between the late phase of preparation and execution for the respective hand. Error bars represent SEMs (three-point star $p = 0.05$, four-point star $p < 0.05$, five-point star $p < 0.01$, six-point star $p < 0.001$)

hand. In this example, the subject was required to flex the right hand to the far left target. Measures of MEP amplitude and SEV were obtained for the contralateral, non-responding hand and analysed in the same manner as above.

FCR MEP amplitude

Figure 6a shows the pooled data for the non-responding hand FCR MEP amplitude in the four time bins following the imperative signal, for each of the three target conditions. There was a significant difference between hemispheres ($F_{1, 13} = 4.89$, $p < 0.05$), a main effect of *target* ($F_{2, 26} = 13.2$, $p < 0.01$), and a main effect of *time* ($F_{3, 39} = 4.711$, $p < 0.01$). There was also a significant *target* \times *time* interaction ($F_{6, 78} = 2.66$, $p < 0.05$) and a significant *hemisphere* \times *target* \times *time* interaction ($F_{6, 78} = 3.55$, $p < 0.01$). When the responding hand flexed to

the far target, the FCR of the non-responding hand showed no significant modulation during RT or during movement. When the responding hand flexed to the near target, there was a significant increase in MEP amplitude in the non-responding FCR during RT for stimulation of the left hemisphere ($t_{13} = 2.54$, $p < 0.05$) as well as the right hemisphere ($t_{13} = 2.22$, $p < 0.05$), but not during movement. When the responding hand extended to the target, there was a significant increase in the non-responding FCR MEP amplitude during RT for left hemisphere stimulation only ($t_{13} = 3.21$, $p < 0.01$), but not during movement.

ECR MEP amplitude

There was a significant main effect of *time* ($F_{3, 39} = 15.9$, $p < 0.01$). The main effect of *hemisphere* was not significant ($F_{1, 13} < 1$), nor was the effect of *target* ($F_{2, 26} = 1.40$,

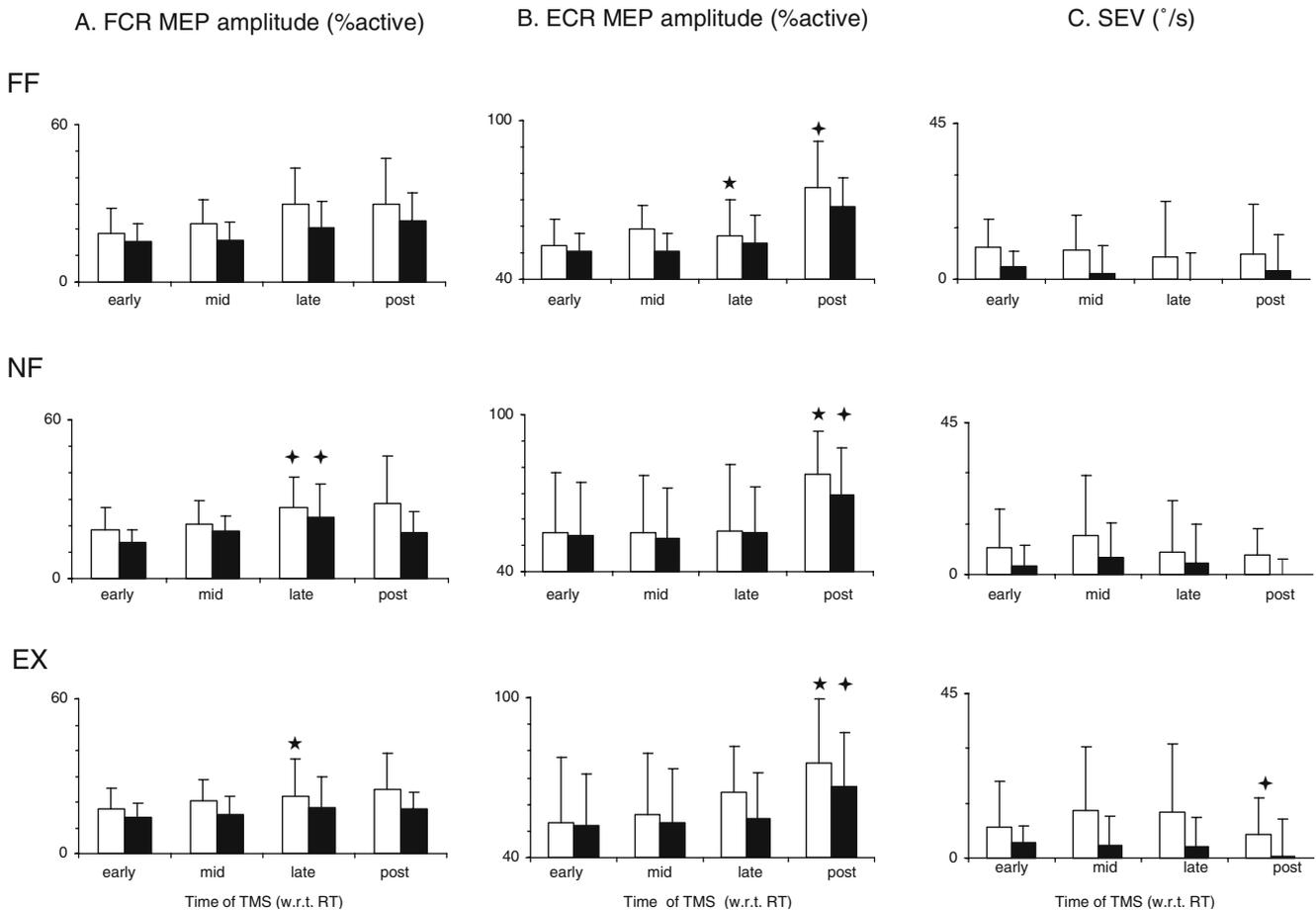


Fig. 6 a and b Non-responding hand MEP amplitudes (% active) in the FCR and ECR muscles, respectively. **c** Non-responding hand stimulus-evoked velocity (SEV) (°/s). A positive SEV value indicates flexion; a negative SEV value indicates extension. Right-hand responses (open bars). Left-hand responses (filled bars). The x-axis depicts the time of TMS when presented early; middle; or late within RT; or following electromyography onset (post). FF flexion

to the far target; NF flexion to the near target; EX extension. Symbols over the late condition depict a significant difference between the early and the late phases of movement preparation for the respective hand. Symbols over the post condition depict a significant difference between the late phase of preparation and execution for the respective hand. Error bars represent SEMs (four-point star $p < 0.05$, five-point star $p < 0.01$)

$p > 0.1$), or any of the interactions. As shown in Fig. 6b, in the condition in which the responding hand was required to flex to the far target, there was a significant increase in the MEP amplitude of the non-responding ECR during RT with left hemisphere stimulation ($t_{13} = 3.71$, $p < 0.01$). This was not significant with right hemisphere stimulation ($t_{13} = 1.16$, $p > 0.1$). When the responding hand was required to flex to the near target, there was no significant modulation in MEP amplitude of the non-responding ECR during RT with stimulation over either hemisphere ($t_{13} < 1$ for both). In the condition in which the responding hand was required to extend, the increase in MEP amplitude in the non-responding ECR was not significant with either right ($t_{13} = 2.01$, $p = 0.07$) or left ($t_{13} = 1.31$, $p > 0.1$) hemisphere stimulation. There was a significant increase in the MEP amplitude of the non-responding ECR with the onset of the movement of the responding hand in all but one condition (left hemisphere—FF: $t_{13} = 2.19$, $p < 0.05$; NF: $t_{13} = 4.04$, $p < 0.01$; EX: $t_{13} = 3.51$, $p < 0.01$;

right hemisphere—FF: $t_{13} = 1.82$, $p = 0.09$; NF: $t_{13} = 2.55$, $p < 0.05$; EX: $t_{13} = 2.37$, $p < 0.05$).

Stimulus-evoked velocity

Analysis of SEV for the non-responding hand revealed a significant main effect of *target* ($F_{2, 16} = 4.68$, $p < 0.05$). The main effect of *time* neared significance ($F_{3, 24} = 2.48$, $p = 0.06$). There was no effect of *hemisphere* ($F_{1, 8} = 3.05$, $p > 0.1$). There was a significant *hemisphere* \times *target* interaction ($F_{2, 16} = 6.16$, $p < 0.05$), a significant *target* \times *time* interaction ($F_{6, 48} = 2.66$, $p < 0.05$), and a significant *hemisphere* \times *target* \times *time* interaction ($F_{6, 48} = 2.77$, $p < 0.05$). As shown in Fig. 6c, there was no significant modulation in SEV in any of the conditions during RT (all $p > 0.1$ except as below). For stimulation over the right hemisphere, there was a non-significant trend for SEVs towards *extension* ($t_8 = 2.02$, $p = 0.08$) in the condition in which the responding hand prepared to

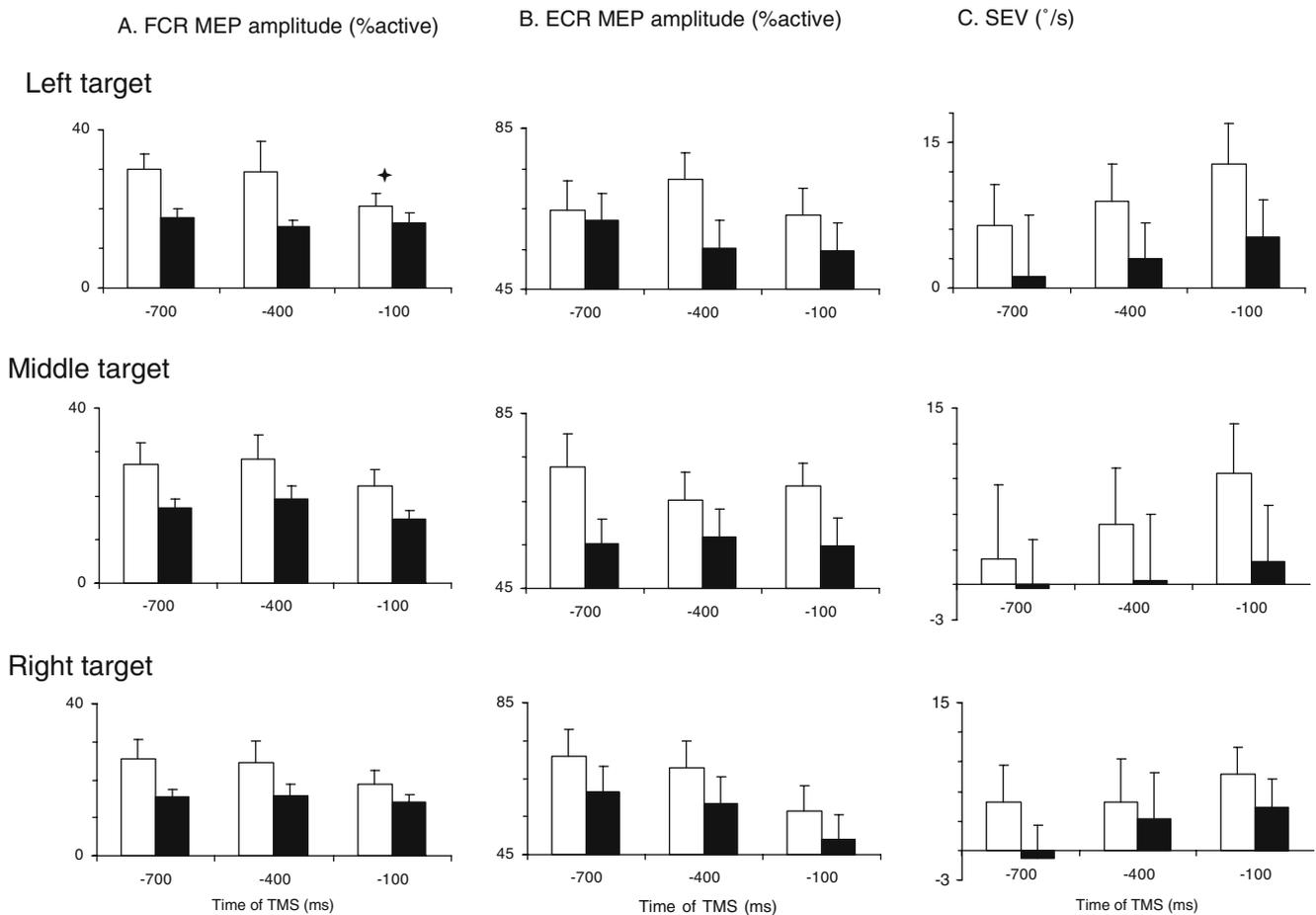


Fig. 7 a FCR and b ECR MEP amplitude (% active) and c stimulus-evoked velocity (SEV) (°/s) when TMS was presented 700, 400, and 100 ms before the end of the 800-ms foreperiod. A positive SEV value indicates flexion; a negative SEV value indicates extension. Right-hand responses (open bars). Left-hand responses

(filled bars). Left target, Middle target, and Right target refer to the target which was illuminated in the cue. Four-point star ($p < 0.05$) indicates significant difference between the early (–700) and late (–100) foreperiod. Error bars represent SEMs

flex to the far target. For stimulation over the left hemisphere, there was a non-significant trend for SEVs towards *flexion* ($t_8 = 1.96$, $p = 0.09$) in the condition in which the responding hand prepared to *extend*. Following the onset of movement in the responding hand, SEV tended towards extension in the EX condition in which the responding hand when stimulation was presented over the left hemisphere only ($t_8 = 2.36$, $p < 0.05$, all other $p > 0.1$).

Foreperiod

FCR MEP amplitude

There was a significant main effect of *hemisphere* ($F_{1, 13} = 7.99$, $p < 0.01$), and a significant main effect of *time* ($F_{2, 26} = 3.57$, $p < 0.05$). There was no main effect of *target* ($F_{2, 26} = 1.92$, $p > 0.1$), and none of the interactions were significant. Figure 7a shows the FCR MEP amplitude at 700, 400, and 100 ms prior to the imperative signal onset, in each of the three target conditions. There was a significant decrease in MEP amplitude during the foreperiod in the condition in which the cue indicated a movement towards the left target (left-hand extension or right-hand far flexion), but only for left hemisphere stimulation ($t_{13} = 1.84$, $p < 0.05$, all other $p > 0.1$).

ECR MEP amplitude

There was a significant main effect of *time* ($F_{2, 26} = 4.26$, $p < 0.05$), but no significant effect of *hemisphere* ($F_{1, 13} = 2.49$, $p > 0.1$) or *target* ($F_{2, 26} < 1$). None of the interactions were significant. As is shown in Fig. 7b, none of the planned contrasts were significant (all $p > 0.1$).

Stimulus-evoked velocity

The SEV of the hand contralateral to the TMS pulse showed no significant effect of *hemisphere* ($F_{1, 8} < 1$), or *time* ($F_{2, 16} = 2.05$, $p > 0.1$), however, there was a significant effect of *target* ($F_{2, 16} = 4.23$, $p < 0.05$) during the foreperiod. There were no significant interactions, nor were any of the contrasts significant (all $p > 0.1$; Fig. 7c).

Discussion

Reaction times without TMS

In non-stimulated trials, RT was significantly shorter in the NF and EX conditions than in the FF condition, while the difference between NF and EX was not significant. Reaction time was longest in the FF condition

and this target required the largest movement amplitude. Accuracy requirements were held constant in this experiment rather than scaled to be proportional as a function of distance. Thus, the difference in RT for the two flexion conditions may be due to a 'speed-accuracy trade-off'. However, this finding should be interpreted with caution since accuracy was not measured throughout the experiment. Another possibility is that the middle target always specified the NF condition and could permit a pre-specification of a small amplitude flexion movement with either hand whereas either 'outside' target would require either large amplitude flexion (FF) of one hand or small amplitude extension (EX) of the other. However, since EX and NF required movements of equivalent amplitude and did not differ in terms of RT, it seems more likely that speed-accuracy is better able to account for differences. Finally, RTs were also shorter for right-hand responses than for left-hand responses. This may reflect an effect of hand dominance in combination with the cueing technique (although this is not well supported by the literature, see Carson et al. 1995).

The foreperiod

Using a unimanual RT task, corticospinal excitability decreases during a foreperiod when the target location is specified, regardless of whether or not the stimulated muscle will be used in the subsequent volitional movement (Hasbroucq et al. 1999). Consistent with these findings, we observed a significant decrease in MEP amplitude in both FCR and ECR muscles during the foreperiod, and neither the FCR nor the ECR MEP amplitude data showed a significant effect of *target*. The decrease in excitability might reflect recruitment of inhibition to prevent response prior to the imperative signal.

One puzzling aspect, however, is that many single-cell recording studies in monkeys have shown directional tuning of the neurons within the shoulder muscle representation of the motor cortex during delayed response tasks (Georgopoulos et al. 1989). It is possible this may reflect a global descending inhibitory influence to the spinal motor neuron pool, to prevent movement, while response-specific preparatory (facilitatory) processes are recruited to support a subset of possible actions.

A more striking effect of the present study was the overall greater level of excitability throughout the foreperiod maintained in the left hemisphere than the right, which may have subserved the RT advantage of the right hand. Responses obtained in the right FCR (following left hemisphere stimulation) were greater than those obtained in the left FCR (following right hemisphere stimulation). The asymmetry suggests a greater increase in excitability, and dominant role of the left hemisphere, during movement preparation. Note that during the foreperiod, subjects were unaware of which hand was required to respond. Therefore, this increase in

excitability does not necessarily suggest a greater activation of the left hemisphere in controlling ipsilateral hand movements per se (cf. Ziemann and Hallett 2001). Rather, it suggests a more general asymmetry between the two hemispheres in terms of response planning, an issue we return to below.

Modulation of excitability in the responding hand during movement planning

Consistent with a large body of evidence (Rossini et al. 1988; Starr et al. 1988; Pascual-Leone et al. 1992a; Tomberg 1995; Hoshiyama et al. 1996; Chen et al. 1998; Leocani et al. 2000; Burle et al. 2002; McMillan et al. 2004), we showed a significant increase in corticomotor excitability directed towards the responding agonist during the RT interval. This was evident in the FCR and ECR in both hands.

Using TMS alone, it is difficult to determine the site at which this modulation of excitability occurs. Given that EMG activity remained at resting levels, it is likely that the increase in MEP amplitude during RT arises from an increase in excitability upstream of the spinal motor neuron pool. Previous studies have shown an increase in the probability of eliciting MEPs during the RT interval when TMS was applied at stimulus intensities below rest threshold (MacKinnon and Rothwell 2000; Pascual-Leone et al. 1992b; Romaiquere et al. 1997; Rossini et al. 1988). This supports the interpretation that there is a cortical contribution to the increased excitability, assuming that the stimulation well below threshold elicits no descending volleys and thus has no influence on spinal excitability. Intracortical recordings also point to a cortical locus given that pyramidal cell firing increases 150 ms prior to movement onset (Evarts 1966, 1968). The increase in MEP amplitude may also result from a decrease in cortical inhibition rather than an increase in excitability. Using paired-pulse TMS, Reynolds and Ashby (1999) reported that increases in MEP amplitude during the RT interval are accompanied by decreases in intracortical inhibition.

Other studies have shown an increase in H-reflex amplitude preceding voluntary movement (Hasbroucq et al. 2000; Kato and Kasai 2000), which would suggest an increase in excitability below the level of M1. This phenomenon however appears elusive, with some evidence suggesting that the increased reflex sensitivity is also observed after EMG onset (MacKinnon and Rothwell 2000). In the present study, there was no significant modulation in the antagonist muscle during RT.

The velocity of wrist flexion and extension at the time of absolute peak acceleration during the stimulus-evoked twitch (SEV) was employed as a measure of directional tuning. In support of the earlier findings of Sommer et al. (2001), the present study showed an increase in SEV in the direction of the upcoming movement in the responding hand, prior to EMG onset.

Modulation of excitability in the non-responding hand during movement planning and execution

We outlined three hypotheses concerning how corticomotor excitability of the non-responding hand might be modulated during the preparation and execution of a response with the other hand. First, if the modulation of excitability were deferred until the responding hand had been specified (some time after the imperative signal), then there may have been a decrease in excitability, at least prior to movement onset (Leocani et al. 2000), i.e. the preceding-inhibition hypothesis. Second, modulation of the non-responding hand might mimic that observed in the responding hand due to neural coupling between homologous muscles (Burle et al. 2002; Hess et al. 1986; Muellbacher et al. 2000; Stedman et al. 1998; Stinear et al. 2001; Tinazzi and Zanette 1998; Ziemann and Hallett 2001), i.e. the homologous-muscle hypothesis. Third, the modulation in the non-responding hand might depend on the direction of the response should that hand have been used to execute the response, i.e. the common-direction hypothesis. This hypothesis is based on the idea that, once the target location is specified, planning occurs in parallel for both possible responses, perhaps as a way to meet the speed requirements emphasised by our instructions. By having a choice-hand RT task involving three target locations, we were able to pit these hypotheses against one another.

In the condition in which the responding hand was required to flex to the near target, both the homologous-muscle hypothesis and the common-direction hypothesis predicted an increase in excitability in the non-responding FCR. This was confirmed with both the left and the right hemisphere stimulation (Fig. 6a—NF). This result is at odds with the preceding-inhibition hypothesis. MEPs following ipsilateral stimulation were larger rather than smaller compared to baseline.

The critical conditions for discriminating *between* the homologous-muscle and the common-direction hypotheses are the FF and EX conditions. When the responding hand prepared to flex to the far target and stimulation was presented over the left hemisphere, there was a significant increase in excitability (MEP amplitude) in the non-responding extensor (Fig. 6b—FF). This result supports the common-direction hypothesis as the excitability of the non-responding hand suggests preparation of an extension movement. The common-direction hypothesis was also supported by the significant increase in MEP amplitude of the non-responding FCR in the condition in which the responding hand was preparing to extend (Fig. 6a—EX).

Interestingly, the two results supporting the common-direction hypothesis were limited to blocks in which stimulation was over the left hemisphere. There was no modulation of excitability in either the FCR or ECR when stimulation was presented over the right hemisphere. Various lines of evidence suggest that during the ipsilateral movements, the left hemisphere, at least for right-handers, is preferentially engaged compared to the

right hemisphere (e.g. Kim et al. 1993). This recruitment has been hypothesised to indicate some contribution of control over ipsilateral movements (Kagerer et al. 2003; Verstynen et al. 2005). The current results suggest another contributing factor namely, that goal-based representations are preferentially instantiated in the left hemisphere, and this leads to the parallel activation of potential movements with either hand that might achieve that goal (see Chen et al. 1997). By this reasoning, excitability in the non-dominant hemisphere is not modulated by direction-based planning because of the absence of strong goal-based representations within this hemisphere. Note that the specification of the response hand involved a highly symbolic cue (i.e. colour). Maintaining the stimulus–response mapping with such cues may be verbally mediated, thus favouring the recruitment of left hemisphere processes.

The MEP amplitudes in the muscles of the non-responding hand over the RT interval must also be interpreted with respect to changes that occur during the foreperiod (see also Hasbroucq et al. 1999). It is evident from inspection of Figs. 6 and 7 that the *increase* in MEP amplitude that occurred during RT occurs within the range of MEP amplitude *decrease* that occurred during the foreperiod. Therefore, the MEP amplitude increase during RT does not represent strict facilitation per se, but rather a recovery from a preparatory decrease which is then modulated differentially based on target and direction. As such the findings provide some support for the preceding-inhibition hypothesis, prior to increases in corticomotor excitability directed towards the non-responding hand during RT. This was more often observed in the FCR of the non-responding hand.

Following movement onset, there was a significant increase in the excitability of the non-responding ECR muscle during all conditions. During extension, the homologous-muscle hypothesis is supported. However, during flexion, the facilitation of non-responding ECR is less clear (Fig. 6b). It is possible this reflects facilitation of homologous muscles since the antagonist extensor in the responding hand is also recruited very close in time, in order to halt the rapid flexion movement. The present study cannot resolve why the ECR MEP amplitude increased in the non-responding hand following both flexor and extensor muscle activation in the responding hand (Fig. 6b). A number of studies have concluded that there is a suppression of excitability of (or an inhibition directed toward) a particular muscle preceding (Hasbroucq et al. 2000; Leocani et al. 2000) and during (Liepert et al. 2001; Warbrooke and Byblow 2004) activation of the homologous contralateral muscle in order to prevent mirror movements. The increase in excitability of the ‘would-be’ antagonist muscle in order to prevent mirror movement, is a finding novel to the present study, and may serve a similar purpose. Given that there was an increase in the excitability of the extensors during activation of the contralateral flexors, the mechanism appears similar to the *flexion withdrawal—crossed extensor reflex*, and may arise through a pathway of similar origin.

Summary

In support of a large body of evidence (Burle et al. 2002; Chen et al. 1998; Hoshiyama et al. 1996; Leocani et al. 2000; McMillan et al. 2004; Rossini et al. 1988; Starr et al. 1988; Pascual-Leone et al. 1992b), the present study showed a significant increase in the excitability of the corticomotor pathway innervating the agonist muscle during the RT interval. Consistent with previous studies (e.g. Sommer et al. 2001), the present findings indicated directional tuning of the responding hand during RT, resulting in selective muscle activation.

The novel findings of this study concern the modulation of corticomotor excitability of the non-responding hand. We hypothesised three possible mechanisms on which the modulation of excitability in the non-responding hand would be dependent. The present findings suggest that during RT, the corticomotor excitability of the non-responding hand is dependent upon both homologous-muscle and common-direction constraints, depending on the circumstances of the movement. Preceding flexion, the increase in excitability in the non-responding hand mirrored that of the responding hand; preceding extension, there was an increase in directional tuning towards the target. Another novel finding was an increase in the excitability of the ‘would-be’ antagonist of the non-responding hand following the onset of movement of the contralateral hand. This may reflect bilateral cross-talk of a braking mechanism, and the origin or level of modulation of this effect might well bear further investigation. In the present study, single-joint movements were performed in either of two directions (flexion or extension). In future research, movements with a greater number of degrees of freedom should be investigated to further elucidate interhemispheric constraints during the planning of goal-oriented actions.

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