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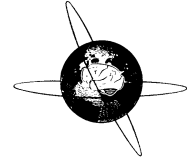
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Influence of task-related ipsilateral hand movement on motor cortex excitability

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Abstract

Objective: The time course of the right motor cortex excitability in relation to a task-related voluntary right thumb twitch was studied using sub-threshold transcranial magnetic stimulation (TMS) to the right motor cortex.

Methods: Motor excitability was studied in 8 adult subjects who made a brief right thumb twitch to the predictable omission of every fifth tone in a series of tones 2.5 s apart. This paradigm avoided an overt sensory cue, while allowing experimental control of TMS timing relative to both movement and the cue to move. Motor excitability was characterized by several measures of motor evoked potentials (MEPs) recorded from the left thenar eminence in response to TMS over the right scalp with a 9 cm coil: probability of eliciting MEPs, incidence of MEPs and amplitude of MEPs.

Results: All subjects showed suppression of motor excitability immediately following a voluntary right thumb twitch (ipsilateral response), and up to 1 s after it. However, two distinctly different effects on motor excitability were observed before the response: two subjects showed excitation, beginning about 500 ms before response until 300 ms after it, followed by the post-movement suppression; 6 subjects displayed pre-movement suppression, beginning about 600 ms before the response and persisting for the duration.

Conclusions: The net effect of an ipsilateral response on motor cortex can be either inhibitory or excitatory, changing with time relative to the response. These findings are compatible with two separate processes, inhibitory and excitatory, which interact to determine motor excitability ipsilateral to the responding hand. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Transcranial magnetic stimulation; Motor evoked potential; Human

1. Introduction

Since the early days of transcranial magnetic stimulation (TMS) the inhibitory and excitatory influences on motor excitability in humans have been the focus of numerous studies. Facilitation of motor-evoked potentials (MEPs) by weak voluntary contraction of the recorded muscle has been attributed to both spinal and cortical mechanisms (Hess et al., 1986; Thompson et al., 1991; Maertens de Noordhout et al., 1992; Mazzocchio et al., 1994; Ridding et al., 1995; Mills and Kimiskidis, 1996). MEP facilitation by voluntary contraction of muscles ipsilateral to TMS (contralateral to the recorded muscle) has also been reported (Hess et al., 1986; Zwarts, 1992; Meyer et al., 1995; Stedman et al.,

1998; Tinazzi and Zanette, 1998; Muellbacher et al., 2000). In contrast, others (Chiappa et al., 1991; Samii et al., 1997) found no MEP facilitation during activation of the same muscle in the opposite limb (homologous muscle activation).

All studies on the excitatory influence of homologous muscle activation used supra-threshold TMS intensities and it has been suggested that only intensities in excess of 120% of MEP threshold can reveal the facilitatory effect (Muellbacher et al., 2000), and that at lower intensities the effect can be missed (Chiappa et al., 1991; Samii et al., 1997). Observing the facilitatory effect is also dependent on forceful contraction of the homologous muscle (Chiappa et al., 1991; Samii et al., 1997; Muellbacher et al., 2000).

The mechanism of the facilitatory effect of homologous muscle contraction on motor excitability is still under debate. Some attributed the facilitatory effect of voluntary homologous muscle contraction to increased spinal motor neuron excitability resulting in more effective descending activation at the spinal level (Hess et al., 1986; Zwarts, 1992). Others have suggested that a large portion of the

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facilitation occurs at the cortical level (Stedman et al., 1998; Tinazzi and Zanette, 1998). Others yet have attributed a large portion of the facilitatory effect of homologous muscle contraction to the spinal level, with a contribution at the cortical level (Muellbacher et al., 2000).

Using supra-threshold TMS intensities to study motor cortex results in MEP recruitment as the main expression of excitability. At threshold and supra-threshold intensities, the probability of evoking MEPs is typically 50–100%. This narrow range limits the use of MEP probability as a measure of motor cortex excitability because it saturates after a moderate increase. Using sub-threshold TMS intensities, the probability of MEPs is typically lower than 50%, allowing both increase and decrease of this measure to be registered over a wide range of change. The possible increase in the variability of measures of motor cortex excitability when sub-threshold stimuli are used may be compensated for by the statistics of multiple measurements. Therefore, rather than using only measures of MEP size to supra-threshold stimulation, sub-threshold TMS allows additional assessment of motor cortex excitability using probability and incidence measures of eliciting MEPs. The combined amplitude and probability measures thus reflect both the amount of recruitment within a neuronal core (amplitude) as well as the probability of excitation of its motor neurons.

Motor cortex excitability is influenced by multiple inputs that may vary depending on the task (Chen et al., 1998; Seyal et al., 1999), preparation for voluntary movement (Hoshiyama and Kakigi, 1999) and sensory input (Furubayashi et al., 2000; Tokimura et al., 2000). Electroencephalographic (Pfurtscheller et al., 1996; Leocani et al., 1997), magnetoencephalographic (Nagamine et al., 1994, 1996) and event-related potentials (Shibasaki and Rothwell, 1999; Hoshiyama and Kakigi, 1999) evidence suggest pre-movement changes (bilateral in case of ERPs) hundreds of ms before and after a voluntary response. A study on human corticospinal excitability on the side of movement and contralateral to it, during reaction time tasks (Leocani et al., 2000), revealed MEP facilitation on the side of movement, while the resting side showed inhibition.

In this study, the influence of a task-related right thumb twitch on right motor cortex excitability was studied using sub-threshold TMS to the right scalp. This right thumb twitch (homologous muscle contraction) was with ordinary force. Thus, subtle changes under normal functional conditions could be examined, reflecting the variety of influences on motor excitability.

2. Subjects and methods

2.1. Subjects

Eight right-handed healthy normal volunteers (7 men and one woman) from the staff of the U.C.I. Evoked Potentials Laboratory, ranging in age between 21 and 52 (mean 33)

years, participated in this study. Four of the subjects underwent two repetitions of the experimental procedures.

2.2. Experimental procedure

Self-adhesive surface EMG electrodes were applied over the left and right thenar eminence and the distal phalanx of the respective thumb, with a ground electrode 5 cm proximal to the right wrist, for recording the EMG from abductor pollicis brevis. During the experiment subjects lay supine on an examination table with their hands resting flat against their abdomen. They were asked to keep both hands relaxed and to avoid any feedback noise from an electromyograph audio output, except for a brief burst when responding with their right thumb (see Section 2.5). Each experimental session lasted approximately 3 h.

2.3. Transcranial magnetic stimulation

TMS was delivered using a 9 cm round coil attached to a 3-dimensionally adjustable mechanical arm. The coil was placed at the position over the right scalp optimal for recording MEPs from the left abductor pollicis brevis muscle, with the induced current running from front to back ('B' side of the coil facing up). The coil was then secured in place by fixing the mechanical arm and strapping with padded Velcro strips around the subject's head. Motor threshold was determined at rest and defined as the minimum intensity required to evoke MEPs of more than 50 μ V in 5 of 10 trials. The intensity used throughout the experiment was 5% below threshold, and this intensity, at rest, typically evoked MEPs in about 20% of trials.

2.4. EMG recording

EMG was recorded from both hands with an electromyograph set to a bandpass of 100–10 000 Hz and a sensitivity of 100 μ V/division. The audio output of the electromyograph was used to assure muscle relaxation during the recording. The amplified and filtered analog two-channel signals were digitized (sampling rate: 10 000/s; bandpass: 100–3000 Hz) by a computer and stored for further, off-line analysis. Absence of EMG other than MEPs in the left hand channel, and absence of MEPs in the right hand were verified.

2.5. Experimental paradigm

During the experiment subjects listened to a series of 1000 Hz tones with an interstimulus interval of 2.5 s. Every fifth tone was omitted, and the subject's task was to press the right thumb briefly against the abdomen at the time estimated by the subject to coincide with the fifth omitted tone. Each run included 60 omitted tones. TMS was delivered to the right scalp at a preset time relative to the omitted ('missing') fifth tone. The experimental setup is summarized in Fig. 1: right-hand EMG associated with the subject's response was recorded in one channel, and the left-hand

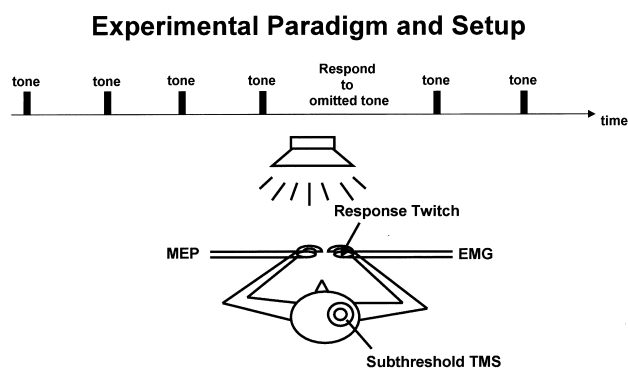


Fig. 1. The experimental paradigm (top) and recording setup (bottom) used in this study. Subjects listened to a series of tones at regular intervals, in which every fifth tone was omitted. The subject's task was to twitch the right thumb at the exact time of the omitted tone. Sub-threshold TMS was delivered to the right motor cortex (contralateral to the one initiating the response) at different times relative to the omitted tone. EMG of the response twitch in the right hand, as well as the MEP evoked by TMS in the left hand, were recorded from the respective thenar eminences. EMG was also recorded from the left hand to verify its relaxation and the unilateral nature of the response.

MEP (evoked by sub-threshold TMS to the right scalp) was recorded in the second channel. In all, 6 runs, each with 60 omitted tones were recorded, and TMS delivery was 600 ms before each omitted tone in the first run, and 200 ms later in each of the following runs, so that in the last run TMS was delivered 400 ms after each omitted tone. At the beginning of the experiment, subjects were not told what their task was, and listened passively to the tones with full relaxation. TMS was delivered at sub-threshold intensity. This sub-threshold intensity evoked MEPs (greater than 50 μV) on the average in 22% of trials (range 2–41%; mean of 14 MEPs in a run of 60 trials). Thus, using an intensity of 5% below threshold, coupled with the moderate baseline probability of evoking MEPs to this intensity, allowed sensitive detection of both increase and decrease in cortical excitability.

In order to control for possible changes in motor cortex excitability that may have occurred during the course of the experiment, MEP threshold was verified not to have changed before each run. In addition, the control run with the subject passively listening to the tones without motor response, was repeated at the end of the session and its measures compared with the initial control run. In some of the subjects the experimental runs in which the subject actively responded to the omitted tones were preceded by runs with the same stimulus parameters and the subject was not required to respond. In the few cases when a threshold change was noted, data were not included in the analysis.

2.6. F-wave measurement

F-waves were recorded from the thenar eminence of the left hand using supra-maximal electrical stimulation of the median nerve at the wrist both when the subject performed

the task by twitching the homologous right thumb and while the subject listened passively. In all, 369 F waves were recorded: 254 with response and 115 without. F-wave amplitude was measured for each trial and amplitudes with and without a response were compared.

2.7. Data analysis

EMG data were analyzed off-line, beginning with segmentation of the continuous digitized EMG data. In the initial run, in which the subject was instructed to relax and no response to the missing stimulus was required, the analysis period was 400 ms beginning 200 ms before TMS. The absence of any muscle tension during this period was verified. In the other runs, in which the subject was instructed to respond, analysis periods lasted 3 s beginning 1.5 s before the delivery of TMS. This analysis period was necessary to include both the TMS-evoked MEP and the EMG of the subject's response at the estimated time of the omitted tone. The timing of the response to the omitted tone varied, reflecting the variability in the subject's accuracy. The timing of TMS delivery was systematically varied before and after the omitted tone, over a 1000 ms interval (see Section 2.5). The combined effect of these two timing variations was a scatter of TMS delivery times across a period beginning 1 s before until 1 s after the subject's response.

MEP latency relative to TMS, peak-to-peak amplitude and latency relative to the response EMG's peak and nearest edge (recorded in the other channel) were measured. EMG nearest edge was defined as EMG onset in trials with TMS before EMG onset, and EMG cessation in trials with TMS delivery after EMG cessation. When TMS was delivered during the subject's response, EMG edge latency was considered 0 because of the ambiguity in choosing the EMG edge nearest to the MEP. In addition, the incidence of MEPs in each experimental run was determined. In trials in which MEPs were not evoked, the temporal relation of TMS and the subject's response was measured.

2.8. Statistical analysis

Cortical excitability was determined using 3 measures: (1) probability of evoking MEP; (2) MEP incidence; and (3) MEP amplitude.

Probability of evoking MEP was defined as the percentage of trials in which an MEP was evoked out of the total number of trials in a given condition. The probabilities for evoking an MEP by TMS in runs in which the subject was not required to respond, as well as in runs when a response was required were calculated. Probability was calculated for each individual subject, as well as for the pooled data across subjects. To determine whether the subject's response had an excitatory or suppressive effect, normalized probability was used. This measure was defined as the ratio between MEP probability when a response was made and its counterpart when no response was required. Normalized probability greater than 1 indicates an excitatory effect while a value

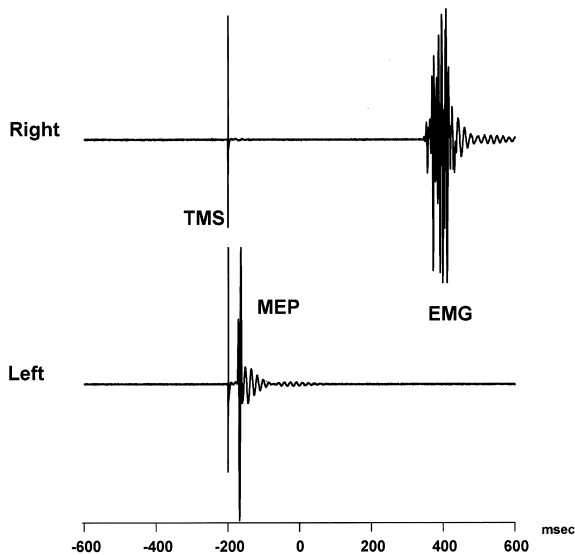


Fig. 2. Example of a single trial from a run in which the subject was required to respond with the right hand and MEP was evoked in the left hand. The EMG of the subject's response, in the right hand, occurred 400 ms after the omitted tone. Time 0 is the time of the omitted tone, and TMS was delivered to the right motor cortex 200 ms before it. Thus, TMS was delivered 600 ms before the subject's response. EMG and MEP are followed by some ringing in the amplifiers

less than 1 suggests suppression. MEP probability as a function of time relative to the response could not be followed because of the low incidence of MEPs in specific time bins, particularly when suppression was involved.

Incidence of MEPs was measured by counting the number of MEPs in specific time bins over a time period beginning 1 s before until 1 s after response EMG edge or peak. It was used to study the temporal changes in motor excitability, as well as to differentiate between excitation and suppression. Incidence was calculated for each subject separately using bins of 300 ms, as well as across all subjects and across all runs using 50 ms bins. The duration of bins was determined so as to allow a meaningful count in each bin: in individual subjects this dictated wider bins than in the pooled data across all subjects. To differentiate excitatory from suppressive effects of the subject's response, incidence of MEPs when subjects were responding was normalized by dividing this incidence by its counterpart when the subject was not responding. This ratio was greater than 1 with excitation and less than 1 with suppression.

MEP amplitudes as a function of their time relationship to the EMG nearest edge and peak were plotted as scatter diagrams. To correct for intersubject differences in MEP amplitudes, their values in the runs in which the subject responded with a thumb twitch were divided by average MEP amplitude in the run in which the subject was not required to respond. Thus, a normalized MEP amplitude measure was obtained, whereby normalized amplitudes greater than 1 suggest excitation, while normalized amplitudes less than 1 indicate suppression.

Single-factor analysis of variance (general linear model) with MEP probability as the dependent variable and subjects as factor was conducted to assess possible excitability differences between subjects. Differences in motor excitability with and without a homologous response were assessed by paired Student's *t* test, comparing MEP probability in runs when a response was present with its counterpart when no response was required. The significance of excitability changes was assessed by comparing the normalized MEP probability and normalized MEP amplitude to a value of 1.0 using one-sample Student's *t* test. Probabilities less than 0.05 were considered significant.

3. Results

An example of a single trial from a run in which the subject was required to respond and MEP was evoked is presented in Fig. 2. In this case, the peak of the subject's response EMG (top trace, recorded from the right hand) occurred 400 ms after the time of the omitted tone (time 0) while TMS was delivered 200 ms before the omitted tone. Thus, in this trial TMS was delivered 600 ms before the subject's response EMG peak (550 ms before EMG onset edge).

In general, all 8 subjects displayed suppression of right motor cortex excitability after a response in the right thenar eminence (homologous muscle), but two distinctly opposite patterns of results preceding this response: two of the subjects showed an excitatory effect before the homologous response, while 6 subjects showed a suppressive effect. The average probability for evoking MEP in subjects with an excitatory effect rose from 3% when no response was required, to 14% when the subjects responded. In contrast, in subjects that showed a suppressive effect probability dropped, on average, from 27% without an ipsilateral response to 6% when the subjects responded. Fig. 3 presents the normalized MEP probability across the 8 subjects. Subjects 1–6 displayed a decrease in normalized probability of MEPs in runs in which a response was made compared to runs without a response. In contrast, subjects 7 and 8

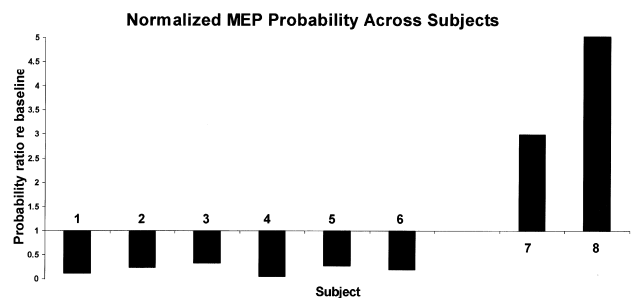


Fig. 3. The normalized MEP probability (MEP probability with a response as a fraction of its counterpart with no homologous response) across the 8 subjects. Subjects 1–6 displayed a decrease in normalized probability of MEPs, while subjects 7 and 8 displayed a marked increase in normalized MEP probability.

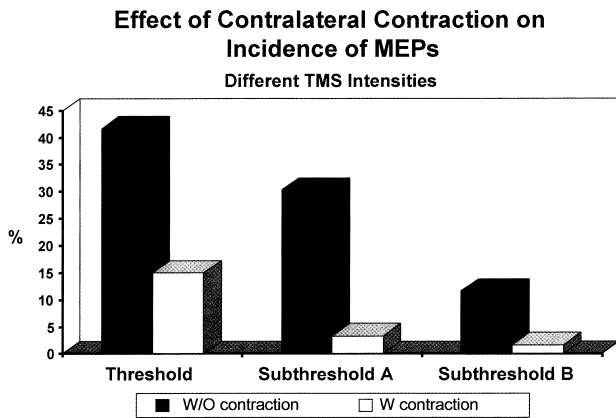


Fig. 4. The effect of homologous response (contralateral contraction) on incidence of MEPs in response to 3 TMS intensities presented to the same subject in two sessions. The suppressive effect of a homologous response was consistent across all conditions.

displayed a marked increase in normalized MEP probability when they responded. A highly significant effect of subject ($F(7, 34) = 5.25$; $P < 0.0005$) on normalized MEP probability was indicated by analysis of variance. Post hoc procedures revealed that subjects 7 and 8 were different than the other subjects, and when they were removed from the analysis, no significant subject effect ($F(5, 24) = 1.30$; $P < 0.3$) was observed for the remaining 6 subjects. The normalized probability of evoking an MEP in all runs of the latter 6 subjects was significantly lower ($t(13) = -22.13$; $P < 0.0000001$) than 1. The suppressive or excitatory effect of a homologous response on motor excitability was consistent in subjects across sessions, and was not related to the intensity of TMS. Fig. 4 presents the effect of homologous (contralateral) response on incidence of MEPs in one subject in response to 3 TMS intensities presented in two sessions. Note the consistent suppressive effect of the homologous response across all conditions.

The probability of evoking MEP among the two subjects who displayed an excitatory effect increased significantly ($t(12) = 2.03$; $P < 0.03$) between runs in which no response was required and runs when the subject responded with a thumb twitch. The probability of evoking MEP among the 6 subjects that displayed a suppressive effect decreased significantly ($t(13) = -5.83$; $P < 0.00003$) between runs in which no response was required and runs when the subject responded with a thumb twitch.

3.1. Suppressive effects of the homologous muscle response

The effect of timing relative to the edge and peak of the voluntary right thumb twitch (homologous response) EMG on the amplitude of the left thumb MEP in the subjects displaying suppression, is presented in Fig. 5. The scatter plots relative to EMG edge or peak showed the same decrease of normalized amplitude below its level when no response was made (horizontal line indicating a value of 1).

Normalized amplitude was significantly smaller ($t(80) = -2.24$; $P < 0.02$) than 1 between 800 ms before and 800 ms after the time of response. The few larger amplitude MEPs tended to concentrate more than 500 ms before the time of response and around the response. The increased amplitudes before the response were mostly due to a single subject who in some of the trials tended to respond late relative to TMS and the omitted tone. This subject's normalized MEP amplitude showed a marked increase (excitation) earlier than 500 ms before the response, followed by a marked decrease (suppression) to below 1.0, similar to the other subjects.

Incidence of MEPs was determined by counting the number of MEPs at different time bins before and after the homologous response EMG edge or peak. Fig. 6 shows the overall low incidence of MEP in these subjects to occur between 700 ms before the response up to about 700 ms after it. The envelope of the incidence histograms resembles the effect of timing on MEP normalized amplitude (Fig. 5): Asymmetry relative to the time of response

Normalized MEP Amp vs Temporal Distance

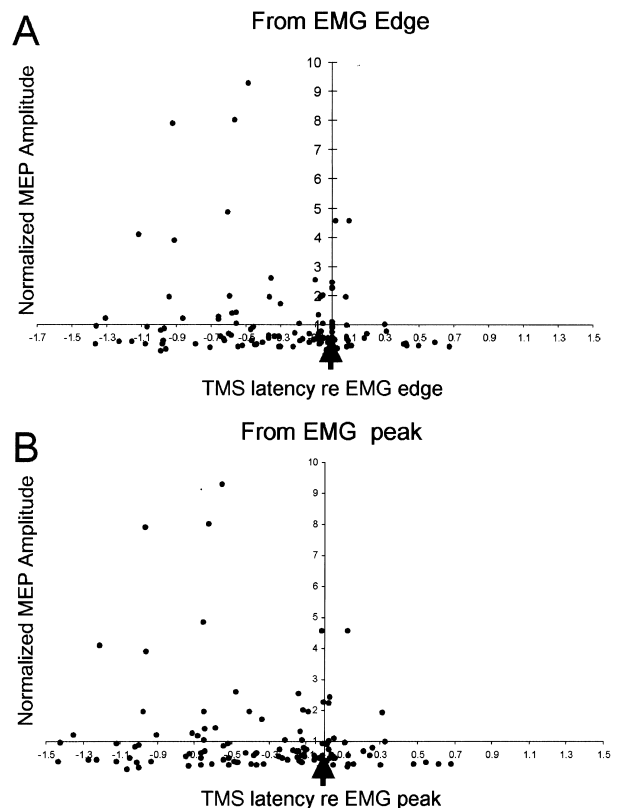


Fig. 5. The effect of TMS timing relative to the homologous response EMG edge (top) and peak (bottom), marked by the small arrow, on normalized MEP amplitude. The horizontal abscissa, indicating a value of 1, marks the normalized amplitude when no response was made. The decrease of normalized amplitude below this value of 1 is evident between 500 ms before the response until the end of the analysis period. In addition, increased excitability is indicated in the period preceding 500 ms before the response.

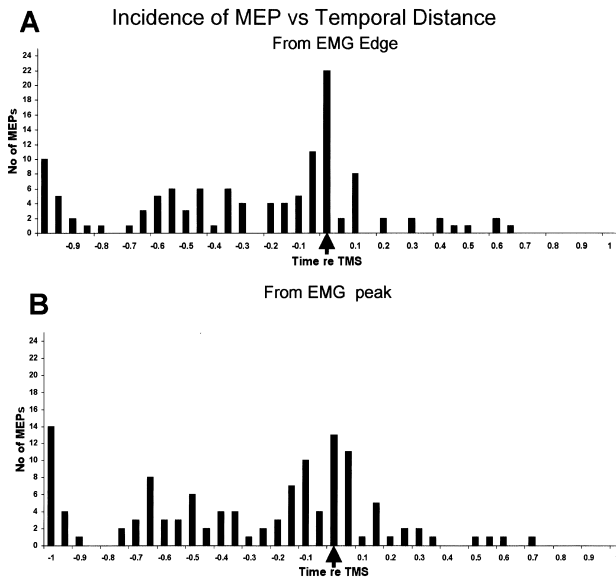


Fig. 6. Incidence of MEPs at different time bins before and after the homologous response EMG edge (top) or peak (bottom), marked by the small arrow. A low incidence of MEP was noted over the period between 700 ms before the response up to about 700 ms after it. Note the asymmetric envelope of the histograms relative to the time of response, with more suppression after the response.

with more suppression after the response. At bins earlier than 800 ms before response, incidence of MEPs increased.

3.2. Excitatory effects of the homologous muscle response

Two subjects showed a marked excitatory effect of the homologous response on motor excitability preceding the response. Due to the small number of subjects and MEPs that were evoked, no normalized amplitude measures were derived. However, as shown above, probability of evoking MEPs and normalized incidence of MEPs were both clearly increased in these two subjects

The effect on MEP amplitude of its timing relative to the edge and peak of the homologous response EMG for these subjects is presented in Fig. 7. The scatter plots relative to EMG edge or peak showed elevation of MEP amplitude between 600 ms before and 300 ms after the response, followed by complete absence of MEPs at later times. The elevation of amplitude peaked with the response or slightly before it and sharply declined thereafter.

Incidence of MEPs was determined by counting the number of MEPs at different time bins before and after the homologous response EMG edge or peak. Fig. 8 shows increased incidence of MEP in these two subjects, beginning up to 600 ms before the response, peaking with the response, and sharply decreasing to reach zero 300–400 ms after the response.

3.3. F-wave measurements

No significant differences were found in amplitudes of F waves recorded from the left hand when subjects were

passively listening compared to when they were responding with a right thumb twitch.

4. Discussion

In this study motor excitability before and after a task-related voluntary right thumb twitch was assessed with sub-threshold TMS to the right motor cortex. The ‘omitted tone’ paradigm and the long intervals between stimuli that were used in this study allowed follow-up of motor excitability without task-related sensory input interference and over longer time periods than in earlier studies. TMS does produce sensory stimuli (sound from the discharging coil and proprioceptive afferent input when the excited muscle twitches) and as such may bias the subjects to respond to it rather than to the omitted tone. However, with the possible exception of one subject, this was not the case in this study, as evident from the evenly distributed latencies of TMS relative to the response EMG.

The effects observed cannot be attributed to the omission of the tone from the regular series preceding it as all measures were normalized to their counterparts in the control condition. In the control condition the tone was also omitted and the only difference between the experimental condition and control was the subject’s motor response to the omitted tone. Three measures were used to assess cortical excitability: MEP amplitude, incidence of evoking MEP and probability of evoking MEPs. Studying task-related cortical excitability allowed measurement of multiple influ-

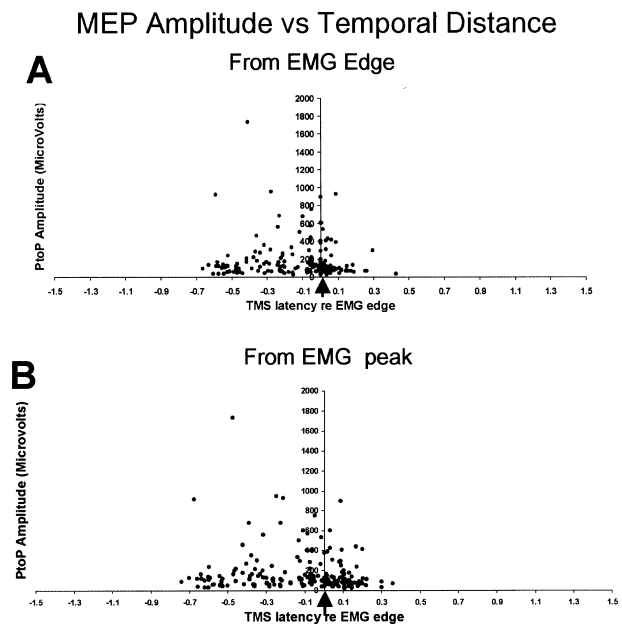


Fig. 7. The effect on MEP amplitude of its timing relative to the edge (top) and peak (bottom), marked by the small arrow, of the homologous response EMG in the two subjects that showed pre-movement increased excitability. The scatter plots show elevation of amplitude beginning 600 ms before the response, peaking with the response or slightly before it and sharply declining until 300 ms after the response, followed by complete absence of MEPs.

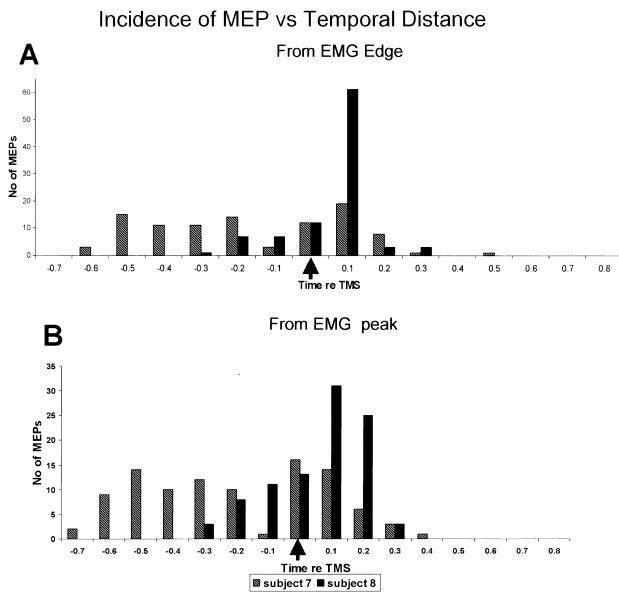


Fig. 8. Incidence of MEPs at different time bins before and after the homologous response EMG edge (top) or peak (bottom), marked by the small arrow, in the two subjects that showed increased excitability before the response. Incidence increased beginning 600 ms before the response, peaking with it, and sharply decreased to total suppression 300–400 ms after the response.

ences on motor cortex that may not be controlled with self-paced movement or with continuous contraction. Supra-threshold stimuli can manipulate the extent of motor activity that is executed while other influences on cortical excitability may only marginally modulate excitability. In contrast, sub-threshold excitation, as used in this study, may or may not evoke a movement, depending on the other influences on motor cortex excitability. Thus the appearance of an MEP in response to sub-threshold TMS can sensitively reflect the integrative influences on movement execution. Moreover, sub-threshold TMS with its added statistical measures of MEP probability and incidence may add information on motor cortex excitability not available using only MEP amplitude measures to supra-threshold stimulation. In general, the paradigm, measures and stimuli that were used in this study allowed a reliable follow-up of motor excitability over a wide time period before and after a voluntary response ipsilateral to the stimulated cortex, minimizing sensory interference.

4.1. Excitatory and suppressive effects of a response

All 8 subjects in this study showed suppression of motor excitability immediately following an ipsilateral response, and two distinctly different effects on motor excitability before the response: excitation and inhibition. This difference was subject-related, as shown by analysis of variance. Although the average probability of evoking MEP when no response was made was lower on average in the subjects with an excitatory effect, in all 12 runs that they were exam-

ined (in subject 8 on two separate dates) the same clear excitatory effect was consistently observed. Similarly, subjects with a suppressive effect showed the same effect across different TMS intensities and sessions (Fig. 4). Moreover, some of the subjects with a suppressive effect had similarly low probabilities when no response was required, and this low probability was further suppressed to as low as zero. These findings do not support differences in sub-threshold baseline excitability as the underlying cause for this grouping of subjects. Rather, the difference between groups may be related to their experience with performing the task. Subjects 7 and 8 were over-trained in the performance of reaction time tasks, while the other subjects were relatively inexperienced.

4.2. Inhibitory effect of a response

The results of this study showed inhibitory changes in motor excitability before and after ipsilateral task-related muscle activation in 6 of the 8 subjects. This effect was statistically significant and consistent across 3 measures of excitability: MEP normalized amplitude, MEP incidence and probability. Suppression of motor excitability in these subjects was throughout the period beginning 700 ms before the response until 1 s after. Although TMS was delivered at all times before and after the response, all 3 measures of excitability indicated asymmetrical suppression before and after the response: suppression was more pronounced after the response. Moreover, even the two subjects that displayed ipsilateral excitatory effects before the response showed post-movement suppression beginning 300 ms after the response. This uniformity across subjects in post-movement inhibition, and the variable inhibition preceding and accompanying movement indicate the involvement of at least two processes in these effects.

4.3. Excitatory effect of a response

Two of our subjects showed facilitation of motor excitability in conjunction with a response ipsilateral to the stimulated cortex. This facilitation was asymmetrically distributed before, during and after the response, beginning 700 ms before the response, declining sharply during the 300 ms after it, to be replaced by suppression. The only parameter distinguishing these subjects from the other subjects who showed inhibition throughout was their experience in performing the task. The two subjects that showed increased excitability were very experienced in the performance of the task. Such ipsilateral excitation has been described by others only with suprathreshold TMS (Hess et al., 1986; Zwartz, 1992; Tinazzi and Zanette, 1998; Muellbacher et al., 2000).

4.4. The role of motor cortex

Our results on motor excitability do not support spinal contributions to the effects observed. Hundreds of F-wave

recordings from the left hand using the exact same experimental procedures, with and without a response with the right hand, were indistinguishable. This finding in conjunction with the significant motor excitability changes observed in this study support a largely cortically mediated effect.

Spinal cord was suggested to be the main contributor to facilitation of motor excitability during ipsilateral hand movement (Hess et al., 1986; Zwartz, 1992) using different experimental procedures and supra-threshold TMS intensity. In contrast, stimulation over the spinal cord failed to induce motor facilitation that was observed with TMS (Stedman et al., 1998). In another study, comparing electrical and magnetic stimulation, differentially activating corticospinal neurons in the white matter and transsynaptically, respectively, a cortical mechanism was suggested (Tinazzi and Zanette, 1998). A mixed effect, consisting largely of spinal contributions with possible cortical influence, using considerably supra-threshold TMS intensities has also been suggested (Muellbacher et al., 2000).

The results of this study differ from some earlier results in supporting a cortical mechanism for the effects of ipsilateral movement on motor excitability. This difference may be attributed to the use of sub-threshold TMS and task-related contraction at normal force. Sub-threshold TMS intensities, as was the case in this study, preferentially evoke indirect (I) MEP waves transsynaptically within the motor cortex. Using higher intensities, corticospinal activation just below the cortex is affected, resulting in direct (D) waves. Thus, earlier studies may have accentuated the subcortical contributions, whereas our protocol preferentially examined cortical effects. The task-related nature of the movement, involving preparation for movement, attention, expectancy and such factors affecting background motor excitability may have contributed to the dominance of cortical effects over any observable effect at the spinal level.

The possible mechanism by which movement affects ipsilateral motor cortex excitability deserves discussion. Possible pathways that mediate changes in motor cortex excitability by ipsilateral hand movement may include cortico-cortical callosal inhibitory as well as excitatory connections which have been described in humans (Preilowski, 1995; Cracco et al., 1989; Pandya and Seltzer, 1986; Jeeves et al., 1988; Meyer et al., 1995; Bonato et al., 1996). Movement can affect the motor cortex ipsilateral to it by changing the net effect of transcallosal flow from the motor cortex contralateral to the movement. Our results show that the net effect of an ipsilateral response on motor cortex can be either inhibitory or excitatory, and changes with time relative to the response. This suggestion is in agreement with findings of two separate processes, inhibitory and excitatory, which interact to determine motor excitability (Reynolds and Ashby, 1999; Floeter and Rothwell, 1999). Support for this interplay between excitation and inhibition derives from results of a study on human corticospinal excitability using TMS during different reaction time paradigms (Leocani et al., 2000). In that study, for

all paradigms, MEP amplitudes on the side of movement increased before EMG onset, while the resting side showed inhibition. Furthermore, corticospinal inhibition on the side not to be moved was more efficient for right- than for left-side movements in right-handed subjects, compatible with left hemisphere dominance for movement. Our results further suggest that the balance between facilitation and suppression may vary under the very same task demands, depending on proficiency in task performance: two experienced subjects showed pre-movement facilitation while the other 6 showed suppression. This suggestion, however, must be further examined as the number of observation in this study was small.

Another explanation for the influence of an ipsilateral response on motor cortex derives from the known ipsilateral motor pathway in humans. Ipsilateral pathways are the only possibility in explaining recovery after hemispherectomy, and in explaining bilateral MEPs using TMS to the remaining hemisphere (Cohen et al., 1991; Benecke et al., 1991). The role of ipsilateral pathways was also suggested in recovery from stroke (Turton et al., 1996) and in patients with cerebral gliomas (Caramia et al., 1998). The role of such pathways in the effects observed in this study deserves further study.

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