Title
Time course of motor excitability before and after a task-related movement

Journal
Neurophysiologie Clinique, 33(3)

ISSN
0987-7053

Authors
Zaaroor, M
Pratt, H
Starr, A

Publication Date
2003-06-01

DOI
10.1016/s0987-7053(03)00029-7

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neurophysiologie clinique 33 (2003) 130–137
NEUROPHYSIOLOGIE CLINIQUE
CLINICAL NEUROPHYSIOLOGY
www.elsevier.com/locate/neucli

Time course of motor excitability before and after a task-related movement

M. Zaaroor [a], H. Pratt [b,*], A. Starr [c]

[a] *Department of Neurosurgery, Rambam Medical Center and Technion – Israel Institute of Technology, Haifa, Israel*
[b] *Evoked Potentials Laboratory, Behavioral Biology, Gutwirth Building, Technion – Israel Institute of Technology, Haifa 32000, Israel*
[c] *Department of Neurology, University of California, Irvine, CA 92697, USA*

Abstract

***Aims of the study*. –** The time course of motor excitability during a task-related unilateral right thumb movement was studied using sub-threshold transcranial magnetic stimulation (TMS) to the contralateral left motor cortex. The level of stimulation evoked a motor evoked potential (MEP) in the thumb when the subject was at rest in approximately 10% of the trials.

***Methods*. –** Subjects made a brief right thumb movement to the predictable omission of regularly presented tone bursts allowing experimental definition of TMS relative to the cue to move. Motor cortical excitability was characterized by amplitude and/or probability of eliciting MEPs.

***Results*. –** There were four periods of altered motor excitability during task performance compared to a control resting state: a first period of weak facilitation before movement between –500 to –200 ms, a second period without increased excitability approximately 150 ms before movement onset when MEPs amplitude was below that seen in rest, a third period of strong facilitation between – 100 ms before movement and +200 ms after facilitation and a fourth period of weak facilitation between +200 to +500 ms.

***Conclusion*. –** These results show that during performance of a task requiring a motor response, motor cortical excitability is increased above resting for hundreds of millisecond before and after the response, except for a transient period between 75 and 150 ms prior to movement onset. The temporal pattern of these excitability changes is compatible with multiple excitatory and inhibitory inputs interacting on motor cortex.

Résumé

***Objectif de l'étude*. –** Étudier le décours temporel de l'excitabilité motrice pendant une tâche de mouvement du pouce droit, en délivrant une stimulation magnétique transcranienne (TMS) à un niveau infra-liminaire sur le cortex moteur contralatéral. À ce niveau de stimulation, nous avons obtenu l'apparition d'un potentiel évoqué moteur (PEM) dans le pouce, avec les sujets au repos, dans 10 % des essais.

***Méthodes*. –** Les sujets faisaient un bref mouvement du pouce droit en réponse à l'omission (prédictible) de bruits blancs présentés régulièrement. Ceci nous a permis de définir différentes fenêtres d'application de la TMS, avant ou après le mouvement du doigt. L'excitabilité motrice corticale était alors définie par l'amplitude et/ou la probabilité de produire un PEM.

***Résultats*. –** Il est apparu 4 périodes au cours desquelles l'excitabilité motrice était altérée en comparaison à un niveau de repos : une première période de faible facilitation avant le mouvement, entre –500 et –200 ms, une seconde période sans augmentation de l'excitabilité, environ 150 ms avant le début du mouvement (l'amplitude des PEM étant inférieure à celle pendant les périodes de repos), une troisième période de forte facilitation entre –100 ms avant le mouvement et +200 ms après la facilitation, enfin une quatrième période de faible facilitation entre +200 et +500 ms.

***Conclusion*. –** Ces résultats montrent que, pendant la réalisation d'une tâche nécessitant une réponse motrice, l'excitabilité corticale est augmentée au dessus du niveau de repos pendant quelques centaines de ms avant et après la réponse, excepté pendant une période de transition se situant entre 75 et 150 ms avant le début du mouvement. Le décours temporel de ces changements dans l'excitabilité corticale est compatible avec la théorie des multiples entrées excitatrices et inhibitrices interagissant dans le cortex moteur.

Keywords: Transcranial magnetic stimulation; Motor evoked potential; Cortical excitability

* Corresponding author.
E-mail address: hillel@tx.technion.ac.il (H. Pratt).

doi:10.1016/S0987-7053(03)00029-7

1. Introduction

Two lines of evidence report the time course of motor excitability. Electroencephalography [14,17], magnetoencephalography [15,16] and event-related potentials (ERP) [13,29] reveal cortical activity changes hundreds of millisecond before and after a voluntary movement. In contrast, transcranial electric and magnetic stimulation (TES and TMS) studies of motor cortex have defined increased motor excitability changes limited to approximately 100–150 ms before and after brief movements [2,21,30]. Some studies have defined the presence of inhibitory influences on motor cortex during motor response preparation. Reduced excitability of the cortico-spinal system was observed during the warning period of a simple reaction time task [33]. Reynolds and Ashby [19] concluded that changes in balance of excitation and inhibition of cortico-spinal neurons were present to account for the changes in motor cortical excitability preceding a voluntary movement.

The discrepancies between transcranial magnetic stimulation (TMS) and ERP results may be related to the neural processes being measured. Electroencephalography, magnetoencephalography and evoked potentials reflect activity in widespread brain regions, whereas TMS affects excitability in a relatively restricted region of the brain.

The level of TMS stimulation can affect motor excitability changes [3]. Therefore, by using sub-threshold TMS intensities the possible involvement of sub-cortical contributions to motor evoked potential (MEP) facilitation may be minimized.

Measures of the effects of TMS on excitability of motor cortex include [1] the probability that TMS will evoke MEPs and [2] the amplitude of the MEP. Since supra-threshold TMS intensities evoke MEPs 100 % of the time, definition of changes of excitability is limited to MEP amplitudes. At threshold and sub-threshold intensities, both MEP probability and MEP amplitude can be used to reveal excitatory and inhibitory changes of motor excitability.

Motor cortex excitability is influenced by several factors that may vary depending on processing involved in performance of the task [2,27], preparations for the voluntary movement [13] and the presence of sensory input [9,32]. For instance, self-paced movements limit experimental control and manipulation of task-related factors since the subject prepares, plans, and decides when the movement is made. To control such factors, experimental paradigms often employ a sensory cue that defines the type and timing of the movement. The use of such a sensory stimulus, may introduce non-specific sensory–motor interactions that affect excitability [25].

The purpose of the present study was to examine motor cortical excitability over a relatively long time period preceding movement. We used an experimental design similar to the one we used in a study of ipsilateral motor excitability during movement [34] that avoids an overt sensory cue, while allowing experimental control of TMS timing relative to both the movement and the cue to move. Sub-threshold TMS was employed to study the time course of motor excitability that was measured by probability of activating motoneurones (MEP probability) and by the degree of motor activation (MEP amplitude) to reveal both excitatory and inhibitory effects.

2. Methods

2.1. Subjects

There were seven right-handed subjects, scientists from the laboratory, whose age was between 21 and 52 (mean 33) years (six men and one woman). All procedures were approved by the institutional review board (Helsinki committee).

2.2. Experimental procedure

Self-adhesive surface EMG electrodes were applied over the right and left 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 the hands relaxed and to avoid moving using the auditory output of the EMG as a guide, except when responding with their right thumb (see Section 2.5, below). Each experimental session lasted approximately 3 h.

2.3. Transcranial magnetic stimulation

TMS was performed using a Magstim 200 with a 9 cm round coil attached to a three-dimensionally adjustable mechanical arm. The coil was placed in the position over the left scalp optimal for recording MEPs from the right abductor policis brevis muscle, with the induced current running from back to front (‘A’ side of the coil facing up). The coil was then secured in place by fixing the mechanical arm and by 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 μV in 50% of trials (five of 10 trials). The intensity was then adjusted to be 10% below “threshold”. This level of stimulation evoked MEPs in subjects at rest in 4.5% of trials, on average (range 0–12%, mean of 2.7 MEPs in a run of 60 trials).

2.4. EMG recording

EMG was recorded with an electromyograph set to a band pass of 100–10,000 Hz and a sensitivity of 100 μV/division. The audio output of the electromyograph was used to ascertain that the muscle was relaxed during the experimental trials. The amplified and filtered analog signal was digitally

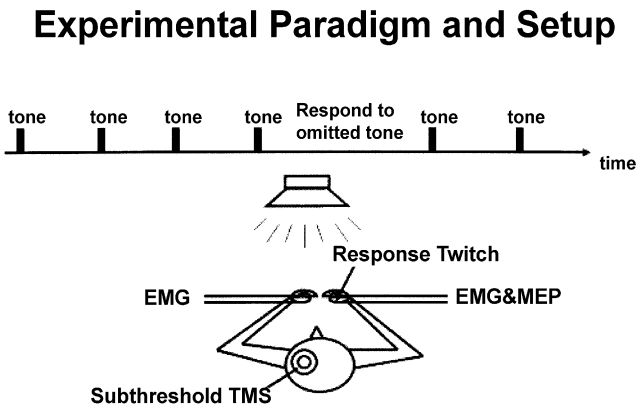


Fig. 1. The experimental paradigm (top) and recording setup (bottom) used in this study. Subjects listened to a series of tones at regular intervals, in which every fifth tone was muted. The subject's task was to twitch the right thumb at the exact time that the fifth tone would have been presented. Sub-threshold TMS was delivered at different times relative to the missing tone, resulting in stimulation of the motor cortex that initiates the response at different times relative to the movement. EMG of the response twitch, as well as the MEP evoked by TMS was recorded from the right thenar eminence. EMG was also recorded from the non-responding left hand to verify its relaxation and the unilateral nature of the response.

filtered and sampled (sampling rate: 10,000 Hz, band pass: 100–3000 Hz) by a computer and stored for further, off-line analysis.

2.5. Experimental paradigm

During the experiment, subjects listened to a series of 1000 Hz tones with 100 ms duration and an inter-stimulus 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 omitted tone. Each experimental run included 60 omitted tones. TMS was delivered at a preset time relative to the omitted tone. The experimental paradigm and setup are summarized in Fig. 1. In all, six runs, each with 60 omitted tones were recorded: 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 set of trials, TMS was delivered 400 ms after each omitted tone. At the beginning of the experiment, subjects were told to "relax and to listen to the tones, and make a thumb movement to the occurrence of the omitted tone". A control set of trials in which the subject was at rest and instructed not to respond to the omitted tones, was then performed to obtain motor excitability measures at rest.

In order to control for the possible changes in motor cortex excitability that may have occurred during the course of the experiment, MEP threshold at rest was verified not to have changed before each run. In addition, a final control set of trials at rest was repeated at the end of the session and the measures compared with the initial control run. In two of the subjects, the experimental runs in which the subject actively responded to the omitted tones were each preceded by runs with the same stimulus parameters and the subject was instructed not to respond and remain at rest. None of the seven subjects included in the analysis exhibited any threshold shift between the beginning and the end of the recording session. One of the subjects underwent three repetitions of the experimental procedures.

2.6. Data analysis

EMG data were analyzed off-line, with analysis periods lasting 3 s beginning 1.5 s before the delivery of TMS. This analysis period included both the TMS–evoked MEP and the EMG of the subject's movement at the approximate time of the omitted tone. Only trials with a flat, baseline recording (except for the response EMG, when movement was required) were accepted for quantification. Trials in which TMS delivery occurred during the subject's movement were also not included in further analysis.

The EMG responses to the magnetic stimulation were quantified with regard to probability of occurrence and maximum peak-to-peak amplitude. The MEP was then categorized with regard to its latency relative to the onset and offset of the motor response's EMG. Only trials in which MEP was clearly discernible over the subject's response EMG were analyzed, and in these cases MEP latency from EMG was defined as zero. In trials in which MEPs were not detected, the temporal relation of TMS and the subject's response EMG was defined and MEP count was zero for that time bin.

2.7. Statistical analysis

Motor excitability was determined using two measures: (1) probability of evoking MEP, and its complement–probability of MEP not being evoked; and (2) MEP amplitude.

Probability was defined as the percentage of trials with MEP out of the total number of stimuli used in each set of trials. Probability was calculated for each individual subject, as well as for the data pooled across subjects. Analysis extended from 1 s before till 1 s after EMG onset in time bins of 25 ms. For each bin, the number of MEPs evoked across all the subjects was determined and expressed as a fraction of the total number of TMS delivered during that time bin. Probability was calculated as the ratio of trials with MEPs out of the total number of TMS delivered. Consequently, if the number of observations used to derive probability was small, spurious values might be obtained. For example, if at a given time bin only one TMS was delivered and it was associated with an MEP, probability would be 1, based on only one observation. For statistical analysis, therefore, only bins containing at least 15 trials were analyzed.

The use of sub-threshold TMS resulted in low probability of MEPs, which further decreased when suppression occurred. When statistically evaluating suppression, numbers of trials in each time bin tended to be small using the probability measure. Therefore, the mirror image of probability–improbability of evoking MEPs (constituting of large numbers of trials, particularly when suppression was involved) was used as a complementary measure.

MEP amplitude as a function of the time difference between MEP to the response EMG nearest edge (onset or end) was plotted in a scatter diagram. To correct for intersubject differences in MEP amplitudes, amplitudes in the runs in which the subject responded with a thumb twitch were divided by the average MEP amplitude in the run in which the subject was not required to respond, the relaxed condition. Thus, a normalized MEP amplitude measure was obtained, whereby normalized amplitudes greater than 1 reflect MEP amplitude increase relative to when subjects were not responding.

The effects on MEP normalized amplitude of subject, TMS timing relative to the missing tone and TMS timing relative to the subject's response EMG (edge and peak) were assessed using three-way analysis of variance (general linear model). In addition, the effect of TMS timing relative to the subject's response EMG on MEP normalized amplitude, on probability of TMS trials that did not evoke MEPs (MEP improbability) and on probability of TMS trials that did evoke MEPs (MEP probability) were assessed using a single factor analysis of variance (general linear model). In order to include sufficient numbers of observations, in the statistical analysis, the time bins of 25 ms were grouped together to form 100 ms time bins. Differences in these measures between specific time periods were assessed using Student's two-sample t-test, verifying sample sizes of at least 15 values in each time period. Bonferroni correction for multiple comparisons was applied when appropriate. Probabilities below 0.05 were considered significant.

3. Results

Examples of a single trial in which the subject's response EMG occurred before TMS, and of a trial in which the subject's response EMG occurred after TMS are presented in Fig. 2. In the top trace, the subject's EMG response ended 150 ms prior to the omitted tone, indicated by 0 on the abscissa. The TMS on this trial was delivered 400 ms after the omitted tone, resulting in a delay of 550 ms between the subject's response EMG offset and the subsequent TMS delivery. In the bottom trace TMS was delivered 200 ms before the omitted tone, while the subject responded about 100 ms before the missing tone, resulting in a delay of about 100 ms between TMS and the subject's response EMG.

Fig. 3 compares MEP probability while relaxed and while responding for each subject (top) and for the average across subjects (below). On average, there was a 4.5–fold increase in MEP probability when the subject responded, with individual increases ranging between 2.2– and 55.2–fold.

The data from all subjects were combined to assess the effect on MEP probability of MEP timing relative to the motor response (Fig. 4). Prior to 600 ms before movement bins did not include the minimum number of trials [15] needed for statistical analysis, and thus these bins are not displayed. The probability for evoking an MEP ranged from 0.1 to 0.35 (2–4 times the value at rest) between 500 and

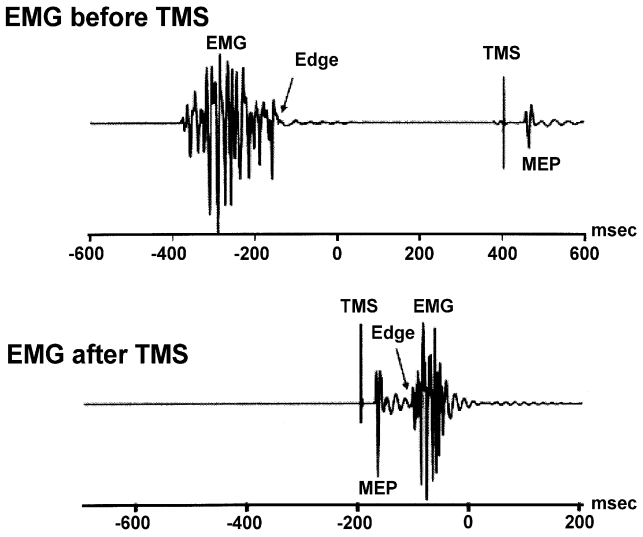
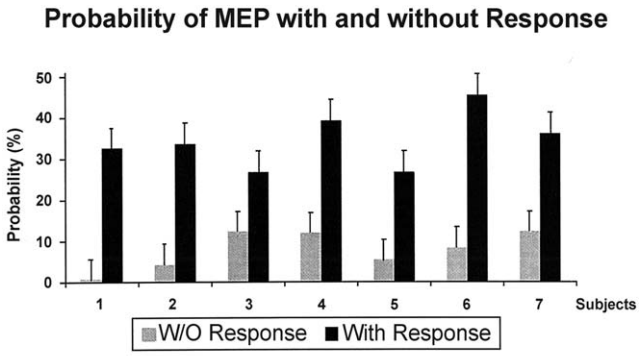


Fig. 2. Examples of single trials in which the subject's response EMG occurred before TMS (top) and after (bottom) TMS. The 0 on the abscissa refers to the time when the omitted tone would have occurred. EMG edge is indicated by the arrows. EMG and MEP are followed by some ringing of the amplifiers due to the high-pass filter used. Note that when TMS was temporally closer to the EMG, MEP was larger.

250 ms before the movement. Between about 200 and 100 ms before movement, a transient period without increased probability preceded a rapid rise in probability from about 100 ms before movement, reaching 0.97 when MEP coincided with the onset of the response EMG. The decline in probability after the offset of the response EMG (right part of the figure) reached 0.25 at approximately 200 ms and fluctuated around this level till 600 ms, the last time bin for which we had sufficient trials for analysis. Analysis of variance using 100 ms bins revealed a significant effect of MEP timing on probability ($F(15,24) = 2.92$; $P < 0.01$). Post hoc analysis revealed significant differences between the 100 ms period coincident with the response EMG and the other time bins up to 500 ms both before and after the response. In order to include sufficient numbers of observations, in the statistical analysis of the time period immediately adjacent to movement onset, the time bins of 25 ms were grouped together to form 50 ms time bins. When probability differences between specific 50 ms bins were evaluated, a significant ($P < 0.01$ after Bonferroni correction) increase during the 100 ms around the movement was found, confirming the above post hoc results. In addition, a significant increase in MEP probability with movement, compared to probability at rest, in the control runs when subjects were not required to respond, was observed in the time period extending beyond 100 ms before or after movement, up to 500 ms before ($P < 0.03$, after Bonferroni correction) and after ($P < 0.003$, after correction) the EMG, respectively. MEP probability in the 100 ms around 150 ms was significantly lower than in the immediately preceding 100 ms ($P < 0.02$).

The absence of increased excitability in the period around 150 ms before movement was verified by another measure reflecting motor excitability change across time: the prob-



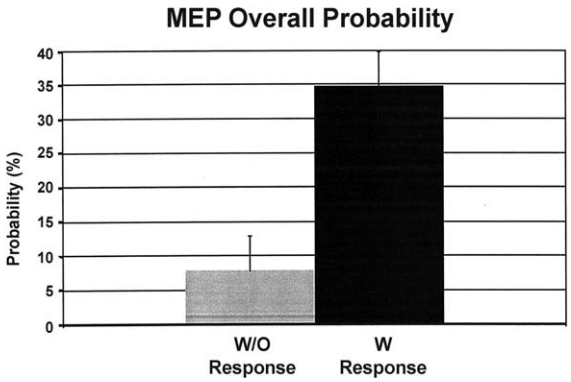


Fig. 3. The probability of evoking MEP when the subject responded (solid bars) and when the subject was not required to respond (hatched bars) in the individual subjects (top) and pooled across all the subjects (bottom). Error bars denote one standard deviation.

ability for trials in which TMS did not evoke MEP. This measure is the complement of MEP probability and with sub-threshold TMS includes many more trials than probability. Hence, this probability has an advantage as a measure of excitability. Increase in this probability may indicate inhibition while its decrease indicates excitation. The probability for TMSs that did not evoke MEPs (improbability of evoking MEPs) at different time bins relative to the subject's response EMG showed a dip coincident with the onset of the response EMG (indicating excitation). In addition, an increase approximately 150 ms before response EMG indicated inhibition. Improbability of evoking an MEP during the 100 ms period around 150 ms before response EMG was significantly higher than in the immediately preceding 100 ms ($P < 0.05$).

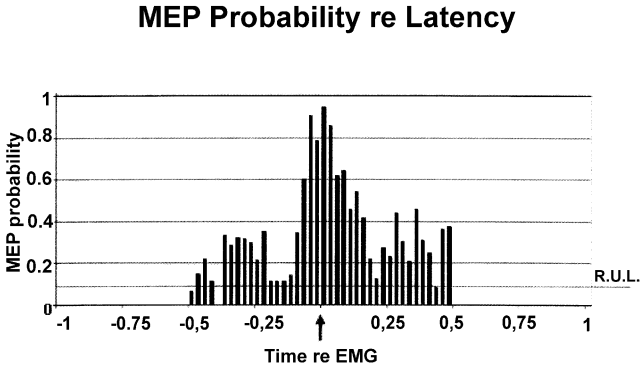


Fig. 4. The effect of TMS timing relative (re) to response EMG onset or offset on MEP probability. Time scale is in seconds and the arrow marks the time of response. R.U.L. indicates the upper limit of probability of evoking EMG when no response was required observed in any of the subjects (i.e. the highest probability observed in any subject during the control run). Note the asymmetrical probability change: with the decline after the movement more gradual than the increase preceding it and the decline in probability around 150 ms before movement.

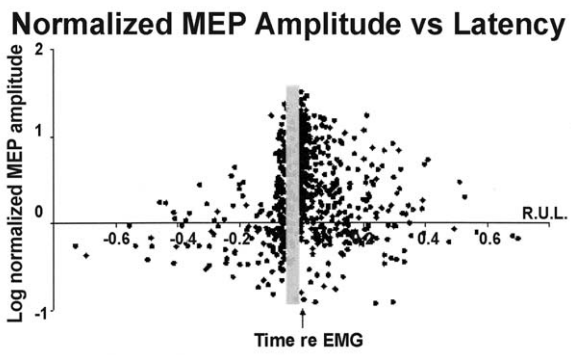


Fig. 5. Normalized MEP amplitude (on a logarithmic scale) at different times relative to the response EMG, across all the subjects. Time scale is in seconds and the arrow marks the time of movement. The horizontal line marks a normalized value of 1.4– the maximum normalized amplitude value that was obtained from any subject at rest. This value is called R.U.L. (i.e. the highest normalized amplitude observed in any subject during the control run). The gray area marks the time range immediately before movement when discrimination of the evoked MEP from the response EMG was ambiguous and MEP amplitude measurement was often unreliable. Note the elevation of many MEP amplitudes above the maximum level ever observed when no response was required, beginning 0.5–0.6 s before movement, separated from a marked further increase (approximately 100 ms before movement) by a short decrease in amplitude which was minimal 150 ms before movement. Also note the asymmetrical change in normalized amplitude about movement: decline after movement, until 600 ms was more gradual than the increase preceding it.

A second measure of excitability, normalized MEP amplitude, was used to correct for intersubject differences in MEP amplitudes: amplitudes in the runs in which the subject responded with a thumb twitch were divided by the average MEP amplitude in the run in which the subject was not required to respond, the relaxed condition. Thus, a normalized MEP amplitude measure was obtained, whereby normalized amplitudes greater than 1 reflect MEP amplitude increase relative to when subjects were not responding. Normalized MEP amplitude was also affected by the timing of TMS relative to the motor response (Fig. 5). The definition of MEP amplitudes was not possible in those trials when the timing of TMS was close to the motor response time and is signified by the gray zone in the figure. The scatter plot of normalized MEP amplitude, expressed in logarithmic values, for each trial showed many points above the highest value observed at rest (rest upper limit–R.U.L.), indicating increased excitability compared to rest, beginning 500 ms

before movement. This elevation further increased approximately 150 ms before movement, peaked with the movement and gradually declined until 600 ms after movement. Note the asymmetrical changes of amplitude (motor excitability) before and after response EMG and the two phases of amplitude change before movement: the first starting 500 ms before movement, separated from the second period of amplitude increase which peaked with the movement by a transient period of about 100 ms of decreased amplitude, beginning at 200 ms and minimal at about 150 ms. Analysis of variance found the effect on MEP normalized amplitude of stimulus timing relative to response EMG to be significant ($F(14,753) = 6.54$; $P < 0.0001$). MEP normalized amplitudes around 150 ms before movement were significantly smaller ($P < 0.05$) than amplitudes in the 200–350 ms period preceding it.

When the combined effects of subject, TMS timing relative to the omitted tone and MEP timing relative to the subject's response EMG on MEP normalized amplitude were assessed together using a three-factor analysis of variance, a significant TMS timing by MEP timing interaction was observed ($F(70,138) = 2.22$; $P < 0.000001$). MEP amplitudes were increased close to the omitted tone even when the overt motor response was inaccurately timed. In addition, MEP amplitudes were increased when they occurred close to the motor response EMG, even when it was inaccurately timed.

4. Discussion

The results of this study indicate an increase in motor excitability when performing a task compared to a control resting state. Motor excitability increase prior to the movement occurred in two phases separated by a short dip approximately 150 ms prior to the movement onset. Excitability peaked with EMG onset and gradually decreased thereafter.

4.1. Factors contributing to motor excitability

This study manipulated a number of factors that may affect motor excitability. Motor response in the hand contralateral to the active cortex was associated with increased probability of evoking MEPs by sub-threshold TMS (Fig. 4). In theory, this increase in probability may result from (a) an increase in excitability of the motor cortex related to the preparation for the movement and inputs from associated structures such as the supplementary motor area and premotor cortex; (b) disinhibition of motor cortex by otherwise ineffective or weak synapses becoming disinhibited ("unmasked") such that they influence cortical activity [20,26]; or (c) increased sub-cortical excitability at the spinal level. Spinal contribution to excitability changes may be due to corticofugal influences before movement or to afferent inputs following the movement. Spinal facilitation has been demonstrated only between 50 and 100 ms before EMG onset [6,11] and thus cannot explain the excitability changes beyond this time period. The effect of afferent inputs after movement is unlikely because afferent inputs have been shown not to affect spinal motoneuron or interneuron excitability [20].

Analysis of variance indicated a highly significant interaction on MEP amplitude of both the time of occurrence of the omitted tone and of the TMS timing relative to onset of the motor response. Moreover, MEP incidence was higher when TMS was delivered close to the omitted tone. These two findings indicate a central facilitatory effect resulting in improved performance. This central facilitatory effect complements earlier reports on such effects at the spinal level, indicating a peripheral inhibition aimed at increasing spinal motoneuron sensitivity to the descending activation of a forewarned movement [12,18]. This latter effect has been shown to result in improved performance.

Timing of TMS relative to response EMG was the factor affecting motor excitability, which was of primary interest in this study. The effect of timing relative to the movement manifested in probability of evoking an MEP and in MEP amplitude and was found significant. This effect, with somewhat different time courses, has already been reported using transcranial electrical stimulation [21,30] as well as magnetic stimulation [2]. The results of this study extend the time period of increased motor excitability to about 500 ms before, until about 600 ms after the subject's response.

4.2. Time course of pre-movement excitability

MEP probability indicated that readiness for a movement was marked by increased excitability beginning 500 ms before movement, with a short pre-movement period without increased excitability, between 100 and 200 ms before movement, followed by a steep increase in excitability peaking with the movement. MEP amplitude also showed a similar pattern with a significant sustained increase beginning 500 ms before movement, a transient decrease below resting values peaking at 150 ms before movement, and then sharply increasing again to reach a maximum with the onset of movement.

Additional evidence for these effects derives from probability of trials in which MEPs were not evoked by the sub-threshold stimuli. Probability of trials without MEPs was relatively stable, under 0.7, then increased to close to 0.9 immediately preceding movement, followed by a sharp decrease with movement. Increased probability of trials without MEP indicates inhibition, while decreased probability of MEP absence corresponds to excitation. These changes, therefore, mirror the excitability changes indicated by MEP probability and MEP amplitudes.

Earlier studies reported increased cortical excitability beginning only about 80–100 ms before EMG onset [2,13]. Transcranial electric stimulation [21,30] showed similar results. Recordings from simian motor cortex (e.g. [7,8,10]) showed that from 70–100 ms before movement, neuronal activity increased up to movement onset. In contrast, movement-related evoked potentials studies show that motor preparation begins 1.5–2 s before self-paced movement, with

three distinct components: (1) the readiness potential starting 1–2 s before movement; (2) negative slope between 300 and 500 ms before movement; and (3) motor potential 50–100 ms before EMG onset (e.g. [5,28,29,31]). These temporal relations led to the conclusion that motor preparation before self-paced movement is not associated with increased cortical excitability and that only the motor potential is associated with increased excitability of cortico-spinal neurons or interneurons closely connected to them [2]. The results of this study extend the time frame of increased motor excitability up to 500 ms before movement. The explanation for this new finding is twofold: the paradigm used in this study enabled scanning a wider time frame than the earlier reaction time studies that were limited by the duration of reaction time following the go signal. Furthermore, this study used multiple measures of motor excitability, increasing confidence in small changes.

4.3. Pre-movement inhibition

The short pre-movement decrease in probability of MEPs at approximately 150 ms before movement may not be due to inhibition but to a delay in movement following TMS when subjects are preparing to respond [4,22]. According to this explanation, it is more difficult to evoke MEP in the time bins near movement onset because TMS delays initiation of the movement. However, the dip in MEP probability, in normalized MEP amplitudes and the increase in MEP improbability at this time period suggest a role for inhibition.

Earlier studies, using other paradigms have reported both excitation and inhibition preceding voluntary movement. Reduced excitability of the cortico-spinal system was observed during the warning period of a simple reaction time task [33]. MEPs in the responding muscles were significantly suppressed from 125 ms after a warning stimulus until the time of a cutaneous shock to the contralateral arm, to which the subjects were to respond. If the task was changed to a choice reaction, in which the imperative stimulus (but not the warning signal) indicated whether to flex or extend the wrist, then there was no change in the MEPs in the warning period. Thus, cortical suppression has been shown to precede the response in a simple reaction time task, when a preceding warning stimulus was presented. In a study on inhibition in the human motor cortex before and during voluntary movements [19], inhibition of the extensor MEP was shown to decline about 95 ms before the onset of the agonist EMG activity. The study concluded that changes in the balance of excitation and inhibition of cortico-spinal neurons associated with a voluntary movement precede the movement. In another study, the area of the human cortex from which inhibition and facilitation of cortico-spinal neurons could be obtained was examined [1]. The inhibition and facilitation of cortico-spinal neurons projecting to a given muscle were shown to arise from small areas close to those cortico-spinal neurons. Thus, the findings of the present study, showing excitatory and inhibitory influences on the motor cortex during the period immediately preceding the response in a simple reaction time task are in line with earlier studies using other paradigms.

4.4. Post-movement excitability

Our results show that within the time window of 1 s following the response, execution of the response was associated with peak excitability that gradually declined but was still significant up to 600 ms following the response. Earlier studies using event-related synchronization have shown the post-movement 20 Hz synchronization to begin around 750 ms after EMG onset [14]. This synchronization correlated with an idling motor area [17] and had a somatotopic organization [23,24]. These findings are, therefore, in agreement with the time course suggested by our results.

Another sub-threshold TMS study on post-movement motor excitability [2] found two phases of cortico-spinal excitability in a reaction–time task: between 0 and 100 ms, and from 100 to 160 ms after EMG onset, with a return to baseline after 160 ms. The probability curves of our study suggest a possible drop in motor excitability at about 200 ms, resembling a biphasic curve for post-movement excitability. This effect, however, was not observed in other measures such as MEP amplitude and probability of trials without MEP. The period of post-movement excitability, extending in our study to 600 ms, may be related to the different paradigms used in this study compared to the previous one.

In conclusion, this study showed that during the performance of a task requiring a motor response, motor cortical excitability is increased above resting for hundreds of millisecond before and after the response, except for a transient period between 75 and 150 ms prior to the movement onset. The temporal pattern of these excitability changes is compatible with multiple excitatory and inhibitory inputs interacting on motor cortex.

Acknowledgements

The tireless help of Dr. Ronald Gordon with technical and software aspects of this study, as well as the willing participation of the staff of the University of California, Irvine, Evoked Potentials Laboratory are gratefully acknowledged. The study was supported by NIH grant AI34250 from the National Institute for Health.

References

[1] Ashby P, Reynolds C, Wenneberg R, Lozano AM, Rothwell J. On the focal nature of inhibition and facilitation in the human motor cortex. Clin Neurophysiol 1999;110:550–5.

[2] Chen R, Yaseen Z, Cohen LG, Hallett M. Time course of corticospinal excitability in reaction time and self-paced movements. Ann Neurol 1998;44:317–25.

[3] Day BL, Dressler D, Maertens de Noordhout A, Marsden CD, Nakashima K, Rothwell JC, et al. Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. J Physiol (Lond) 1989;412:449–73.

[4] Day BL, Rothwell JC, Thompson PD, Maertens de Noordhout A, Nakashima K, Shannon K, et al. Delay in the execution of voluntary movement by electrical or magnetic brain stimulation in intactman. Evidence for the storage of motor programs in the brain. Brain 1989; 112:649–63.

[5] Deecke L, Scheid P, Kornhuber HH. Distribution of readiness potentials, promotion positivity, and motor potential of the human cerebral cortex preceding voluntary finger movements. Exp Brain Res 1969; 7(2):158–68.

[6] Eichenberger A, Ruegge DG. Relation between the specific H reflex activation preceding a voluntary movement and movement parameters in man. J Physiol (Lond) 1984;347:545–59.

[7] Evarts EV. Pyramidal tract activity associated with a conditioned hand movement in the monkey. J Neurophysiol 1966;29:1011–27.

[8] Fetz EE, Finocchio DV. Operant conditioning of isolated activity in specific muscles and precentral cells. Brain Res 1972;12(40):19–23.

[9] Furubayashi T, Ugawa Y, Terao Y, Hanajima R, Sakai K, Machii K, et al. The human hand motor area is transiently suppressed by an unexpected auditory stimulus. Clin Neurophysiol 2000;111: 178–83.

[10] Godschalk M, Lemon RN, Nijs HG, Kuypers HG. Behaviour of neurons in monkey peri-arcuate and precentral cortex before and during visually guided arm and hand movements. Exp Brain Res 1981;44:113–6.

[11] Gottlieb GL, Agarwal GC, Stark L. Interactions between voluntary and postural mechanisms of the human motor system. J Physiol (Lond) 1970;33:365–81.

[12] Hasbroucq T, Kaneko H, Akamatsu M, Possama CA. The time-course of preparatory spinal and cortico-spinal inhibition: an H–reflex and transcranial magnetic stimulation study in man. Exp Brain Res 1999; 124:33–41.

[13] Hoshiyama M, Kakigi R. Shortening of the cortical silent period following transcranial magnetic brain stimulation during an experimental paradigm for generating contingent negative variation (CNV). Clin Neurophysiol 1999;110:1394–8.

[14] Leocani L, Toro C, Manganotti P, Zhuang P, Hallett M. Event-related coherence and event-related desynchronization/synchronization in the 10 Hz and 20 Hz EEG during self-paced movements. Electroenceph Clin Neurophysiol 1997;104:199–206.

[15] Nagamine T, Toro C, Balish M, Deuschl G, Wang B, Sato S, et al. Cortical magnetic and electric fields associated with voluntary finger movements. Brain Topogr 1994;6:175–83.

[16] Nagamine T, Kajola M, Salmelin R, Shibasaki H, Hari R. Movement-related slow cortical magnetic fields and changes of spontaneous MEG– and EEG–brain rhythms. Electroenceph Clin Neurophysiol 1996;99:274–86.

[17] Pfurtscheller G, Stancak A, Neuper C. Post-movement beta synchronization. A correlate of an idling motor area? Electroenceph Clin Neurophysiol 1966;98:281–93.

[18] Requin J, Brener J, Ring C. Preparation for action. In: Jennings JR, Coles MGH, editors. Handbook of cognitive psychophysiology: central and autonomic nervous system approaches. New York: John; 1991. p. 357–448.

[19] Reynolds C, Ashby P. Inhibition in the human motor cortex is reduced just before a voluntary contraction. Neurology 1999;53:730–5.

[20] Ridding MC, Brouwer B, Miles TS, Pitcher JB, Thompson PD. Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. Exp Brain Res 2000;131:135–43.

[21] Rossini PM, Zarola F, Stalberg E, Caramia M. Pre-movement facilitation of motor-evoked potentials in man during transcranial stimulation of the central motor pathways. Brain Res 1988;458:20–30.

[22] Rothwell JC, Day BL, Thompson PD, Marsden CD. Interruption of motor programmes by electrical or magnetic brain stimulation in man. Prog Brain Res 1989;80:467–72.

[23] Salmelin R, Hari R. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. Neuroscience 1994;60(2):537–50.

[24] Salmelin R, Hamalainen M, Kajola M, Hari R. Functional segregation of movement-related rhythmic activity in the human brain. Neuroimaging 1995;2:237–43.

[25] Sawaki L, Okita T, Fujiwara M, Mizuno K. Specific and non-specific effects of transcranial magnetic stimulation on simple and go/no-go reaction time. Exp Brain Res 1999;127:402–8.

[26] Sanes JN, Donoghue JP. Organization and adaptability of muscle representations in primary motor cortex. In: Caminiti R, Johnson PB, Burnod Y, editors. Control of arm movement in space: neurophysiological and computational approaches. Berlin: Springer–Verlag; 1992. p. 103–28.

[27] Seyal M, Mull B, Bhullar N, Ahmad T, Gage B. Anticipation and execution of a simple reading task enhance corticospinal excitability. Clin Neurophysiol 1999;110:424–9.

[28] Shibasaki H, Barrett G, Halliday E, Halliday AM. Cortical potentials following voluntary and passive finger movements. Electroencephalogr Clin Neurophysiol 1980;50(3–4):201–13.

[29] Shibasaki H, Rothwell JC. EMG–EEG correlation. In: Deuschl G, Eisen A, editors. Recommendations for the practice of clinical neurophysiology: guidelines of the international federation of clinical neurophysiology. Amsterdam: Elsevier; 1999. p. 269–74.

[30] Starr A, Caramia M, Zarola F, Rossini PM. Enhancement of motor cortical excitability in humans: non-invasive electrical stimulation appears prior to voluntary movement. Electroenceph Clin Neurophysiol 1988;70:26–32.

[31] Tarkka IM, Hallett M. Topography of scalp-recorded motor potentials in human finger movements. J Clin Neurophysiol 1991;8(3):331–41.

[32] Tokimura H, Di Lazzaro V, Tokimura Y, Oliviero A, Profice P, Insola A, et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J Physiol 2000;523:03–13.

[33] Tomberg C, Caramia MD. Prime mover muscle in finger lift or finger flexion reaction time: identification with transcranial magnetic stimulation. Electroenceph Clin Neurophysiol 1991;81(4):319–22.

[34] Zaaroor M, Pratt H, Starr A. Influence of task-related ipsilateral hand movement on motor cortex excitability. Clin Neurophysiol 2001;112: 908–16.