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# The dual nature of time preparation: neural activation and suppression revealed by transcranial magnetic stimulation of the motor cortex

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**Keywords:** cortical activation, cortico-spinal inhibition, motor evoked potential, primary motor cortex, silent period

## Abstract

Single-pulse transcranial magnetic stimulations (TMSs) of the motor cortex (M1) were performed in order to decipher the neural mechanisms of time preparation. We varied the degree to which it was possible to prepare for the response signal in a choice reaction time (RT) task by employing either a short (500 ms) or a long (2500 ms) foreperiod in separate blocks of trials. Transcranial magnetic stimulations were delivered during these foreperiods in order to study modulations in both the size of the motor evoked potential (MEP) and the duration of the silent period (SP) in tonically activated response agonists. Motor evoked potential area and silent period duration were assumed to reflect, respectively, the excitability of the cortico-spinal pathway and the recruitment of inhibitory cortical interneurons. Shorter reaction times were observed with the shorter foreperiod, indicating that a better level of preparation was attained for the short foreperiod. Silent period duration decreased as time elapsed during the foreperiod and this decrement was more pronounced for the short foreperiod. This result suggests that time preparation is accompanied by a removal of intracortical inhibition, resulting in an activation. Motor evoked potential area decreased over the course of the short foreperiod, but not over the long foreperiod, revealing that time preparation involves the inhibition of the cortico-spinal pathway. We propose that cortico-spinal inhibition secures the development of cortical activation, preventing erroneous premature responding.

## Introduction

In the reaction time (RT) paradigm, the processing mechanisms sustaining time preparation become manifest through the manipulation of the interval between a precue and the response signal, an interval termed the 'foreperiod'. Reaction time lengthens as the duration of the foreperiod is increased, provided that this manipulation is performed across blocks of trials (Woodrow, 1914). It can be inferred from this finding that (i) time preparation is set according to the subject's expectations concerning the time of occurrence of the response signal and (ii) the accuracy of this timing decreases as the time elapsed since the precue lengthens (Requin *et al.*, 1991).

Results indicate that time preparation is implemented via an activation of central structures (see, e.g. Van Boxtel & Brunia, 1994a; Van Boxtel & Brunia, 1994b), though the identification of which specific structures remains to be ascertained. Other results suggest that suppression mechanisms also play a role in time preparation (see, e.g. Brunia, 1984; Hasbroucq *et al.*, 1997; Prut & Fetz, 1999). In particular, the size of the motor potential evoked by single-pulse transcranial magnetic stimulation (TMS) decreases during foreperiods

allowing optimal time preparation. The motor evoked potential (MEP) is due to the direct or transynaptic recruitment of cortico-spinal neurons (see Terao & Ugawa, 2002). The size of the MEP reflects the degree of cortico-spinal excitability and hence, the decrease in MEP amplitude during the foreperiod reflects a diminution of the excitability of the cortico-spinal pathway.

Transcranial magnetic stimulation can further reveal changes in cortical excitability through the study of the silent period (SP) that follows the MEP in the ongoing electromyogram (EMG) when the response agonists are tonically contracted (Burle *et al.*, 2002). While the initial part of the SP can be a direct consequence of the MEP (refractory period of neurons involved in the MEP, pause in spindle firing, or Renshaw inhibition), the later part results from the stimulation of inhibitory interneurons of the motor cortex (Uncini *et al.*, 1993; Schnitzler & Benecke, 1994; Terao & Ugawa, 2002). Furthermore, SPs can be obtained with TMS intensities weaker than those necessary to elicit MEPs (e.g. Rossini *et al.*, 1995) and the latency of SPs elicited at such intensities is longer than that of near-threshold MEPs (Davey *et al.*, 1994). Thus, there is a delay between the initial recruitment of cortico-spinal neurons (revealed by the MEP) and the recruitment of inhibitory interneurons (revealed by the late part of the SP).

As results obtained with other methods show an excitability of central structures (e.g. Niemi & Näätänen, 1981), preparatory

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activation may reduce inhibition at the cortical level and thus decrease the duration of the late part of the SP. The present study was intended to test this hypothesis. Changes in SP duration were investigated during two foreperiods allowing the subjects to attain different levels of preparation; a short, optimal foreperiod (500 ms), and a long, non-optimal foreperiod (2500 ms). Silent period duration was predicted to decrease during the foreperiod and this decrease was expected to be more pronounced for the short than for the long foreperiod.

## Materials and methods

### Subjects

The subjects (five females and three males, aged 23–46; mean, 30 years; SD, 7) were healthy, right-handed, volunteers with normal or corrected-to-normal vision. Informed written consent was obtained according to the Declaration of Helsinki and the local ethics committee (CCPPR3, Marseille, France) approved the experiment.

### Behavioural setup

Subjects were seated in a comfortable chair in a darkened room with supports for hands and arms. They faced a black panel, 1 m away at eye level, and gripped two cylinders, vertically fixed 12 cm apart on a pull-out table. The distal phalanx of each thumb touched a force sensor fixed on the top of the cylinder. After a blue light-emitting diode (LED) at the top of the panel was lit, isometric presses exerted on the sensors allowed the subject to initiate a trial. This self-initiation procedure was intended to generate a background EMG activity necessary to observe a SP. Three horizontal rows of two LEDs, separated by 2 cm, were positioned at the centre of the panel. Neighbouring LEDs of the same row were 4 cm apart. The two central LEDs (green) displayed the response signal. The response was a compatible isometric press with the right or the left thumb on the force sensor according to the spatial location of the response signal. The response force was recorded and digitized on line (A/D rate 2 kHz). The two upper and

the two lower LEDs (red) corresponded to the force exerted on the left and right sensor. The lower LEDs lit up red when the force exerted on the sensor by the two thumbs was in the predefined range of force required to initiate the trial (from 10 to 20 N). The upper LEDs turned red if the force exceeded a value of 20 N.

### Trial events

The trial events are schematically represented in Fig. 1. After the blue LED was lit, the subject initiated the trial by exerting an isometric press on both sensors. The trial began when the correct force was attained, then the subject was to maintain this force during 3 s. This period of time corresponded to the isometric press and to the foreperiod durations. If the force was (over or below) the predefined range before the end of the 3-s period, the subject should initiate another correct isometric press for a 3-s period. The foreperiod duration was varied between blocks. In the short foreperiod condition, the beginning of the foreperiod was signaled by an auditory signal 2500 ms after the beginning of the trial. Five hundred milliseconds later, one of the two possible imperative stimuli (right or left) lit up in red. In the long foreperiod condition, the beginning of the foreperiod was signaled by an auditory signal 500 ms after the beginning of the trial. Two thousand, five hundred milliseconds later, one of the two possible imperative stimuli lit up in red (see Fig. 1). This procedure ensured that the duration of the isometric contraction was identical across foreperiod conditions. When the subject reacted by producing an isometric press stronger than 20 N on one of the force sensors, an auditory signal corresponding to the recording of the answer was given. If the time allowed to respond (1000 ms) was bypassed, the display was turned off. To initiate a new trial, the subject should wait a minimum intertrial interval of 1500 ms.

### Design

Before the experiment, subjects practiced a training session to reach a stable level of RT performance. During this session, blocks of 96 trials

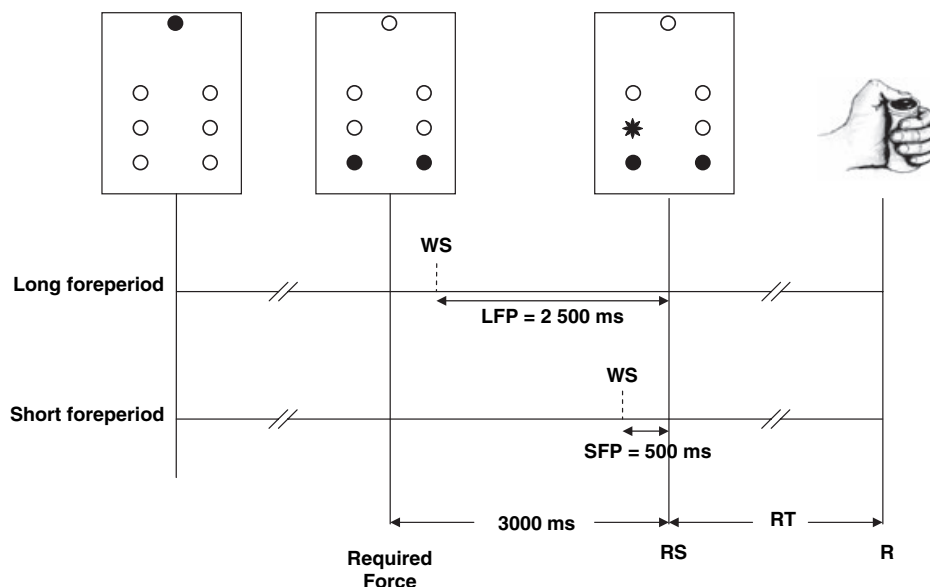


FIG. 1. Schematic representation of the time course of experimental events. At the top of the figure, the circles represent the light-emitting diodes (white, extinguished; black, lighted) and the star represents the lighting of the response signal. The upper trace represents the time course of the trial for long foreperiod and the lower trace represents the time course of the trial for the short foreperiod. WS, warning signal; RS, response signal; R, mechanical response; LFP, long foreperiod; SFP, short foreperiod.

were performed, alternating between short foreperiod (500 ms) and long foreperiod (2500 ms) conditions. The training was considered complete when, during two consecutive blocks (i) the error rate was less than 5% and (ii) the coefficient of variation of RT (standard deviation divided by the mean) was at most 0.15. No TMS was delivered during the training session; however, EMG was recorded in order to estimate the voluntary EMG onset latency of the individual distributions (see Burle *et al.*, 2002).

There were two sessions, an experimental session and a sham session, each ran on a different day. In the experimental session, five blocks were, respectively, performed in short and long foreperiod conditions, alternated every other block. In the sham session, three blocks were performed in each foreperiod duration condition. A block consisted of 96 trials, and within a block each response signal (right or left) occurred 48 times in an unpredictable order. During a block, a single pulse TMS was delivered, over the hand area of the left motor cortex (M1), according to seven stimulation times distributed either during the preparatory period or during the RT. Note that when the stimulation was delivered during the foreperiod, the subjects were unaware as to the effector involved in the to-be-performed response. The trials during which the stimulation was delivered were intermixed with no-stimulation trials (6% of the trials). During the experimental session, there were 30 stimulations per stimulation time, foreperiod duration and effectors.

The scalar property of timing refers to the fact that although time judgements are accurate on average, the variability of these estimates increases linearly with the duration of the to-be-estimated interval (reviewed in Allan, 1992). The timing variability is therefore a constant proportion of the duration to be estimated (but its absolute value increases with increasing durations). Absolute accuracy thus decreases when the duration increases and equivalent levels of timing accuracy are achieved at different moments when short and long durations are used. To take into account the scalar property in the present design, the stimulation times, delivered during the foreperiod, correspond, respectively, to the warning signal, half, three-eighth, one-quarter, one-eighth of the foreperiod duration and to the response signal.

To this end, the EMG activities and the force signals recorded during each trial were displayed on a computer screen aligned to the onset of the imperative stimulus, the onsets of the changes in activity were determined visually and then marked with the computer mouse. Although labourious, this method was preferred to an automated one because it allows precise detection provided that the EMG is recorded at a high sampling rate with an antialiasing filter frequency (Van Boxtel *et al.*, 1993; Staude, 2001).

### EMG recording

Two electrodes glued 2 cm apart on the thenar eminences recorded EMG activity of the flexor pollicis brevis. This activity was amplified, filtered (low/high frequencies cut-off at 10 Hz/1 kHz), and digitized on-line (A/D rate 2 kHz). The experimenter continuously monitored the EMG signal.

### Transcranial magnetic stimulation

Magnetic stimulation was delivered using a Magstim 200 (Magstim, UK) connected to a figure-of-eight coil (double 70 mm in diameter coil, maximum output intensity 2.2 T; stimulus duration < 1 ms). During the experimental session, the coil was placed tangentially on the head over the hand area of the left M1. The coil was first centred over the primary motor cortex of the right hand, approximately 6 cm

to the left of the vertex (Cz, 10/20 Electrode System, Jasper, 1958). Next, the coil was moved in the antero-posterior and coronal directions until the lowest threshold spot for activating the right flexor pollicis brevis was reached. The stimulation intensity range was set on an individual basis. In this end, computer-piloted series of adjustment trials were performed to adjust the intensity of TMS stimulation for each subject individually. During each series of adjustment trials, the subject was asked to exert a constant press (between 10 and 20 N) on the sensors and received 20 stimulations delivered in a pseudo-random temporal sequence. After the last stimulation of a series, the EMG signal, averaged over the trials and time-locked to the occurrence of the stimulation, was displayed on the computer screen to be visually examined. The TMS intensity was adjusted as the minimal intensity to produce a MEP of approximately 100  $\mu$ V peak-peak amplitude (on the trace averaged over the 20 adjustment trials) and set 5% above this value for the experiment. This value corresponded to 35–45% of the maximum stimulator output (mean 38%; SD 4). The coil was held in position by a clamp mounted on a mechanical arm with six degrees of freedom and bolted on the back of the chair. A vacuum controlled head support assured a light and comfortable maintaining of the head of the subject. During sham session, the coil was positioned at Pz location (10/20 electrode system; Jasper, 1958). The stimulation intensity was the same as that used in the experimental session.

### Signal processing

The RT was measured between the onset of the imperative signal and the mechanical response (a press stronger than 20 N on one of the force sensors). For each subject, the 960 trials recorded during the experimental session were averaged time locked to the stimulation time. Then, the average EMG curve (non-rectified) was used to estimate individually the time of occurrence and the duration of the response evoked by TMS.

This time interval will hereafter be termed the 'evoked response window' (see Table 1). Next, a computer program was used to estimate, trial by trial, the area under the rectified EMG trace within the evoked response window (the rectification was thus performed off-line). This index will hereafter be termed 'MEP area'. The duration of the SP was visually inspected on the EMG signal time locked to the time stimulation, and marked with the computer mouse from the TMS onset to the return of uninterrupted tonic EMG activity (Fig. 2). The scoring was made on a trial by trial basis for each subject by an examiner unaware of the stimulation time to which the trace corresponded. Trials were excluded when the end of the SP was

TABLE 1. The stimulation intensity was the lowest intensity inducing a MEP in preactive flexor pollicis brevis

Subjects	Stimulation intensity (% of max. output)	Start of the evoked response window (ms)	Duration of the evoked response window (ms)
1	35	19	33
2	35	24	34
3	35	21	40
4	35	20	33
5	40	22	33
6	35	21	32
7	45	20	36
8	40	25	35

The beginning and the end of the evoked response window are given for each subject.

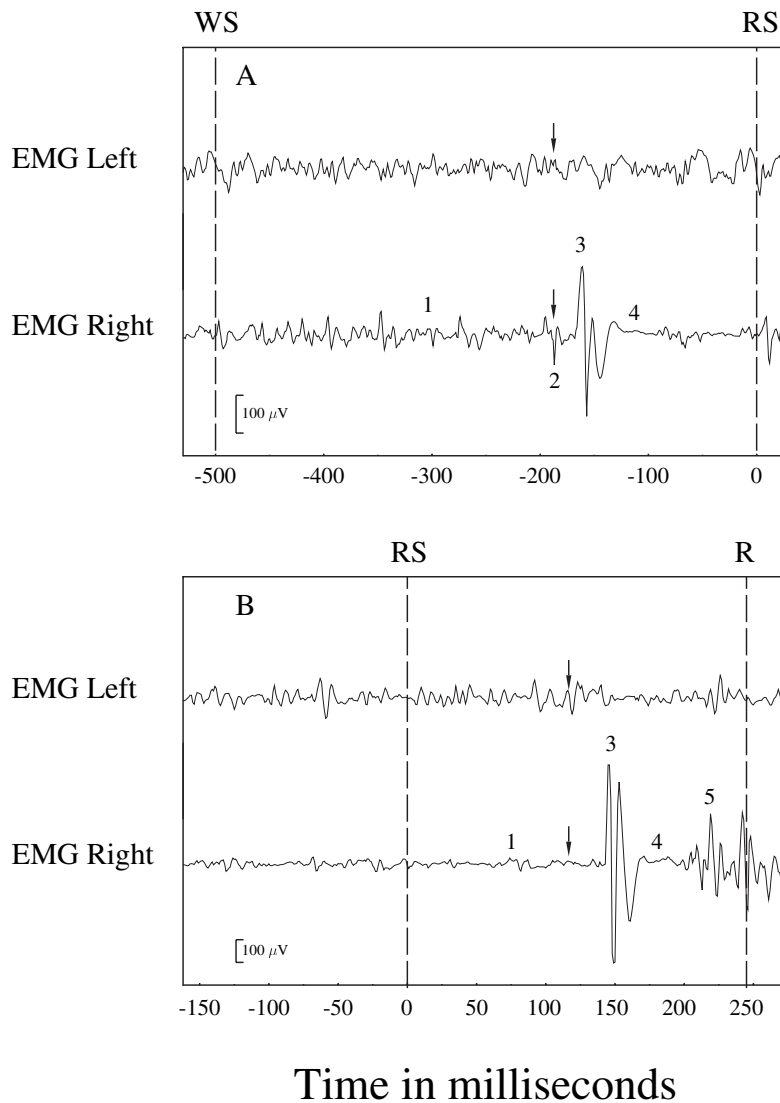


FIG. 2. Examples of recorded traces. (A) TMS delivered during the 500-ms foreperiod. (B) TMS delivered during RT. On each graph, the upper trace represents the EMG activity of the left thumb and the lower trace represents the EMG activity of the right thumb. The arrows represent the time of occurrence of the TMS. (1) Baseline EMG activity reflecting the pre-activation of the muscles. (2) Artefact due to the TMS (note that this artefact is only visible on the right EMG trace of A). (3) Motor evoked potential after the TMS, visible on the right trace only, as the coil is over the left primary motor cortex. (4) SP following the TMS. (5) Onset of the EMG activity involved in the voluntary motor response. For A, the SP is followed by an EMG activity of the right thumb equivalent to the EMG activity observed before the occurrence of the TMS. In B, the SP was interrupted by the onset of the EMG involved in voluntary response execution and could not be included in subsequent analyses. WS, warning signal; RS, response signal; R, mechanical response.

interrupted by the voluntary contraction (see Fig. 2), or when the end of the SP was obscured by the loss of EMG caused by the relaxation of hand muscles. Moreover, the SP after the response stimulus was not analysed, because in this situation it was too often interrupted by the voluntary response (see Results section).

#### Data analysis

Although MEPs were usually present in all subjects, MEP areas varied considerably across subjects. In order not to give too much weight to particular subjects, the MEP areas were converted into Z scores. This was performed in the following way; the mean and the standard deviation of the MEP areas were computed for a given subject, regardless of the stimulation time and the foreperiod duration.

Thereafter, the Z score was computed for each individual data. The mean Z scores were then averaged separately for each stimulation time and foreperiod duration. As a result of this transformation, all subjects had the same weight in the subsequent analysis. For the same reasons, the raw SP durations were Z-transformed in the same way as the MEPs.

#### Results

##### Errors

Incorrect overt responses, anticipation ( $RT < 100$  ms) and omission errors occurred in only 0.6% of the total number of trials recorded during stimulation and sham sessions. This percentage was judged too low for an analysis.

### Reaction time

The mean RT per subject and condition for the trials during which no TMS was delivered was submitted to an analysis of variance (ANOVA), that involved session (experimental, sham) and foreperiod duration (short, long) as within-subject variables. There was no session effect ( $F_{1,7} = 1.02$ ,  $P = 0.35$ ). Reaction time was shorter for the short (279 ms) than for the long foreperiod (339 ms,  $F_{1,7} = 36.76$ ,  $P < 0.001$ ). There was no hint of interaction between the two factors ( $F < 1$ ).

### Mean motor evoked potential area

On average, the beginning of the analysed MEP window was 22 ms after the stimulation (range 19–25 ms) and the end was 35 ms (range 32–40 ms). For each subject, the MEP area was evaluated in his/her individual time window (Table 1).

The MEP area was 1.80 mV on average (range 0.34–4.92 mV). First, we intended to determine whether the MEP area, recorded during the short and the long foreperiod, diminished between the warning signal and the response signal, as reported in previous studies. To do this, the standardized MEP area recorded when the stimulation was delivered at the occurrence of the warning signal was compared with the standardized MEP area recorded at the occurrence of the response signal. The results relative to the MEP area are illustrated in Fig. 3. The ANOVA included stimulation time (t1, warning signal; t6, response signal) and foreperiod duration (short, long) as within-subject factors.

There was a main effect of foreperiod duration ( $F_{1,7} = 11.10$ ,  $P < 0.05$ ) but no noticeable main effect of stimulation time ( $F_{1,7} = 1.44$ ,  $P = 0.27$ ). The two-way interaction between these factors was significant ( $F_{1,7} = 6.09$ ,  $P < 0.05$ ). Newman–Keuls analysis revealed that the MEP area at the occurrence of the warning signal was similar for the two foreperiod conditions (short, 1.68 mV; long, 1.92 mV). For the short foreperiod, the MEP area decreased between presentation of the warning signal and the response signal (diff =  $-0.11$  mV,  $P < 0.05$ ), whereas it remained stable for the long foreperiod (diff =  $+0.07$  mV,  $P = 0.65$ ).

Next, the MEP areas were analysed separately for each foreperiod. The design of the ANOVAs involved stimulation time during the foreperiod as a within-subject factor (t1, warning signal; t2, t3, t4, t5 and t6, response signal). For the long foreperiod, the MEPs were unaffected by the stimulation times ( $F_{5,35} < 1$ ). For the short foreperiod, as a decrease in cortico-spinal excitability was predicted on the basis of previous results, we used a one-tailed  $F$ -test. Although the effect of stimulation was in the predicted direction, it fell short of significance ( $F_{5,35} = 1.85$ ,  $P = 0.06$ ).

Finally, we intended to determine whether the MEP area, recorded for the short and long foreperiod duration, increased during RT, as has been reported in previous studies (see, e.g. Romaiguère *et al.*, 1997). To examine this, the MEP area recorded when the stimulation was delivered at the occurrence of the response signal was compared with the MEP area recorded for last stimulation time (first decile of the distribution of the voluntary EMG onset latency for the last two blocks of the training session). The ANOVA included stimulation time (t6, response signal; t7, first decile) and foreperiod duration (short, long) as within-subject factors. There was a main effect of foreperiod duration ( $F_{1,7} = 27.87$ ,  $P < 0.05$ ). MEP area was greater for the long foreperiod (1.99 mV) than for the short foreperiod (1.67 mV). There was no noticeable effect of stimulation time ( $F_{1,7} = 0.27$ ,  $P > 0.05$ ). There was a trend for an interaction between stimulation time and foreperiod duration ( $F_{1,7} = 3.95$ ,  $P = 0.09$ ). Newman–Keuls analyses revealed that MEP area was larger for the long (1.98 mV) than for the short (1.60 mV) foreperiod at the occurrence of the response signal ( $P < 0.05$ ), but not at the first decile of the RT interval (long, 1.99 mV; short, 1.74 mV;  $P = 0.28$ ).

### Silent period duration

The duration of the SP was 107 ms on average (range 70–147 ms). The results relative to the SP duration are illustrated in Fig. 4. Note that for the last stimulation time (first decile of the distribution of the voluntary EMG onset latency for the last two blocks of the training session), the SP duration could not be analysed because the end of the SP was too frequently (72% of the trials) concealed by the beginning

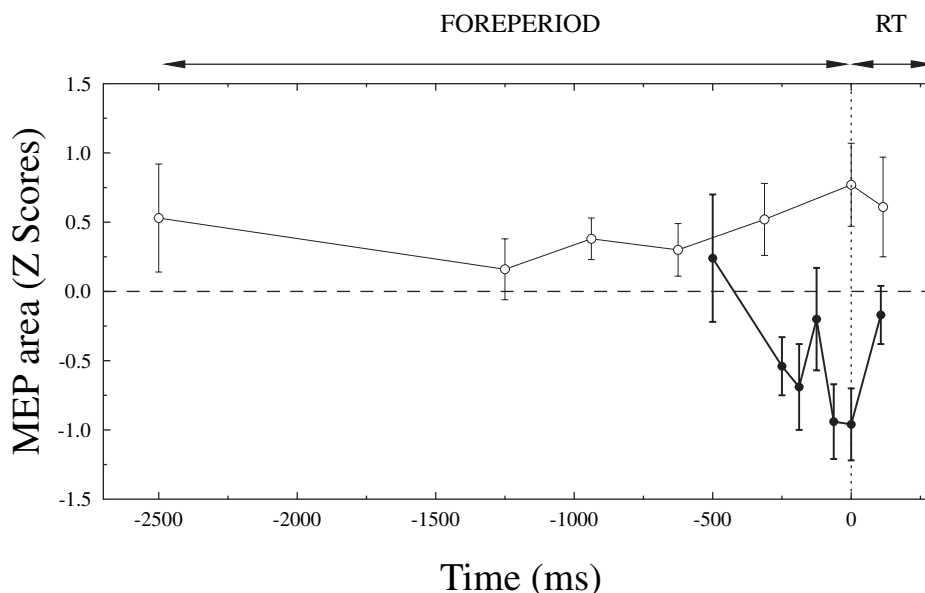


FIG. 3. Evolution of MEP mean area (in Z score values) recorded for both sessions as a function of stimulation times for the short foreperiod (black dots) and long foreperiod (white dots). Vertical lines depict standard error of mean MEP amplitude value for each condition.

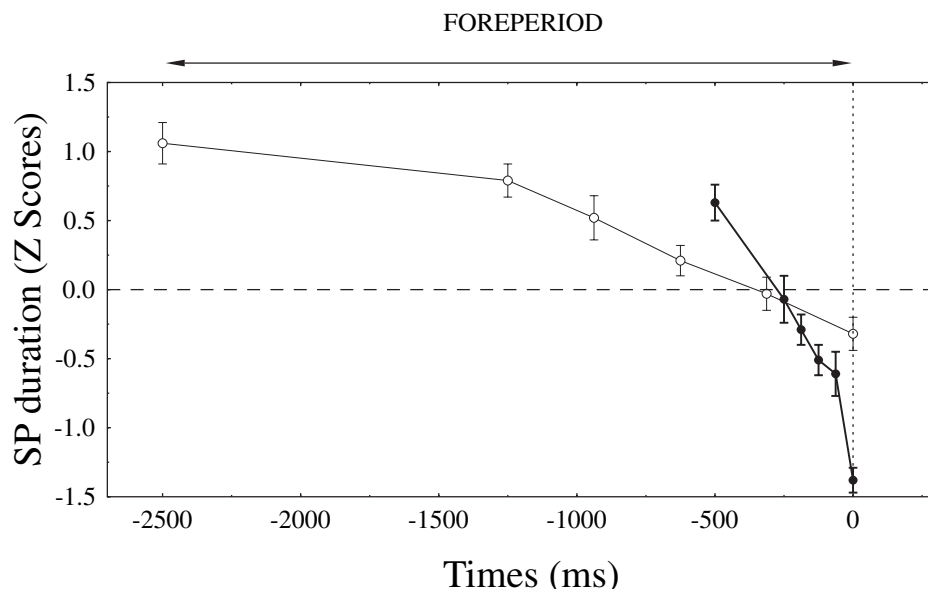


FIG. 4. Evolution of SP duration (in Z score values) for the short foreperiod (black dots) and long foreperiod (white dots). Vertical lines depict standard error of mean SP duration value for each condition. Note that for the last stimulation time (during the RT) the SP duration could not be analysed because the beginning of the voluntary EMG activity too frequently concealed the end of the SP.

of the voluntary EMG activity. As for the analyses carried out on the MEP, we intended to determine whether the SP duration changed between the warning and the response signal, and whether the SP evolution depended on foreperiod duration. We therefore compared the mean SP duration recorded when the stimulation was delivered at the occurrence of the warning signal or at the occurrence of the response signal. The ANOVA included stimulation time (t1, warning signal; t6, response signal) and foreperiod duration (short, long) as within-subject factors. This analysis reveals a main effect of stimulation time ( $F_{1,7} = 74.84$ ,  $P < 0.001$ ), but no effect of foreperiod duration ( $F_{1,7} = 3.34$ ,  $P = 0.11$ ). There was an interaction between these two factors ( $F_{1,7} = 10.21$ ,  $P < 0.05$ ). Newman-Keuls analysis indicates that the SP duration decreased between the warning signal (113 ms) and the response signal (102 ms) and that the evolution differed according to the foreperiod duration. The SP duration at the occurrence of the warning signal was similar for both foreperiod durations. Thus, the SP duration decreased during both foreperiod durations, but the reduction was greater (14 ms) for the short foreperiod compared to the long one (10 ms).

Next, the SP duration was analysed separately for each foreperiod in order to specify the dynamics of SP evolution. The ANOVAs included stimulation time during the foreperiod as within-subject factor (t1, warning signal; t2, t3, t4, t5 and t6, response signal). SP duration was affected by stimulation time for both foreperiod durations ( $F_{5,35} = 11.10$ ,  $P < 0.001$  and  $F_{5,35} = 6.49$ ,  $P < 0.001$  for the short and the long foreperiod, respectively). Furthermore, the overall effect of stimulation time on SP was linear for both foreperiod durations (linear component  $F_{1,7} = 25.58$ ,  $P < 0.001$ ;  $F_{1,7} = 33.34$ ,  $P < 0.001$  for short and long foreperiod, respectively; quadratic component  $F_{5,7} < 1$ ).

#### Correlation between MEP area and SP duration

Correlation coefficients, for the eight subjects pooled together, were computed in the 12 basic conditions; six stimulation times  $\times$  2 foreperiod durations.

TABLE 2. Summary of correlations between the dependent variables for the first six stimulation times and for the short and long foreperiod

Stimulation time	MEP-SP	
	Short foreperiod	Long foreperiod
t1	-0.02	-0.05
t2	0.00	-0.02
t3	0.02	0.01
t4	-0.04	0.01
t5	-0.03	0.03
t6	0.04	-0.16*

\* $P < 0.01$ .

The mean correlation between these two indices was never significant for the short foreperiod duration. There was a correlation between MEP area and SP duration for the long foreperiod for the sixth stimulation times, only (see Table 2). The coefficient was weak (-0.16) and in the context of previous experiments, which failed to demonstrate a statistical link between the two variables (Triggs *et al.*, 1993; Wilson *et al.*, 1993; Burle *et al.*, 2002), this negative relationship may be a chance finding. An ANOVA, which included stimulation time during the foreperiod (t1, warning signal; t2, t3, t4, t5 and t6, response signal) and foreperiod duration (short, long) as within-subject factors revealed no main effects of stimulation time and foreperiod duration ( $F_s < 1$ ) nor interaction between these factors ( $F_{5,30} = 1.07$ ,  $P = 0.39$ ).

#### Discussion

In the present experiment, the degree to which it was possible to prepare temporally for the response signal was varied by employing either a short (500 ms) or a long (2500 ms) foreperiod in separate blocks of trials. As anticipated on the basis of previous results, slower RTs were observed with the longer foreperiod, consistent with the view that (i) the

precision of the time estimates of the response signal decreases with longer durations and (ii) a better level of preparation is attained for short than for long foreperiods. It is to be noted that this result was similar for the sham session, which indicates that the TMS of the motor cortex did not modify the preparation strategies of the subjects.

Single-pulse TMS of the motor cortex was used to probe two opposite influences on the corticospinal tract. By delivering TMS while the subjects were tonically contracting their response agonists during the foreperiod. In such conditions, the MEP is followed by a SP in the ongoing EMG. Modulations in SP duration can be attributed to variations of the late part of this period, which results from the stimulation of inhibitory interneurons of the motor cortex (see [Terao & Ugawa, 2002](#)). It can thus be conjectured that reductions in SP duration reflect activation mechanisms through the release of intracortical inhibition, while decreases in MEP area reflect a suppression in the activity of the cortico-spinal pathway. This dissociation is possible because the MEP and the SP are asynchronous; the changes in MEP area occur prior to modulation of SP duration. The two variables therefore reflect influences exerted on the corticospinal tract at different times after the stimulation has been delivered. In the following paragraphs, we shall examine each of these influences and propose a tentative explanation for such modulation.

#### *Neural suppression during preparation*

The MEP amplitude decreased over the course of the short foreperiod, but not over the long foreperiod, which replicates previous data from our group ([Hasbroucq \*et al.\*, 1997](#)). This decrease in MEP amplitude reflects the inhibition of the cortico-spinal pathway, thereby revealing a suppression component of time preparation (for similar results, see [Touge \*et al.\*, 1998](#)). This modulation suggests that inhibitory processes occur in parallel with the activation mechanisms reflected by the changes in SP duration, and indicates that optimal time preparation is accompanied by a suppression in activity of the cortico-spinal pathway.

Other results also indicate that suppression plays an important role in time preparation. Notably, the amplitude of monosynaptic reflexes triggered in a response effector decreases during the foreperiod (reviewed in [Requin, 1969](#); [Brunia, 1984](#)). This reflex depression has initially been attributed to the presynaptic inhibition of the motoneurons' somesthetic afferents ([Schieppati, 1987](#)).

A possible interpretation suggested by [Touge \*et al.\* \(1998\)](#) is that the suppression revealed by the MEP depression serves to hold back response execution during the foreperiod. Using single cell recording techniques in monkeys, [Prut & Fetz \(1999\)](#) observed that most of the preparatory modulations of the spinal interneuron's activity were inhibitory and proposed an interpretation of such modulations in line with the suggestion of [Touge \*et al.\* \(1998\)](#). According to Prut and Fetz, inhibitory modulations are part of a general braking mechanism suppressing the tendency to initiate a response during the foreperiod. Such a braking would be implemented both at the spinal and central level and would be released during the RT, after the occurrence of the response signal. This notion was further promoted by [McMillan \*et al.\* \(2006\)](#) who proposed that 'it is possible that this (the MEP depression) may reflect a global descending influence to the spinal motor neuron pool, to prevent movement...'

#### *Neural activation during preparation*

Silent period duration decreased as time elapsed during the foreperiod and this decrement was more pronounced for the short foreperiod, that is when the subjects were better prepared. This modulation indicates

that time preparation is accompanied by a removal of intracortical inhibition, resulting in an overall activation. The neurons that receive projections from the inhibitory interneurons affected by TMS were more activated when the level of preparation was higher. This result is compatible with previous findings obtained with other techniques. First, the amplitude of long latency reflex responses, which are considered to reflect changes in excitability in central structures that affect spinal excitability, has been reported to increase during the foreperiod ([Bonnet \*et al.\*, 1982](#)). These findings suggest that time preparation is implemented by a progressive increment of supra-spinal neural activity. Second, research on event related potentials (ERPs) supports this notion. [Walter \*et al.\* \(1964\)](#) described a sustained negative change in brain potentials during the foreperiod; the contingent negative variation (CNV). This composite wave (see, e.g. [van Boxtel & Brunia, 1994a, 1994b](#)) is a meaningful index of time preparation. In terms of the threshold regulation theory ([Birbaumer \*et al.\*, 1990](#)) its development could manifest an increase of excitability of the underlying neural structures. While long-latency reflexes and CNV data are in favour of excitatory modulations, these modulations likely rely on the contribution of motor and non-motor neural populations. These previous results were therefore inconclusive regarding the structures mediating such increases in neural activity. As TMS is relatively focal, our data suggest that the increase occurs in particular at the level of the motor cortex. Furthermore, as the decrease in SP duration was more pronounced for the short than for the long foreperiod, the present findings demonstrate that SP duration is linked to RT performance and thus to the level of preparation attained in the two foreperiod conditions.

The reduction in SP duration, which reflects a preparatory increase in neural activity, can be interpreted in terms of the proposal of [Näätänen \(1971\)](#) (see also [Niemi & Näätänen, 1981](#)). Näätänen proposed a simple scheme that relates time preparation to RT performance. Accordingly, time preparation increases neural activation during the foreperiod. When the increase in preparatory neural activation bypasses a threshold, termed 'motor action limit', an overt response is triggered. Reaction time depends on the distance between the motor action limit and the level of neural activation attained during the foreperiod. If this distance is large, the RT is long; in contrast, when the distance is short, the RT is short. When subjects expect the stimulus, they attempt to adjust neural activation close to the motor action limit. The decrease in SP duration observed in the present study may thus reflect a reduction of the distance between preparatory neural activation and the motor action limit. Given that the accuracy of this adjustment depends on the precision of time estimation, neural activation is on average higher at the time of occurrence of the stimulus when the foreperiod is short than when it is long. One may therefore expect that the activation necessary to implement the response during the RT is smaller when the level of preparation during the foreperiod is high than when it is low.

Note that previous results relative to the processes implemented during the RT are compatible with such an outcome. [Mattes & Ulrich \(1997\)](#) analysed the force spontaneously generated to execute the response and reported that this force was weaker for short than for long foreperiods ([Mattes & Ulrich, 1997](#); see, however, [Van Den Heuvel & Van Gemmert, 2000](#)). In previous EEG studies, by estimating the surface Laplacian, we have shown that the negative wave that develops over the motor cortex during RT is smaller and better time-locked to the onset of the response when the foreperiod is short than when it is long ([Tandonnet \*et al.\*, 2003, 2006](#)). These results converge with those of [Mattes & Ulrich \(1997\)](#) in suggesting that the excitability of the motor cortex during RT is less pronounced when the level of preparation attained during the foreperiod is high.



### Reconciling activation and suppression

The increase in cortico-spinal inhibition counteracts the increase in excitation of cortical neurons, which may seem odd at first sight. However, these opposite modulations concern different neuronal populations that influence the cortico-spinal pathway at different times

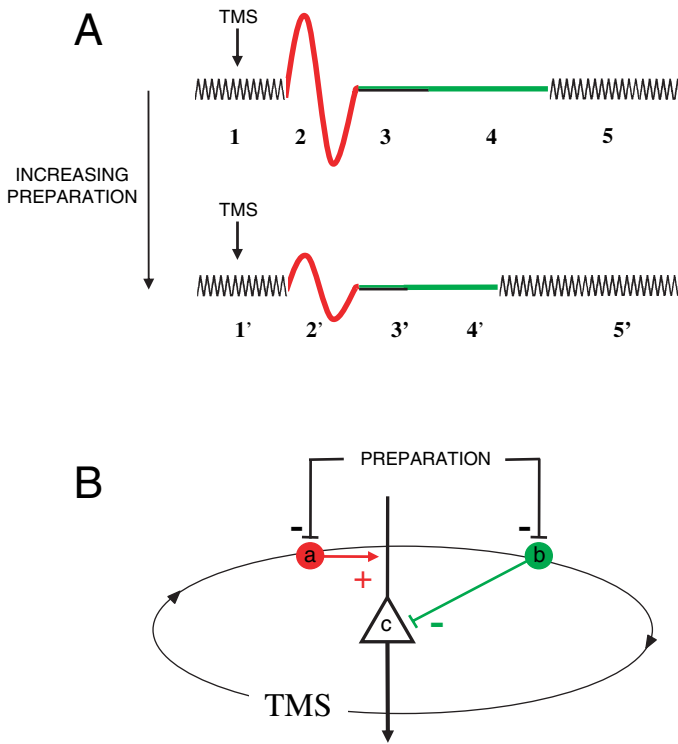


FIG. 5. Tentative schema portraying the evolution of motor evoked potentials and silent periods during the foreperiod and the interplay of excitatory and inhibitory modulations at the motor cortex level during time preparation. (A) Motor evoked potential and silent period in the ongoing EMG as a function of preparation. 1 and 1', tonic activation of the flexor pollicis brevis when TMS is delivered; 2 and 2', MEPs, 3 and 3' (black lines), early SPs; 4 and 4' (green lines), late SPs; 5 and 5', return to basic tonic activity. As preparation increases, both MEP (2' vs. 2) and SP decrease (4' vs. 4). Note that, as the early and late part of the SP are not distinguishable with single-pulse TMS, only variations in duration of the late part of the SP (of cortical origin) are detected. Now, because of the direct relationship between the MEP and the early SP (Terao & Ugawa, 2002), the duration of the early SP should also decrease (3' vs. 3) when preparation increases. (B) Hypothetical neuronal arrangement accounting for the empirical observations. Excitatory (a) and inhibitory (b) interneurons project onto cortico-spinal neurons (c). When TMS is delivered, the excitatory synapse (between neurons a and c) is activated first, which evokes the MEP, while the inhibitory effects of TMS [through recruitment of neurons (b), involved in the late SP] are not yet effective as indicated by the fact that the cortical component of the SP occurs later than the MEP (Davey *et al.*, 1994). Preparation could correspond to the joint inhibition of excitatory (a) and inhibitory (b) interneurons. When preparation increases, the inhibition of excitatory neurons (a) is manifest through the decrease in MEP amplitude, which is the first effect to occur after the stimulation. As the recruitment of inhibitory interneurons (b) is delayed, the inhibition of such neurons occurs later, during the SP. Inhibition of inhibitory neurons releases the inhibition, resulting in an activation of the cortico-spinal neuron (c). This effect is manifest through the decrease in duration of the late SP. The hypothetical synaptic connections represented here capitalize on the results of paired TMS experiments showing that when the delay between the two TMS is short enough, the second TMS does not evoke a MEP, even when the first conditioning TMS is under MEP threshold (Kujirai *et al.*, 1993; Di Lazzaro, 2004). This finding suggests that the test TMS occurs while the inhibitory effects of the conditioning TMS on neurons (b) are effective and strong enough to prevent the generation of a second MEP. A location of the inhibitory synapse close to or on the soma of the cortico-spinal neurons would be most efficient to implement an inhibition strong enough to prevent the generation of a second MEP.

after the TMS (e.g. Davey *et al.*, 1994; Priori *et al.*, 1994; Classen & Benecke, 1995; Bonhage *et al.*, 1996). The recruitment of cortico-spinal neurons (revealed by the MEP) precedes the recruitment of inhibitory interneurons (revealed by the late part of the SP).

Note that, in the present experiment, as in previous ones (Burle *et al.*, 2002; Triggs *et al.*, 1993; Wilson *et al.*, 1993), the absence of correlation between MEP amplitude and SP duration on a trial-by-trial basis is compatible with a simple model according to which time preparation correspond to the joint inhibition of excitatory and inhibitory interneurons projecting onto the corticofugal cells. This tentative model is presented in Fig. 5.

This organization may provide a clue for interpreting the functional interplay of inhibitory and excitatory modulations. Indeed, the stronger the suppression, the higher the activation can get without triggering premature responding. In other words, suppression allows for the build-up of a high level of cortical excitability. Suppression thus appears as the functional counterpart of activation; it secures the development of cortical excitability, preventing erroneous responding.

Although, we have outlined a tentative schema portraying the interplay of excitatory and inhibitory modulations at the motor cortex level, such an interplay may occur in several motor structures from associative cortical areas to the spinal cord, regardless of their relative synaptic distance from the muscle (Alexander & Crutcher, 1990; Prut & Fetz, 1999). The preparatory modulations observed in the present study could potentially occur at different levels of the neuroaxis. The coexistence of suppression and activation mechanisms at different levels would subserve a distributed functional organization of motor preparation (Jaeger *et al.*, 1993).

### Removal of neural suppression during reaction time

Finally, a comment relative to the MEP amplitude when the TMS was delivered during the RT interval is in order. Several studies have established that during this interval, MEP amplitude increases as the stimulation gets closer in time to the voluntary EMG onset (Tomberg & Caramia, 1991; Pascual-Leone, *et al.*, 1992a, b) and, whenever several responses are possible, this increase is non-specific to the to-be-performed response (Romaiguère *et al.*, 1997; Burle *et al.*, 2002). In a typical RT experiment, the MEP thus decreases during the foreperiod and thereafter increases during the RT interval. The influence of time preparation on this pattern, however, remains unknown. A secondary aim of the present experiment was to start documenting this issue. For this reason, the last stimulation was delivered during the RT interval (first decile of the distribution). This important issue shall be explored further in future studies.

At this time, MEP amplitude was similar for both foreperiods. In contrast, at the occurrence of the response signal, MEP amplitude was larger for the long than for the short foreperiod, hence the MEP increase was largest in the short foreperiod. When the level of preparation is higher, the cortico-spinal suppression could therefore to be removed earlier during the RT (see Fig. 3). Because of the variability of the data (see Fig. 3), this conclusion must, however, be considered as only tentative. Future research should confirm this result more conclusively, and address the influence of preparation on changes in excitability during this time interval in more detail.

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## Abbreviations

EMG, electromyogram; LED, light-emitting diode; M1, motor cortex; MEP, motor evoked potential; RT, reaction time; SP, silent period; TMS, transcranial magnetic stimulation.

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