Paired-Pulse Transcranial Magnetic Stimulation During Preparation for Simple and Choice Reaction Time Tasks

Oscar Soto,1 Josep Valls-Solé,2 and Hatice Kumru3

1Neurology Department, Clínica Teknon; 2Electromyography and Motor Control Unit, Neurology Department, Hospital Clinic, Institut d’Investigació Biomèdica August Pi i Sunyer, Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas, Universitat de Barcelona, Barcelona; and 3Department of Neurology, Institut Guttmann, Badalona, Spain

Submitted 20 July 2009; accepted in final form 24 June 2010

Soto O, Valls-Solé J, Kumru H. Paired-pulse transcranial magnetic stimulation during preparation for simple and choice reaction time tasks. J Neurophysiol 104: 1392–1400, 2010. First published June 30, 2010; doi:10.1152/jn.00620.2009. Motor preparation for execution of both simple and choice reaction time tasks (SRT and CRT) involves enhancement of corticospinal excitability (CE). However, motor preparation also implies changes in inhibitory control that have thus far been much less studied. Short-interval intracortical inhibition (SICI) has been shown to decrease before CE increases. Therefore we reasoned that, if SICI contributes to inhibitory control of voluntary movement during the preparatory phase, it would be larger in CRT than in SRT because of the need to keep the movement unreleased until the uncertainty resolves on which task is required. We measured changes in SICI and in CE at different time points preceding motor reaction in normal subjects. Single-pulse transcranial magnetic stimulation (spTMS) and paired-pulse transcranial magnetic stimulation (ppTMS) produced time-dependent changes in both SRT and CRT, with shortening when applied close to the presentation of the imperative signal (“early”) and lengthening when applied near the expected reaction (“late”). In addition, at all stimulation time points, reaction time was shorter with ppTMS than with spTMS, but there was no consistent association between the amount of SICI and reaction time changes. At early stimulation time points, CE was reduced in CRT but not in SRT. However, SICI in CRT was not different from SICI in SRT. At late stimulation time points, SICI decreased just before enhancement of CE. Our findings indicate that inhibitory circuits other than SICI are responsible for setting the level of CE at earlier parts of the reaction time period. Although the decrease in SICI may contribute to the increase in CE at the last part of the premotor period, the two phenomena are not dependent on each other.

INTRODUCTION

Preparation for execution of a motor task requires setting a motor plan, which comprises all the intentions, expectations, rules, and strategies that apply to a defined behavioral context. This includes an appropriate balance between excitation and inhibition of structures implied in task execution (Ridderinkhof 2002). In reaction time tasks, where the subjects are prepared to react to an imperative signal (IS), the amount of on-line inhibitory control might modulate the amount of excitation. However, the balance between excitation and inhibition might differ according to the reaction time paradigm. Indeed, inhibition should contribute more to choice reaction time (CRT), in which erroneous outcome has to be avoided (Burle et al. 2004; Carbonnell et al. 2004; Davranche et al. 2007; Hashbroucq et al. 1997, 1999b; Vidal et al. 2003), than to simple reaction time (SRT), in which the stimulus drives an overlearned response (Henderson and Dittrich 1998; Luce 1986).

The excitability of the motor pathway can be examined using transcranial magnetic stimulation (TMS). It is known that, in ballistic movements, corticospinal excitability (CE), measured with subthreshold or suprathreshold single-pulse TMS (spTMS), shows a progressive increase beginning at about 100 ms preceding movement onset (Burle et al. 2002; Chen et al. 1998; Hoshiyama et al. 1996, 1997; Leocani et al. 2000; McMillan et al. 2004; Pascual-Leone et al. 1992c; Rossini et al. 1988; Starr et al. 1988). The inhibitory aspect of motor preparation has received relatively less attention. However, Reynolds and Ashby (1999) reported a decrease in short-latency intracortical inhibition (SICI), examined with paired-pulse TMS (ppTMS) according to the technique described by Kujirai et al. (1993), preceding the increase of CE in SRT. This suggests that SICI might be actively suppressing unwanted motor cortical output in the premotor time and needs to be removed before the arrival of the excitatory drive to the motor cortex (Floeth and Rothwell 1999).

A study of the changes in the motor evoked potential (MEP) with reaction time paradigms cannot be separated from that of the effects induced by TMS on reaction time. Suprathreshold spTMS causes a lengthening of reaction time, which is more marked with stimuli applied closer to the expected onset of electromyographic (EMG) activity (Berardelli et al. 1994; Burle et al. 2002; Day et al. 1989; Leocani et al. 2000; Pascual-Leone et al. 1992a; Priori et al. 1993; Romaiguere et al. 1997; Rothwell et al. 1989; Ziemann et al. 1997). On the contrary, subthreshold or slightly suprathreshold spTMS causes the opposite effect, i.e., reaction time shortening, when applied together with IS or at a short interval afterward (Burle et al. 2002; Hallett et al. 1991; Hashimoto et al. 2004; Leocani et al. 2000; Molinuevo et al. 2000; Pascual-Leone et al. 1992a,b, 1994; Romaiguere et al. 1997; Terao et al. 1997; Ziemann et al. 1997). Because SICI modifies motor cortical excitability, we considered the possibility that SICI circuits contribute to modulation of reaction time by TMS.

We carried out the present study under a double aim: First, we wanted to know whether SICI is responsible for inhibitory control during movement preparation in reaction time paradigms. If this is the case, we would expect SICI to be larger in CRT tasks than that in SRT tasks because of more inhibitory control required in the former than in the latter. Second, we hypothesized that some of the effects of TMS on reaction time may be mediated by activation of intracortical inhibitory cir-
cuits. If this is the case, we would expect SICI to vary in parallel with reaction time (i.e., larger SICI in trials with reaction time delay and vice versa). Both hypotheses were tested using spTMS and ppTMS during SRT and CRT paradigms.

**Methods**

**Subjects**

We studied 11 healthy volunteers (7 males; mean age, 34.3 yr; range, 23–55 yr). The Ethical Committee of the Hospital Clinic approved the study protocol and all subjects gave written informed consent. Nine subjects were right-handed and two strongly left-handed (Oldfield 1971).

**Transcranial magnetic stimulation**

TMS was performed using two magnetic stimulators (Magstim, Dyfed, UK), which output was conveyed through a single figure-of-eight coil (9-cm external diameter) connected via a BiStim device. The acquisition program triggered both the sweeps and stimulators. The coil was placed tangential to the skull on the side opposite to the dominant hand, at the optimal site for eliciting a MEP in the first dorsal interosseous (FDI) muscle, with the handle held in a posterior and slightly lateral position. The position was marked on the skin and continuously monitored throughout the experiments. The resting motor threshold was considered to be the minimal stimulation intensity at which the MEP amplitude exceeded 50 µV in at least three of six trials in the resting muscle. The active motor threshold was considered to be the minimal stimulation intensity at which the MEP amplitude exceeded 200 µV in at least three of six trials, whereas subjects exerted a slight contraction of the target muscle. We used two TMS methods: 1) spTMS at a stimulus intensity of 1.2-fold resting motor threshold; and 2) ppTMS at an interstimulus interval of 2.5 ms, in which the intensity for the first stimulus was 0.9 active motor threshold and that for the second was 1.2 resting motor threshold.

**Recording**

Recordings were done with Ag–AgCl electrodes attached in a belly-tendon arrangement over the FDI muscle of the dominant hand. We used a Mystro5Plus EMG with a recording window of 500 ms and a band-pass frequency filter between 50 Hz and 1 kHz.

**Behavioral task**

Subjects were sitting on a comfortable chair, facing a computer monitor with its center at eye level at a distance of 1.2 m. A warning signal, consisting of a 1-cm “X”, was displayed in the center of the monitor over a black background. The IS was a 5 × 5 cm white square, which appeared after a random interval of 500–1,800 ms on one side of the warning stimulus. Subjects were informed as to the type of paradigm required: in SRT the IS appeared only at the side of the responding hand (dominant hand); in the CRT paradigm, it appeared randomly on either the right or the left side and the subject had to respond with the hand ipsilateral to the IS. The required response consisted of isometric squeezing of a solid plastic cylinder between thumb and index finger, “as quickly as possible.” The intertrial interval was variable between 10 and 20 s.

**Experimental procedure**

The experiment was divided in two sessions, carried out in random order: in one, subjects were requested to perform SRT and in the other they were requested to perform CRT. A schematic representation of the paradigm used is shown in Fig. 1. In each session, after a period of practice and when reaction times were considered stable (coefficient of variation [CV] <20%), we recorded 15 to 25 trials to compute the mean baseline reaction time for both SRT and CRT. These were considered the reference values to set the individual time points for TMS, which was applied at IS and at −125, −100, −75, −50, and −25 ms with respect to either baseline SRT or baseline CRT. For each stimulation time point we collected 24 trials, randomly mixing the following conditions until we obtained six trials in each one of them: spTMS at rest (spTMS was applied with no preceding warning or IS), ppTMS at rest (ppTMS was applied with no preceding warning or IS), spTMS during reaction (spTMS was applied at the predetermined time point with respect to IS), and ppTMS during reaction (ppTMS was applied at the predetermined time point with respect to IS). Trials with anticipation or with any EMG activity preceding the presentation of the TMS pulse were disregarded on-line and repeated.

**Data reduction and statistical analysis**

Our study implied six experimental conditions in three domains: activation (Rest vs. React), paradigms (SRT vs. CRT), and stimuli (spTMS vs. ppTMS) and six tests on each condition (the specific stimulation time points referred to earlier). The primary outcome variables for each condition were the MEP amplitude and the reaction time.

**Motor evoked potential**

We measured the MEP amplitude (in microvolts), peak-to-peak in each recording, and calculated the mean value among the six trials obtained at each stimulation time point for each of the four different types of trials (spTMS at Rest, ppTMS at Rest, spTMS during React, and ppTMS during React). The derived variables used for statistical analysis resulted from calculations carried out according to the following scheme. We defined CE as the quotient obtained by dividing the amplitude of the MEP to spTMS during React by that at Rest in the specific stimulation time point at study. In this way, values <1 would represent an increase and those >1 a decrease. In the case of SICI, we performed a two-step calculation: We first calculated separately the quotient between ppTMS and spTMS for Rest and for React and expressed SICI as the differences between that quotient and 1, in such a way that the value of 1 would represent maximal effect (complete suppression of the MEP), whereas the value of 0 would represent no suppression. Finally, we divided the value obtained during React by that obtained at Rest. CE and SICI changes with reaction time were determined for each stimulation time point in SRT and CRT. Statistical analyses were carried out on data obtained in the
responding hand during SRT and, in both the responding and the nonresponding hands, during CRT. For statistical analysis of CE changes, we used a one-factor repeated-measures ANOVA to test the effects of stimulation time point (IS, −125, −100, −75, −50, −25) on CE during React. To assess the significance of differences in CE between the Rest and React conditions, we used a paired t-test on data obtained at each stimulation time point, applying the Bonferroni correction for multiple comparisons to the P value. For statistical analysis of changes in SICI, we used the two-factor repeated-measures ANOVA to test the effects on SICI of either activation condition (Rest, React) or paradigm (SRT, CRT) as one of the factors and stimulation time points (IS, −125, −100, −75, −50, −25) as the other factor and the post hoc analyses were conducted using the Scheffé test. For graphical display of SICI values were normalized to resting SICI at each stimulation time point, such that 1 represents no changes in SICI relative to Rest and values below or above would represent a decrease or increase relative to resting SICI, respectively.

**Reaction time**

We measured reaction time as the latency (in milliseconds) of the first burst of EMG activity following IS presentation. Data obtained at each stimulation time point were normalized by subtracting the individual’s baseline values for either SRT or CRT from the reaction time of each single trial in the corresponding paradigm. Pooling data from all subjects for each paradigm (SRT, CRT) and TMS method (spTMS, ppTMS) at each stimulation time point produced normalized reaction time distributions, in which negative values indicated a shortening effect of TMS, whereas positive values indicated a lengthening effect. Preliminary analyses showed the distribution of reaction time values to be nonnormal (Shapiro–Wilks test, P < 0.001). Therefore we applied a square-root transformation of normalized reaction time data (Sokal and Rohlf 1995) before analysis. For graphical display of the data, we made groups of 10-ms time bins in a range from 100 ms before to 100 ms after baseline SRT or baseline CRT, to obtain a curve of response probability corresponding to each stimulation time point (Burle et al. 2002; Pascual-Leone et al. 1994). Statistical analyses on reaction times were done using two-factor repeated-measures ANOVA. In one test we used the TMS method (spTMS, ppTMS) and stimulation time point (IS, −125, −100, −75, −50, −25) as factors and, in another test, we used paradigm (SRT, CRT) and stimulation time point (IS, −125, −100, −75, −50, −25) as factors. For post hoc analyses we used the Scheffé procedure for multiple comparisons.

To analyze the relationship between changes in reaction time and the size of the MEP, we computed the Pearson’s correlation coefficient between the normalized reaction time (ms) and the MEP amplitude (µV). We report the mean correlation coefficient across subjects and stimulation time points, for both stimulation methods and experimental paradigms. Significance for all statistical analyses was set at 95%. All numerical values and graphical displays express data as means ± SE.

**Results**

The mean intensities of TMS used in the study, in percentage of maximum stimulator output, were 64.7 (range, 47–90) for spTMS and the test stimulus of the ppTMS, and 36.4 (range, 23–55) for the conditioning stimulus of ppTMS. Representative examples of MEP recordings are shown in Fig. 2 for all experimental conditions at the stimulation time points −100 and −25 ms.

**Baseline responses**

**AMPLITUDE OF THE MEP.** In spTMS trials, the grand mean of the MEP amplitude was 1,593.2 ± 288.7 µV (range, 697.1 to 4,011.8 µV) and its mean CV across all stimulation time points was 23.5 ± 1.83%. In ppTMS trials, the motor evoked potential amplitude was markedly reduced (497.33 ± 45.4 µV), corresponding to a mean percentage SICI of 0.68 (range between 0.82 and 0.62). Its mean variability across stimulation time points was 43.0 ± 3.15%.

**REACTION TIME.** Baseline SRT was 170.6 ± 3.3 (range, 123–240 ms), whereas baseline CRT was 194.6 ± 5.3 (range, 125–299 ms). In both paradigms the CV values showed a low and uniform RT variability (0.12 ± 0.009; range, 0.08–0.15 for SRT and 0.15 ± 0.01; range, 0.11–0.2 for CRT).

**Data from the responding hand in SRT and CRT**

CE. CE increased progressively toward the time of expected onset of EMG activity in both SRT and CRT. Figure 2 shows examples of recordings at two stimulation time points, whereas Fig. 3 shows the mean change in the normalized React/Rest...
FIG. 3. Cortical excitability (CE; filled squares and continuous lines) and short-latency intracortical inhibition (SICI; empty diamonds and dotted lines) represented as the ratio between the values calculated in React with respect to Rest as a function of stimulation time points. Values $< 1$ indicate decrease and values $> 1$ indicate increase, compared with Rest. In SRT (A), CE is kept unchanged until it increased significantly at $-50$ and $-25$ ms before onset of EMG activity. In CRT (B and C), CE was significantly suppressed at early stimulation time points (IS, $-125$, $-100$) in the responding and the nonresponding hands. It also subsequently increased in the responding hand to significant change from Rest at $-50$ and $-25$ ms. On the contrary, it remained mostly unchanged in the nonresponding hand (C). The changes in the SICI React/Rest ratio slightly preceded those seen in CE in SRT and in the responding hand in CRT (A and B). However, SICI remained unchanged in the nonresponding hand during CRT except for a slight decrease at $-25$ ms (C).

EFFECTS OF SP TMS AND PP TMS ON REACTION TIME. As expected, the presence of TMS modified reaction time. Changes in the same direction were induced by both spTMS and ppTMS in both SRT and CRT. The mean deviations from baseline reaction time values were $-32.0$ ms (SE $= 1.67$ ms) for SRT and $-26.32$ ms (SE $= 2.42$ ms) for CRT, when TMS (combining both spTMS and ppTMS) was applied at IS and $+58.04$ ms (SE $= 9.81$ ms) for SRT and $+68.23$ ms (SE $= 6.5$ ms) for CRT at stimulation time point $-25$ ms. Figure 4 shows the cumulative response probability curves as functions of stimulation time points for each of the four possible combinations. At all stimulation time points, mean reaction time was shorter with ppTMS than that with spTMS (Fig. 5), with a mean difference of 22.52 $\pm$ 1.6 ms for SRT and 25.86 $\pm$ 2.77 ms for CRT. A two-factor repeated-measures ANOVA showed significant effects of stimulation time points on SRT [$F(5,50) = 10.0; \ P = 0.001$] and on CRT [$F(5,50) = 10.1; P = 0.001$]. Similarly, there were significant effects of stimulation type on SRT [$F(1,10) = 7.58; \ P = 0.008$] and on CRT [$F(1,10) = 4.9; P = 0.03$ for CRT]. However, there were no significant main effects of paradigm [$F(1,10) = 0.55; P = 0.46$] and no significant interaction effects between stimulation type and stimulation time points for CRT [$F(5,50) = 0.05; P = 1.0$; for CRT: $F(5,50) = 0.001; P = 1.0$].

A weak correlation was found between MEP amplitude and reaction time, with $r = 0.31$ for spTMS and $0.13$ for ppTMS in SRT and $0.04$ for spTMS and $-0.24$ for ppTMS in CRT. None of these correlations was statistically significant ($P > 0.05$ for all comparisons). To further examine whether the effects of TMS on reaction time had any correlation with differences in MEP amplitude, we analyzed all data from stimulation time point $-25$ ms, in which SICI was physiologically removed. As reported earlier, the MEP amplitude was not different between spTMS and ppTMS for SRT ($P = 0.26$) or CRT ($P = 0.1$). However, mean RT with ppTMS was significantly shorter than that with spTMS for both SRT, with a difference of $25 \pm 5.5$ ms, and CRT, with a difference of $36 \pm 8.4$ ms ($P < 0.001$ for both).

Data from the nonresponding hand in CRT paradigms

CE. In CRT, data were collected for the nonresponding hand in trials in which the subject had to respond with the nonmonitored hand. In this condition, the MEP amplitude was reduced with respect to Rest at all stimulation time points (Fig. 3C). A two-factor ANOVA showed a significant effect of condition $[F(1,10) = 63.8; P < 0.001]$ and of stimulation time point $[F(5,50) = 15.4; P = 0.001]$, as well as a significant interaction $[F(5,50) = 17.5; P = 0.001]$. Post hoc analyses showed significantly reduced mean SICI in React with respect to Rest at stimulation time points $-75$, $-50$, and $-25$ ($P < 0.001$ in all). The mean SICI value decreased from 0.81 $\pm$ 0.06 at IS to 0.15 $\pm$ 0.11 at stimulation time point $-25$ in SRT and from 0.79 $\pm$ 0.04 at IS to 0.22 $\pm$ 0.07 at stimulation time point $-25$ in CRT, with no statistically significant differences between SRT and CRT values at any stimulation time point ($P > 0.05$ for all comparisons). There were no significant differences in the size of the MEPs obtained at stimulation time point $-25$ ms between baseline condition and either SRT ($t$-test, $P = 0.93$) or baseline and CRT ($t$-test, $P = 0.88$).
DISCUSSION

The results reported in our study, apart from being confirmatory to some previously reported findings in the relationship between TMS and reaction time, bring novel observations that are summarized as follows. 1) We found no difference between SRT and CRT with respect to the time course of changes in percentage SICI in cortical motor representations contralateral to the responding hand during the premotor time of reaction time paradigms. This occurred in spite of differences in CE at early stimulation time points, suggesting that SICI does not essentially contribute to differential regulation of CE during motor preparation. 2) We found that ppTMS induced more marked reaction time shortening than spTMS, whereas there was no correlation between reaction time modulation and the amount of SICI. These findings indicate that TMS-induced reaction time changes may be contributed by mechanisms independent from those related to SICI.

CE and SICI during motor preparation

The modulation of CE during motor preparation (Logan 1981) may be dependent on the behavioral attributes of the task, including time expectation (Hasbroucq et al. 1997, 1999a; van Elswijk et al. 2007) and its perceptual and motoric complexity (Wijnen and Ridderinkhof 2007). This “task set” may reflect strategic options for compliance with the required task (Ridderinkhof 2002). In our paradigm, both tasks met with similar time constraints (short foreperiods of variable duration), suggesting that the reduced CE in CRT with respect to SRT is due to differences in the perceptual and motoric requirements of the task rather than to differences in time expectation. Along a framework that divides motor reactions to external stimuli into “automatic” and “controlled” (Shiffrin and Schneider 1984), SRT tasks may be considered as automatic (i.e., requiring no additional processing after the external stimulus), whereas the CRT task requires extra processing to decode the stimulus and select the appropriate response. Thus the task set in CRT may be characterized by an increased inhibitory control compared with SRT (Ridderinkhof 2002) that may be necessary to prevent the untimely release of the motor action (Carbonnell et al. 2004) and likely similar to what is observed in Go/No-Go tasks (Hoshiyama et al. 1996, 1997;
Kumru et al. 2006). The CE decrease that we found in CRT is consistent with the findings reported by other authors in CRT (Burle et al. 2004; Carbonell et al. 2004; Davranche et al. 2007; Hasbroucq et al. 1997, 1999b), and Go/No-Go tasks (Hoshiyama et al. 1997), which may reflect changes in the excitability at cortical and subcortical levels. A decrease in the amplitude of the MEP has been also reported by Touge et al. (1998) and Sinclair and Hammond (2008) during the preparatory period of SRT. However, these authors studied the effects of TMS before IS in experimental conditions in which the presence of catch trials could have led to incomplete motor preparation (Kumru et al. 2006; Valls-Solé 2004). Task set-related preparatory inhibition has been documented at spinal (Bonnet et al. 1981; Brunia 1983; Burle et al. 2004; Duclos et al. 2007; Hasbroucq et al. 1999b; Prut and Fetz 1999; Touge et al. 1998) and brain stem levels (Kumru et al. 2006). Similar to other authors before (Sinclair and Hammond 2008; van Elswijk et al. 2007), we found no changes in SICI, indicating that the relative CE decrease in CRT most probably occurs not at a motor cortical level but at a subcortical level or it is due to cortical inhibitory mechanisms other than SICI.

**Suppression of nonresponding effector during CRT**

In line with previous reports, we found that the amplitude of the MEP to spTMS in the nonresponding hand was decreased with respect to Rest at the earliest stimulation time points (Duque et al. 2005; Hasbroucq et al. 1999b; Leocani et al. 2000). This suppression is thought to be necessary to prevent unwanted activation (Carbonell et al. 2004; Vidal et al. 2003). It has been suggested to be largely of cortical origin (Weiss et al. 2003) and appears to be highly specific for the homologous motor representation and related to shared kinematic aspects of the task between the two hemispheres (Duque et al. 2005). However, our results show that SICI in the nonresponding muscles remained unchanged relative to baseline values at the time when CE is decreased. Therefore it does not seem to contribute much to the inhibitory control of CE in CRT. It is possible that other inhibitory systems play a role. Interhemispheric inhibition is highly modulated during motor preparation. The net effect, whether excitatory or inhibitory, may depend on hemispheric dominance (Duque et al. 2007). SICI has been reported to be reduced by interhemispheric inhibition (Daskalakis et al. 2002; Florian et al. 2008). Nonetheless, we did not observe significant differences in the amount of SICI between motor representations of responding and nonresponding muscles, suggesting a limited involvement of interhemispheric inhibition in the observed suppression of CE or, alternatively, it acts through an interaction with SICI. Inhibition of CE can take place at a subcortical level. In a between-hands CRT task, inhibition of monosynaptic reflexes of the nonresponding muscle has been reported at points in time immediately preceding onset of EMG activity (Hasbroucq et al. 2000), which suggests that spinal inhibitory processes may contribute to the suppression of ipsilateral representations. We think that cortical systems different from SICI, or subcortical inhibitory mechanisms, are responsible for the suppression of CE in the nonresponding hand in the CRT paradigm.

**Is SICI just a cortical brake?**

At present, the physiological role of SICI remains incompletely understood. SICI measures the excitability of a cortical inhibitory circuit that reduces the number or size of I-waves in the descending corticospinal volley. As a consequence, there is less temporal summation in spinal motoneurons from corticospinal input after cortical stimulation (Di Lazzaro et al. 1998).

Removing SICI may be required for execution of a motor action (Floeter and Rothwell 1999), whereas its restoration may be necessary for movement cancellation (Coxon et al. 2006). Preparatory removal of SICI might help to focus the excitatory drive onto those motor representations required for the behavioral task (Floeter and Rothwell 1999). One possible role of SICI might be to suppress excessive cortical excitation, as supported by the finding of decreased SICI modulation in focal dystonia (Gilio et al. 2003).

In line with previous reports, we found that, in the responding hand, CE was facilitated and SICI was reduced (i.e., there was less inhibition), just before onset of EMG activity in both SRT and CRT. However, in the nonresponding hand, CE remained suppressed and SICI remained unchanged, along the entire premotor time. This temporal pattern of events is similar to that reported for imagined movements (Kumru et al. 2008). Thus the removal of SICI preceding enhanced CE may be a prerequisite to achieve a net increase in CE, regardless of the behavioral paradigm, but has no role in the premotor decrease of CE. Currently, SICI is postulated as a cortical braking mechanism, which needs to be released before the arrival of the

![FIG. 5. Mean (±SE) reaction time of pooled data from all subjects in simple SRT (top) and CRT (bottom) paradigms. The horizontal axis represents the mean normalized RT, whereas the vertical axis represents stimulation time point. Positive values represent shortening, whereas negative values represent shortening relative to the baseline reaction time (0). With ppTMS (filled circles) mean reaction time was consistently shorter by about 20 ms relative to spTMS (empty circles) at all stimulation time points in both SRT and CRT paradigms.](http://jn.physiology.org/DownloadedFrom/10.1152/jn.00142.2010)
excitatory drive to the motor cortex (Floeter and Rothwell 1999). Although our data confirm SICI removal as a necessary step for excitation, they also suggest a parallel action of different inhibitory processes during motor preparation at earlier periods. The main physiological action of SICI on reaction time may be tightly linked to the subsequent excitatory inputs, whereas other inhibitory mechanisms, working in parallel with SICI, would be more dependent on the behavioral context of the task.

Cortical and spinal modulatory systems during motor preparation

In SRT paradigms, stimulus decoding and response selection can be carried out before stimulus presentation, resulting in significant shortening of processing time (Henderson and Dittrich 1998). On the contrary, in CRT paradigms, these premotor processes cannot be started until the IS appears, resulting in consistently longer reaction times (Henderson and Dittrich 1998; Luce 1986). Interestingly, our data showed that TMS similarly affected reaction times in both SRT and CRT paradigms. This suggests that the effect of TMS on reaction time takes place in processes common to both paradigms, probably in late motoric processes, as opposed to earlier processes, such as perceptual and decisional processes, which are known to be significantly different between SRT and CRT (Hackley and Valle-Inclan 1998; Henderson and Dittrich 1998; Luce 1986). At present, the mechanisms responsible for TMS-induced reaction time shortening remain incompletely clarified (Burle et al. 2002; Molinuevo et al. 2000; Pascual-Leone et al. 1994; Terao et al. 1997; Ziemann et al. 1997). Some authors suggest that the effect can be attributed predominantly to the phenomenon of intersensory facilitation (Burle et al. 2002; Nickerson 1973; Terao et al. 1997), whereas others see it as a specific action of TMS on the motor cortex (Pascual-Leone et al. 1992a, 1994) or subcortical motor structures (Molinuevo et al. 2000). Intersensory facilitation, in which an accessory sensory stimulus presented temporally close to the IS induces reaction time shortening, is thought to reflect faster processing during perceptual or decisional (early) phases, but not (late) motoric ones (Hackley and Valle-Inclan 1998). Thus although we cannot rule out that intersensory facilitation has an important contribution to the phenomenon of TMS-induced reaction time modulation, we are inclined to believe that the major part of the effect takes place at the motor pathway (Pascual-Leone et al. 1992a). Suprathreshold spTMS causes reaction time shortening (Day et al. 1989; Pascual-Leone et al. 1994; Terao et al. 1997; Ziemann et al. 1997). Reaction time shortening could be due to the action of the stimulus on some inhibitory system preventing the translation of the motor memory to output structures (Day et al. 1989). An alternative framework proposes a continuous monitoring of outputs during motor preparation, in which reaction time delay reflects the extra time taken to repair errors in the motor program (Churchland and Shenoy 2007). Our results bring relevant data for further speculation opposing this framework: We found that, whatever the paradigm and conditions, reaction time was significantly shorter with ppTMS than that with spTMS. This indicates that the lengthening can be partially compensated with the addition of a subthreshold stimulus (i.e., ppTMS), which would probably act facilitating the translation of motor commands. The fact that differences in the effects of the type of stimulation on reaction time were still present at the stimulation time point –25 ms, where SICI was physiologically removed, indicates that the modulatory effect is due to the stimulus composition and not to the size of the responses. We must take into account, however, that removal of SICI may be contaminated by an increase in short-interval intracortical facilitation that may come into play mainly at late time points, just preceding the onset of EMG activity (Ortu et al. 2008; Peurala et al. 2008).

Although suprathreshold TMS nonselectively activates excitatory and inhibitory local cortical modulatory circuits, each of which has distinct connectivity and pharmacological properties (Chen 2004), subthreshold TMS activates selectively cortical inhibitory circuits (Chen 2004). The inhibitory effect is maximal at the interval used in our experiments (2.5 ms) and with the subthreshold stimulus intensity, as used in our study (Fischer et al. 2002; Ilíć et al. 2002). The effects of TMS on reaction time correlate with those seen in the duration of the cortical silent period (Ziemann et al. 1997). Such a relationship is present only for muscles participating in the task (Burle et al. 2002), supporting a true physiological interaction. The facilitatory effect of ppTMS on reaction time is similar to the effects induced by subthreshold TMS on the cortical silent period generated during sustained voluntary contraction: A shortening effect is induced with subthreshold TMS applied at the onset of the cortical silent period (Shimizu et al. 1999; Trompetto et al. 2001), whereas a lengthening effect is induced when TMS is applied some 15–20 ms after onset of the cortical silent period (Shimizu et al. 1999). Subthreshold TMS induces a rebound increase in corticospinal excitability, beginning 50–60 ms after the stimulus (Boniface et al. 1994; Davey et al. 1994; Mills et al. 1991; Valls-Solé et al. 1992). Therefore it could be speculated that such increased excitability might result in facilitation of cortical processing, allowing a faster transfer of motor command to output structures (Day et al. 1989).

In line with previous observations (Burle et al. 2002; Rojamguere et al. 1997), we did not find a clear association between reaction time and MEP amplitude or the amount of SICI. This finding suggests that the neural structures responsible for the disruptive effect of TMS on reaction time are different from those responsible for the effects of subthreshold TMS on the size of the MEP and that the two phenomena are not physiologically related.

In conclusion, the data gathered in the present study indicate the following. 1) Part of the inhibitory control involved in motor preparation relates to differences in the task set of the experimental paradigm: with all experimental conditions being equal, decreased CE was found in CRT but not in SRT. 2) There is no significant contribution of SICI on inhibition of CE during early premotor periods in CRT; the same amount of SICI was found in the agonist muscle in SRT and CRT and in the nonactive muscle in CRT. 3) The decrease in SICI may indeed contribute to the increase in CE at the end of the premotor time, when both changes occur in parallel and slightly earlier in SICI than in CE. 4) TMS-induced reaction time changes may partly be mediated by the same circuits that produce SICI, but other mechanisms are likely to participate as well. 5) Reaction time disruption by TMS is not dependent on MEP size.
Acknowledgments
The authors acknowledge the financial support of Marato TV3 Grant 071930 to J. Valls-Solé.

Disclosures
No conflicts of interest, financial or otherwise, are declared by the author(s).

References


