Top–Down Inhibitory Control Exerted by the Medial Frontal Cortex during Action Selection under Conflict

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Abstract

■ Top–down control is critical to select goal-directed actions in changeable environments, particularly when several conflicting options compete for selection. In humans, this control system is thought to involve an inhibitory mechanism that suppresses the motor representation of unwanted responses to favor selection of the most appropriate action. Here, we aimed to evaluate the role of a region of the medial frontal cortex, the pre-SMA, in this form of inhibition by using a double coil TMS protocol combining repetitive TMS (rTMS) over the pre-SMA and a single-pulse TMS over the primary motor cortex (M1) during a visuomotor task that required participants to choose between a left or right button press according to an imperative cue. M1 stimulation allowed us to assess changes in motor excitability related to selected and nonselected (unwanted) actions, and rTMS was used to produce transient disruption of pre-SMA functioning. We found that when rTMS was applied over pre-SMA, inhibition of the nonselected movement representation was reduced. Importantly, this effect was only observed when the imperative cue produced a substantial amount of competition between the response alternatives. These results are consistent with previous studies pointing to a role of pre-SMA in competition resolution. In addition, our findings indicate that this function of pre-SMA involves the control of inhibitory influences directed at unwanted action representations. ■

INTRODUCTION

At every moment, we are faced with a choice of actions, the majority of which are incompatible. A critical question is therefore how one action is selected in favor of another. Models of decision making postulate that any action ultimately performed results from a competition between several potential options whose neural representations are activated in parallel by current external stimuli and internal biases (Cisek, 2012; Doya & Shadlen, 2012; Klein, Olivier, & Duque, 2012; Oliveira, Diedrichsen, Verstynen, Duque, & Ivry, 2010). In many variants of such models, the accumulation of activity for each potential response is accompanied by inhibitory interactions between their distinct representations (Duque et al., 2008; Brown & Heathcote, 2005b; Usher & McClelland, 2004). That is, each candidate not only accrues supporting "evidence" but also inhibits the other options (Seeley et al., 2012; Coles, Gratton, Bashore, Eriksen, & Donchin, 1985). Accordingly, the cortical representation of nonselected responses is systematically suppressed during action selection (van de Laar, van den Wildenberg, van Boxtel, Huizenga, & van der Molen, 2012; Duque et al., 2007; Wijnen & Ridderinkhof, 2007; Meckler et al., 2010; Duque, Mazzocchio, et al., 2005; Burle, Vidal, Tandonnet, & Hasbroucq, 2004). This phenomenon, referred to as "inhibition for competition resolution" (Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010), helps to ensure that inappropriate responses fail to reach a selection threshold (Munakata et al., 2011; Tandonnet, Garry, & Summers, 2011; van den Wildenberg et al., 2010; Goghari & Macdonald, 2009; Munoz & Everling, 2004).

Converging lines of evidence indicate that a region within the medial frontal cortex, the pre-SMA, plays a key role in the process of resolving competition between action contingencies so that suitable behavior may emerge (Swann et al., 2012; Nachev, Kennard, & Husain, 2008; Isoda & Hikosaka, 2007). As such, pre-SMA is highly active during choice behaviors in humans (Nachev, Rees, Parton, Kennard, & Husain, 2005) and monkeys (Isoda & Hikosaka, 2007). Moreover, a lesion of this area in patients (Nachev, Wydell, O'Neill, Husain, & Kennard, 2007) or following TMS in healthy volunteers (Taylor, Nobre, & Rushworth, 2007) alters the ability to choose appropriate actions, especially when selection occurs under situations of conflict (but see also Grinband et al., 2011) such as following incongruent stimuli (Taylor et al., 2007), stop signals (Cai, George, Verbruggen, Chambers, & Aron, 2012; Chen, Muggleton, Tzeng, Hung, & Juan, 2009), or during task-switching in humans (Rushworth, Hadland, Paus, & Sipila, 2002). Interestingly, it has usually been assumed that pre-SMA resolves competition by "inhibiting" inappropriate or prepotent actions (Schall & Godlove, 2012; Hsu et al., 2011; Hikosaka & Isoda, 2010; van Gaal, Ridderinkhof, Scholte, & Lamme, 2010). However, whether such an "inhibitory function" of pre-SMA is associated with

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an inhibitory physiological mechanism has been unclear (Neubert, Mars, Buch, Olivier, & Rushworth, 2010; Mars et al., 2009; Aron, 2007), and it is notable that some models of action selection emphasize activation, rather than inhibition, as the selective agent (Brown & Heathcote, 2008).

In the following three experiments, we aimed at testing the hypothesis that pre-SMA is implicated in the control of "inhibition for competition resolution" during action selection. We used a combined on-line rTMS and single-pulse TMS (sTMS) procedure, recently introduced (Duque, Labruna, Verset, Olivier, & Ivry, 2012), and in which, during a two-choice RT task, a high-frequency rTMS train was delivered over pre-SMA and then followed by sTMS applied over M1. The rTMS train was used to produce transient disruption of pre-SMA during response preparation. M1 stimulation provided an assessment of changes in corticospinal (CS) excitability of selected and nonselected responses.

The task required participants to choose a response based on the color of an imperative cue (a circle), which was presented at the center of a computer screen. In the main experiment, the color of this circle was barely distinguishable. Importantly, based on a parallel organization of sensorimotor processes where stimulus identification and action selection processes overlap (Heekeren, Marrett, & Ungerleider, 2008), we assume that the ambiguity of the circle color led to a significant degree of competition between response alternatives in motor-related areas (Cisek, 2012). We also tested a low-competition control condition in which the color of the imperative cue was very salient.

We reasoned that if pre-SMA was the source of an inhibitory process involved in competition resolution, a virtual lesion of this region should degrade the inhibition of the nonselected response representation in M1. We predicted that this effect would be particularly pronounced following ambiguous imperative cues, given the established role of pre-SMA in conflict resolution.

METHODS

Participants

A total of 15 right-handed healthy volunteers (11 women; 28 ± 1.4 years old) participated in the present study. Handedness was determined by means of a short version of the Edinburgh Handedness inventory (Oldfield, 1971). Participants were naive to the purpose of the study and were financially compensated for their participation; all gave written informed consent. The protocol was approved by the institutional review board of the Université Catholique de Louvain.

Hand Selection Task

Participants performed a two-choice RT task, which was implemented by means of Matlab 6.5 (The Mathworks, Natick, MA) and Cogent 2000 toolbox (FIL, LON, and ICN at the Wellcome Department of Imaging Neuroscience, London, UK). The task required the participants to perform fast left or right index finger abduction movements depending on the color of the imperative cue, a small circle (blue or red, respectively), briefly presented at the center of a computer screen positioned at about 60 cm in front of them.

The time course of a trial is depicted in Figure 1A. The color of the imperative cue was obtained by increasing, above a neutral value (=127), the saturation of either the red (R) or blue (B) channel in the RGB (red, green, blue) model. Before each experiment, we determined the smallest saturation level for which the participants were able to discriminate the circle color with fewer than 10% errors. On average, the RGB values for the blue and red circles equaled [127, 127, 134 ± 0.4] and [134 ± 0.4, 127, 127], respectively (n = 15) and were kept constant for the whole experiment. The use of barely discernible colors made the stimulus identification quite difficult, a situation thought to induce a significant amount of competition between response alternatives in the motor cortex (Cisek, 2012; Heekeren et al., 2008).

Each trial started with the brief presentation (200 msec) of a fixation cross, displayed at the center of the screen. After a blank screen of 700 msec, a precue was presented for 200 msec. This precue was always uninformative ("!"; see Figure 1A) and was followed by another blank screen for a fixed delay of 700 msec. Note that the precue was not really necessary here given that it was uninformative. Yet, we decided to keep it to allow easier comparisons with our previous studies (Duque et al., 2010, 2012; Duque & Ivry, 2009). Then, an imperative cue appeared (blue or red circle), which remained visible for 500 msec. The participant was instructed to move the appropriate index finger as quickly as possible, following the onset of the imperative cue. After the imperative cue, there was an intertrial interval of 4500–5000 msec. The duration of this intertrial interval was set based on safety guidelines for the use of rTMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009).

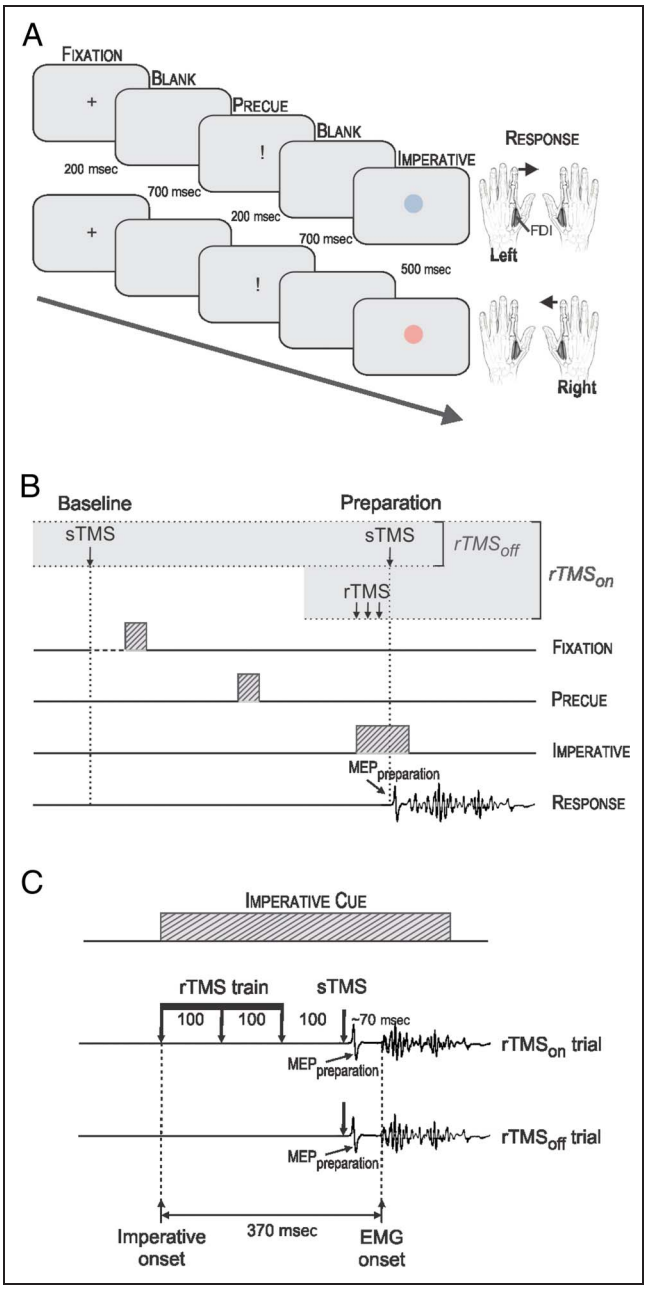
TMS Protocol

We used a double coil design combining sTMS and high-frequency rTMS (Figures 1B, C and 2A) while participants performed the choice RT task, similar to a previous study (Duque et al., 2012). The sTMS was used to probe CS excitability during response selection (Chen & Hallett, 1999). To do so, the sTMS coil was positioned over the right M1 to elicit motor-evoked potentials (MEPs) in the left first dorsal interosseous (FDI), a muscle agonist of index finger abduction. We focused on the left hand because MEP suppression during movement preparation is generally thought to be more pronounced in the nondominant hand (Duque et al., 2007; Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000). The rTMS was used to produce a transient virtual lesion in predefined cortical regions

(e.g., Taylor et al., 2007; Davare, Andres, Cosnard, Thonnard, & Olivier, 2006). To do so, the rTMS coil was placed over pre-SMA or a control site overlying the parieto-occipital cortex (POC; see below) in two separate sessions on different days and in a counterbalanced order.

sTMS

The sTMS was applied over M1 by placing a 70-mm figure-of-eight coil connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK) tangentially on the scalp. The handle was oriented toward the back of the head and laterally at a 45° angle away from the midline, approximately perpendicular to the central sulcus (Figure 2A).



After fitting the participant with a tight EEG cap, we identified the optimal location (hotspot) for eliciting MEPs in the left FDI. This location was marked on the EEG cap to provide a reference point throughout the experimental session. The resting motor threshold (rMT) was defined at the hotspot as the minimal TMS intensity required to evoke MEPs of about 50 μV peak-to-peak in the left FDI in 5 of 10 consecutive trials. The mean rMTs were 39% ($SE = 2.3$, $n = 15$) and 38% ($SE = 1.8$, $n = 15$) of maximum stimulator output in the pre-SMA and POC sessions, respectively; the intensity of the sTMS pulse was set at 120% of the rMT in all sessions.

rTMS

Trains of rTMS were applied using a second 70-mm figure-of-eight coil connected to a rapid Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). Each rTMS train consisted of three pulses at 10 Hz (200 msec train duration) at an intensity of 51 ± 3.0% and 51 ± 2.3% of maximum stimulator output in the pre-SMA and POC sessions, respectively, corresponding to 110% of the "rTMS rMT." The latter was obtained by increasing the rMT measured with the sTMS coil by 20% (Duque et al., 2012). This is because there is a loss of power when a coil is powered by a rapid (biphasic pulse) stimulator (see http://www.magstim.com/).

The orientation of the coils and location of stimulation sites are shown on Figure 2A, B. For pre-SMA (Figure 2A, left, and Figure 2B), the coil was placed as close as possible to a position 4 cm anterior to the vertex, with the handle pointing forward (Mars et al., 2009; Taylor et al., 2007; Rushworth et al., 2002). This coil position was controlled in 13 participants using a neuronavigation method (Duque et al., 2009, 2012; Noirhomme et al., 2004). Average Montreal Neurological Institute (MNI) coordinates for

Figure 1. (A) Illustration of trials requiring a left (blue circle, upper trace) or a right (red circle, lower trace) index finger response. Each trial consisted in the sequential presentation of a fixation cross, a first blank screen, a precue ("!"; always uninformative), a second blank screen and then an imperative cue indicating a left or right response (blue or red circle respectively, less salient in the main experiment). (B) An sTMS was applied over the right M1 at two possible timings (baseline or preparation). The pulse at $TMS_{preparation}$ was preceded by an rTMS train on half of the trials ($rTMS_{on}$ trials). On the other half of the trials, the sTMS pulse was presented alone ($rTMS_{off}$ trials). (C) Schematic representation of the TMS protocol when MEPs were elicited at $TMS_{preparation}$ in the $rTMS_{on}$ (upper trace) and $rTMS_{off}$ (lower trace) trials. The sTMS pulse was always applied 70 msec before the mean RT estimated in the no-TMS block. In the $rTMS_{on}$ trials, the rTMS train consisted of three pulses elicited at 10 Hz (200 msec), with the last pulse always elicited 100 msec before the sTMS. Therefore, the onset of the rTMS train was always set to fall 370 msec before the estimated RT. In the current example, the participant's RT was estimated at 370 msec and thus the onset of the rTMS train coincided with the onset of the imperative cue. For longer RTs, the onset of the rTMS train was delayed accordingly with respect to the imperative onset (maximum 40 msec).

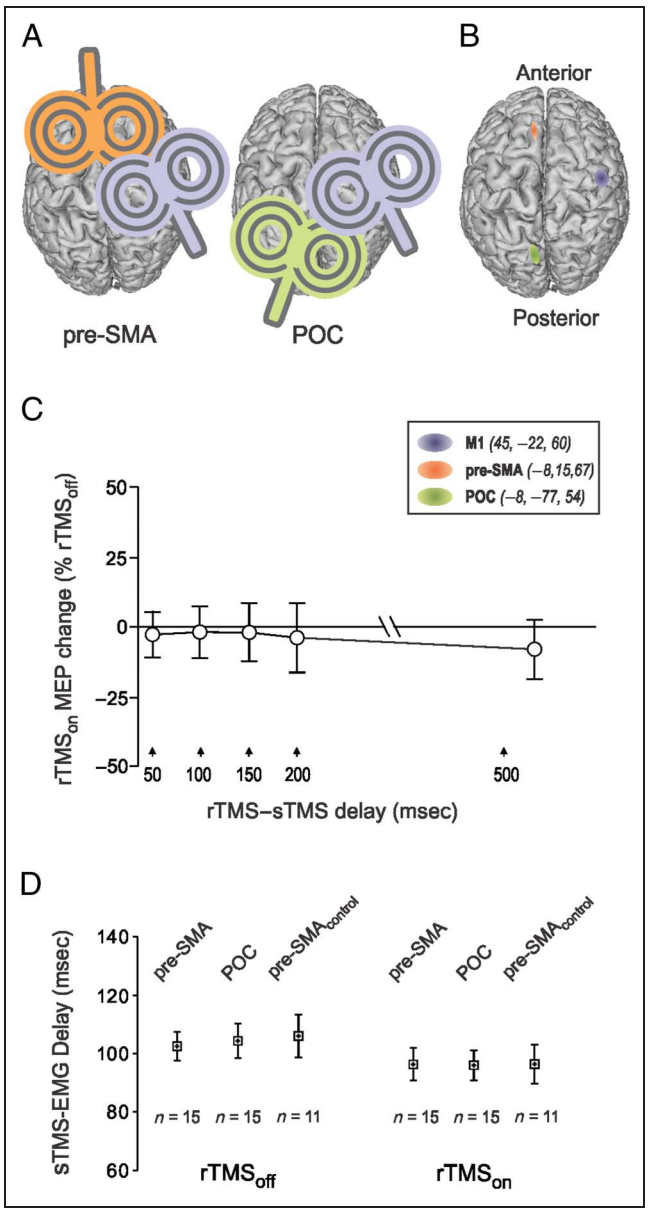


Figure 2. (A) Location and orientation of the sTMS coil over primary motor cortex (M1, purple) and the rTMS coil over pre-SMA (orange: left) or POC (green: right). (B) Actual MNI coordinates of the stimulation sites. Each ellipse is centered on the mean MNI coordinates of pre-SMA, POC, and M1 stimulation points, and their surface shows the 95% confidence interval of the normalized coordinates calculated for each participant. (C) Effect of rTMS over pre-SMA on CS excitability at rest. MEPs are elicited by a test sTMS stimulation over right M1 following conditioning stimulation consisting of rTMS over pre-SMA (10 Hz, three pulses). Conditioned MEPs ($rTMS_{on}$) are expressed with respect to MEPs evoked in the absence of conditioning stimulation ($rTMS_{off}$). The *x* axis indicates the delay between the conditioning (last pulse of the rTMS train) and test stimuli. At rest, rTMS over pre-SMA did not alter MEPs. (D) Mean delay between the $sTMS_{preparation}$ occurrence and the EMG onset for the $rTMS_{off}$ (left plots) and $rTMS_{on}$ (right plots) trials of the two sessions in the main experiment (pre-SMA and POC) and the control experiment ($pre\text{-}SMA_{control}$) after cleaning of the MEP data ("advanced MEP cleaning"; see Methods).

the coil position were [−8, 15, 67 mm] and clearly fell within pre-SMA (Picard & Strick, 1996), slightly to the left of the midline. Because of the size of the TMS coils, it was not possible to place the two coils simultaneously over pre-SMA and M1 of the right hemisphere. The stimulation site for POC [−8, −77, 54 mm] was the same as in a recent study (Taylor et al., 2007; Figure 2A, right, and B). The choice of POC as the control site was based on three reasons. First, it was approximately at the same distance from M1 as the pre-SMA stimulation site, allowing us to control for nonspecific spread of the rTMS induced current. Second, it meant that rTMS in both the POC and pre-SMA conditions was applied about 5 mm to the left of the midline; hence, the sound associated with the two rTMS sites should induce similar laterality effects, if any. Third, it ensured that the control site rTMS was applied over a region that has not been associated with the mediation of response conflict (Liston, Matalon, Hare, Davidson, & Casey, 2006; Rushworth, Krams, & Passingham, 2001).

Effect of High-Frequency rTMS Trains over Pre-SMA at Rest

The protocol used in this study combined two TMS procedures applied jointly: high frequency on-line rTMS over pre-SMA to induce a "virtual lesion" (10 Hz, 200 msec) and sTMS over M1 to assess CS excitability. While these procedures have been employed separately in many TMS experiments (e.g., Taylor et al., 2007; Duque, Vandermeeren, et al., 2005), very few studies have used them simultaneously. Given this, in a subset of participants ($n = 10$), we first examined the effects of high-frequency rTMS over pre-SMA on CS excitability when the participants were at rest. This preliminary session served to identify potential rTMS effects that were not task-specific. To do so, left FDI MEPs were elicited by right M1 sTMS at one of five delays (50, 100, 150, 200, and 500 msec) after the last pulse of the rTMS train over pre-SMA ($rTMS_{on}$ trials; see Figure 2C). MEPs were also recorded in the absence of rTMS ($rTMS_{off}$ trials) and were used as baseline. The $rTMS_{on}$ (five delays) and $rTMS_{off}$ (baseline) trials were intermingled within two blocks of 48 MEPs each. A total of 16 MEPs were elicited for each condition.

Figure 2C shows the change in left FDI MEP amplitudes that occurred when the sTMS pulse was preceded by an rTMS train applied over pre-SMA ($rTMS_{on}$ trials) compared with $rTMS_{off}$ trials, for each of the rTMS–sTMS delay. As shown on this figure, trains of rTMS over pre-SMA did not induce any significant change in CS excitability when participants were at rest. If anything, there was a small tendency for the MEPs to become smaller, although this effect never reached significance (all delay paired $t < 1.5$, all $ps > .17$ when compared with MEPs in $rTMS_{off}$ trials). Hence, these results indicate that a 200-msec rTMS train delivered over pre-SMA does not influence CS excitability at rest.

Experimental Procedure

After a practice period during which we set individually the color of the two imperative cues (red and blue circles), the experiment began. First, participants performed a no-TMS block (42 trials). This block was used to estimate the individual RT. This RT served to determine, for each individual, the timing of the sTMS application during the preparation period (see below). Then, the main phase of the TMS experiment began during which participants performed four blocks of 42 trials. Each block lasted approximately 5 min.

Only one sTMS pulse was applied in each trial, with two possible timings (see Figure 1B). To establish a baseline ($TMS_{baseline}$), the sTMS probe was delivered during the intertrial interval (i.e., 100–500 msec before the onset of the fixation cross; 6 trials/block = 24 MEPs in total). To probe CS excitability during movement preparation, the sTMS pulse was applied after the onset of the imperative cue ($TMS_{preparation}$), when the left FDI was selected (following a blue circle; 16 trials/block = 64 MEPs total) or nonselected (following a red circle; 16 trials/block = 64 MEPs total). This timing was adjusted on an individual basis so that, for each participant, it occurred about 70 msec before the mean RT (EMG onset) estimated in the unstimulated trials of the no-TMS block (Duque & Ivry, 2009; Duque, Mazzocchio, et al., 2005; see Figure 1C). Each block also comprised four "catch trials" with no TMS.

Importantly, in half of the $TMS_{preparation}$ trials, the sTMS probe was preceded by an rTMS train applied, in separate sessions, over pre-SMA or POC. The starting time of this rTMS train was fixed so that it terminated 100 msec prior to the sTMS pulse (as shown on Figure 1B, C), similar to a previous study (Duque et al., 2012). Hence, the first pulse of the rTMS train always occurred about 370 msec (200 + 100 + 70) before the mean time of the participant response measured in the no-TMS block (Figure 1C). For participants with a mean RT longer than 370 msec, a short delay was added between the onset of the imperative cue and that of the rTMS train. This delay never exceeded 40 msec in our participants (see also RTs in Results section). In contrast, in the few participants (n = 2) who showed a mean RT shorter than 370 msec, an exception was made and the sTMS was set to fall closer to the EMG onset (50 msec in both participants) to allow the whole TMS procedure to fit within the response preparation period; the rTMS train never started before the onset of the imperative cue.

To analyze MEPs elicited at $TMS_{preparation}$, we applied a post hoc cleaning procedure. First, an "initial MEP cleaning" was done to exclude the outliers. It comprised the three following steps: (1) We excluded trials in which the sTMS pulse fell after EMG onset as well as trials with background EMG activity (see EMG Recording section). (2) We then excluded trials in which the delay between the sTMS pulse and EMG onset fell outside a ±2.5 standard deviation window centered on the mean delay for that condition. (3) Finally, we excluded trials in which the MEP amplitude was outside a ±2.5 standard deviation window centered on the mean amplitude for that condition.

Even if we set the timing of the sTMS probe at a given latency with respect to the mean EMG onset estimated in the no-TMS block, the actual RTs and therefore the actual delay between the sTMS application and EMG onset still varied quite a lot from trial to trial. This variation had to be taken into account while analyzing data because the amplitude of MEPs strongly depends on their time of occurrence with respect to EMG onset (Chen & Hallett, 1999). Thus, to correct for this variation, we performed a further post hoc trimming of the MEP data (Duque & Ivry, 2009; Duque, Mazzocchio, et al., 2005). This "advanced MEP cleaning" comprised the following steps: (1) We calculated the mean delay between sTMS occurrence and EMG onset across the POC and pre-SMA sessions, for each of the four experimental conditions ($rTMS_{off\text{-}selected}$, $rTMS_{off\text{-}non\ selected}$, $rTMS_{on\text{-}selected}$, $rTMS_{on\text{-}non\ selected}$). (2) We then only included trials for which the delay between the sTMS occurrence and EMG onset fell within a ±2.5 standard deviation window of this mean delay. (3) Finally, within this window, we only included MEPs such that their average delay was as close as possible (provided that a minimum of eight MEPs remained) to the average of the participant across sessions. On average, 13.3 MEPs (SE = 0.74, n = 15) remained after the "advanced MEP cleaning."

This "advanced MEP cleaning" was done to ensure that MEPs recorded across sessions were representative of CS excitability changes occurring at the exact same time with respect to movement onset. As such, following this procedure, the mean delays were equivalent across sessions for each condition (mean delay = 99 msec [SE = 5.3, n = 15] and 100 msec [SE = 5.4, n = 15] in the pre-SMA and POC sessions, respectively). Importantly, the goal of this advanced cleaning procedure was to match delays across sessions but not across conditions. In fact, the mean delays were globally shorter in the $rTMS_{on}$ (mean delay across sessions = 96 msec) than in the $rTMS_{off}$ trials (103 msec, both session $p < .05$; see Figure 2D), probably because rTMS shortened RTs (see Results section). Finally, the mean delays were globally shorter for MEPs in the nonselected condition (right hand responses, mean delay across sessions = 87 msec) than in the selected condition (left-hand responses, 113 msec, both session $p < .0002$, not shown on Figure 2D), probably because sTMS delayed RTs when MEPs were elicited in the selected hand.

Control Experiment

In the main experiment of the present study, we found that rTMS over pre-SMA alters CS excitability variation that normally occurs during response preparation (see Results section). One important question is whether this effect was related to the need to select an action in a conflicting setting (due to the use of barely distinguishable colors)

or whether it would also have occurred in a situation without conflict. To test this idea, a subset of 11 participants (who were all part of the main experiment) was tested in an additional control experiment where rTMS was applied over pre-SMA while they performed the same task but with very salient colors (R or B channel always set to 127 + 30 = 157). All other aspects of this pre-SMA control experiment (pre-$SMA_{control}$) were similar to the main experiment except for one point. That is, our TMS stimulation procedure (rTMS train + sTMS) applied during the preparation period, required RTs to last for at least 370 msec, whereas the use of salient colors strongly reduced RTs. We therefore had to find a way to lengthen RTs in the control experiment. To do so, we asked participants to respond as quickly as possible but only after the offset of the imperative cue. The duration of the imperative cue presentation was adjusted on an individual basis to match RTs in the main experiment (delay between the onset of the imperative cue and the EMG response). Importantly, the time of rTMS application also matched that used for each participant in the main experiment. Hence, the delay between the onset of the imperative cue and that of the rTMS train was never longer than 40 msec (see Experimental Procedure section). All other aspects of the control task were similar to the main experiment, including the number of trials and the procedure used to analyze MEPs. The mean delay between sTMS occurrence and EMG onset after the "advanced MEP cleaning" equalled 101 msec (SE = 7.0, n = 11). In addition, similar to the two sessions in the main experiment, this delay was globally shorter in $rTMS_{on}$ (96 msec) than $rTMS_{off}$ (106 msec; $p < .02$; see Figure 3D) trials and was shorter for nonselected (90 msec) compared with selected MEPs (112 msec; $p < .006$).

We recognize that the need to lengthen artificially the RT in the control experiment might have biased other aspects of the task than the degree of competition. In fact, previous investigation of this task (Duque et al., 2010, 2012) instead suggests that this paradigm is an especially apt and close control task because the instructed movement preparation period entails inhibition of the prepared movement. However, this inhibition is functionally distinct to the modulation of competitive inhibition that was investigated in the main experiment. Hence, we believe that if pre-SMA is involved in the generation of these inhibitory influences, its transient disruption should induce visible changes in MEP amplitudes in this protocol too (see full argument in Discussion section).

EMG Recording

EMG activity was recorded from surface electrodes placed over the left and right FDI muscles. Each EMG recording lasted 3600 msec such that the rTMS train, the sTMS, and the motor response were visible on all sweeps. The EMG signals were amplified and band-pass filtered on-line (10–500 Hz; Neurolog; Digitimer, Hertfordshire, UK) and digitized at 2 kHz for off-line analysis. The EMG signals were used to determine the RT and to measure the MEP peak-to-peak amplitude. The RT was computed for each trial and corresponded to the delay between the onset of the imperative cue and the time at which the EMG signal became larger than 50 μV. Trials with background EMG activity greater than 100 μV in the 200-msec window preceding the sTMS pulse were considered as outliers and thus excluded from the analysis. This was done to prevent contamination of the MEP measurements by significant fluctuations in background EMG (Duque & Ivry, 2009; Duque et al., 2007).

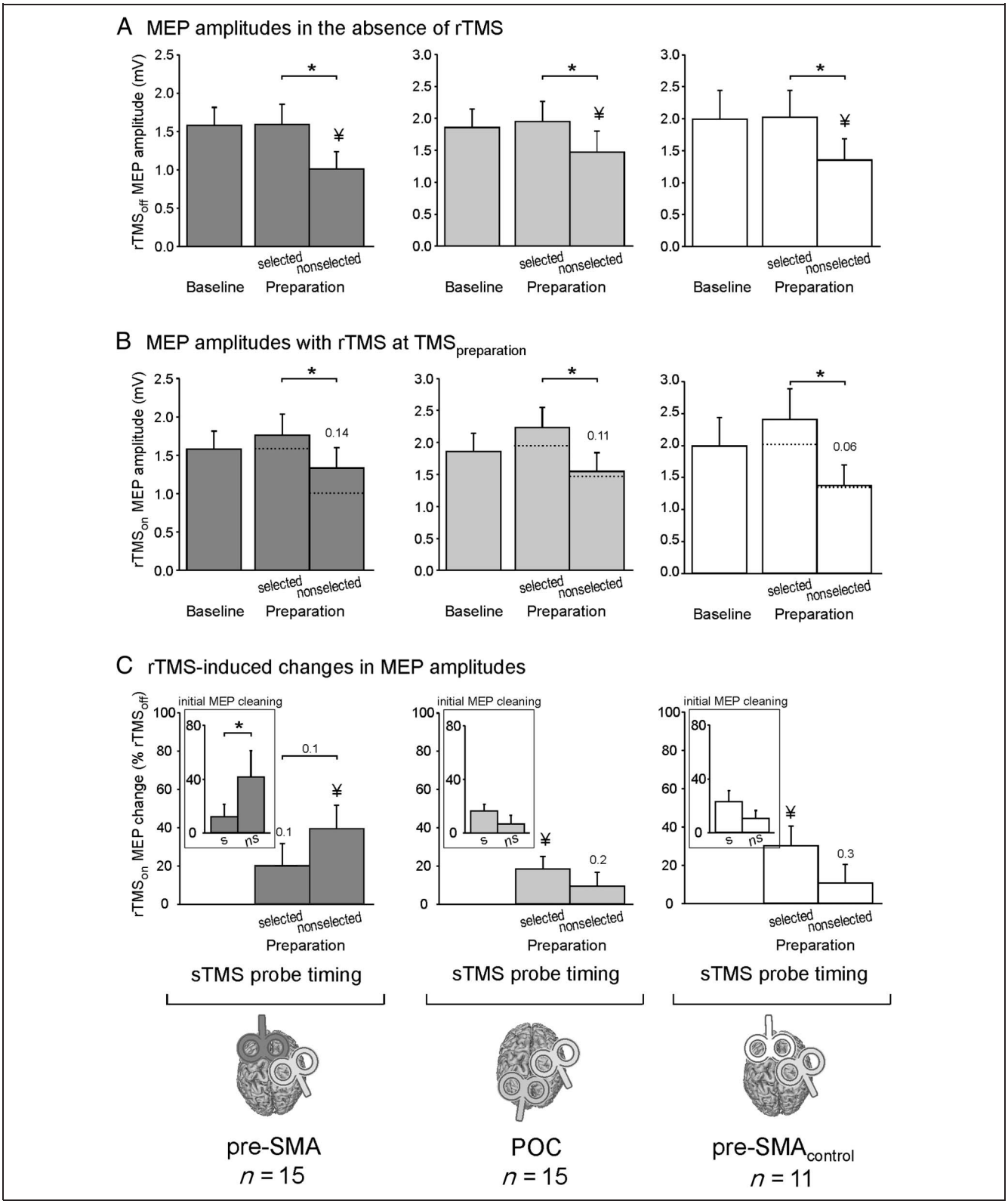
Statistical Analysis

We first analyzed MEPs in the absence of rTMS ($rTMS_{off}$ trials) to describe CS excitability changes occurring in a selected or nonselected hand at $TMS_{preparation}$. To do so, we used a series of one-way repeated-measure ANOVAs ($ANOVAs_{RM}$), one for each session (pre-SMA, POC, pre-$SMA_{control}$), with the factor Condition ($TMS_{baseline}$, $TMS_{selected}^{rTMSoff}$, $TMS_{non\text{-}selected}^{rTMSoff}$). Then, several analyses were run to investigate MEPs at $TMS_{preparation}$ in $rTMS_{on}$ trials. As a first step, we used another series of one-way $ANOVAs_{RM}$ with the factor Condition ($TMS_{baseline}$, $TMS_{selected}^{rTMSon}$, $TMS_{non\text{-}selected}^{rTMSon}$). Then, left FDI MEPs in the $rTMS_{on}$ trials were expressed with respect to the corresponding MEPs recorded in the $rTMS_{off}$ trials ($([rTMS_{on}] - [rTMS_{off}]/[rTMS_{off}])$. This normalized score was then used in paired t tests to compare the rTMS effect in the selected and nonselected hands for each session. Finally, to compare the effect of the rTMS train across sessions, we used two-way $ANOVAs_{RM}$ with the factors Session (pre-SMA, POC, pre-$SMA_{control}$) and Condition

Figure 3. (A) Amplitude of MEPs (mV) recorded during the intertrial interval ($TMS_{baseline}$) or during the preparation period ($TMS_{preparation}$) in the absence of rTMS ($rTMS_{off}$ trials). For the latter, the data are separated for trials in which left FDI was associated with a selected or nonselected response. Left, middle, and right panels are for the pre-SMA (n = 15), POC (n = 15), and pre-$SMA_{control}$ (n = 11) sessions, respectively. Note the use of different scales to facilitate the comparison of MEP changes at $TMS_{preparation}$ across sessions. ¥ indicates significant differences with respect to baseline. (B) Amplitude of MEPs (mV) recorded during the intertrial interval ($TMS_{baseline}$) or during the preparation period ($TMS_{preparation}$) following rTMS ($rTMS_{on}$ trials) in the pre-SMA (left), POC (middle), and pre-$SMA_{control}$ (right) sessions. The dotted lines indicate mean MEP amplitudes in $rTMS_{off}$ trials. Note the use of different scales to facilitate the comparison of MEP changes at $TMS_{preparation}$ across sessions. (C) Percent change in MEPs at $TMS_{preparation}$ following $rTMS_{on}$ over pre-SMA (left), POC (middle), and pre-$SMA_{control}$ (right). All values are expressed with respect to MEPs in $rTMS_{off}$ trials. The insets display the MEP data without "advanced MEP cleaning" ("initial MEP cleaning" only; see Methods). *$p < .05$. ¥ indicates significant differences with respect to $rTMS_{off}$ trials.

($TMS_{selected}$, $TMS_{non\text{-}selected}$) to analyze MEPs in $rTMS_{off}$ trials (expressed in percent of MEPs elicited at $TMS_{baseline}$) as well as rTMS-induced changes in $rTMS_{on}$ trials ($[rTMS_{on}] - [rTMS_{off}]/[rTMS_{off}]$) in the participants who participated in the control experiment ($n = 11$).

RTs and errors were analyzed to assess the effect of rTMS on the participants' behavior. To do so, we included the data from all the $TMS_{preparation}$ trials of the main experiment in a three-way repeated-measure $ANOVA_{RM}$ with Session (pre-SMA, POC), rTMS-Condition ($rTMS_{on}$,



$rTMS_{off}$) and Hand (left, right) as factors ($n = 15$). To further analyze the effect of rTMS on behavior, RTs in the $rTMS_{on}$ trials were expressed with respect to the corresponding RTs recorded in the $rTMS_{off}$ trials ($[rTMS_{on}] - [rTMS_{off}]/[rTMS_{off}]$). This normalized score was analyzed using two-way repeated-measure $ANOVA_{RM}$ with Session (pre-SMA, POC) and Hand (left, right) as factors. Additionally, in the participants who performed the control experiment, we performed the same analyses but with a factor Session including the $pre\text{-}SMA_{control}$ experiment. Post hoc comparisons were conducted using the Fisher's LSD procedure. All of the data are expressed as mean ± *SE*.

RESULTS

MEP Measurements

At $TMS_{baseline}$, left FDI MEPs equalled 1.6 mV ($SE = 0.23$ mV, $n = 15$), 1.9 mV ($SE = 0.29$ mV, $n = 15$), and 2.0 mV ($SE = 0.45$ mV, $n = 11$) in the pre-SMA, POC, and $pre\text{-}SMA_{control}$ sessions. Figure 3A shows the mean MEP amplitudes at $TMS_{baseline}$ and $TMS_{preparation}$ in the absence of rTMS ($rTMS_{off}$ trials). The factor Condition was significant for each session (all Fs > 4.85, all ps < .02). Consistent with many previous reports, left MEPs were larger when the left hand was selected (on average 110 ± 9.0% of baseline; Figure 3A) compared with when the left hand was nonselected (right response, 74 ± 6.2%; all ps < .008); as such, "nonselected MEPs" were systematically suppressed with respect to the baseline (all sessions $p < .03$). Note that "selected MEPs" were not different from the baseline value (all session $p > .57$), probably because premovement CS facilitation mostly occurred at later time points, closer to EMG onset (McMillan, Ivry, & Byblow, 2006; Chen, Yaseen, Cohen, & Hallett, 1998).

The mean MEP amplitudes at $TMS_{baseline}$ and at $TMS_{preparation}$ after rTMS ($rTMS_{on}$ trials) are shown in Figure 3B. Here again, the factor Condition was significant for each session (all Fs > 3.35, all ps < .05) with "selected MEPs" always larger than "nonselected MEPs" (all session $p < .02$). However, rTMS seemed to increase the amplitude of MEPs at $TMS_{preparation}$. The suppression of "nonselected MEPs" did not reach the significance threshold anymore (all session $p > .06$ when compared with the baseline value) and "selected MEPs" seemed to be more facilitated (but still not significantly larger than baseline in all sessions, $p < .29$).

To evaluate this rTMS effect, we computed the change in MEP amplitude following rTMS ($rTMS_{on}$ trials), relative to the MEP amplitude when rTMS was absent ($rTMS_{off}$ trials). Figure 3C shows this normalized score for the selected and nonselected hands in each session. In the selected hand, the rTMS train tended to increase MEP amplitudes in all sessions (18–30% increase, all $t > 1.74$, all ps < .1). This nonspecific rTMS-related MEP increase could be due to an arousal effect of the rTMS sound on premovement CS excitability changes (Mock, Foundas, & Golob, 2011) because such an effect was found in all conditions. Consistently, MEPs at $TMS_{preparation}$ were elicited closer to movement onset in trials with rTMS compared with $rTMS_{off}$ trials (see Methods and Figure 2D). Yet, in contrast to the selected hand, the effect of rTMS on "nonselected MEPs" varied across experimental sessions. The rTMS train induced a specific attenuation of MEP suppression in the pre-SMA session ($t = 3.21$, $p = .006$); left MEPs were 39% larger in the $rTMS_{on}$ (i.e., 85 ± 8.7% of baseline) compared with the $rTMS_{off}$ trials (i.e., 68 ± 9.6% of baseline). Note that this pre-SMA rTMS increase in "nonselected MEPs" was 19% larger than that found for "selected MEPs" ($t = 1.75$, $p = .10$). The rTMS effect was not significant for the nonselected hand of the POC and $pre\text{-}SMA_{control}$ sessions (both $t < 1.29$, both $p > .22$). In fact, in these sessions the rTMS effect seemed to be larger in the selected compared with the nonselected hand, but this effect was not significant (both $t < 1.46$, both $p > .18$).

We also checked the rTMS effect when the analysis of MEPs at $TMS_{preparation}$ did not account for possible differences in RTs across sessions ("initial MEP cleaning" only; see Experimental Procedure in Methods). This allowed us to consider a larger number of MEPs and to account for a possible bias in the selection procedure of the "advanced MEP cleaning." Importantly, similar results were obtained when analyses were performed on these data (see insets of Figure 3C). Nonselected MEPs were found significantly increased by rTMS (MEP suppression was attenuated) in the pre-SMA session only (42% larger in $rTMS_{on}$ compared with $rTMS_{off}$ trials), and this effect was larger than that found for the selected hand (12% increase; $t = 2.27$, $p < .04$).

The specificity of the rTMS effect was further investigated by comparing the changes induced by rTMS across the three sessions in the 11 participants who performed the control experiment (see "Control experiment" section). Figure 4A shows the mean MEP amplitudes at $TMS_{preparation}$ (expressed in percentage of the baseline) in the absence of rTMS ($rTMS_{off}$ trials). Consistent with the analyses described above, $ANOVA_{RM}$ revealed a main effect of Condition on left FDI MEPs; "selected MEPs" were larger than "nonselected MEPs," $F(1, 10) = 37.28$, $p = .0001$. The Condition × Session interaction was not significant, $F(1, 10) = 0.66$, $p = .53$, suggesting that MEP changes at $TMS_{preparation}$ were comparable in $rTMS_{off}$ trials of all sessions. We assume that the small differences across sessions are indicative of the variation classically observed in MEPs when recorded on different days.

The effects of rTMS-induced transient disruption on MEPs elicited at $TMS_{preparation}$ in the pre-SMA, POC, and $pre\text{-}SMA_{control}$ sessions are shown in Figure 4B. Similar to Figure 3C, the data are presented as a change in MEP amplitude following rTMS ($rTMS_{on}$ trials), relative to the MEP amplitude when rTMS was absent ($rTMS_{off}$ trials). $ANOVAs_{RM}$ revealed a significant Condition × Session interaction on rTMS-related effects, $F(2, 20) = 4.2$, $p = .03$. In the selected hand, the rTMS effect was comparable in

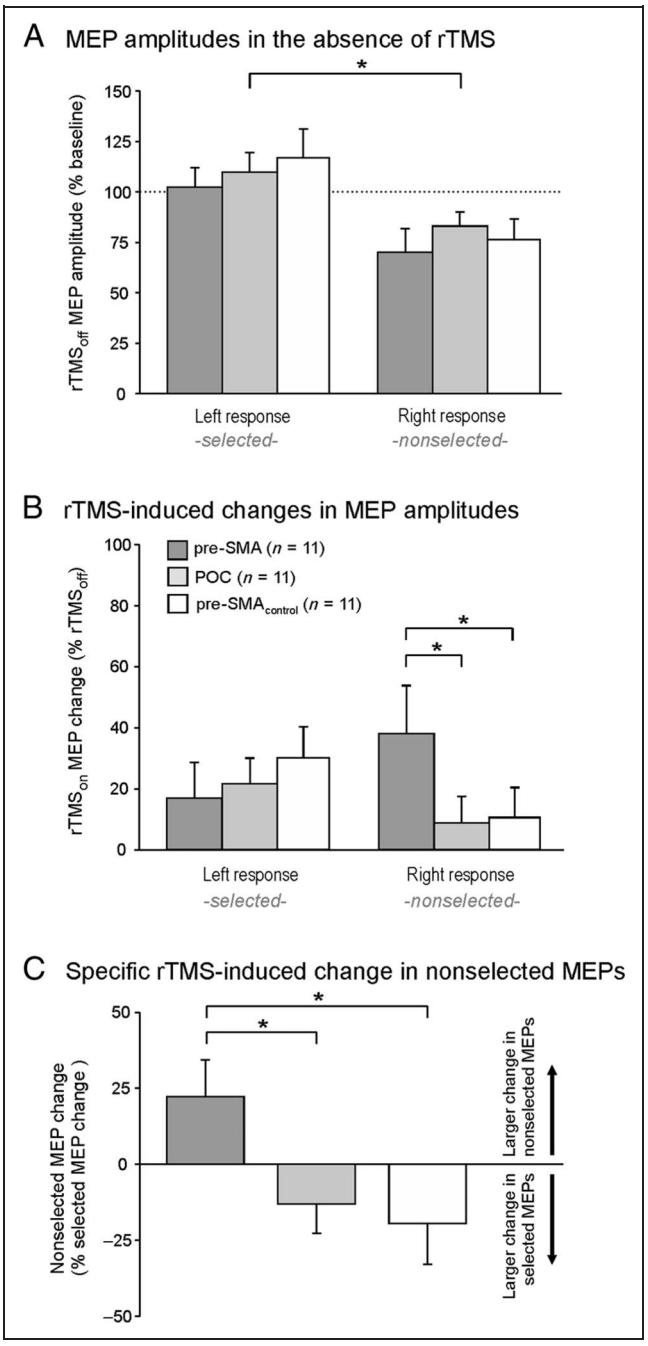


Figure 4. (A) Left FDI MEP amplitude at $TMS_{preparation}$ (expressed in % of MEPs elicited at $TMS_{baseline}$) in the $rTMS_{off}$ trials of pre-SMA, POC, and pre-$SMA_{control}$ sessions for the participants who participated both in the main and the control experiments (n = 11). Data are separated for trials in which left FDI was associated with a selected (left side) or nonselected (right side) response. (B) rTMS-induced change in MEPs (expressed with respect to MEPs in $rTMS_{off}$ trials) elicited in a selected or nonselected muscle, for pre-SMA, POC, and pre-$SMA_{control}$ sessions. Note the specific release in MEP suppression in the nonselected condition of the pre-SMA session. (C) Specific rTMS-induced change in MEPs elicited in a nonselected muscle (expressed with respect to the change induced in MEPs elicited in a selected muscle). *p < .05.

the pre-SMA, POC, and pre-$SMA_{control}$ experiments (all ps > .20). In contrast, the effect of rTMS on nonselected MEPs was significantly larger in the pre-SMA session compared with the POC (p = .01) and the pre-$SMA_{control}$ (p = .02) sessions. As a consequence, the hand specific rTMS effect (change in "nonselected" with respect to "selected MEPs") was different across the three sessions, $F(2, 20)$ = 4.22, p = .03 (see Figure 4C). It was positive in the pre-SMA session (larger increase in nonselected MEPs) but negative (larger increase in selected MEPs) in the POC (p = .03 when compared with the pre-SMA session) and the pre-$SMA_{control}$ sessions (p = .01 when compared with the pre-SMA session).

Behavior

In the main experiment (n = 15), error rates were less than 5%, and this value did not differ between the POC and pre-SMA sessions and did not increase in trials with rTMS (Session × rTMS Condition: $F(1, 14) = 0.07$, p = .79, n = 15). RTs averaged 393 msec (SE = 11.9, n = 15) across conditions in which only sTMS was applied ($rTMS_{off}$ trials; see Figure 5A). In $rTMS_{on}$ trials, RTs were even shorter (385 msec, SE = 11.8; $F(1, 14) = 13.2$, p < .002; see Figure 5B, C), most probably because the sound of the rTMS primed the participants to respond faster. In addition, as expected in right-handers, right-hand responses were overall faster than left-hand responses, $F(1, 14) = 23.4$, p < .001. Yet, note that the occurrence of MEPs in the left hand is likely to have contributed to this effect as MEPs can delay responses in a hand in which they occur (Duque & Ivry, 2009; Davare, Duque, Vandermeeren, Thonnard, & Olivier, 2007). Finally, neither the Session × rTMS Condition interaction nor the Session × rTMS Condition × Hand interaction were found significant (both F < 1.20, p > .29). We also computed a score of the rTMS effect (change in RTs following rTMS [$rTMS_{on}$ trials], relative to the RTs when rTMS was absent [$rTMS_{off}$ trials]), but the $ANOVA_{RM}$ performed on these data did not reveal any effect of Session, $F(1, 14) = 0.89$, p = .36, or Session × Hand interaction, $F(1, 14) = 0.22$, p = .65. However, we would like to mention that the fastening effect of rTMS was significant for the left-hand RTs (hand in which the MEPs were elicited), in the POC session (p < .007) but not for the pre-SMA session (p = .18, see Figure 5C). We recognize that this result is weak given the absence of significant effect in the $ANOVA_{RM}$, but it suggests nevertheless that the pre-SMA transient disturbance might have slightly affected RTs, leading to a reduction in the priming effect of the rTMS sound.

RTs in the control experiment (pre-$SMA_{control}$; n = 11) averaged 403 msec in the $rTMS_{off}$ trials (left hand: 411 msec, SE = 10.6; right hand: 395 msec, SE = 11.9) and were shortened by rTMS (main effect of rTMS Condition; $F(1, 10) = 20.9$, p < .002), similar to the main experiment. However, in contrast to the two main sessions (Session × Hand interaction; F = 8.8, p < .002), the left and right hand

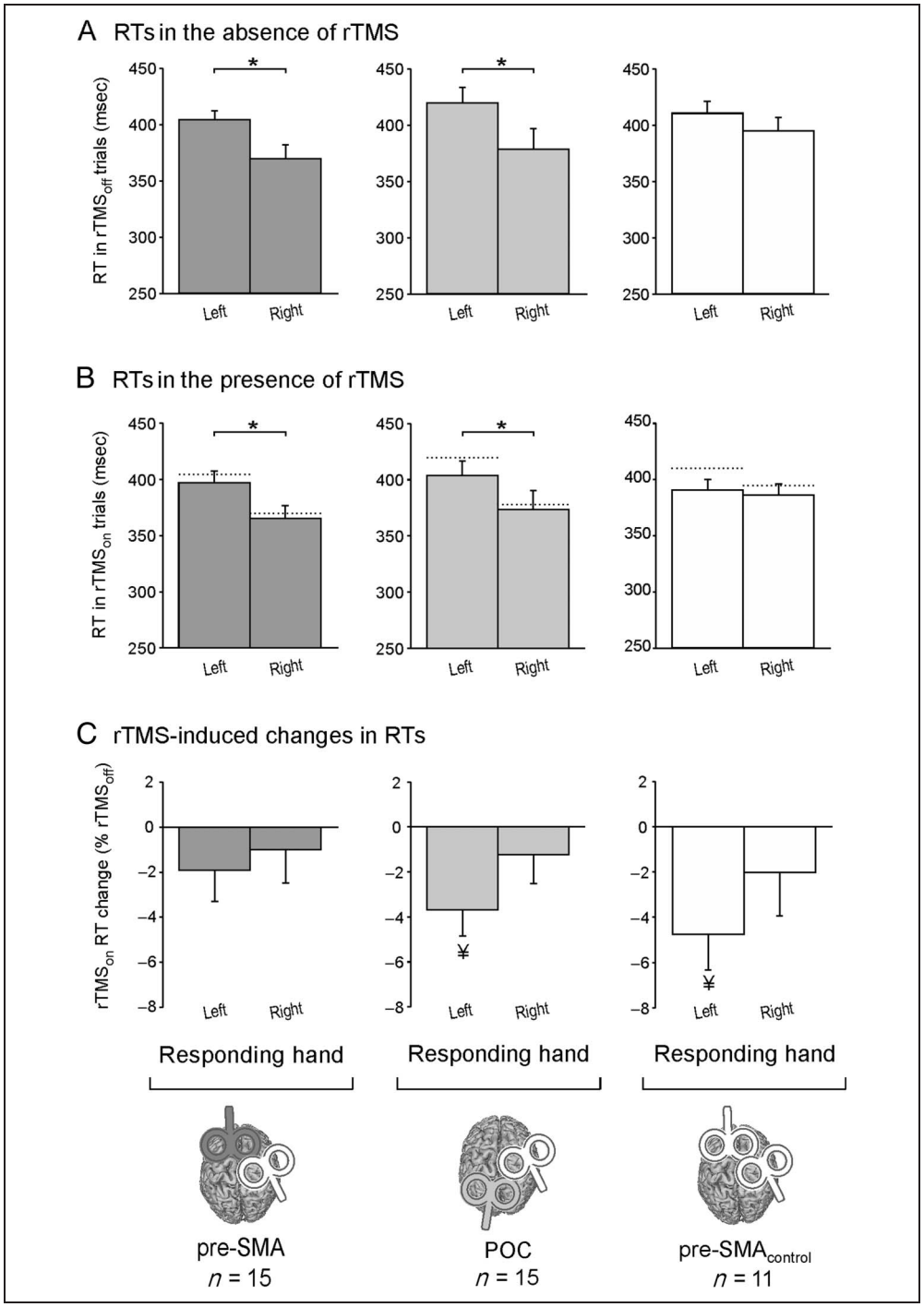


Figure 5. (A) RTs (msec) recorded for trials in which sTMS was applied during the preparation period ($TMS_{preparation}$) in the absence of rTMS ($rTMS_{off}$ trials). The data are separated for left and right hand responses. Left, middle, and right panels are for the pre-SMA (n = 15), POC (n = 15), and pre-$SMA_{control}$ (n = 11) sessions, respectively. (B) RTs (msec) recorded for trials in which sTMS was applied during the preparation period ($TMS_{preparation}$) following rTMS ($rTMS_{on}$ trials) in the pre-SMA (left), POC (middle), and pre-$SMA_{control}$ (right) sessions. The dotted lines indicate RTs in $rTMS_{off}$ trials. (C) Percent change in RTs following rTMS over pre-SMA (left), POC (middle), and pre-$SMA_{control}$ (right). All values are expressed with respect to RTs in $rTMS_{off}$ trials. *$p < .05$. ¥ indicate significant differences with respect to $rTMS_{off}$ trials.

RTs were not significantly different in the pre-$SMA_{control}$ session ($p > .05$), most probably because the instructions to respond only after the offset of the imperative cue homogenized RTs across hands. Neither the Session × rTMS Condition interaction, nor the Session effect for the analysis of the normalized RT scores were significant (both $F(1, 10) < 0.59$, $p > .56$). However, note that in the pre-$SMA_{control}$ session, similar to the POC session in the main experiment, the rTMS fastening effect on left-hand RTs was significant ($p = .01$), contrasting again with the absence of significant effect in the pre-SMA session of the main experiment (Figure 5C).

DISCUSSION

rTMS over pre-SMA attenuated MEP suppression in a non-selected hand; that is, it reduced "inhibition for competition resolution." This was true when the cue was difficult to discriminate, producing a substantial amount of competition between response alternatives, but not when the

cue was unequivocal. These findings corroborate the view that pre-SMA is involved in conflict resolution. More importantly, our results indicate that this role entails the control of inhibitory influences directed at unwanted responses.

In the absence of rTMS, left MEPs were significantly suppressed when the imperative cue designated a right response, thus indicating that the left hand should not be selected. This finding is consistent with many previous studies, which have reported inhibitory changes in nonselected effectors following an imperative cue (van den Wildenberg et al., 2010; Meynier, Burle, Possamai, Vidal, & Hasbroucq, 2009; Duque, Mazzocchio, et al., 2005; Burle et al., 2004). This effect is called "inhibition for competition resolution" and is thought to assist response selection (Duque et al., 2010, 2012). In the main experiment, rTMS applied over pre-SMA specifically attenuated the MEP suppression. As such, when the imperative cue indicated a right hand response, left MEPs were significantly larger (less suppressed) when the sTMS pulse was preceded by an rTMS train applied over pre-SMA, compared with when the sTMS pulse was applied alone or compared with rTMS over a control site. rTMS over pre-SMA did not induce any specific change in left MEPs, compared with rTMS over a control site or over pre-SMA in a control condition, when the precue had indicated that the left hand was to be selected for the forthcoming response.

These findings point to a role of pre-SMA in the control of inhibitory influences directed at unwanted action representations. Specifically, it is usually assumed that, at the onset of the imperative cue, a competition is triggered between preparatory processes associated with right and left hand responses (Brown & Heathcote, 2005a; Usher & McClelland, 2004; Coles et al., 1985), with each preparatory process producing some inhibition of the other alternative (Seeley et al., 2012). Over time, the dynamics will favor the response indicated by the imperative cue, and the unwanted responses will remain inhibited (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004).

Importantly, the imperative cue was ambiguous in the main experiment, eliciting a significant amount of competition between alternatives (Cisek & Kalaska, 2010; Heekeren et al., 2008). We then included a control experiment in which the cue was unequivocal. Interestingly, in that situation, rTMS over pre-SMA did not alter inhibition. That is, rTMS over pre-SMA did not induce any specific change in non-selected MEPs, similar to the effects of rTMS over the control site in the main experiment. These findings suggest that pre-SMA is only implicated in "inhibition for competition resolution" under situations of conflict, and it is not implicated in other aspects of inhibitory control such as those entailed by preparation of action prior to its release.

Converging lines of evidence point to a cardinal role of pre-SMA in conflict resolution (van Gaal et al., 2010; Chen et al., 2009; Aron & Poldrack, 2006; Rushworth et al., 2002). Pre-SMA is highly active during conflicting choices (Isoda & Hikosaka, 2007; Nachev et al., 2005), and a lesion to this area in patients (Nachev et al., 2007, 2008) or following TMS in healthy volunteers (Taylor et al., 2007) alters the ability to choose between appropriate actions (Cai et al., 2012; Chen et al., 2009), especially when selection occurs under situations of conflict such as following incongruent stimuli (Taylor et al., 2007) or during task-switching (Rushworth et al., 2002). In humans, lesions of pre-SMA can lead to alien limb syndrome, with some patients demonstrating involuntary actions such as grasping nearby objects without ever intending to do so (Feinberg, Schindler, Flanagan, & Haber, 1992; Della Sala, Marchetti, & Spinnler, 1991). Finally, microstimulation of pre-SMA in monkeys affects tasks requiring the inhibition of a planned saccade to execute an alternative saccade (Isoda & Hikosaka, 2007; Stuphorn & Schall, 2006).

More interestingly, our results support the idea that pre-SMA is implicated in conflict resolution because it controls inhibitory influences directed at unwanted action representations, presumably to sharpen the selectivity of motor activations in a competitive setting. Previous work (Taylor et al., 2007) showed that an rTMS-induced pre-SMA disruption alters the selectivity of motor activations (assessed by recording lateralized readiness potentials [an EEG measure of relative levels of activity in left and right motor areas]) during response conflict. However, from that study, it was not possible to tell whether the role of pre-SMA consisted in inhibiting unwanted responses or facilitating desired responses. Our results provide strong support for the former "inhibition" option. Also especially relevant to the current issue are two recent studies (Neubert et al., 2010; Mars et al., 2009) which, by means of paired-pulse TMS, assessed the strength of a short latency inhibitory link originating in two regions of the frontal cortex and directed at response representations in M1 during conflict resolution. Interestingly, the authors revealed a strong inhibitory link for a region in the lateral frontal cortex, also consistent with a recent study (Duque et al., 2012), but not for pre-SMA (Mars et al., 2009). Yet, when rTMS was applied over pre-SMA the inhibitory effect of lateral frontal cortex on M1 during conflict resolution was attenuated (Neubert et al., 2010). Unlike in the current study, these experiments did not evaluate the effect of rTMS on the actual amount of inhibition of CS excitability (MEP amplitudes). Instead, all the analyses were made on parameters that reflected changes in the strength of the connectivity between each of the two frontal regions and M1 (paired-pulse/single-pulse MEP ratios). Because these cortico-cortical connectivity indices changed in similar ways for both M1 areas, both contralateral to the selected and the unselected action, it was again not possible in those studies, unlike in the present one, to assess whether pre-SMA had a particular role in inhibiting the unwanted action. The present study provides strong support for this idea. Finally, it was important to assess whether pre-SMA is an important source of within-trial inhibitory

influence over M1; the directness of the top–down influence over action control has been questioned for adjacent medial frontal areas, such as the supplementary eye field (Stuphorn, Brown, & Schall, 2010).

Nonselected responses were always inhibited, even in the control experiment where competition was minimal. This finding is consistent with previous reports (Tandonnet et al., 2011; Duque, Mazzocchio, et al., 2005; Burle et al., 2004) and indicates that "inhibition for competition resolution" is recruited whenever selection between several options is required. Yet, one would expect the inhibition to be stronger in situations of conflict compared with when the choice is easy, reflecting the recruitment of additional inhibitory resources to suppress incompatible responses. Surprisingly, the degree of MEP suppression was similar in the main and control experiments of the present study. One possibility is that the amount of inhibition is independent of the degree of conflict during competition resolution. Yet, we believe this is unlikely given our rTMS result; the unique impact of rTMS over pre-SMA in the main experiment strongly points to the generation of further inhibitory influences under situations of conflict. It is important to keep in mind that the MEP measure always reflects the combined effects of both facilitatory and inhibitory changes in the excitability of CS fibers. Now, if the presence of conflict induces the recruitment of additional inhibitory resources, it will also yield a larger facilitation of incompatible response representations. Thus, it is possible that nonselected responses were in fact more inhibited in the main experiment even if it was not apparent from global MEP measures.

Finally, we think that the absence of behavioral change following rTMS over pre-SMA is likely due to the simplicity of the task, an aspect that allowed us to obtain clean MEP data but reduced the sensitivity at the behavioral level. In fact, rTMS tended to shorten RTs in all conditions, most probably because the sound of the rTMS primed the participants to respond faster. However, we would like to point out that this shortening effect tended to be less pronounced for the pre-SMA session compared with the sessions in which rTMS was applied over a control site or in a control task. This suggests that the rTMS-induced transient disturbance of pre-SMA might have slightly affected conflict resolution, increasing RTs, even in this simple task.

How does pre-SMA exert its inhibitory influence over M1? A set of studies (Neubert et al., 2010; Mars et al., 2009) suggest that pre-SMA works in concert with the lateral PF to resolve conflict. The implication of lateral PF in "inhibition for competition resolution" is consistent with a recent study in which we showed that rTMS over this region attenuates MEP suppression in a nonselected effector, even in the absence of conflict (Duque et al., 2012). Pre-SMA may thus exert control over lateral PF to boost "inhibition for competition resolution" specifically when a conflict is detected. It is possible that pre-SMA reinforces mutual inhibitory interactions between competing representations. Alternatively, this area could directly control the exertion of additional top–down inhibitory influences over unwanted representations (Nigbur, Cohen, Ridderinkhof, & Sturmer, 2012). This control mechanism is also likely to recruit cortico-basal ganglia loops (Isoda & Hikosaka, 2011; Obeso & Olanow, 2011; Hikosaka & Isoda, 2010; Aron & Poldrack, 2006). Future experiments are required to characterize the time course of the rTMS effect found in the present study, possibly by applying shorter rTMS trains at different time points during the preparation period.

Methodological Considerations

The technical requirements of our TMS protocol precluded us from using the exact same task in the control experiment as in the main experiment. As a consequence, other aspects of the task than the degree of competition might differ between the experiments. It is thus critical to consider the possibility that a bias occurred in our data, invalidating our conclusions. One important question is whether the rTMS-related disturbance of activity in pre-SMA overlapped with the selection period in this control experiment. We believe it did for the following reasons. First, similar to the main experiment, rTMS was applied very close to the onset of the imperative cue. This means that, even if the decision was faster to make in the control experiment (easier color discrimination), selection could not have occurred before the rTMS application. One might then propose that selection occurred after the rTMS effect in the control experiment? Indeed, the time pressure was decreased in the control experiment with respect to the main experiment and participants might have taken their time to choose a response. However, previous studies have shown that participants do select their response after a cue, even if they are asked to postpone the initiation of the movement (Duque & Ivry, 2009; Davranche et al., 2007). In addition, in a recent study we showed that the effect of an rTMS train extends beyond the time of its application (Duque et al., 2012). Hence, even if participants were slower in choosing their response in the control experiment, it is very unlikely that the time of the rTMS effect did not overlap with the selection process. Another important concern is whether the nonselected MEP suppression found in the control experiment really reflects "inhibition for competition-resolution." Because the choice was easier to make in the low competition control task, selection was probably over at the time we elicited our MEPs. However, importantly, results from several recent studies indicate that the effect of "inhibition for competition resolution" can remain for some time after the actual period during which an action is selected. For example, nonselected MEPs are still suppressed 400 msec (Duque et al., 2012) or even 800 msec (Duque et al., 2010; Duque & Ivry, 2009) after an obvious informative cue. This was also confirmed in the present study as nonselected MEPs were found suppressed in our

control task. This indicates that "inhibition for competition resolution" can be investigated for some time after the selection is over and that an alteration to this process should be evident in our "late" premovement measurements (about 300 msec after the onset of the imperative cue) even if selection occurs "early" in the control experiment.

Finally, the attenuation of inhibition for competition resolution in the nonselected effector (left FDI) resulted from the application of rTMS over the left, ipsilateral, pre-SMA. We expect we would have observed similar effects if the rTMS train was directed at right pre-SMA (in the same hemisphere as M1 sTMS). Homologous regions of pre-SMA may work in concert via transcallosal fibers to produce inhibition for competition resolution (Hofer & Frahm, 2006; Marconi, Genovesio, Giannetti, Molinari, & Caminiti, 2003). However, the size of the coils precludes a direct test of this hypothesis with the current procedure (Neubert et al., 2010; Mars et al., 2009; Taylor et al., 2007).

Conclusion

In conclusion, the specific release of inhibition following rTMS over pre-SMA in the main experiment suggests that this region is implicated in a process that assists response selection, specifically under situations of conflict, by ensuring further inhibitory influences directed at unwanted response representations.

Acknowledgments

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