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TRACKING POST-ERROR ADAPTATION IN THE MOTOR SYSTEM BY TRANSCRANIAL MAGNETIC STIMULATION

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Abstract—The commission of an error triggers cognitive control processes dedicated to error correction and prevention. Post-error adjustments leading to response slowing following an error (''post-error slowing''; PES) might be driven by changes in excitability of the motor regions and the corticospinal tract (CST). The time-course of such excitability modulations of the CST leading to PES is largely unknown. To track these presumed excitability changes after an error, single pulse transcranial magnetic stimulation (TMS) was applied to the motor cortex ipsilateral to the responding hand, while participants were performing an Eriksen flanker task. A robotic arm with a movement compensation system was used to maintain the TMS coil in the correct position during the experiment. Magnetic pulses were delivered over the primary motor cortex ipsilateral to the active hand at different intervals (150, 300, 450 ms) after correct and erroneous responses, and the motor-evoked potentials (MEP) of the first dorsal interosseous muscle (FDI) contralateral to the stimulated hemisphere were recorded. MEP amplitude was increased 450 ms after the error. Two additional experiments showed that this increase was neither associated to the correction of the erroneous responses nor to the characteristics of the motor command. To the extent to which the excitability of the motor cortex ipsi- and contralateral to the response hand are inversely related, these results suggest a decrease in the excitability of the active motor cortex after an erroneous response. This modulation of the activity of the CST serves to prevent further premature and erroneous responses. At a more general level, the study shows the power of the TMS technique for the exploration of the temporal evolution of post-error adjustments within the motor system.

Key words: TMS, flanker task, post-error slowing, post-error inhibition, corpus callossum.

INTRODUCTION

Most of our everyday tasks proceed with apparent ease and swiftness, yet errors occur and must be corrected and avoided. Our brain not only has the ability to detect errors during an ongoing task but also to adapt its strategies in order to improve performance. In proof of this, Rabbitt (1966) observed that erroneous responses in reaction time (RT) tasks led to a slowing of the subsequent correct responses. This post-error slowing (PES) has often been attributed to executive control adjustments between trials, and it has been understood as a consequence of an extended processing in trials following an error in order to reduce impulsive responses. The interest in error processing has been revitalized by the discovery of the Error-Related Negativity (ERN) (Falkenstein et al., 1991; Gehring et al., 1993), a component occurring time-locked to the erroneous response in the event-related potential. Since then, researchers have focused on disentangling the neurophysiological mechanisms underlying these adaptive processes.

Neuroimaging studies have evidenced the role of prefrontal areas during error processing (Botvinick et al., 2001; van Veen and Carter, 2002; Kerns et al., 2004; Burle et al., 2008) with the anterior cingulate cortex (ACC) being involved in detecting errors and implementing subsequent cognitive control mechanisms (Ridderinkhof, 2002; Ridderinkhof et al., 2004; Lötcke and Frahm, 2008). The activation of the ACC has been related to a subsequent increase in BOLD activity in right dorsolateral prefrontal cortical areas (rDLPFC), which has been associated with post-conflict/error adjustments (Kerns et al., 2004; Klein et al., 2007). However, it remains unclear how does the interaction between these cognitive control regions (ACC and rDLPFC) and the motor system result in PES.

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Abbreviations: ANOVA, analysis of variance; ACC, anterior cingulate cortex; CST, corticospinal tract; ERN, Error-Related Negativity; FDI, first dorsal interosseous; MEP, motor-evoked potentials; PES, post-error slowing; rDLPFC, right dorsolateral prefrontal cortical areas; RT, reaction time; TMS, transcranial magnetic stimulation.

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Transcranial magnetic stimulation (TMS) has been used to study changes in the excitability of the motor system during the execution of cognitive tasks that involve a motor command (Duque et al., 2005; Duque et al., 2007; van den Wildenberg et al., 2009). Commonly, suprathreshold single-pulses are given in primary motor areas to elicit motor evoked potentials (MEP) in hand muscles contralateral to the stimulation site. The amplitude of the elicited MEP has been considered as a marker of excitability of the corticospinal tract (CST) (Hess et al., 1986; Andersen et al., 1999). In addition, TMS can be applied at different time-points allowing a chronometric analysis of the excitability changes of the motor system, for example during rapid reaction time tasks such as the Flanker paradigm (van den Wildenberg et al., 2009).

Mainly, two different accounts have been proposed to understand the PES phenomena (see Danielmeier and Ullsperger, 2011 for a review). The inhibitory account holds that an increase of strength of selective suppression (or inhibition) is observed in trials immediately following errors (Ridderinkhof, 2002; Marco-Pallarés et al., 2008). Alternatively, the conflict monitoring account (Botvinick et al., 2001) suggests that the commission of errors engages a conflict monitoring system based on the activation of the ACC. Such activation might trigger cognitive control processes by recruiting the rDLPFC, and possibly lead a reduction of the excitatory input to the response level. Despite their differences, both accounts propose that the activation of the motor system might be biased after the commission of an error. Therefore, we hypothesize that the activity on the motor system during the preparation for the following response will be affected by the correctness of the actual response. To validate our hypothesis, we used a flanker task requiring a unimanual choice response and tested motor cortex excitability ipsilateral to the response hand using TMS single-pulses after correct and erroneous responses. This method allows tracking the time-course of changes in the excitability of the CST after stimuli or motor responses (Schneider et al., 2004; van den Wildenberg et al., 2009; Verleger et al., 2009). Hence, increments and decrements in excitability will be apparent through changes in MEP amplitude of target muscles of the inactive hand after stimulation of motor regions ipsilateral to the active hand. Note, that this approach is based on previous findings suggesting a reciprocal relationship of changes of activity in the motor cortex ipsi- and contralateral to the response hand (Vercauteren et al., 2008). Thus, we assume that changes of excitability of the active motor cortex will be mirrored by opposite changes in the non-active motor cortex.

EXPERIMENTAL PROCEDURES

The study comprised three different experiments, two designed to control the results of the initial experiment (Fig. 1). Two different groups of subjects participated in the study: the first took part in experiment 1 and the second group was subjected to experiments 2 and 3. In all settings, participants were seated in a comfortable armchair in front of a computer screen located at a distance of about 1.2 m. The software package Presentation (Neurobehavioral Systems Inc., Albany, CA) was used to present the stimuli, to record the responses and to trigger pulses of the magnetic stimulator.

Experiment 1

Participants. Seventeen right-handed healthy volunteers (9 women, 23.7 ± 2.7 years) were required to abstain from coffee or tea at least 4 h before the experiment. All subjects gave written informed consent, were paid for their participation, and were pre-screened for compatibility with TMS (Rossi et al., 2009). Handedness was assessed using the Edinburgh Handedness inventory (Oldfield, 1971). The study was approved by the ethics committee of the University of Lübeck and was conducted in accordance with the Declaration of Helsinki.

Task and TMS procedures. A version of the Eriksen flanker task was used (Eriksen and Eriksen, 1974). Participants were instructed to focus their attention on the center of the screen and to respond to the central letter of a five-letter array with either the index or middle finger of their right hand using a response box. For technical reasons, correct fixation was not monitored during the task. The four letters flanking the central (target) letter were either compatible (HHHHH, SSSSS) or incompatible (HHSHH, SSHSS). Each stimulus array subtended about 2.5° of visual angle in width. Each stimulus was presented during 100 ms, and the trial duration (accounted as the time elapsed between two consecutive stimulus onsets) was 900 ms. Letter-finger allocations were counterbalanced between participants. To increase the number of errors, 60% of the stimuli were incompatible. Participants were encouraged to rapidly correct their erroneous responses by pressing the button with the corresponding finger (Rodríguez-Fornells et al., 2002). Importantly, participants did not receive any kind of feedback about the correctness of their responses.

A robotized TMS system was employed for precise coil placement (Matthäus, 2008). The system is based on a serial six joint robot (Adept Technology, Inc., Livermoore, CA, USA) and a Polaris infrared stereo-optical tracking system (Northern Digital Inc., Waterloo, Ontario, Canada). As a main feature, the system provides active motion compensation to maintain the coil position throughout the experiment. This enables a more accurate and comparable stimulation setting in contrast to common hand-held approaches (Richter et al., 2013). An individual three-dimensional (3D) digital contour of the participant's head was constructed before stimulation using a GALAXY3D laser scanning system (LAP, Lüneburg, Germany) for head navigation (Richter et al., 2011). A headband with passive marker spheres measured by the tracking system was used for precise

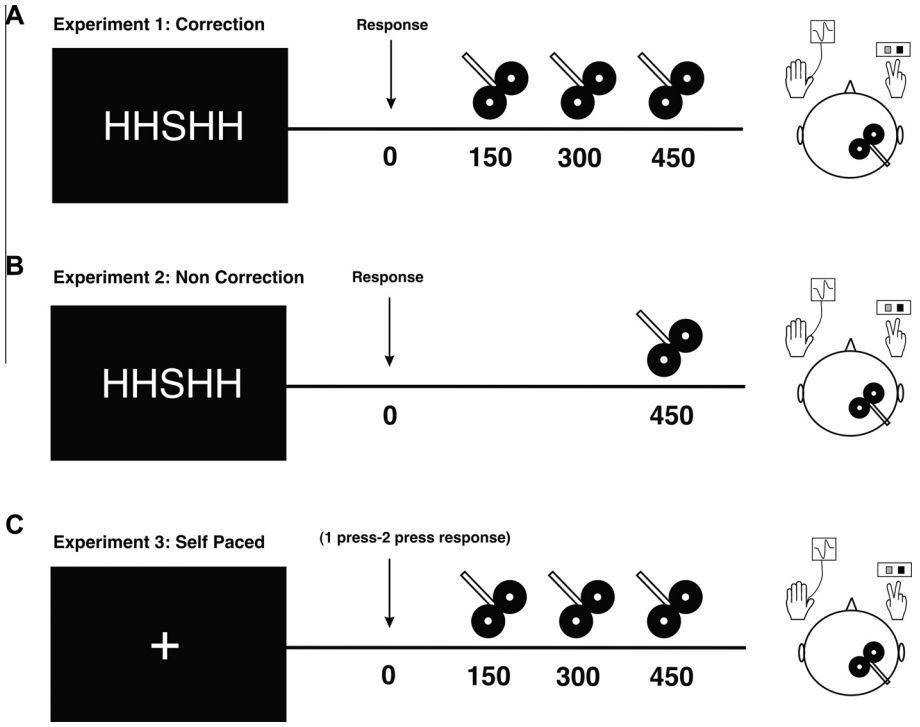

Fig. 1. Schematic representation of the experimental setup. In all experiments, TMS pulses were delivered on the right hemisphere, ipsilateral to the responding (right) hand. Participants were performing a choice reaction time flanker task. MEPs were acquired from the left FDI muscle. (A) In experiment 1 (correction condition), magnetic stimulation of the right hemisphere was delivered at 150, 300 and 450 ms after a correct or erroneous response. Participants were asked to correct the erroneous responses. (B) In experiment 2 (no correction condition) magnetic stimulation of the right hemisphere was performed at 450 ms after the response. Participants were instructed not to correct erroneous responses. (C) In experiment 3 (self-paced condition) magnetic stimulation of the right hemisphere was performed at 150, 300 and 450 ms after self-paced responses (either a single or two successive bouton presses).

head tracking and real-time motion compensation. Prior to stimulation, the head marker was registered to the digital head contour using a pointer. A MCF-B65 figure-of-eight coil was mounted to the robot's end effector and employed for focal stimulation. The coil was connected to a MagProX100 stimulator with MagOption (MagVenture A/S, Farum, Denmark) for biphasic stimulation.

MEPs were recorded from the left first dorsal interosseous (FDI) muscle using surface electrodes in a belly–tendon montage. The EMG signal was amplified and band-pass filtered (10 Hz–10 kHz) using a 2 channel DanTecKeypoint Portable system (Alpine Biomed Aps, Skovlunde, Denmark) at a sampling rate of 50 kHz.

The TMS coil was first placed tangentially on the head near the center of the right M1 approximately 5 cm lateral of the vertex (defined by coordinate Cz of the 10/20 EEG system). The stimulation of the hemisphere ipsilateral to the active hand was chosen in order to evaluate PES effects on the excitability of CST with no artifacts of muscular activation produced by the performance of the task. Subsequently, the coil was moved in the coronal and antero-posterior directions until the spot with the lowest threshold for the activation of the contralateral FDI was reached (Davranche et al., 2007). The resting motor threshold (resting MT) was defined as the lowest stimulation intensity over the optimal scalp position necessary to evoke MEPs of at least 0.05 mV of peak-to-peak amplitude, with a probability of .5 on the relaxed contralateral FDI (Rossini et al., 1994). During this measurement, we stimulated each position 10 times with an imposed inter-pulse time of 5–7 s. Once the resting MT was obtained, the TMS intensity was adjusted to the minimal intensity necessary to produce a MEP with a peak-to-peak amplitude of about 1 mV. This procedure was performed by giving suprathreshold pulses at the previously localized hot-spot, and adjusting the stimulation intensity until five consecutive MEPS of about 1 ± 0.1 mV of peak-to-peak amplitude were obtained.

Participants were asked to allocate both hands on the surface of a table located comfortably in front of them. The left hand was positioned at the same attitude than the right hand during the performance of the task. Importantly, participants were asked to maintain the left upper limb relaxed during the whole procedure and EMG activity of the left FDI was recorded while performing the flanker task.

The whole task was performed in one single session. Pauses were introduced every 5 min and participants decided upon the duration of this pauses, but any pause exceeded in more than 1 min. During the task, TMS pulses were delivered to the right hot spot 150, 300 or 450 ms after correct and erroneous responses. The timing of the delivery of pulses was randomized. These

time points were selected taking into account that the maximum increase of an oscillatory response in the beta EEG band related to PES has been observed 500 ms after the response in Marco-Pallarés et al. (2008). At least six trials were imposed between pulses to avoid possible behavioral interference produced by the previous pulse. Magnetic pulses were only delivered in trials where the RT was shorter than 350 ms. This constraint was considered because in responses with slower reaction times that such cut-off value, the interval between the motor response and the next TMS pulse would have been too short or even could have coincided in time interfering each other. A maximal temporal window of 500 ms after the presentation of the stimulus was provided for the execution of the motor responses.

Twenty pulses were delivered for each condition and TMS intervals, so that 120 pulses were delivered at the end of the task. The task finished when all MEPs were recorded.

Data analysis. The RT differences between correct and erroneous trials as well as RT differences between correct trials following both incorrect and correct trials were analyzed with paired-sample *t*-tests. The RTs of the corrective responses and the percentage of the corrections were assessed. Trials following a pulse were not considered for the RT analysis.

Previous to the analysis of the MEP amplitudes, EMG traces that presented spurious muscular activity previous to the MEP onset were eliminated after visual inspection ($<5\%$ for all subjects), to avoid the inclusion of trials with muscular pre-activation (the same procedure was performed for the analysis in experiments 2 and 3). Additionally, when more than two responses were produced, the corresponding EMG traces were excluded from the analysis. Because of the large inter-subject variability, individual peak-to-peak MEP amplitudes were converted to *z*-scores. This linear transformation is a measure of the number of standard deviations above (positive values) or below (negative values) the mean is placed for each subject. Because of its linearity, this transformation conserves the rank of the values but also the relation between the values of the original sample within each subject. This method has been successfully used in similar TMS studies to compare motor excitability changes across different conditions (Aglioti et al., 2008; van den Wildenberg et al., 2009). Therefore, mean *z*-scores of the MEP amplitudes were analyzed using a 2×3 repeated-measures analysis of variance (ANOVA) with response (correct, error) and TMS interval (150, 300 and 450 ms post-response) as factors. Importantly, the association between the target stimulus (S or H) and the finger response (index finger or middle finger) was counterbalanced across subjects. Additionally, we conducted an analysis to rule out any effect of the finger used to respond in the results. To this aim, we defined a $2 \times 2 \times 3$ repeated-measures ANOVA with factors finger (index vs. middle finger), type of response (correct vs. erroneous) and TMS interval (150, 300 vs. 450 ms). All post hoc comparisons were performed by using paired *t*-tests. The Greenhouse-Geisser epsilon correction was applied when necessary.

Experiment 2

Participants. The participants were 16 new right-handed healthy volunteers (10 women, 25.2 ± 1.9 years) from a different pool than in the experiment 1 who fulfilled the same criteria.

Procedures. Stimuli and TMS location were the same as in experiment 1. However, in this setting participants were asked not to correct their erroneous responses. A pulse was delivered only at 450 ms post-response (see in Results section for the rationale of this time course), after 20 correct and 20 incorrect responses. The aim of this experiment was to evaluate, if the results obtained in Experiment 1 depended on the correction process.

Data analysis. The RT differences between correct and erroneous trials, as well as the RT differences between correct trials following both incorrect and correct trials, were compared as in experiment 1. Also, the percentage of the corrections was assessed to ensure that participants did not perform a significant number of corrections. Trials affected by such corrective responses were excluded from the analysis. RT analysis, MEP quantification and transformation, and statistical analysis were performed analogously to experiment 1.

Experiment 3

Participants. The same group of participants as in experiment 2 took part in this experiment.

Procedures. Participants were asked to perform self-paced right hand button presses: either single presses with the index finger or double presses with the index finger followed by the middle finger were required. Subjects were asked to randomly perform one of these movements every 1–2 s, and were instructed to perform single and double presses in random order in about 50% each. TMS pulses were delivered to the right M1 150, 300 or 450 ms after the index finger response every six to 11 trials to minimize possible effects of a pulse delivery expectation. Pulses were delivered at the same intensity as in experiments 1 and 2. During this task, participants were instructed to fix their gaze to a fixation point, consisting in an uninformative white cross in a black background. For technical reasons, correct fixation was not monitored during the task. The aim of this experiment was to rule out that the results of the previous experiments were related to pure motor activity not associated with the ongoing task.

Data analysis. The percentages of single and double presses were computed as well as the interval between presses in the double presstrials and the average inter-trial time. The number of pulses delivered for each type

of movement and TMS interval was also calculated. Again, *z*-transformed MEP amplitudes were analyzed using a 2×3 ANOVA with factors trial type (single and double presses) and TMS interval (150, 300 and 450 ms post-response). The Greenhouse-Geisser epsilon correction was applied when necessary.

RESULTS

Experiment 1

The mean duration of the experiment (the flanker task) was 30.61 min (minimum 21.11, maximum 65.57).

Behavioral data. As expected, RTs were significantly faster for erroneous than correct responses (Table 1). Moreover, RTs of correct responses following an error were significantly slower than RTs of correct responses after a correct response, i.e. there was PES.

MEP amplitude. Resting MTs ranged between 38% and 60% of the maximum output intensity ($M = 52 \pm 5\%$). Individual stimulation intensity was kept constant throughout the experiment. For all participants, intensity ranged between 47% and 75% of the maximum output intensity ($M = 61 \pm 6\%$) that corresponded to $127 \pm 12\%$ of the resting MT (range between 110% and 152%). The average time elapsed between two consecutive pulses was 15.19 s (maximum 35.88 s, minimum 10.19 s). Fig. 2a shows the averaged MEP amplitudes with the TMS intervals aligned to the response. The repeated-measures ANOVA yielded a significant interaction between response and TMS interval [$F(2,32) = 4.37$, $\varepsilon = 0.72$, $p = .035$]. A significant difference in the MEP amplitudes elicited by the 450 ms post-response pulse was found between erroneous and correct responses [$t(16) = 2.58$, $p = .02$]. A marginally significant increase between the MEP amplitudes elicited by the pulses at 300 and 450 ms was found for erroneous responses [$t(16) = 2.06$, $p = .056$] as well as a slight decrease between the MEP amplitudes elicited 300 and 450 ms following correct responses [$t(16) = -1.86$, $p = .081$]. No other comparisons proved significant or marginally significant. No effect of finger ($p > .5$) or interaction with the factor finger was found significant ($p > .7$ for all interactions).

Experiment 2

The mean duration of the experiment (the flanker task) was 12.42 min (minimum 10.43, maximum 14.24).

Behavioral data. As in experiment 1 RTs were significantly faster for erroneous responses and significant PES was present (Table 1). We did not find differences between RTs obtained in Experiments 1 and 2 [$t(34) = 0.64$, $p = .76$)].

MEP amplitude. The stimulation intensity was kept constant in each participant and ranged between 44% and 73% of the maximum output intensity ($M = 60 \pm 7\%$) whereas resting MTs ranged between 39% and 57% ($M = 52 \pm 7\%$). In terms of the percentage of the resting MT, stimulation intensity was $121 \pm 8\%$ (range between 113% and 138%). The average time elapsed between two consecutive pulses was 15.53 s (maximum 22.22 s, minimum 10.63 s).

The rationale of this experiment was to ensure that differences in MEP amplitudes obtained at 450 ms after correct and error responses in experiment 1 were not an effect of the demanded correction of the error response. To this aim, in this experiment we asked participants not to correct the response in case it was an erroneous response, and the pulses were only delivered 450 ms post-response. Fig. 2b shows the averaged MEP amplitudes produced by pulses delivered at 450 ms post-response. Similar to the experiment 1, MEP amplitudes of erroneous responses were significantly increased compared to correct responses [$t(15) = 2.42$, $p = .02$]. No effect of finger ($p > .6$) nor finger by type of response interaction ($p > .4$) was found.

Experiment 3

The mean duration of the experiment (the flanker task) was 25.21 min (minimum 21.23, maximum 29.56).

Behavioral data. Single button presses were observed in 57.5% ($SD = 13.00$) of trials. The average inter-trial interval was 1.23 s ($SD = 0.22$) and the mean interval between presses in the double press condition was 153 ms ($SD = 34$). At least 13 pulses were delivered per trial type and TMS interval.

MEP amplitude. The average time elapsed between two consecutive pulses was 9.61 s (maximum 12.66, minimum 6.33). Fig. 2c shows the averaged MEP amplitudes produced by pulses delivered after 150, 300 and 450 ms after the self-paced single or double button presses. In case of the double presses the initial response was taken as a time-lock point. A repeated-measures ANOVA did neither reveal an effect of trial type (single vs. double) [$F(1,15) = 1.4$, $p = .43$], nor an

Table 1. Summary of the behavioral results for experiments 1 and 2. Error rate (%), reaction times (RT) in correct and erroneous trials (ms), RT of correct trials after correct trials and correct trials after error trials (ms), correction rate (%) and correction speed (ms) are shown

	Error rate	RT Error/correct	RT Correct after error/correct after correct	Correction rate	Correction speed
Exp. 1	18.8 (9)	309 (37)/387 (40)**	401 (23)/371 (10)*	83.7 (21)	260 (41)
Exp. 2	19.2 (9)	337 (35)/396 (34)**	387 (43)/365 (36)*	6.5 (3)	–

* $p < .01$.
** $p < .05$.

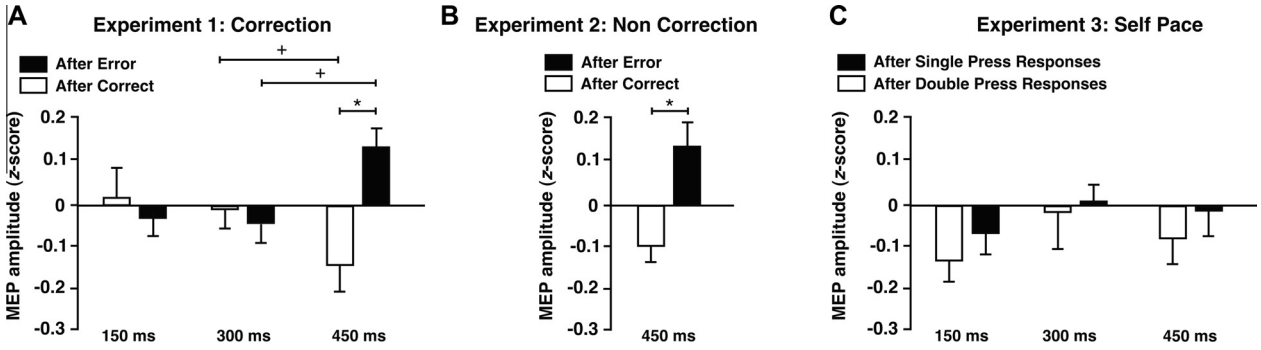

Fig. 2. Normalized MEP amplitude (*z*-score with SEM in brackets) for experiments 1 (A), 2 (B) and 3 (C). Positive *z* values correspond to those MEP amplitudes greater than the mean, whereas negative *z* values correspond to those MEP amplitudes lesser that the mean. There is an increase of the MEP amplitude at 450 ms after erroneous responses and a decrease of the MEP amplitude at the same time-interval after correct responses (A). Results were neither dependent on the correction of erroneous responses (B) nor due to the effects of single or double mere motor commands (C). For clarity purposes and given that post hoc comparisons did not reveal significance in the conditions after error vs. after correct at 150 nor at 300 ms, only statistically significant post hoc comparisons are indicated in the figure. $+.05 < p < .1$; $^{*}p < .05$.

effect of TMS interval [$F(1,15) = 0.9$, $p = .61$] or an interaction between trial type (single vs. double press) and TMS interval [$F(2,30) = 0.71$, $p = .78$]. These results indicate that MEP amplitudes neither depended on the kind of response performed nor the time elapsed between the response and the application of the pulse.

DISCUSSION

This study aimed to elucidate whether the post-response excitability of the CST is modulated by the correctness of the response by stimulating the primary motor cortex with single TMS pulses delivered with different delays after correct and incorrect hand motor responses in a flanker task. Three different experiments were performed to test our hypothesis. In the first experiment, we found that pulses delivered at 450 ms after erroneous responses (but not after 150 and 300 ms) elicited greater MEP amplitudes in the left FDI muscle than those after correct responses. Moreover, MEP amplitudes elicited at 450 ms were larger than those elicited at shorter delays. Participants in experiment 1 were encouraged to correct their errors (see Rodríguez-Fornells et al., 2002, for a comparison of ‘‘correction encouraged’’ and ‘‘correction forbidden’’ conditions in an event-related potential experiment), which might have influenced the activation level, more particularly after errors which were in most cases (83.7%) associated with a second (corrective) motor response. Therefore, a control experiment (Experiment 2) was performed in a different group of participants demonstrating that the MEP facilitation after errors at 450 ms was also present when the correction of the error was forbidden and thus could not be due to the corrective response. In addition, results from experiment 3 revealed that MEP amplitude remained unchanged over time after a mere self-paced motor response, regardless of a single or a double button press (mimicking the successive erroneous and corrective responses in experiment 1). This outcome rules out the possibility that the results of experiments 1 and 2 are driven by differences in motor preparation, or an effect of a pure motor command not related to the task.

Clearly, the results of Experiments 1 and 2 demonstrate differences in the excitability of cortico-spinal motor systems not directly involved (ipsilateral to the active hand) in the execution of the response as a function of whether or not the immediately pre-TMS response was an error or not. Because the TMS pulses were varied in time relative to the participant’s motor response, the differential dynamics of the motor system after correct and erroneous responses could be tracked. The different TMS intervals presumably coincided with the different stages of the preparation for the response of the subsequent trial. Critically, we found an increase of the MEP amplitude 450 ms after an erroneous response. In imaging studies, activations ipsilateral to the motor response have been observed during the performance of complex motor tasks (Banich, 1998; Verstynen et al., 2005; Welcome and Chiarello, 2008). Previous studies have shown that the commission of an error engaged several regions involved in performance monitoring which resulted in either decreased activation or increased inhibition of the contralateral motor cortex (Marco-Pallarés et al., 2008; Danielmeier and Ullsperger, 2011), which presumably might lead to the increase of excitability of the ipsilateral motor cortex shown in our data. Indeed, the reciprocal activation/inhibition of the two hemispheres is thought to be mediated via transcallosal connections featuring inhibitory $GABA_B$ receptors (Irlbacher et al., 2007; Palmer et al., 2012). Importantly, MEPs in Experiments 1 and 2 were elicited after stimulation of the right hemisphere and acquired from the left FDI muscle, whereas all motor responses involved the left hemisphere/right hand. This was done to avoid influences on the MEP amplitude by facilitation that had occurred if we recorded from the response hand (Hess et al., 1986; Andersen et al., 1999). Because of this setup, the MEP results obtained by stimulating the hemisphere ipsilateral to the subject’s response might be interpreted in terms of the reciprocal activation and inhibition of the left and right motor cortex. In this sense, functional imaging studies have demonstrated that unilateral movements are often associated with

activations in the ipsilateral sensorimotor cortex (Shibasaki and Nagae, 1984; Rao et al., 1993; Caramia et al., 2000; Chen et al., 2002; Kobayashi et al., 2003; Kim et al., 2004). Also, magnetoencephalographic recordings of movement-related fields have demonstrated a bilateral activation of motor areas at about 500 ms prior to self-paced unilateral movements (Cheyne et al., 1991; Salmelin et al., 1995; Tandonnet et al., 2003). Nevertheless, previous TMS studies have yielded contradicting results showing that the excitability of the hemisphere ipsilateral to a movement was increased (Hoshiyama et al. 1996; Muellbacher et al., 2000), decreased (Leocani et al., 2000; Duque et al., 2007) or unchanged during the performance of unilateral movements (MacKinnon and Rothwell, 2000). However, in a recent study Tandonnet et al. (2010) showed that the amplitude of the MEP decreased for the ipsilateral motor cortex (corresponding to the non-responding hand in a choice reaction time paradigm) after 130 ms post-stimulus presentation. This result suggests that the gradual increase of activation of the motor cortex executing the choice response is mirrored by a decrease of activation of the opposite hemisphere. This supports an active suppression mechanism of the incorrect response (Hasbroucq et al., 2000). A similar decrease in the MEP has been observed on successfully stopped trials in a stop-paradigm, reflecting a reduction of the excitability of the CST about 180 ms after the presentation of a stop signal (van den Wildenberg et al., 2009). Similarly, paired-pulse TMS has revealed that intracortical inhibitory circuits in M1 might contribute to the suppression of activation in no-go trials (Waldvogel et al., 2000) and when preventing the initiation of a response (Coxon et al., 2006). Kiçic et al. (2008) combined TMS and EEG recordings to investigate unilateral movements and showed a bilateral increase in the excitability of the sensorimotor cortex, evidenced by increases of MEP amplitudes. A smaller increase in the ipsilateral hemisphere was attributed to the fact that the excitation in the ipsilateral hemisphere coincided with additional inhibitory processes related to the suppression of mirror movements. In addition, with regard to MEP amplitudes, an amplitude increase was found prior to the movement when the contralateral (active) hemisphere was stimulated but not when the ipsilateral hemisphere was stimulated. Therefore, the increase of excitability at the ipsilateral motor cortex observed in our data at 450 ms could be taken as a marker of the reduction of excitability on the contralateral (active) motor cortex at this time. In this sense, our data are in agreement with the previously hypothesized modulation of the activity of the motor system by the commission of errors (Danielmeier and Ullsperger, 2011).

Additionally, we found a trend to reduction of the MEP amplitudes 450 ms after correct responses. Previous studies have reported evidences of reduction of response thresholds during repetitive manual or saccadic movements, producing therefore shorter reaction times in subsequent trials (Bertelson, 1961; Kirby, 1976; Soetens and Hueting, 1985; Soetens, 1998; Dorris et al., 1999; Jentzsch and Sommer, 2002; Vercauteren et al., 2008). In the same line, increasing of the activation of motor neurons involved in repeated movements has also been reported (Dorris et al., 2000). Previous EEG studies, using the amplitude of the lateralized readiness potential (LRP) as a measure of movement preparation in humans, have shown that the LRP amplitude does not return to baseline levels if the current response is the same as the preceding one, showing that response activation in the current trial is superimposed on residual activation left from previous trials (Jentzsch and Sommer, 2002). Applying these findings to our paradigm, we suggest that increase of motor activation in the contralateral motor cortex after a correct response might induce greater transcallosal inhibition in the ipsilateral motor cortex, resulting in less activation of the ipsilateral motor cortex to the active hand.

Another important aspect regards the timing of the TMS effects observed at about 450 ms after the response, even though a more extensive temporal sampling might reveal an even later peak of the effect. A possible explanation for this timing might be given on the basis of the known dynamics of error detection, error correction and post-error behavioral adjustments. A direct relationship between our findings at 450 ms and the error detection processes indexed by the ERN might be unlikely since the peak of this ERP component appears before 100 ms post-response (e.g., Rodríguez-Fornells et al., 2002). A neurophysiological marker more closely associated in time with our TMS finding is the error-related oscillatory brain activity observed by Marco-Pallarés et al. (2008). In this multimodal study, a frontocentral increase of beta power starting at about 400–500 ms after an erroneous response showed a positive correlation with PES on the next correct trial. Importantly, this beta oscillatory component (13–30 Hz) has been linked to motor inhibition (Whittington et al., 2000; Alegre et al., 2004; Kramer et al., 2009; Swann et al., 2009; Walsh et al., 2010). Our results might be compatible with these findings, since the increase of excitability of the ipsilateral motor cortex at 450 ms occurred roughly at the same time as the beta-oscillatory component associated to PES (see Danielmeier and Ullsperger, 2011 for a discussion). However, to firmly establish a relationship between these two phenomena, MEP changes and variations in oscillatory brain activity will need to be measured simultaneously in future studies.

Although our results suggest a modulation of the excitability over the motor system as a function of the correctness of the response, this study presents a set of limitations or caveats that require further discussion. First, our results are not sufficient to disentangle whether such modulatory effects presumably tied to the correctness of responses are purely intracortical or they might be associated to other non-cortical regions. In this sense, paired-pulse intracortical excitability measures (combining conditioning and test stimuli in the right and also in the left M1 cortex) might be necessary to establish a concrete role of the motor cortex underlying such

modulation. A second important limitation of this study is that these results are mainly based on the transcallosal modulation hypothesis, which has not been yet fully demonstrated and it should be taken carefully. In this context, inter-hemispheric inhibition measured through paired-pulse techniques between the right and the left primary motor areas (Duque et al., 2005; Duque et al., 2007; Vercauteren et al., 2008) might allow translating the increase (decrease) of MEP amplitudes measured following errors (correct) into a decrease (increase) of transcallosal suppression over the M1 contralateral to the responding hand. A third caveat corresponds to the lack of knowledge of the modulation of the excitability of the motor system measured by delivering pulses on the motor cortex contralateral to the active hand. Therefore, future studies will be devoted to compare the effects of post-response corticospinal excitability probed from the hemisphere involved in the actual and factual response to those homolog systems of the opposite hemisphere in different blocks. Mirror symmetric changes as those here reported might corroborate our given interpretation of these data. Although the activation of these muscles might interfere the recording of MEP amplitudes, several alternative options to pinpoint the activity of the motor system contralateral to the active hand could be considered. One way to eliminate the effect of spurious muscular activation during the record of the MEPs might be to ask participants to maintain a constant pre-activation of the active hand during the whole task. This method could allow assuming the same level of noise in all conditions causing a cancellation of the effects of this noise in data. Another possibility might be to test a right hand muscle non directly involved in the activation of the index or middle finger entailed by the response, such as the abductor pollicisbrevis (APB) or the abductor digitiminimi (ADM), not likely activated during these finger presses. In addition, due to the fact that several hand muscles present an overlapped representation in the primary motor cortex (Penfield and Boldrey, 1937; Wilson et al., 1993; Plow et al., 2010), the activity of several muscles of the right hand could be monitored at the same time by pulses in the same hotspot location. A third strategy for subsequent studies might be to implement tasks involving non-manual responses, such as verbal or saccades, to evaluate the activity in other motor areas underlying these post-error adaptation mechanisms. These methods might allow ruling out whether PES specifically affects the mechanism engaged in a given response or might be related to a more general motor planning phenomenon. A final limitation of this study concerns the lack of knowledge of the changes of excitability of the motor system respect the intended (corrective) response. In the present study we ruled out the possibility that the observed changes in the excitability of the motor cortex as a function of the correctness of the response were dependent on planning a corrective response. However, the similarity of results from the experiment 1 and 2 might arise by the fact that the distribution of the correction times is similar in all time-intervals when pulses are delivered (respect the first response), canceling a possible specific effect of the correction in the MEP amplitudes. Therefore, exploring the evolution of the excitability of the motor cortex as a function of the corrective response might be considered. Indeed, further studies could be conducted delivering pulses in time-intervals locked to the corrective response to measure possible changes in the excitability associated with the correction.

A remaining open question concerns to the brain networked areas that might cause the changes of the excitability of the CST here reported. We found changes in the modulation of this activity at 450 ms post-response indicating the influence of a series of a priori unknown areas that converge in the CST at that specific time-interval. However, little information can be extracted about which regions are previously engaged and their specific time-course of activation. In agreement with Ridderinkhof (2002), one possible explanation could be that regions from the frontal lobe might suppress the excitatory input to the corticospinal system and, therefore, modulate its excitability. A second alternative explanation would suggest that the modulation of the excitability of the CST might be triggered by the output of a conflict monitoring system involving the DLPFC and the ACC (Botvinick et al., 2001). Previous studies administered single or brief burst of high-frequency magnetic pulses to different regions of the brain in specific time intervals respect to an event in order to momentarily disrupt the corresponding neural activity at specific stages of the task (Desmurget et al., 1999; Pascual-Leone et al., 2000; Vesia et al., 2010). Particularly, applying single pulses to these regions at specific time intervals respect to the commission of mistaken responses might help to disentangle i) their functional role by measuring the behavioral effect of the suppression of its activity and (ii)the exact time-course of their activation. Additionally, little is known about potential role of other areas of the frontal lobe that might be involved in these post-error adjustments. Neubert et al. (2010) reported evidences of the contribution of the inferior frontal gyrus as well as other non-primary areas of the motor system such the pre-supplementary motor area (pre-SMA) and the pre-motor cortex of the ipsilateral hemisphere in task switching and motor inhibition that might be also be implicated in the modulation of the excitability of the corticospinal system. Furthermore, other areas outside the frontal lobe, such as the intra-parietal sulcus implicated in sensory visual feedback and integration (Gréa et al., 2002; Wolynski et al., 2009), might project to the DLPFC in the frontal lobe and ultimately to pre-motor and motor systems. Interestingly, single and brief-bursts of TMS pulses could allow us to test the potential role of these structures, as well as their time-course respect to the motor response.

CONCLUSION

This study provides a new way to examine the cognitive control mechanisms underlying post-error adjustments. Using TMS we demonstrated excitability changes of the

motor cortex ipsilateral to the response hand in a choice reaction time task. These indicate that about 450 ms after an error the excitability of the active motor cortex is adjusted in order to prevent premature responding on the next trial and thus to prevent further errors.

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