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Release of premotor activity after repetitive transcranial magnetic stimulation of prefrontal cortex

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In the present study we aimed to explore by means of repetitive transcranial magnetic stimulation (rTMS) the reciprocal influences between prefrontal cortex (PFC) and premotor cortex (PMC). Subjects were asked to observe on a computer monitor different pictures representing manipulations of different kind of tools. They had to produce a movement (go condition) or to keep the resting position (no-go condition) at the appearance of different cue signals represented by different colors shown alternatively on the hands manipulating the tools or on the picture background. Motor evoked potentials (MEPs) were collected at the offset of the visual stimuli before and after a 10 minute, 1 Hz rTMS train applied to the dorsolateral PFC (Experiment 1), to the PMC (Experiment 2) or to the primary motor cortex (Experiment 3). Following rTMS to the PFC, MEPs increased in the go condition when the cue for the go command was presented on the hand. In contrast, following rTMS to the PMC, in the same condition, MEPs were decreased. rTMS to the primary motor cortex did not produce any modulation. Results are discussed according to the presence of a visual-motor matching system in the PMC and to the role of the PFC in the attention-related processes. We hypothesize that the perceptual analysis for action selection within the PFC was modulated by rTMS and its temporary functional inactivation in turn influenced the premotor areas for motor programming.

INTRODUCTION

Prefrontal cortex (PFC) can be conceived as a set of cortical areas connected with all sensory and motor systems (Elliott, Dolan, & Frith, 2000; Fuster, 1989; Miller, 2000). This wide network provides the ideal structure for controlling important functions, namely working-memory processes

(Goldman-Rakic, 1987), emotion-related behaviors (Bechara, Damasio, & Damasio, 2000) intentional self-generated actions (Jahanshahi & Frith, 1998), planning of high-level processes or simple motor tasks (Miller, 2000). Patients with a PFC impairment could fail to pursue appropriate strategies, be bound to follow wrong rules and be unable to change them when they are required to

plan multiple, complex cognitive processes (Luria, 1966). In the same fashion, PFC patients seem to be unable to select sensory information during the planning and execution of motor tasks because they are captured by useless "sensory cues that reflexively elicit strongly associated actions" (Miller, 2000). During the execution of motor tasks, a PFC elaboration is indeed necessary at multiple levels in order to monitor the ongoing status of both the environment and the action (Petrides & Pandya, 1999). The connections between PFC, visual and sensory cortices make this function possible (Pandya & Yeterian, 1998; Petrides & Pandya, 1999; Rao, Rainer, & Miller, 1997).

In the early 1980s Lhermitte described a group of patients suffering from extensive uni- or bilateral lesions of the PFC, mainly in the basal and lateral areas of the rostral portion of frontal lobe, characterized by the compulsive tendency to interact with every object that was presented to them (Lhermitte, 1983, 1986; Lhermitte, Pillon, & Serdaru, 1986). Lhermitte's patients considered every object falling in their visual field as a potential target for a possible action (utilization behavior) or were compelled to replicate movements executed in front of them without any evident necessity to do it (imitation behavior). Years later, other authors confirmed these observations (Cambier, 1999; Shallice, Burgess, Schon, & Baxter, 1989). However, despite the growing number of new anatomical and neurophysiological evidences on the PFC functions, the mechanism responsible of such behavior has not been yet understood. Lhermitte himself tried to explain this syndrome by attributing the automatic, compulsive tendency to imitate actions or execute movements to an imbalance between the reduced activity of a lesioned PFC and the normal activity of parietal areas functionally related to PFC (Lhermitte, 1983, 1986; Lhermitte et al., 1986).

In recent years, Rizzolatti and his group have shown that mirror neurons localized in the ventral portion of primate PMC automatically fire not only during the actual execution of a movement but also during its passive observation, without the production of an actual movement (DiPellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti & Fadiga, 1998). Several subsequent experimental evidences in humans have shown a comparable activation of motor and PMC areas during observation of actions executed by others.

This internal PMC representation is probably used for their understanding (Buccino et al., 2001; Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995; Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Grèzes, Armony, Rowe, & Passingham, 2003; Grèzes, Costes, & Decety, 1999; Hari et al., 1998; Iacoboni et al., 1999; Kohler et al., 2002; Maeda, Kleiner-Fisman, & Pascual-Leone, 2002). This passive automatic activation of PMC-motor circuits, without the production of an actual movement, seems to be the counterpart of the compelling tendency to move of the PFC-lesioned patients.

Moving from these considerations we hypothesize a possible functional relation between PFC and PMC mirror activity. The present study aimed to explore these possible interactions. We model, in healthy subjects, the behavior observed in PFC-lesioned patients by means of repetitive transcranial magnetic stimulation (rTMS). We asked them to execute a go/no-go task on the presentation of pictures reproducing hands manipulating tools. Stimuli were specifically designed to demand both the PFC functions and to evoke the activation of the PMC mirror system by changing the way of analyzing and processing some of their key features (Gentilucci, Benuzzi, Bertolani, Daprati, & Gangitano, 2000; Gentilucci, Daprati, & Gangitano, 1998; Grafton et al., 1996; Kiefer, Marzinzik, Weisbrod, Scherg, & Spietzer, 1998; Konishi et al., 1999; Liddle, Kiehl, & Smith, 2001).

In order to differentiate the single contributions of PFC and PMC in task execution rTMS was employed. rTMS has been shown to be an effective tool in investigating functions of discrete regions of cortex (Hallett, 2000; Pascual-Leone, Batres-Faz, & Keenan, 1999; Pascual-Leone, Walsh, & Rothwell, 2000; Rothwell, 1991; Walsh & Cowey, 2000; Walsh & Rushworth, 1999). In particular, we used a low-frequency (1 Hz) of rTMS, which is thought to depress the excitability of the stimulated cortex for a short period of time after the completion of the train itself (Chen et al., 1997; Hallett, 2000; Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994; Walsh & Cowey, 2000). Employing a pre–post paradigm, the effects on behavior and on cortical excitability were observed, along three different experiments, before and after the delivering of rTMS over the PFC, PMC and primary motor cortex, respectively.

MATERIALS AND METHODS

Subjects

A total of 24 subjects were studied in three different experiments. In Experiment 1 we enrolled 8 males and 1 female, mean age 27.2 ($\pm$1.4 years). In Experiment 2 we enrolled another 8 males and 1 female, mean age 31.2 ($\pm$4.3 years). Finally, in Experiment 3 we enrolled 5 males and 1 female, mean age 33.0 ($\pm$3.7 years).

All subjects were right-handed according to the Edinburgh Inventory (Oldfield, 1971) and without any history of neurological diseases or vision impairments. All subjects gave written informed consent to the study, which was conducted according to the declaration of Helsinki and had been approved by the local Institutional Review Board (IRB).

Apparatus and stimuli

Subjects were seated in a dimly illuminated room, 80 cm in front of a computer screen (Macintosh, iMAC, Apple Computers Cuppertino, CA, USA) used for presentation of visual stimuli.

Stimuli consisted of digital images of right hands manipulating different tools (i.e., pliers, scissors, pen, screwdriver, knife, etc.). SuperLab pro, v1.74 (Cedrus Corp., San Pedro, CA, USA) was used for stimuli presentation and reaction time (RT) recording. The images were elaborated using Adobe Photoshop (v5.5).

In different visual stimuli, the hands or the background were painted with one of the following colors (see Figure 1, panel A): (a) red; or (b) one of three colors chromatically close to the red (pink, orange, and purple); or (c) one of three other colors chromatically different from the red and easily distinguishable from it (green, blue, and yellow). Their chromatic properties were assessed according to the RGB scale. The meaning of the colors, regardless of which part of the stimulus (hand or background) was colored, was to convey the instruction for the task that the subjects had to accomplish: red for the go signal, all the other colors for the no-go signal (see procedure below).

Such colors were chosen in order to increase the demands during the perceptual elaboration of the stimuli and thereby, presumably, to modulate the amount of activity within the PFC. We hypothesized that, if the delivering of rTMS can modulate the supposed PFC–PMC functional circuitry, it would be possible to reproduce some features of the unwilling tendency to move of Lhermitte's patients, and that such an effect would be stronger when the stimulus analysis become more difficult (i.e., at presentation of colors chromatically closer to the red) that is when a greater involvement of PFC resources was required. Furthermore, requiring to focus alternatively different part of stimuli, our prediction was likely to induce the subjects to pay more attention to a relevant (at the hand observation) or non-relevant (at the background observation) feature for mirror activation and consequently to change the strength of the mirror effect. In this way, we speculated that we would be able to observe a possible modulation of PFC on the PMC mirror system. Finally, the rationale for the use of static stimuli instead of moving hands was to allow the locking of the evoked activity within the PMC-motor circuit to the time of the TMS pulse.

Procedure

A go/no-go paradigm was employed. Subjects were asked to execute two different tasks: (1) press with the right index finger the space-bar on a computer keyboard every time the red color was presented, either on the hand or on the background (go condition); (2) maintain the resting position every time any color other than red was presented, either on the hand or on the background (no-go condition). The computer keyboard (extended keyboard, Apple Computers, Cuppertino, CA, USA) was used to collect the responses and the RTs in the go condition. Given the employed setup, resolution on RT measures was $\pm$16 ms. The position of the index finger on the keyboard and of the wrist on the table was marked for each subject and kept constant across the experimental sessions.

Each experimental session (before and after rTMS) was composed of 144 trials. For the no-go condition subjects completed 96 trials, 16 for each of the six presented colors, that is 8 trials in which the informative color was presented on the hand (colored-hand condition) and 8 trials in which the color was presented on the background (colored-background condition). For the go condition subjects completed 48 trials, 24 for each one of
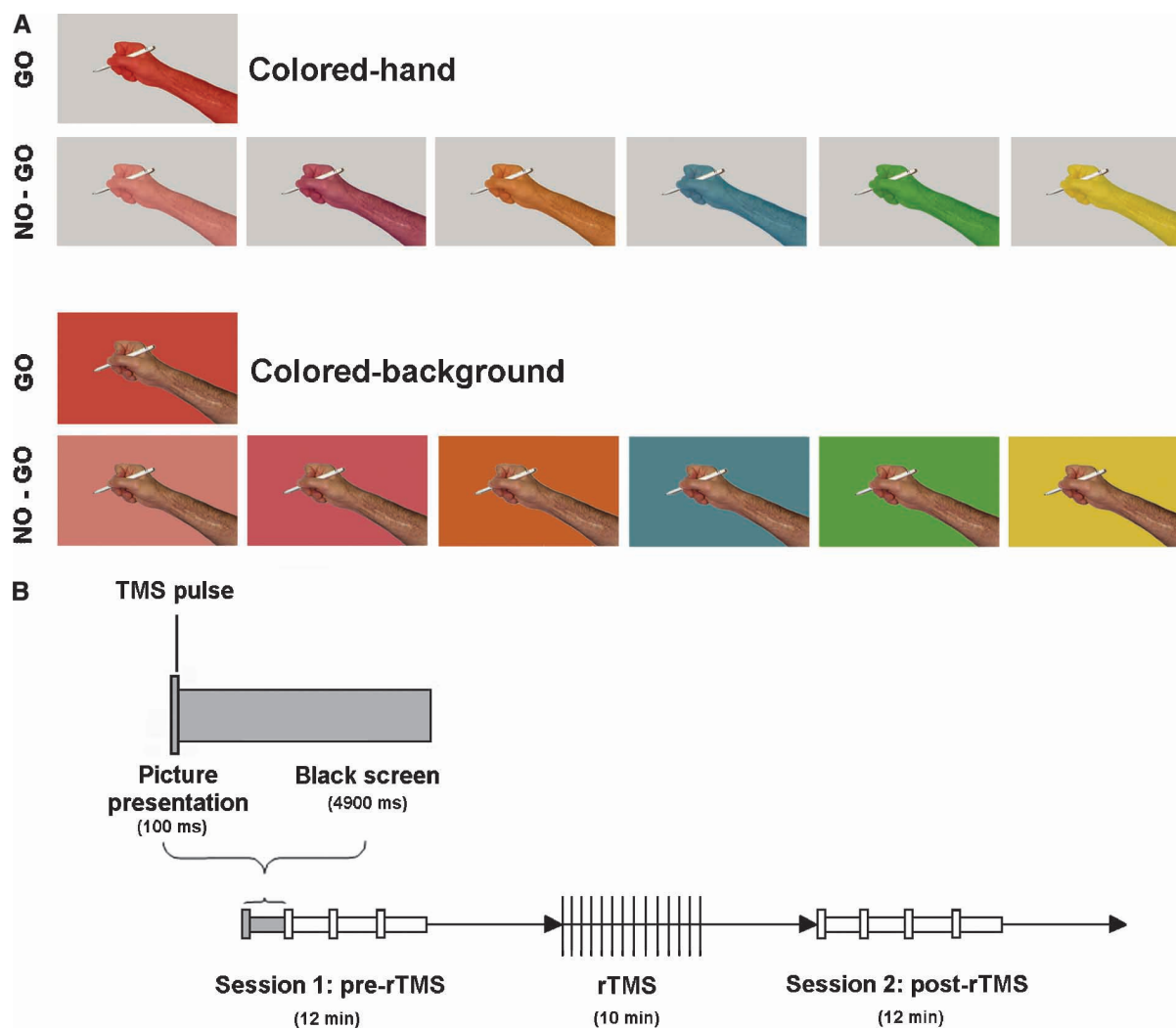
Figure 1. Representative examples of the presented stimuli (panel A) and a schematization of the task design (panel B) are shown. Subjects were requested to press (go) or not to press (no-go) the space-bar of a PC keyboard on the basis of the colors presented on the pictures. Colors were alternatively shown on the hand (first row: "colored-hand" condition) or on the background (second row: "colored-background" condition). Each experiment consisted of two sessions executed before and after rTMS over the dorsolateral PFC (Experiment 1), PMC (Experiment 2) and primary motor cortex (Experiment 3). Stimuli were presented for 100 ms and were followed, for 4900 ms, by a central fixation-cross on a black screen. At the pictures offset a single TMS pulse was delivered on the optimal spot for FDI. One hundred forty-four trials were serially executed in 12 minutes. At the end of this period rTMS was applied for 10 minutes. rTMS was immediately followed by a new execution of the task. For further details see text.

the two kinds of stimuli (colored-hand and colored-background). The order of stimuli was randomized. No-go trials were made more frequent in order to increase the elaboration within the PFC (Jahanshahi & Frith, 1998). The duration of a single trial was 5 s: images were shown for 100 ms and at their offset a central fixation-cross appeared on a black screen for 4900 ms (see Figure 1, panel B). Therefore, each experimental session lasted 12 minutes.

During each trial, when the picture disappeared from the screen, a single magnetic pulse was delivered to the optimal representation of the

right first dorsal interosseus (FDI) muscle in the left primary motor cortex (see TMS procedure below). Times for stimuli presentation and TMS were chosen in order to explore the early cortical elaboration before the response generation. Previous EEG (Thut et al., 2000) and TMS single-pulse studies (Hoshiyama et al., 1997; Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000) employing visuo-motor tasks have shown the activation of the PMC-motor cortices 100–200 ms after stimulus perception. Other studies employing go/no-go paradigms have shown the modulation of MEPs in the interval between

120 and 300 ms after the signal (Yamanaka et al., 2002). In choosing the timing of the TMS we tried to avoid any interference of the single TMS pulses with the impending response movement. Nevertheless, the possible presence of a close muscular activity was checked by recording the EMG trace for a period 50 ms antecedent and 200 ms subsequent to the TMS pulse. The interval between each TMS pulse was at least 5 s in order to avoid any interference between two subsequent stimuli.

Each experiment was divided into two sessions, serially executed. In the first session (pre-rTMS) the basal data were collected. The second session (post-rTMS) was preceded by a 10-minute train of rTMS applied at a frequency of 1 Hz and 90% motor threshold intensity. The cortical area targeted by this rTMS train varied in the three experiments. In Experiment 1 we targeted the left dorsolateral PFC. In Experiment 2, rTMS was applied to the PMC area—Brodmann area (BA) 6. Finally, in Experiment 3, rTMS was applied to the primary motor cortex. These different cortical targets were defined anatomically using each subject's brain MRI to verify the placement of the TMS coil on the scalp (see below for details). In all experiments, the pre-rTMS session was proceeded by a short practice session in which the subjects became familiar with the stimuli and the task.

TMS stimulation

Single-pulse TMS and repetitive TMS were performed using a Magstim Super-Rapid Transcranial Magnetic Stimulator (Magstim Company, Whitland, UK) and a 70 mm figure-of-eight coil. For the purpose of single-pulse TMS and induction of motor-evoked potentials (MEPs) TMS was delivered to the scalp position from which TMS induced MEPs of the maximal amplitude in the contralateral FDI muscle. This position was marked on a tightly fitting Lycra swimming cap placed on the subject's head. The coil was held tangentially to the subject's head, with the handle pointing occipitally, positioned at 45 degrees with respect to the mid-sagittal axis of the subject's head. This coil orientation elicits the maximal response with a predominant, indirect, pyramidal-cells activation (Brasil-Neto, McShane, Fuhr, Hallett, & Cohen, 1992; Mills, Boniface, & Schubert, 1992).

Two surface electrodes were placed on the belly and tendon of the right FDI muscle, the finger used for the response. Electrodes were connected to a Dantec Counterpoint Electromyograph (Dantec, Skovlunde, Denmark) in order to collect the MEPs. The EMG signal was amplified (to 1 mV), filtered (band pass of 20–1000 Hz) and digitized using PowerLab 16S (AD Instruments Limited, Hastings, UK) at the sampling rate of 2 KHz and stored on a computer for subsequent off-line analysis.

Subjects' motor threshold (MT) was initially assessed, before the rTMS application. MT was defined as the minimal intensity of stimulation capable of inducing MEPs greater than $50 \mu V$ peak-to-peak in at least five out of ten consecutive trials (Rossini, 1994). MT was used as a reference value to set the single-pulse intensity and rTMS intensity. For the single pulse the intensity was set at 110% of the individual's MT.

Repetitive TMS was delivered at 90% of the individual's MT with a frequency of 1 Hz for 10 minutes, for a total of 600 stimuli. This kind of stimulation conforms to current safety guidelines (Wassermann, 1998). For Experiment 1, the stimulation site for rTMS was established using the optimal spot of FDI motor response and moving the coil 5 cm anterior along a line parallel to the mid-sagittal line in order to target the dorsolateral PFC (BA 9/46). Coil orientation during rTMS was the same as during the assessment of MT. In Experiment 2, rTMS was applied to the caudal PMC (BA 6). This point was defined by moving the coil 2 cm forward from the optimal spot for FDI responses, along a line parallel to the mid-sagittal line. Finally, in Experiment 3 rTMS was delivered to the primary motor cortex itself. This third experiment was conducted because given the anatomical proximity during rTMS of the premotor (Experiment 2) a spread of stimulation to the motor cortex, which could account for the results, cannot be completely excluded (Pascual-Leone et al., 1994). In all three experiments, the anatomical location of the stimulation points was verified by obtaining an anatomical MRI of the brain.

MRI procedure

In order to verify the anatomical correctness of coil placement during rTMS a 3D-MPRAGE MRI scan (160 sagittal slices 1 mm apart with an in-plane resolution of $256 \times 256 \, \text{mm}^2$) was

obtained at the end of the post-rTMS session in four subjects in each of the three experiments. Vitamin E capsules were placed on the scalp to mark the site of rTMS stimulation. Additional markers were placed above Cz of the 10–20 EEG system, on the nasion, on the inion and on the tragus bilaterally. The actual location of the coil position on the scalp with respect to the frontal gyrus was subsequently assessed using MRIcro (Chris Rorden, UK, Version 1.23).

As illustrated in Figure 2, images showed that the targeted TMS scalp positions were indeed above the rostral part of the gyrus frontalis medium (presumed to correspond in most subjects with BA 9/46; Experiment 1) on the rostral part of the precentral gyrus (presumed to correspond with BA 6; Experiment 2) and on the anterior bank of the central sulcus (primary motor cortex, BA 4; Experiment 3). The inter-individual variability of the anatomical targets
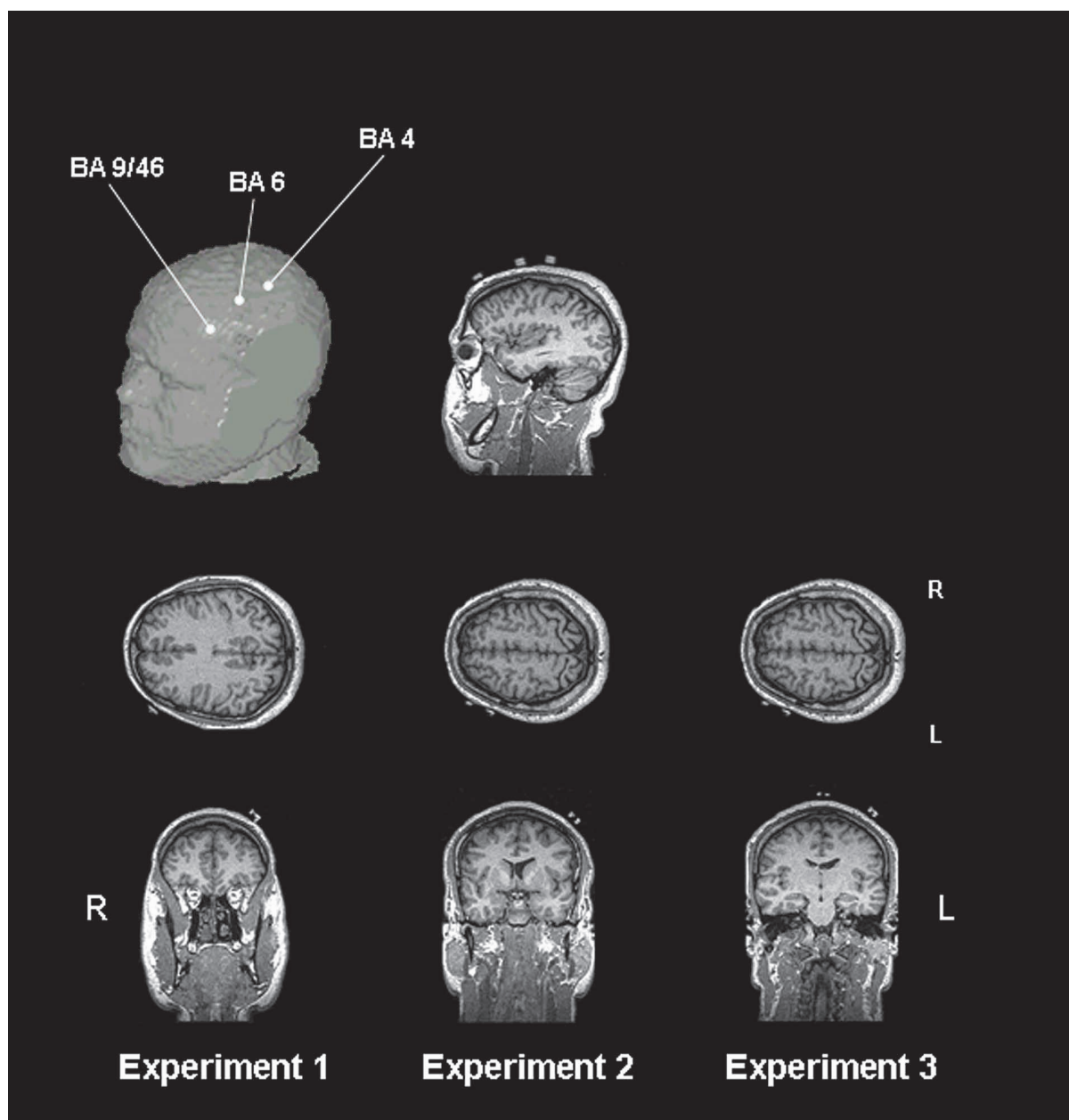

Figure 2. MRI scans obtained from a representative subject who participated in Experiment 1 are shown. Coil placement over the left dorsolateral PFC (BA 9/46), PMC (BA 6) and primary motor cortex (BA 4) was confirmed using a 3D MRI sequence with vitamin E capsules in place. Details are reported in the text.

was well within the presumed spatial resolution of the rTMS with the employed coil (1–1.5 cm).

Data analysis

MEPs, responses in the go condition, and response times (RTs) were collected and analyzed. MEPs were rectified and the area under the curve was calculated. Two different analyses of variance (ANOVA) were executed. In the first analysis the no-go trials were collapsed. Data were averaged across the subjects and submitted to a $2 \times 2 \times 2$ ANOVA, using as within-subjects factors the Stimulation Condition (pre-rTMS vs. post-rTMS), the Colored Section of Stimuli (colored-hand vs. colored-background) and the Response Condition (go vs. no-go). The second ANOVA was carried out contrasting the presented colors separately. A $2 \times 2 \times 7$ design was employed using as factors the Stimulation Condition, the Colored Section of Stimuli and the seven Presented Colors. In all analyses Newman-Keuls test was employed post hoc for the multiple comparisons. Significance level was set at $p < .05$. Errors in the pre- and post-rTMS sessions were compared by means of two-tailed t-tests. Errors were considered the space-bar pressure in the no-go condition and the absent response in the go condition. Finally, RTs for each trial in the go condition were submitted to a 2×2 ANOVA using as factors the Stimulation Condition (pre or post-rTMS) and Colored Section of Stimuli (colored-hand or colored-background).

RESULTS

Experiment 1: rTMS applied to the PFC

Colors chromatically close to the red didn't produce any modulation of cortical excitability, neither before nor after rTMS. A $2 \times 2 \times 7$ ANOVA analyzing the influence of single colors on MEP size did not show any effect either when they were presented on the hands or on the background.

After rTMS, a significant increase of the motor excitability was present across all experimental conditions as indexed by the increase in the MEPs size, pre-rTMS: $2.51 \, mm \times mV$, post-rTMS: $3.39 \, mm \times mV$, $F(1, 8) = 5.92$; $p < .041$. Mean values for each condition are shown in Figure 3A. The post hoc analysis confirmed the

overall facilitation of the MEPs after rTMS (all the post-rTMS conditions are significantly different from the pre-rTMS ones; all ps < .05). However, after rTMS, the go condition with the cue signal presented on the hands induced a greater activity than alternative conditions (go with cue signal on the background, all no-go conditions), as shown by the significant 3-way interaction between stimulation condition, colored section of stimuli condition and response condition, $F(1, 8) = 6.19$; $p < .038$.

No differences in number of errors and RTs were found across all conditions (see Table 1). The EMG recording didn't show any trial contaminated by any early muscular activity that could have interfered with the MEPs.

Experiment 2: rTMS applied to the PMC

No variation of the overall motor excitability was found after rTMS. As in the Experiment 1, in this experiment the 3-way interaction between stimulation condition, colored section of the stimuli condition and response condition was significant, $F(1, 8) = 29.29$; $p < .001$. However, differently from Experiment 1, in which a greater activity after rTMS was observed in the go condition when the hand was painted in red as compared with the other conditions, in this experiment the size of the MEPs was modulated in the opposite fashion becoming smaller (see Figure 3B). A significant effect was observed also in the 2-way interaction between stimulation condition and colored section of stimuli, $F(1, 8) = 5.35$; $p < .05$. The hands were less effective in modulating MEPs size than background. Similar to the findings in Experiment 1, no differences were present among different colors in the no-go condition. No differences in number of errors and RTs before and after rTMS were found (see Table 1).

Experiment 3: rTMS applied to the motor cortex

In this final experiment, rTMS was applied to the motor cortex in order to control for the possible spread of the rTMS effects from the PMC to the motor cortex during Experiment 2. After rTMS an overall, but non-significant trend to MEPs suppression (see Figure 3C) was observed. In contrast to Experiments 1 and 2, no modulation of the MEPs' size across the post-rTMS conditions was present. Interaction
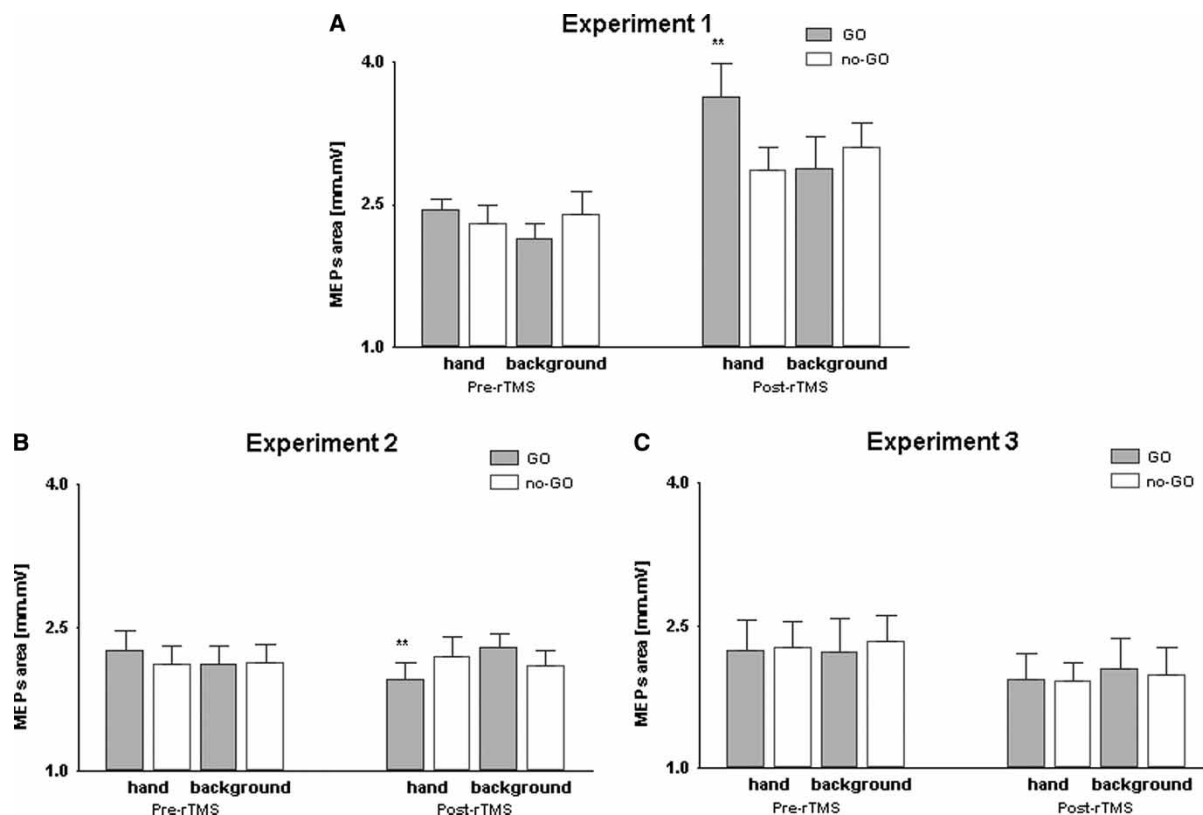
Figure 3. MEPs from FDI collected before and after rTMS for the two conditions of color presentation in the go and no-go tasks during Experiment 1 (rTMS over PFC, panel A), Experiment 2 (rTMS over PMC, panel B) and Experiment 3 (rTMS over primary motor cortex, panel C). Histograms refer to the MEPs area-under-the-curve, averaged across the subjects. Whiskers are standard error of means (*SEM*). **($p < .05$) refers to the significant variation in post-rTMS conditions with respect to the pre-rTMS conditions.

between stimulation condition, colored section of the stimuli and response condition was not significant, $F(1, 5) = 1.28$, $p = .31$. RTs collected in the pre-rTMS session were significantly shorter than RTs after rTMS, $F(1, 5) = 6.26$, $p = .05$, but we found no significant effect of rTMS on the number of errors (see Table 1).

DISCUSSION

Effects on cortico-spinal excitability

Several different results of the present study deserve mention and discussion. First, rTMS resulted in differential effects on cortico-spinal

TABLE 1
Mean values of reaction times and number of errors in the go condition

| | RTs (ms) | | | | Errors (n) | |
| | Red hand | | Red background | | | |
	Pre-rTMS	Post-rTMS	Pre-rTMS	Post-rTMS	Pre-rTMS	Post-rTMS
Experiment 1	439.3 (24.8)	426.6 (36.2)	440.5 (24.1)	435.2 (35.2)	4.0 (1.3)	4.6 (1.8)
Experiment 2	431.2 (42.5)	416.3 (48.0)	437.6 (42.7)	424.7 (53.1)	4.3 (0.7)	3.0 (0.5)
Experiment 3	376.9 (26.7)	390.6 (31.9)	405.6 (44.2)	436.7 (50.1)	4.8 (0.5)	4.2 (0.6)

Notes: RTs = reaction times. Data are collected in the go condition before and after rTMS over the dorsolateral PFC (Experiment 1), PMC (Experiment 2) and primary motor cortex (Experiment 3). For each value the corresponding standard deviation is shown in parentheses.

excitability depending on the targeted cortical region. In Experiment 1, rTMS of the PFC caused an overall increase of MEPs (Figure 3A). Such an effect was not found after rTMS applied over the PMC (Experiment 2, Figure 3B) whereas only a trend toward suppression was found after rTMS over the primary motor cortex (Experiment 3, Figure 3C).

Although the suppression of cortico-spinal excitability following low-rate rTMS of the motor cortex in Experiment 3 is consistent with other observations (Chen et al., 1997; Hallett, 2000; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000b; Pascual-Leone et al., 1999, 2000; Rothwell, 1991; Walsh & Cowey, 2000) the lack of similar effects in Experiment 2 (when the rTMS was applied to the PMC) is surprising in light of findings that have shown the presence of a robust decrease of cortico-spinal excitability after 1 Hz rTMS to the PMC (Gerschlager, Siebner, & Rothwell, 2001) when intensities of 90% of motor threshold has been employed (Rizzo et al., 2003). Other studies employing low intensities of stimulation (80% MT) on the same premotor spot have shown small or no modulatory effects on MEP amplitude (Münchau, Bloem, Trimble, & Rothwell, 2002). It is possible that in our study the relatively short duration of the rTMS train may not have been sufficient to induce a more robust modulation of cortico-spinal excitability. More important is the fact that subjects were engaged in preparing a motor response. This probably may have modified the rTMS effects.

The main finding in our results is the demonstration of a facilitation of cortico-spinal excitability following rTMS to the PFC. Several anatomical studies can support this hypothesis. The PFC is connected to PMC by means of indirect cortico-cortical, i.e., through the parietal lobe (Pandya & Yeterian, 1998; Petrides & Pandya, 1999) or subcortical projections, i.e., through the basal ganglia (Alexander, DeLong, & Strick, 1986; Alexander, Cructher, & DeLong, 1990); other direct connections are between the dorsolateral PFC and rostral part of the PMC. On the basis of these connections, premotor areas can be subdivided into several different subregions endowed with different properties (see Schubotz & von Cramon, 2003, for a review on this argument). In sum, rTMS over the dorsolateral PFC could have influenced the rostral PMC and, from there, the primary motor cortex. Alternatively, rTMS

could have primarily exerted an influence on the PFC-connected areas (e.g., the parietal cortex), feeding back to the PMC.

However, we believe that the increase in cortico-spinal excitability following rTMS to the PFC (Experiment 1) could be explained by hypothesizing a suppression of PFC facilitating in turn the activity of the primary motor cortex only when subjects were already engaged by a task that might facilitate the motor cortical outputs. According to this hypothesis, the PFC has a pure modulatory role. This point will be further discussed below. We can exclude that these effects are the consequence of a spread of rTMS from PFC to the nearby premotor and motor cortices. In fact, a different modulation was found after the direct application of rTMS over these sites. The same explanation excludes the presence of a possible "order effect" due to the fixed sequence of sessions.

Interaction between prefrontal and premotor cortices

Against our initial prediction, before rTMS, in all three experiments, we failed to detect any modulation of MEPs when subjects were required to orient their attention toward features capable of evoking (attention toward the hands) or not evoking (attention toward the background) the mirror effect. MEPs collected across the two conditions of color presentation (hand or background colored), were indeed similar. In addition, no significant modulation of the MEPs in the no-go condition for the color group closer to the red was observed. Moreover, our subjects were still able to properly judge the instruction conveyed from the stimuli, and differently from prefrontal-lesioned patients described by Lhermitte no "compulsion to move", revealed by changes in RTs, was ever induced by rTMS when colors close to red were presented.

However, in despite of these apparently negative evidences, a noticeable effect was found. In Experiment 1, after rTMS, MEPs in the go condition increased significantly when the hands conveyed the information for the impending task. We believe that this effect was task specific. This assumption is supported by the following considerations. (i) Although an overall increase of cortical excitability was present after rTMS over dorsolateral PFC, the existence of two opposite modulations in Experiments 1 and 2 (i.e., the

3-way interaction, see Results) indicates that the effect was induced by the visual elaboration of the stimuli. After targeting the premotor areas, we found a decrease of MEPs in the same condition (go with colored hand) that was enhanced in Experiment 1 (see Figure 3A and 3B). The presence of this "reverse-effect" makes a non-specific or artifactual modulation quite improbable. (ii) Methodological biases, like the presentation of non-natural colors that could have surprised the subjects inducing an involuntary muscle contraction can be safely excluded as well. Such a kind of perceptual influence was controlled against by allowing subjects to become familiar with the stimuli before the execution of the task. (iii) A muscle preactivation induced by the preparation of the motor response can be excluded as well because it should have affected all conditions and this was not the case. Furthermore, our on-line EMG recording ruled out any contraction of the target muscles before or after the single TMS pulses.

Our first hypothesis is that such an effect could be attributed to the changes of properties within the circuitry linking the dorsolateral portion of the PFC and the PMC and in turn influencing the mirror system within the PMC. In recent years, a growing number of studies on monkeys have described two different populations of premotor neurons, the canonical and mirror neurons, both of them endowed with similar visuo-motor properties for the programming of goal-directed movements (Fogassi et al., 2001; Rizzolatti & Fadiga, 1998). However, differently from canonical neurons, mirror neurons are activated not only during the execution of actual movements but also when the monkey observes another individual executing an action in front of it (Gallese et al., 1996). It has been proposed that mirror neurons generate the internal representation of the observed action used in movement recognition and imitation processes (Fadiga, Fogassi, Gallese, & Rizzolatti, 2000; Iacoboni et al., 1999; Kohler et al., 2002). TMS and ERP studies have confirmed that analogous properties can be found in humans (Fadiga, Craighero, Buccino, & Rizzolatti, 2002; Fadiga et al., 1995; Gangitano, Mottaghy, & Pascual-Leone, 2001; Hari et al., 1998; Nelissen, Luppino, Vanduffel, Rizzolatti, & Orban, 2005; Strafella & Paus, 2000). In general, a mirror neuron discharges at the observation of "biological" movements (e.g., the movement of an arm or of a hand executed by another animal or by a human being). It has been shown that

human mirror system may be more capable than monkey mirror system of processing abstract visual representation of actions (Saygin, Wilson, Hagler, Bates, & Sereno, 2004) and that a mirror effect can also be evoked at the observation of static stimuli suggesting the idea of actions, like pictures of hands holding or manipulating objects (Gentilucci et al., 1998, 2000; Grafton et al., 1996) that is the same kind of stimuli that we used. In our study, it is possible that mirror activity was enhanced by the temporary failure of PFC. The mirror effect (i.e., difference between hand and background condition) was evident only when the activation within the PMC was maximal, that is when it was recruited for the preparation of a motor act (the go response). This explanation can take into account both the overall increase in excitability of the primary motor cortex and the selective modulation in the condition in which the colored hand was analyzed for the go response.

However, we have to consider that mirror recruitment was revealed only by the MEPs modulation in the red-hand condition. Moreover, neither a significant change in the RTs nor in the number of errors was found throughout all experiments. In Experiment 3, the increase in RTs can be explained considering a compromising of motor function induced by an inhibitory frequency of stimulation delivered directly on the primary motor cortex (Pascual-Leone et al., 1994). Consequently, it is possible that the observed effect was caused by the modulation of PFC on the primary motor cortex without the involvement of the PMC mirror system.

PFC plays a key role in the guidance of complex behaviors such as working memory (Elliott et al., 2000; Fuster, 1989; Miller, 2000; Petrides & Pandya, 1999) or decision-making tasks (Frith, 1991; Hyder et al., 1997; Jahanshahi & Frith, 1998). PFC is recruited either when different alternative responses have to be chosen or when an action has to be selected and performed (Miller, 2000). In both cases, signal elaboration within PFC seems to proceed according a common schema. When a non-motor act is required, PFC elaborates and filters information stored elsewhere (Grafman, 1995) making possible the choice between "more than one equally appropriate responses" (Frith, 1991; Jahanshahi et al., 1998; Jahanshahi & Rothwell, 2000). During the execution of motor tasks, PFC helps the analysis, the selection and the focusing of sensorial inputs relevant to the aim of the impending action whether voluntary or automatic

(Norman & Shallice, 2000; Seitz, Stephan, & Binkofski, 2000). Left dorsolateral PFC is engaged in elaborating signals from sensory processing areas during perceptual decision making (Heekeren, Marrett, Ruff, Bandettini, & Ungerleider, 2006; Rorie & Newsome, 2006). Information related to object properties are integrated along pathways linking the parietal the PFC and the PMC (Boussaoud, 2001; Rao et al., 1997). Particularly, the posterior and the dorsal portions of the lateral PFC are involved in the visuo-spatial and motor processing, whereas the ventral PFC regions seem to be particularly interested in information about visual form and stimulus identity (Pandya & Yeterian, 1998). On the other hand, recent evidence from studies of both humans and monkeys may indicate that the dorsal PMC, besides its traditional function in movement planning and execution plays a role also in attention and working-memory functions. Furthermore, PMC seems to be endowed with pure perceptual functions such as speech perception (Wilson, Saygin, Sereno, & Iacoboni, 2004) or sensory-attentional processes for motor programming such as recognition and prediction of sequential motor patterns (Schubotz & von Cramon, 2002). Attention-related properties seem to be relatively segregated to the more rostral portion of lateral PMC whereas the more caudal portion is endowed with intention-related or motor properties (Boussaoud, 2001; Schubotz & von Cramon, 2003; Simon et al., 2002). The specialization of the rostral PMC subregion derives also from the pattern of connections feeding it, receiving projections from both dorsolateral PFC and the parietal cortex. Differently from the caudal subregion, the rostral PMC does not send noticeable projections to either motor cortex or spinal cord (Boussaoud, 2001; Schubotz & von Cramon, 2003; Simon et al., 2002). For these reasons rostral PMC may be conceived as functionally belonging to the PFC cortex whereas caudal PMC could be seen as a true motor area (Schubotz & von Cramon, 2003).

Moving from these considerations, it is possible to offer an alternative explanation for our results. In our task, subjects had to decide what action (pressing the space bar or keeping the resting position) they had to perform on the basis of the visual analysis of a stimulus. rTMS over the PFC could have interfered with the prefrontal-premotor "attentional switch" for sensory elaboration. It is possible that the perceptual analysis of stimuli was less efficient due to the lack of the

PFC sensorial filter, making necessary an over-commitment of the PMC-motor efferent pathway indexed by the increase of MEPs. Hypothetically, the activation in the red-hand condition was more pronounced both because a movement had to be prepared and because hands were more difficult to elaborate. However, this explanation does not take into account the different MEPs modulation in the go condition in Experiment 2 described above. Furthermore, a significant increase in the errors rate after rTMS should be expected and this was not the case.

Lesions of PMC are followed by either deficits in initiation of simple movements or automatic triggering of complex motor acts (Rizzolatti & Luppino, 2001). In the latter case it is possible to observe symptoms like forced grasping, alien-hand syndrome and utilization behavior. It has been proposed that all these neurological signs could be the consequence of a loss of inhibitory afferents to PMC from the PFC and the cingulate control (Rizzolatti & Luppino, 2001). On the other hand, lesions of the mesial cortical areas usually lead to the appearance of negative symptoms like motor inertia. Taken together our results could suggest that rTMS effects on PFC could have produced the release of its inhibitory influence on the premotor activity in turn increasing the excitability of the primary motor cortex. Such modulatory control could be reduced or be absent in patients with PFC lesions hence accounting for their compulsive imitation or utilization behavior. The remarkable behavior of the patients described by Lhermitte (Lhermitte, 1983, 1986; Lhermitte et al., 1986), who depicted their automatic compulsive tendency to imitate actions or execute movements as the direct consequence of an imbalance between parietal and frontal elaboration, could provide clinical support for this hypothesis.

In our study the lack of signs towards a "compulsive tendency to move" stronger than the increase of MEPs could be due to the relative sparing of circuits only partially affected by rTMS capable of "compensating" the transient deficit induced by rTMS on targeted areas. Generally, rTMS was not expected to suppress the function of the targeted brain region, but rather to modulate its activity to a certain degree, by approximately 15 or 20% if consistent with the findings of similar protocols on cortico-spinal excitability (Gangitano et al., 2002; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000a; Romero, Anschel, Sparing, Gangitano, &

Pascual-Leone, 2002). In this sense rTMS effects on PFC can be conceived as the result of the "dynamic" modulation of multiple afferences and efferences in a complex neuronal network (Mottaghy et al., 2000).

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