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Transcranial magnetic stimulation of medial prefrontal cortex modulates face expressions processing in a priming task

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ABSTRACT

The medial prefrontal cortex (mPFC) and the right somatosensory cortex (rSC) are known to be involved in emotion processing and face expression recognition, although the possibility of segregated circuits for specific emotions in these regions remains unclear. To investigate this issue, we used transcranial magnetic stimulation (TMS) together with a priming paradigm to modulate the activation state of the mPFC and the rSC during emotional expressions discrimination. This novel paradigm allows analyzing how TMS interacts with the ongoing activity of different neuronal populations following prime processing. Participants were asked to discriminate between angry and happy faces that were preceded by a congruent prime (a word expressing the same emotion), an incongruent prime (a word expressing the opposite emotion) or a neutral prime. In TMS trials, a single pulse was delivered over the mPFC, rSC or Vertex (control site) between prime and target presentation. TMS applied over the mPFC significantly affected the priming effect, by selectively increasing response latencies in congruent trials. This indicates that the mPFC contains different neural representations for angry and happy expressions. TMS over rSC did not significantly affect the priming effect, suggesting that rSC is not involved in processing verbal emotional stimuli.

1. Introduction

Face expression recognition is a crucial skill for human interactions and adaptive social behaviour (Adolphs, 1999). Converging evidences from functional neuroimaging (Critchley et al., 2000; Davidson & Irwin, 1999; Vuilleumier & Pourtois, 2007) and lesion studies (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Adolphs, Damasio, Tranel, & Damasio, 1996; Philippi, Mehta, Gabrowski, Adolphs, & Rudrauf, 2009) have allowed identifying a cortical–subcortical neural network including regions involved in the perception and processing of facial expressions. These circuits include cortical areas primarily implicated in face processing like the inferior occipital cortex, the superior temporal sulcus, the fusiform cortex (Haxby, Hoffman, & Gobbini, 2000) and regions involved in processing emotional stimuli, like the amygdala, prefrontal cortex, insula and cingulate cortex (Cristinzio, Sander, & Vuilleumier, 2007; Dolan et al., 1996; Morris, Ohman, & Dolan, 1998; Nomura et al., 2004; Phillips, Drevets, Rauch, & Lane, 2003).

The medial prefrontal cortex (mPFC) and the somatosensory cortex (SC) have also been found to play a critical role in emotion discrimination (Adolphs, 2002; Dolan et al., 1996; Kesler-West et al., 2001; Winston, O'Doherty, & Dolan, 2003). In particular, the prefrontal cortex is connected with the amygdala and likely modulates emotional responses through cognitive control (Hariri, Bookheimer, & Mazziotta, 2000; Nomura et al., 2004). Further studies suggest that the prefrontal cortex has a critical role in emotional stimuli processing (Hornak, Rolls, & Wade, 1996), representation of affective states (Davidson & Irwin, 1999) and in processes that allow using emotional stimuli as cues for social behaviour (Damasio, 1994). Neuropsychological studies support these hypotheses by demonstrating that patients with mPFC damage are impaired in recognizing emotional expressions and this deficit is associated with abnormal social behaviour (Mah, Arnold, & Grafman, 2005) and reduced emotional responsiveness (Heberlein, Padon, Gillihan, Farah, & Fellows, 2008).

Recent theories of embodied cognition also emphasize the role of the SC. This area facilitates facial emotion recognition through simulation processes of reactivation of somatovisceral responses associated with early acquisition and production of the perceived emotion (Niedenthal, 2007). In a study with a large sample of brain-damaged patients, Adolphs et al. (2000) reported that the integrity of the right (r)SC was necessary for normal recognition of facial expressions. A more recent transcranial magnetic stimulation (TMS) study supports this conclusion by demonstrating that stimulation of the rSC disrupts discrimination of different facial expressions (Pitcher, Garrido, Walsh, & Duchaine, 2008). In particular, Pitcher et al. (2008) found that stimulation of rSC with repetitive TMS or with double pulse delivered after 100 ms from target onset

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reduced accuracy in discriminating happy, sad, surprise, fear, disgust and angry faces with no expression-specific effect.

Despite the evidence pointing to a crucial role of the mPFC and the rSC in facial emotion processing, one unsolved issue concerns whether these regions contain distinct neural circuits representing different types of emotion. Lesion studies have shown that brain damage can differently affect the ability to recognize specific emotions (Adolphs et al., 1996; Heberlein et al., 2008), but neuroimaging studies have provided conflicting results about the different circuits involved in the processing of specific facial expressions (Kesler-West et al., 2001; Winston et al., 2003). In particular, while evidence concerning amygdala and insula contribution respectively to fear and disgust processing is consistent (Adolphs, Tranel, Damasio, & Damasio, 1994; Calder, Lawrence, & Young, 2001; Morris, Friston, et al. 1998; Phillips et al., 1997), the cortical areas involved in other basic emotions, like anger and happiness, are less clearly defined. Kesler-West et al. (2001) found that angry faces activated the medial region of the superior frontal gyrus while happy faces activated the medial frontal/cingulate sulcus region. By means of an explicit discrimination task during fMRI, Phillips et al. (1998) found a specific signal increase in the anterior and posterior cingulated gyri and in the mPFC when happy facial expressions were presented, while no brain region showed signal increase for sad expressions. In a different fMRI study (Blair, Morris, Frith, Perret, & Dolan, 1999), in which the emotional variable was implicit, the right orbitofrontal cortex responded to angry, but not sad faces. On the contrary, TMS applied over the mPFC increased response times in discriminating angry, but not happy faces (Harmer, Thilo, Rothwell, & Goodwin, 2001).

Concerning the rSC, lesion and functional studies suggest that this area contributes to facial expression processing regardless emotion type (Adolphs et al., 2000; Winston et al., 2003). Consistently with this, repetitive TMS over rSC disrupted accuracy in discriminating all the six basic emotions (Pitcher et al., 2008). However, Pourtois et al. (2004) found that single pulse TMS over rSC selectively interfered with fear but not happy expressions. Conversely, happiness expressions were more affected compared to other emotions in a recognition task when subjects' facial mimicry was blocked by an irrelevant task (as bite a pen with the teeth or the lips) supposed to involve the rSC (Oberman, Winkielman, & Ramachandran, 2007). These contrasting results may depend on different emotions requiring different levels of somatic representation. The rSC activation may thus vary depending on the perceived facial expression. Accordingly, different effect of TMS on rSC in emotional processing may depend on the interaction between the specific stimulation parameters (i.e. intensity, frequency) and the specific level of activation of the rSC region (Hussey & Safford, 2009).

In light of the above, our study aimed at clarifying whether the activation of the mPFC and rSC in emotion processing is specific for type of emotion. To address this issue, we used state-dependent TMS (Silvanto & Pascual-Leone, 2008; Silvanto, Muggleton, & Walsh, 2008), which is based on the assumption that TMS effects depend on the pre-existing activation state of the targeted neural population. Specifically, we used a TMS-priming paradigm (Cattaneo, Rota, Vecchi, & Silvanto, 2008) in which participants were primed with a word related to happiness or anger, and were then asked to indicate whether a face following the prime word was happy or angry (Carroll & Young, 2005). A TMS pulse was delivered before target onset. According to TMS state-dependent view (Silvanto & Pascual-Leone, 2008; Silvanto et al., 2008), combining TMS with a priming paradigm enables to assess the existence of possible functionally distinct neural representations for different emotions within the stimulated cortical area. In particular, a different TMS effect on primed or unprimed targets can reveal that the area contains neural populations that were selectively activated by the different primes processing (Cattaneo et al., 2008; Silvanto, Schwarzkopf, Gilaie-Dotan, & Rees, 2010). On the contrary, if this is not the case and there are no distinct representations within the area, all the neural populations should respond equally regardless of prime category and no interaction between TMS and prime type would appear. Therefore, if the stimulated cortical region contains distinct neural representations for happiness and anger, priming to either one should differentially modulate the initial activation state of these populations, and TMS should interact with the priming effect. Specifically, TMS should have a different effect on emotion recognition depending on whether the prime word and the target face refer to same (congruent trials) or different (incongruent trials) emotions.

In line with previous evidence, we predicted that TMS over the mPFC would have differentially affected performance depending on prime type (see Harmer et al., 2001; Phillips et al., 1998). Predictions for the TMS effects over the rSC are less straightforward: according to Pitcher et al. (2008), TMS should affect emotion discrimination regardless of the emotion type. However, according to other studies (Oberman et al., 2007; Pourtois et al., 2004), rSC recruitment in emotion recognition may vary depending on the extent of facial mimicry induced by different facial emotions presented. If this is the case and the intensity of the single-pulse TMS is sufficient to disrupt embodied representations in rSC, TMS should affect emotion discrimination regardless of prime type, since the area is likely to be activated by faces processing but not by emotional words.

2. Method

2.1. Participants

Twenty healthy volunteers participated in the experiment. All subjects (8 males, 12 females; mean age = 22.3; SD = 2.4) were University students and gave written consent prior to their participation. All participants had normal or corrected to normal vision and no history of mental or neurological illness or other specific contraindications for TMS. The experiments took place in the TMS laboratory of the University Milano-Bicocca with the approval of the local Ethics Committee.

2.2. Material

Eight Italian words were used in the experiment as prime words (see Appendix A). All words were chosen from the Corpus and Frequency Lexicon of Written Italian (COLFIS, see http://www.istc.cnr.it/material/database/colfis/index_eng.shtml), and included four "anger-related" words (rage, ire, aggressiveness, violence) and four "happy-related" words (joy, gaiety, happiness, good cheer). Prime words were chosen on the basis of a preliminary questionnaire administered to 14 undergraduate students (7 male, 7 female, mean age = 24.6), different from those participating in the TMS experiment. Subjects were asked to rate on a four-point Likert scale (1 = "not at all", 2 = "a little", 3 = "enough", 4 = "a lot") the relatedness of each word with anger and happiness. The questionnaire included 16 words for the two emotions; the four words of each emotion with the higher relatedness score for the target emotion and a score <1.5 for the opposite emotion were selected. Independent sample *t*-test on the selected words confirmed that there were no significant differences between the two categories in word length ($p = 0.75$) and total written frequency ($p = 0.64$). The neutral prime consisted of a string of eight "#" (where eight corresponded to the mean number of letters of the emotional prime words). We used a non-word string as neutral prime in line with a previous study (Cattaneo, Devlin, Salvini, Vecchi, & Silvanto, 2010), in order to avoid accidental systematic associations

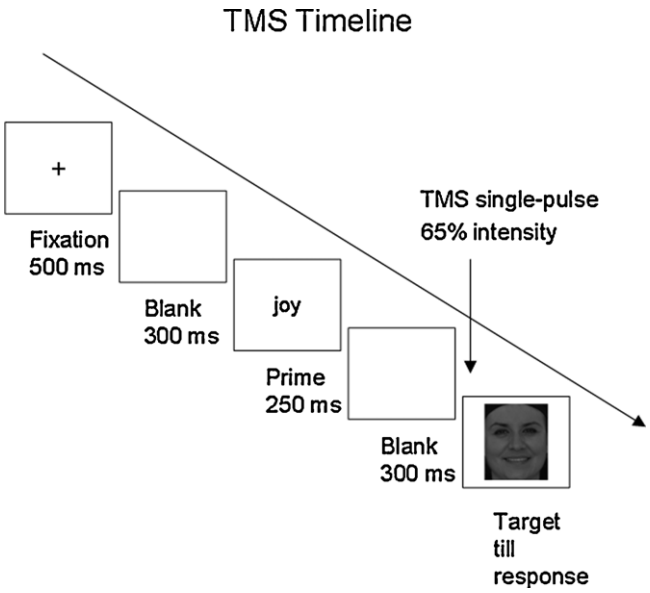

Fig. 1. Timeline of a TMS experimental trial of the main Experiment. In each trial, the prime was a happiness-related word, an anger-related word, or a neutral non-word. The target was a face with either a happy or an angry expression. In the TMS conditions, a single-pulse TMS was applied over the medial prefrontal cortex (mPFC), the right somatosensory cortex (rSC) or Vertex at target onset.

between non-emotional words and individual positive or negative feelings. The face stimuli were coloured photographs of 8 different unknown individuals, 4 males and 4 females, with either an angry or happy face. Photographs were chosen from the Bosphorus 3D Database (Savran et al., 2008) on the basis of a preliminary study with 20 additional students (10 male, 10 female, mean age = 24.1). Photographs were presented on a computer screen, displaying seven different expressions (neutral, anger, disgust, fear, happiness, sadness, surprise) together with the name of the seven emotions; participants were required to match each facial expression with the corresponding name. The photographs of the four individuals whose angry and happy expressions were more consistently identified (mean accuracy score >75%) were selected as stimuli for the main experiment.

2.3. Experimental procedure

Fig. 1 depicts the timeline of an experimental trial. Subjects were asked to judge as fast and as accurately as possible whether the target face expressed anger or happiness, pressing two buttons with the index and middle right hand fingers; response-button correspondence was randomized across subjects. Each experimental trial started with a fixation point in the middle of the screen lasting for 500 ms and followed by a blank screen for 300 ms. Then, the prime word appeared for 250 ms, followed again by a blank screen (300 ms) and the target face stimulus, which remained on the screen until the subject responded. The experimental procedure included eight blocks, two for each stimulation site (mPFC, rSC, Vertex) and two for the baseline no-TMS condition, with a total of 192 trials for each experimental condition. Blocks order was counterbalanced across subjects.

2.4. TMS

In TMS trials a single-pulse TMS was delivered immediately before the target onset by means of a Magstim Standard Rapid magnetic stimulator (Magstim, Whitland, UK) with a figure-of-eight coil (70 mm diameter) at 65% intensity of the maximum stimulator output. A fixed intensity was chosen on the basis of previous studies (e.g. Campana, Cowey, & Walsh, 2002; Cattaneo, Devlin, et al., 2010). The stimulated areas were the mPFC, rSC and the Vertex (control site), in addition to a baseline condition without TMS. The face area of rSC was localized using the SofTaxic Evolution Navigator System (E.M.S., Bologna, Italy). This system allows the co-registration of the coil and subject's head positions and the localization on the scalp of the position corresponding to the cortex area of interest on the basis of the subject's MRI. Four subjects had their own T1-weighted structural MRI. When an individual MRI is not available, Softaxic allows computing an estimate MRI volume on the basis of a set of points registered from the subject's scalp. Talairach's coordinates for rSC ($x = 51$, $y = -13$, $z = 29$) were individualized on the basis of a previous fMRI study (Drevets et al., 2005). For mPFC stimulation, the coil was positioned on the scalp at one-third of the distance between the nasion and the inion on the midline between the left and right periauricular points (see Fig. 2) (see Harmer et al., 2001, for similar procedure). The Vertex was localised as the point falling half the distance between the nasion and the inion on the same midline (Pitcher et al., 2008).

3. Results

Trials were classified as "congruent" when the prime and the target face referred to the same emotion (e.g. joy and happy face), as "incongruent" when the prime and the target face referred to a different emotion (e.g. joy and angry face), and "neutral" when the prime was neutral. Mean percentage accuracy for congruent trials was 95.1% in the baseline, 95.9% in the Vertex, 94.3% in the mPFC and 95.7% in the rSC condition. For incongruent trials, mean percentage accuracy was 95.6% in the baseline, 93.8% in the Vertex, 95.7% in the mPFC and 93.7% in the rSC condition. For neutral trials, mean percentage accuracy was 95.6% in the baseline, 95.5% in the Vertex, 96.6% in the mPFC and 95.5% in the rSC condition.

In order to consider possible TMS effects on both RTs and accuracy we incorporated these two measures in a single analysis by dividing RTs by the proportion of correct responses. This is a standard measure, which allows to combine RTs and accuracy in a single performance score controlling for any potential speed-accuracy trade-offs across participants and conditions (Brozzoli et al., 2008; Igarashi, Kitagawa, Spence, & Ichihara, 2007; Kiss, Driver, & Eimer, 2009; Mevorach, Humphreys, & Shavel, 2006). One subject was excluded because his RTs (adjusted for accuracy) were >2 SD the participants' mean. Hence, all the analyses were carried out on 19 subjects. In the baseline condition the mean adjusted RTs were faster in the congruent trials (532.36 ms) compared to the incongruent (535.14 ms) and the neutral trials (543.82 ms). However, a repeated measures ANOVA with Prime (three levels: congruent, incongruent, neutral) as within-subjects variable revealed that the effect of Prime was not significant [$F(2, 36) = 1.74$, $p = .19$].[1]

To verify that the Vertex could be considered as a control condition, baseline and Vertex stimulation were compared by means of pairwise t-test for each prime type. Vertex and baseline did not differ in any experimental condition (congruent primes [$t(18) = 0.2$, $p = .84$], incongruent primes [$t(18) = -1.33$, $p = .2$], neutral primes [$t(18) = -0.007$, $p = .99$]).

[1] Critically, the same pattern of results was reported in a control behavioural experiment, carried out on 12 new subjects (5 male, 7 female; mean age = 23, SD = 2.98) using the Italian word "neutrale" ("neutral" in English) as neutral prime. Mean RTs (adjusted for accuracy) were faster for congruent trials (568.82 ms) than for incongruent (581.93 ms) and neutral trials (588.55 ms). A repeated measures ANOVA with Prime (three levels: congruent, incongruent, neutral) as within-subjects variable revealed that the effect of Prime was not significant [$F(2, 22) = .82$, $p = .45$]. These data rule out the hypothesis that the effects we reported in the baseline condition of our experiment depend on the use of a non-word neutral prime.

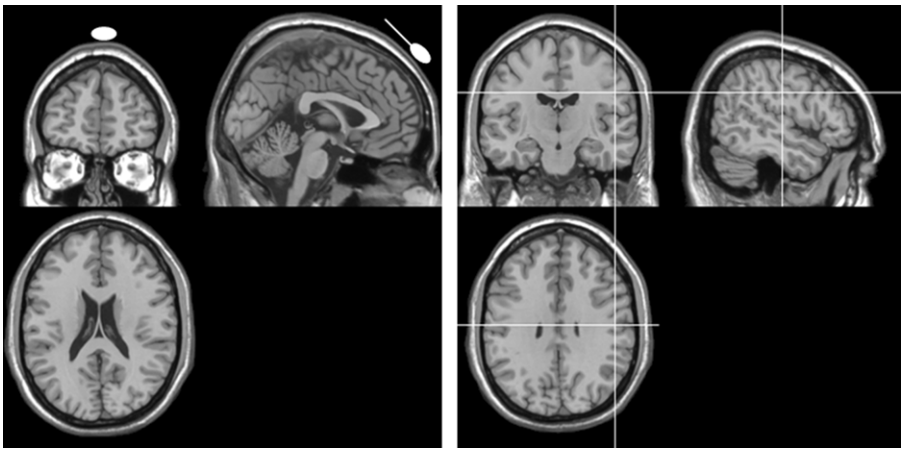

Fig. 2. Normalized locations of mPFC and rSC. mPFC was localized at one-third of the distance from nasion to inion; the coil position is reported (left side). Localization of the face area in the rSC was based on Talairach coordinates 51, −13, 29 (right side).

3.1. The effect of TMS on priming

Since baseline and Vertex did not show any difference, Vertex was used as unique control condition. To investigate whether TMS interfered with the priming effect, the difference between congruent and incongruent trials, considered as a measure of the congruent primes facilitatory effect, was compared among the three TMS conditions. Fig. 3 shows the effect of TMS on the priming benefit. A 3×2 repeated measures ANOVA on the priming effect with TMS (three levels: Vertex, mPFC, rSC) and Emotion (two levels: anger, happiness) as within-subjects variables showed a significant main effect of TMS [$F(2, 36) = 4.45$, $p = .019$], while neither the effect of target Emotion [$F(1, 18) = 0.19$, $p = .67$] nor the interaction [$F(2, 36) = 1.71$, $p = .20$] were significant. Bonferroni post hoc analysis showed a significant difference between Vertex and mPFC conditions [$t(18) = -5.06$, $p < .001$], whereas the difference between Vertex and rSC was not significant [$t(18) = -1.05$, $p = .92$].

To investigate whether the effect of TMS on priming benefit differently affected congruent or incongruent trials, a repeated measures ANOVA with TMS (three levels: Vertex, mPFC, rSC), Emotion (two levels: anger, happiness) and Prime (two levels: congruent, incongruent) as within-subjects variables was performed on the mean response latencies adjusted for accuracy. The analysis showed a significant main effect of TMS [$F(2, 36) = 3.57$, $p = .038$] and a significant interaction TMS × Prime [$F(2, 36) = 4.45$, $p = .019$]. The main effect of Emotion [$F(1, 18) = .02$, $p = .89$] and Prime [$F(1, 18) = .18$, $p = .68$] and the remaining interactions were not significant. Pairwise comparisons on the TMS main effect revealed that adjusted RTs were longer when TMS was applied over the mPFC and the rSC as compared to the Vertex, but such difference was not significant when correcting for multiple-comparisons (mPFC–Vertex [$t(18) = -2.12$, $p = .048$], rSC–Vertex [$t(18) = -2.17$, $p = .043$], significance level <.025, according to Bonferroni's correction). To further investigate the significant interaction TMS × Prime, simple main effect analyses of TMS for each prime were carried out collapsing together the two emotions. TMS was found to significantly affect congruent trials [$F(2, 36) = 4.57$, $p = .017$] but not incongruent trials [$F(2, 36) = 2.03$, $p = .15$] (see Fig. 4). Pairwise t-tests showed that adjusted RTs increased for congruent trials when TMS was applied over mPFC as compared to the Vertex [$t(18) = -3.27$, $p = .004$]. Critically, as shown in Fig. 4, TMS over rSC seems to have an unspecific effect by overall increasing response latency regardless of prime type, although not to a significant extent ([$t(18) = -2.01$, $p = .06$] for congruent trials and [$t(18) = -1.78$, $p = .092$] for incongruent trials).

3.2. Control experiment

In order to exclude the possibility that our results were due to TMS interfering with priming per se rather than specifically with emotional priming, a control experiment was carried out, in which a gender priming task was used and the same cortical sites as in the previous experiment were stimulated.

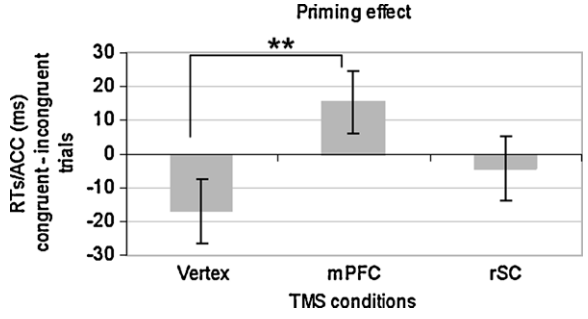

Fig. 3. Priming effect expressed in ms (i.e. difference between RTs adjusted for accuracy in congruent and incongruent trials) in the three TMS conditions. Negative values indicate that target discrimination was faster on congruent trials than on incongruent trials. TMS over mPFC abolished the benefit of the congruent prime; the double asterisk indicates a significant effect ($p < .001$), error bars represent Standard error of the means.

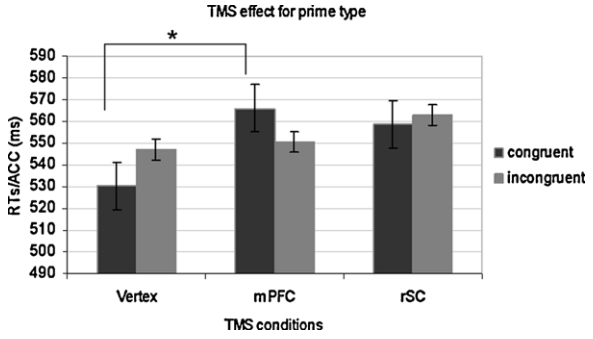

Fig. 4. Effect of prime type on facial expression recognition for the three stimulated sites. TMS over mPFC interfered with facial expression discrimination when targets were preceded by congruent primes; an asterisk indicates a significant effect ($p < .05$), error bars represent Standard error of the means.

4. Method

4.1. Participants

Thirteen subjects participated in this experiment (5 males, 8 females; mean age = 23; SD = 2.8) in the TMS laboratory of University Milano-Bicocca. All subjects had normal or correct to normal vision, no specific contraindication for TMS and they gave written consent to their participation.

4.2. Material and procedure

The same paradigm, TMS sites and procedure of the previous experiment were used, but the task was to judge as fast and as accurately as possible whether the target face was a male or female. The Italian words "maschio" (male) and "femmina" (female) were used as prime words together with the word "vivente" (alive) as neutral prime. We chose this latter word because in Italian it has the same number of letters as the other prime words and carries no gender information. The face stimuli were the same eight individuals photographs from the Bosphorus 3D Database (Savran et al., 2008), but with a neutral expression.

5. Results

Data were analyzed using the same measures, namely RTs adjusted for accuracy, and steps of the affective priming experiment. Trials were classified as "congruent" when the prime and the target face referred to the same gender (e.g. male and male face), as "incongruent" when the prime and the target referred to different gender (e.g. male and female face), and "neutral" when the prime was neutral. Mean percentage accuracy for congruent trials was 97.4% at the baseline, 97.2% during stimulation of the Vertex, 96.4% during stimulation of the mPFC and 97% during stimulation of the rSC. For incongruent trials, mean percentage accuracy was 96.4% at the baseline, 96.4% in the Vertex, 96.9% in the mPFC and 95.8% in the rSC condition. For neutral trials, mean percentage accuracy was 97.8% at the baseline, 96.8% in the Vertex, 97.3% in the mPFC and 96.7% in the rSC condition.

At the baseline with no-TMS, adjusted RTs were 476.70 ms for congruent trials, 489.46 ms for neutral trials, and 491.26 ms for incongruent trials. A repeated measures ANOVA with Prime (three levels: congruent, incongruent, neutral) as within-subjects variable revealed that the effect of Prime was not significant [$F(2, 24) = 1.95$, $p = .16$]. Baseline and Vertex conditions, compared by means of pairwise t-test for each prime type, did not differ in any experimental condition (congruent primes [$t(12) = 0.34$, $p = .74$], incongruent primes [$t(12) = -0.02$, $p = .98$], neutral primes [$t(12) = 1.24$, $p = .24$]); hence, Vertex was used as unique control condition in the following analyses. The potential effect of TMS on priming benefit (difference between congruent and incongruent trials) was compared in the three TMS conditions. A 3×2 repeated measures ANOVA on the priming effect with TMS (three levels: Vertex, mPFC, rSC) and target Gender (two levels: female, male) as within-subjects variables did not lead to any significant effect (TMS [$F(2, 24) = 1.16$, $p = .34$], Gender [$F(1, 12) = .20$, $p = .66$], TMS by target Gender interaction [$F(2, 24) = .06$, $p = .94$]). As for the main Experiment, a further repeated measures ANOVA was carried out on the mean adjusted RTs with TMS (three levels: Vertex, mPFC, rSC), target Gender (two levels: male, female) and Prime (two levels: congruent, incongruent) as within-subjects variables. The analysis showed a significant main effect of Prime [$F(1, 12) = 5.57$, $p = .036$], indicating that adjusted RTs were faster in congruent than in incongruent trials. Neither the effect of TMS [$F(2, 24) = 1.23$, $p = .31$], nor of target Gender [$F(1, 12) = 2.82$, $p = .12$] was significant. None of the interactions reached significance.

6. General discussion

In the present study, we investigated the role of the mPFC and the rSC in discriminating happy and angry expressions by using a TMS-priming paradigm. TMS delivered over the mPFC at target onset was found to significantly interfere with the priming effect, compared to the Vertex. In particular, stimulation of the mPFC selectively interfered with the discrimination of both angry and happy expressions when the prime was congruent with the target, but not when it was incongruent. According to the state-dependent view of TMS (Silvanto et al., 2008), this TMS–prime interaction suggests that the stimulated area contains distinct neural representations for the emotions of anger and happiness that were selectively activated by the prime. In other words, the presentation of a specific prime induced an activation imbalance between specific neural populations mediating the representation of the corresponding emotion within the targeted region, and TMS selectively interacted with this activity imbalance (Silvanto et al., 2008). Conversely, if the mPFC contained a common representation for both emotions, TMS would have affected response latencies regardless of the type of prime. This was indeed the case for rSC stimulation that did not significantly interfere with the priming effect. As shown in Fig. 4, TMS over this region led to a trend for a general impairment compared to the Vertex condition, regardless of the prime used.

Critically, the effects we reported proved to be specific for emotion processing, since TMS did not affect a gender priming task in which the same faces used in the main experiment (but with a neutral expressions) were presented as targets (see Control Experiment).

Our data fit with the hypothesis that the mPFC contains different representations for different emotions, and that these representations can be activated by an emotional word (and not only by presentation of an emotional face). This suggests that the role of the prefrontal cortex in emotion recognition may be related to lexical knowledge of the facial expression. Accordingly, Adolphs et al. (2000) reported that patients with frontal damage failed in a verbal categorization task, in which emotion expressions had to be matched to the correct name. Our results are also in line with Phillips et al.'s (1998) fMRI study that found activation in the middle frontal gyrus (BA 32) during happy face perception and with Kesler-West et al. (2001), who found activation in the mPFC for both angry and happy faces processing. More specifically, Kesler-West et al. (2001) reported activation of BA 32 and 10 for happiness and superiorly in BA 9 for anger. In our experiment, the coil was positioned over the mPFC; based on individual MRI available this area seems to correspond approximately to BA 32. However, considering TMS spatial resolution (Walsh & Cowey, 2000), we cannot exclude that BA 9 and 10 were also affected by stimulation. Our findings extend previous neuroimaging evidence by showing that mPFC plays a causal role in emotion recognition and contains different neural representations for the emotions of anger and happiness.

In a previous TMS study, stimulation of the mPFC was found to selectively affect the processing of angry expressions, whereas happy expressions were unaffected (Harmer et al., 2001). Conversely, our findings suggest that mPFC encodes both happy and angry faces, with different neural representations associated with the two emotions. The use of different methodologies may account for this different outcome. In particular, Harmer et al. (2001) assessed the effect of TMS in discriminating anger and happiness from neutral expressions in two separate tasks. They presented morphed faced with increasing expression intensity and stimuli close to the recognition threshold of each subject were selected for the TMS experiment. This task was probably more difficult than ours, thus possibly leading to a difference in the discrimination between happy and angry faces that did not emerge in our study

(i.e. we did not report a main effect of target emotion). In addition, Harmer et al. used repetitive TMS (four pulses applied at target offset) with a classical "virtual lesion" approach (Walsh & Cowey, 2000), while we assessed both emotional expressions in a single task by means of a TMS state-dependent paradigm. This approach allows a higher functional resolution relative to "virtual lesion" TMS, because one can control which neural population within the stimulated area is facilitated or inhibited by TMS (Silvanto et al., 2008).

TMS over the rSC did not modulate the priming effect, although a trend for an overall impairment on emotion recognition was observed after stimulation of this site (regardless of the prime used and of the target emotion presented). This finding is in line with the hypothesis that rSC plays a role in face expressions recognition but is not differentially activated by different emotions (see Pitcher et al., 2008). The fact that in our experiment TMS over rSC did not result into a clear impairment (as in the case of Pitcher et al., 2008) may be due to the specific TMS timing and parameters: we delivered a single pulse of TMS at target onset, whereas Pitcher et al. (2008) used repetitive TMS. If, as suggested, the rSC cortex plays a role in emotion recognition through mimicry simulation and the reactivation of the somatovisceral sensations linked to the perceived emotion (Adolphs et al., 2000; Adolphs, 1999; Niedenthal, 2007; Oberman et al., 2007), it is likely that our stimulation occurred too early to interfere with this processing. Similarly, the early timing of our TMS stimulation may have prevented possible differences related to the level of simulation induced by different emotions to emerge (see Pourtois et al., 2004). Conversely, our results clearly indicate that the rSC was not differently activated by words conveying an emotional meaning. Thus, it seems that the role played by the rSC in emotion recognition is specific for visual facial expressions and does not extend to more abstract concepts.

Previous TMS state-dependent studies have consistently found that, following adaptation, TMS facilitates the detection of adapted stimuli (e.g. Cattaneo, Rota, Walsh, Vecchi, & Silvanto, 2009; Silvanto, Muggleton, Cowey, & Walsh, 2007), suggesting that TMS preferentially stimulates the less active neural populations relative to more active ones (Silvanto et al., 2008). However, the evidence on how TMS interacts with priming is less clear, with reports of facilitation of unprimed trials (Cattaneo, Devlin, et al., 2010) as well as impairment of primed trials (Silvanto et al., 2010). Our results support the latter solution, since they show that TMS over mPFC affected trials with a congruent prime.

In the baseline no-TMS condition the priming task did not show an evident behavioural effect, since response latencies in congruent and incongruent trials were not significantly different. This may appear at first puzzling. However, similar results were obtained in a previous behavioural study (Carroll & Young, 2005) with affective priming tasks. Indeed, Carroll and Young (2005) found evidence of a facilitation of the congruent condition relative to the neutral condition, but no inhibition in the incongruent condition compared to either the neutral or congruent condition. The authors suggest that this is due to a "leakage" effect between emotions, since emotional categories in part overlap. In other words, an incongruent emotional prime may still prime the following target by activating an "emotional" network, whereas this does not happen in the case of a neutral prime. There may be some degree of priming between emotional prime and incongruent target since face expressions and emotional words are never completely unrelated. Nonetheless, we were interested in assessing whether the mPFC contains separate neural representations for different emotions. Accordingly, analyses were performed on the priming effect (i.e. the difference between congruent and incongruent trials). TMS over the mPFC was found to differently affect emotional processing depending on the prime used, suggesting that anger and happiness words activated at least partially segregated neural circuits within the stimulated region. Notably, similar results have been found in previous studies, which have reported state-dependent TMS effects in spite of weak behavioural effect (Cattaneo, Sandrini, & Schwarzbach, 2010; Cohen Kadosh, Muggleton, Silvanto, & Walsh, 2010).

Our results also shed light on the debate concerning priming mechanisms with affective stimuli. The priming effect in this type of task has been interpreted as due to spreading activation between related concepts in a semantic network (Fazio, Sanbonmatsu, Powell, & Kardes, 1986; Fazio, 2001). According to this explanation related stimuli share some features, so that the congruent prime facilitates target recognition by activating these common features (Masson, 1995). The alternative hypothesis posits that affective priming is due to processes occurring at the response selection stage rather than at the semantic encoding stage, so that the longer latencies in the incongruent trials are due to a Stroop-like response conflict mechanism (De Houwer, Hermans, Rothermund, & Wentura, 2002; Wentura, 1999). Previous studies demonstrated that the mPFC is activated by the Stroop effect (Liu, Banich, Jacobson, & Tanabe, 2004) and is involved in response inhibition and control stimulus–response contingencies (Picton et al., 2007). According to the response-selection account, mPFC-TMS should have increased the priming effect, resulting into a larger difference between congruent and incongruent trials. On the contrary, we found a selective mPFC-TMS effect on congruent trials with longer response latencies when prime and target referred to the same emotion, while incongruent trials were unaffected. This suggests that the priming effect likely depends on spreading activation among related concepts (Masson, 1995).

Finally, our findings confirm the importance of the TMS state-dependent paradigm (Silvanto et al., 2008) as a tool to study high cognitive functions. However, the physiological basis of the state-dependent effects is not completely clear, and future studies should directly investigate how TMS interacts with neural mechanisms involved in affective priming combining TMS with neuroimaging or electrophysiological techniques such as fMRI or electroencephalography (EEG).

In summary, our data contribute to clarify the role of the mPFC and of the rSC in the network underlying affective processes. The mPFC was found to contain selective representations for emotions like anger and happiness; this result supports previous evidence indicating that the mPFC implements both negative and positive emotions (Davidson & Irwin, 1999). On the other side, the rSC did not seem to be involved in representing emotional concepts. Our data also shed light on the mechanisms underlying affective priming, suggesting that priming in this context depends on spreading activation among connected elements (Masson, 1995).

Appendix A.

See Table A1.

Table A1
Words related to anger and happiness used as primes.

Happy words		Angry words	
Italian	English	Italian	English
Gioia	Joy	Aggressività	Aggressiveness
Allegria	Gaiety	Collera	Rage
Contentezza	Happiness	Ira	Ire
Buonumore	Good cheer	Violenza	Violence

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