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Disrupting Pre-SMA Activity Impairs Facial Happiness Recognition: An Event-Related TMS Study

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It has been suggested that the left pre-supplementary motor area (pre-SMA) could be implicated in facial emotion expression and recognition, especially for laughter/happiness. To test this hypothesis, in a single-blind, randomized crossover study, we investigated the impact of transcranial magnetic stimulation (TMS) on performances of 18 healthy participants during a facial emotion recognition task. Using a neuronavigation system based on T1-weighted magnetic resonance imaging of each participant, TMS (5 pulses, 10 Hz) was delivered over the pre-SMA or the vertex (control condition) in an event-related fashion after the presentation of happy, fear, and angry faces. Compared with performances during vertex stimulation, we observed that TMS applied over the left pre-SMA specifically disrupted facial happiness recognition (FHR). No difference was observed between the 2 conditions neither for fear and anger recognition nor for reaction times (RT). Thus, interfering with pre-SMA activity with event-related TMS after stimulus presentation produced a selective impairment in the recognition of happy faces. These findings provide new insights into the functional implication of the pre-SMA in FHR, which may rely on the mirror properties of pre-SMA neurons.

Keywords: facial emotion recognition, happiness, mirror neurons, pre-SMA, transcranial magnetic stimulation

Introduction

Facial expressions are a key feature for communication within and across species (Darwin 1872). This type of non-verbal communication is based on the expression, perception, and recognition of facial emotions. Facial emotion recognition (FER) appears to be closely related to social functioning (Hooker and Park 2002; Addington et al. 2006), and is impaired in a variety of psychiatric and neurological conditions, such as schizophrenia (Bediou, Franck et al. 2005, Bediou et al. 2007), major depressive disorder (Bediou, Krolak-Salmon et al. 2005), Parkinson's disease (Lachenal-Chevallet et al. 2006), as well as fronto-temporal dementia and Alzheimer's disease (Bediou, Ryff et al. 2009). FER is also impaired in healthy individuals with heightened risk for developing schizophrenia (Bediou, Ryff et al. 2009). Hence, better understanding the neural mechanisms implicated in FER is of primary importance.

Numerous imaging studies have investigated the cerebral networks implicated in FER. It has been suggested that complex expressions that contain blends of emotions may fully be recognized by simulating the perceived expression, either overtly or covertly, and sensing the emotion produced by that simulation (Adolphs 2001). Thus, FER mechanisms may involve both facial mimicry (i.e. the motor simulation of another's expression) and empathy (i.e. the sensory simulation of the feelings associated with another's emotional expression; Iacoboni 2009). Motor and somatosensory cortical areas may be involved in the motor components of simulation (e.g. facial mimicry), whereas the amygdala and insula may be involved in the sensory components of simulation (e.g. empathy), and both may contribute to FER (van der Gaag et al. 2007).

Consistent with this embodied view of emotion recognition (Niedenthal 2007), lesion of the somatosensory cortex (Adolphs et al. 2000), amygdala (Adolphs et al. 1994; Calder et al. 1996) and insula (Calder et al. 2000) produces impairments in FER, possibly reflecting the role of the sensory simulation mechanisms or empathy in FER. A peak of activation in the pre-supplementary motor area (pre-SMA) has been observed during a task of facial emotion observation in healthy subjects (Carr et al. 2003), and both the recognition and the generation of happy and sad expressions activate the pre-SMA (Seitz et al. 2008), consistent with a role in motor (mimicry) and sensory (empathy) simulations. The fact that the neural responses to the observation and execution of (dynamic) smiles overlap in the premotor cortex and somatosensory cortex (Hennenlotter et al. 2005) is further consistent with a role for these regions in both the recognition and the motor (mimicry) simulation of this emotion. Furthermore, electrical stimulation of the left pre-SMA with intracranial subdural electrodes in 2 epileptic patients has consistently produced laughter (Fried et al. 1998; Krolak-Salmon et al. 2006). In both studies, laughter was accompanied by a sensation of merriment or mirth, and patients gave a different explanation for it each time. In addition, Krolak-Salmon et al. (2006) recorded intracranial evoked potentials in the same epileptic patient during the presentation of emotional faces. In 2 different blocks, the patient had to pay attention to gender or emotion. Between 150 and 450 ms after the presentation of an emotional face (during both tasks), a selective response to happy facial expression was recorded by the electrode implanted in the left pre-SMA. These studies suggest that the pre-SMA may participate in FER via a mirror communicative activity involved in both the detection and the production of facial emotional

expression, especially happiness/laughter. However, these results were obtained in the epileptic brains. Although the pre-SMA was not a part of the patients' seizures, functional reorganization cannot be excluded. Further studies in healthy subjects are essential to conclude a real and systematic implication of the pre-SMA in FER, and especially in facial happiness recognition (FHR). Because of its cortical location, non-invasive and reversible inhibition of the pre-SMA with transcranial magnetic stimulation (TMS) may be used during an FER task to assess its causal implication in FHR.

At the interface between neuropsychology and functional neuroimaging, TMS appears to be a suitable means to non-invasively investigate the cerebral function. According to Faraday's principle, a brief current flows through the stimulation coil producing a transient magnetic field that penetrates the cranium. As a result of this induced magnetic field, an eddy current occurs in the brain, transiently and reversibly perturbing activity in the affected cortical region. Thus, using a perturb-and-measure approach, TMS gives the opportunity to infer about the necessity (but not the sufficiency) of the integrity of a particular brain region for a given behavior (Paus 2005; Brunelin et al. 2006). For example, TMS over the medial prefrontal cortex has been shown to reversibly modify the analysis of facially expressed anger (Harmer et al. 2001), suggesting a crucial role for this region in the recognition of facial anger. Similarly, TMS over the right occipital face area and TMS over the face region of the right somatosensory cortex (relative to the finger region) have been shown to interfere with the processing of emotional facial expressions but not facial identity (Pitcher et al. 2008). Conversely, TMS of the right superior temporal sulcus impaired the processing of the gaze direction without affecting expression processing (Pourtois et al. 2004). Based on the past results and its excellent temporal resolution, an event-related TMS protocol appears appropriate to investigate the role of the pre-SMA in FER.

Our study aims to clarify the role of the pre-SMA in FHR. Given 1) the robust activation of the pre-SMA in response to happy faces (Krolak-Salmon et al. 2006; Seitz et al. 2008) and 2) the laughter and the merriment sensation elicited by electrical stimulation of the pre-SMA in epileptic patients (Fried et al. 1998; Krolak-Salmon et al. 2006), we hypothesized that the pre-SMA is implicated in FER, especially in the recognition of happiness.

Materials and Methods

Subjects

A total of 20 right-handed (average right-handedness score: 97.10; standard deviation (SD) = 4.81%; *Edinburgh Handedness Inventory*; Oldfield 1971) healthy volunteers (12 males and 8 females) aged between 20 and 34 years (mean age = 24.61; SD = 3.74; and years of education = 17; SD = 2) were enrolled in this single-blind, randomized crossover study in return for payment (100€). Postgraduate and graduate students were recruited through "word-of-mouth," according to the following general non-inclusion criteria, which were evaluated during a medical interview: 1) a story of neurological issues (e.g. epilepsy), 2) a personal or familial psychiatric disorder history (axis I of the diagnostic and statistical manual of mental disorders DSM IV), 3) uncorrected vision, 4) pregnancy, 5) TMS contraindication (e.g. metallic prosthesis, pacemaker), and 6) medication intake. All these exclusion criteria were evaluated during a personal medical interview with a psychiatrist (Personal medical interviews were undertaken by psychiatrists, Emmanuel Poulet and Mohamed Saoud.). Past and current histories of psychiatric disorders were assessed throughout the clinical interview using the Mini-International Neuropsychiatric Interview semi-standardized evaluation (MINI version 4.4). A familial history was evaluated at the knowledge of the participant and consultation of hospital records. All participants were naive to the FER task, the TMS tool, and the presented stimuli. They all gave their written consent after a complete description of the study procedure. A local ethical committee (CPP *Sud-Est IV*) had approved the study design and consent procedure. The subjects were told that they could withdraw from the study at any time, and 1 male subject did so before the TMS protocol ($n = 19$).

Facial Stimuli

The images were taken from a standard set of facial emotion pictures (Ekman and Friesen 1976). Each stimulus was obtained by morphing 2 black and white facial pictures (1 neutral and 1 emotional, in different proportions) from a same identity. Morphing construction permits the creation of an ecological variation in facial emotional intensity and to test the subjects' performances on various levels of difficulties, thus providing a more sensitive FER measure than classical tests (Bediou, Ryff et al. 2009). Moreover, the task should be neither too hard nor too easy to perform to increase the probability of 1) disrupting the psychological process studied and 2) inferring a functional implication of the cerebral area stimulated in the evaluated function. In our study, morphed faces were generated between a neutral face and a happy, angry, or fearful face, for 8 identities (4 men and 4 women). The choice of the relevant morphing proportions was based on the results of a pilot study in an independent sample of 8 healthy volunteers without TMS. Seven levels of morphing between each emotional and neutral faces were used. Our pilot data showed that anger was recognized with greatest difficulty. As a consequence, we used a greater proportion of the expressive face in each anger morphing (20%, 30%, 40%, 50%, 60%, 70%, and 80% for fear and happiness; 30%, 40%, 50%, 60%, 70%, 80%, and 90% for anger), in order to keep task difficulty equal between emotions across intensity levels. The pilot data showed that with these morphing levels, recognition accuracy did not differ significantly between happiness (71.33; SD = 6.53), fear (65.07; SD = 12.72), and anger (66.33; SD = 12.76), $F = 1.19$, $P = 0.34$. The total set of stimuli comprised 168 faces (8 identities × 3 emotions × 7 morphs), the order of which was randomized between series and across subjects. The digitized size, brightness, and contrast of images were standardized.

FER Task

FER task was run by the software "Presentation v0.55" (Neurobehavioral Systems Inc., Canada), which presented the different images, recorded subjects' responses, and controlled the TMS device connected to the computer. Figure 1*A* depicts the timeline of an experimental trial. Each trial started with a central white fixation cross on a dark background (duration: 1000, 1250, 1500, or 1750 ms, randomly selected) attracting subjects' attention while minimizing the response anticipation and motor preparation. Then, a facial stimulus appeared during 50 ms on a black background. Each stimulus was followed by a black screen (500 ms) during which event-related TMS was applied (1 pulse every 100 ms). This was in turn followed by the response screen (2000 ms). Subjects were instructed to maintain fixation, visualize each picture, and judge as quickly and as accurately as possible whether the target face expressed happiness, fear, anger, or neutrality (no emotion), by pressing 1 of 4 possible response buttons (up, down, left, and right arrows) with their right-hand fingers.

Experimental Procedure

In order to standardize experimental conditions, all participants were seated in a padded armchair at a 60 cm distance from the 17-inch computer monitor, with their head held in place comfortably by a headrest. The subject's resting motor threshold (RMT) was determined and study started by a practice block with the same task but with the different stimuli (other identities) and without TMS, in order to familiarize with the task and procedure. Thus, FER under TMS

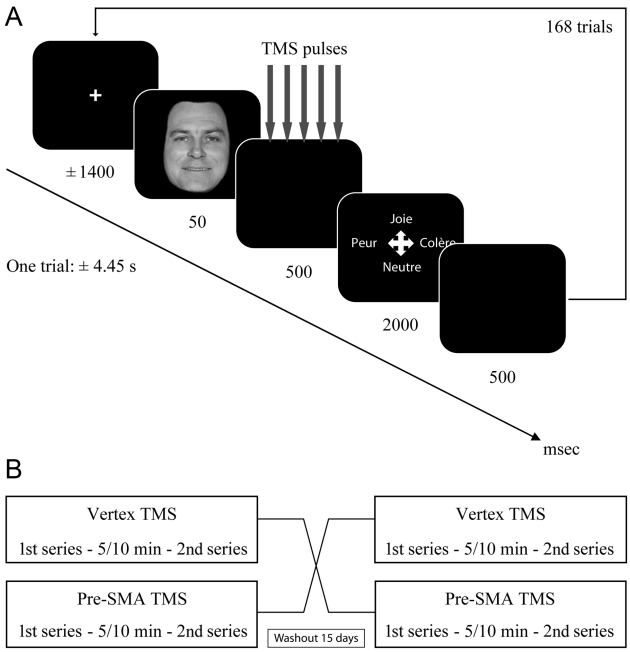

Figure 1. (*A*) Timeline of a TMS experimental trial. Each stimulus appeared during 50 ms and ±1400 ms after crosshair fixation. After stimulus offset, 5 single pulses of TMS were applied during a black screen (500 ms). The subjects were instructed to answer as quickly and as accurately as possible once the response screen appeared (2000 ms or until response). Responses were followed by a black screen (500 ms), preceding the next trial. (*B*) Crossover TMS stimulation protocol. During the first session, a subject received the TMS pulses over the vertex or the left pre-SMA, and inversely during the second session. The two sessions were separated by a washout period of 15 days. Short breaks (5–10 min depending on the subject's comfort) were inserted between each series to avoid fatigue and to prevent overheating of the stimulator. The order of the TMS conditions was randomized between subjects.

treatment was measured on 4 occasions: 2 sessions (pre-SMA and vertex), each comprising 2 series of 168 faces. The 168 faces were randomized. Faces were the same for each series and each session. For the 2 sessions, once the participant had completed the practice block, the FER task started with a first series of 168 stimuli, lasting ~10 min. Then, a second series of the same 168 faces was shown, while TMS was applied on the same site as for the first series. Short breaks (5–10 min depending on the subject's comfort) were inserted between each series to avoid fatigue and to prevent overheating of the stimulator. Thus, for each TMS session, FER was divided into 2 series. Because low frequency (LF) repeated TMS (rTMS) research demonstrated delayed and extended effects in time on several indices of emotional processing (van Honk et al. 2002), the 2 sessions were separated by 15 days. During the first session, the subject received the TMS pulses over the vertex or the left pre-SMA, and inversely during the second session (Fig. 1*B*). The order of TMS stimulation sites (vertex – pre-SMA or pre-SMA – vertex) was randomized between participants. This had 2 main advantages. First, it allowed us to compare the performance in the 2 TMS conditions within the same subjects. Secondly, it allowed us to control for any potential order/training effect.

TMS Procedure

Neuronavigation

We localized the 2 TMS sites using a frameless stereotaxic system (*Softaxic Optic*; http://www.softaxic.com/) to guide the TMS coil positioning over the brain, by means of individual high-resolution T1-weighted magnetic resonance imaging (MRI) transformed in the Talairach space. We targeted the sites based on the Talairach coordinates (*x*, *y*, *z*) for either the left pre-SMA (−6, 15, 58) or the vertex (0, −30, 70). Once MRI co-registration and cortical target localization were successful, infrared tracking was used to monitor the position of the coil with respect to the participant's brain.

Resting Motor Threshold

The RMT was determined as the minimal intensity of electromagnetic stimulation that produced a visible inch adductor contraction in at least 5 times out of 10 TMS pulses. A figure-8 coil was placed over the participant's left motor cortex hand area with the coil held tangentially to the skull and the handle-pointing posterior and down. Single pulses were delivered to the motor cortex, with the intensity of the stimulation adjusted until a muscle movement in the right hand was visually observed. The location of the stimulation was adjusted to locate the inch adductor. Furthermore, it has been demonstrated that rTMS delivered to the primary motor cortex (M1) produces intensity-dependent increases in brain activity locally and has associated effects in distant sites with a known connection (Speer et al. 2003). In order to be the more accurate over the pre-SMA and limit the impact of TMS over the network interconnected to the pre-SMA, the intensity of TMS was fixed to 80% RMT, which is known to produce a more focal effect (Wagner et al. 2009). In addition, a moderate intensity of stimulation tends to limit the peripheral discomforts and muscles contraction.

TMS Pulses

All TMS pulses were delivered by a MagPro X100 magnetic stimulator (MagVenture, Denmark) with a 70 mm figure-8 coil at 80% intensity of each subject's RMT. Stimulations were controlled through the Presentation v0.55 software installed on a computer connected to the stimulator. Based on previous work, (Krolak-Salmon et al. 2006) event-related stimulations were delivered in trains of 5 pulses (1 pulse every 100 ms) during the 500 ms after the picture presentation (i.e. the first pulse was synchronized with the vertical offset). Each participant received 3360 pulses during the whole protocol, which lasted ~2 h (168 stimuli × 5 pulses × 2 series × 2 sessions; 1680 pulses during each session, separated by 2 weeks).

Subjective Ratings

TMS can perturb subjects' mood if used daily and repeatedly (Brunelin et al. 2007). Thus, subjects were asked to report their mood on the Norris' 16-item visual analog scale (VAS; Norris 1971) before, between, and after each series of each session (3 measures for each session).

Data Analysis

Post Experimental Coil Positioning

Post experimental visual inspection of the coil localization was conducted to ensure that the stimulation site corresponded to the desired one. The data from 1 female subject had to be excluded from statistical analysis because the coil localization was substantially different at the end compared with the beginning of the session ($n = 18$; 1 subject having withdrawn before the TMS protocol). As a result, statistical analyses were conducted on data from 18 participants: 10 received TMS over the vertex and then the pre-SMA, and 8 received the inverse sequence (pre-SMA – vertex).

Statistical Analysis

To directly test our *a priori* hypothesis that TMS over the pre-SMA impairs the recognition of happiness selectively, we subtracted data (performances P and reaction times RT) in the vertex condition from data in the pre-SMA condition (see also Romei et al. 2011 for a similar approach). This procedure cancels any individual side-effects due to TMS treatment (e.g. sounds, feelings, stress). The obtained (pre-SMA – vertex) value provides a quantitative measure of the modification in FER induced by pre-SMA stimulation compared with vertex stimulation for each participant. A positive value indicates an increase for the pre-SMA compared with the vertex, whereas a negative value indicates a reduction for the pre-SMA compared with the vertex. Statistical analyses were performed on these pre-SMA – vertex difference scores

for both the performance (i.e., difference in percent correct responses, delta-P) and reaction time (i.e., difference in ms between the response screen onset and the onset of the subject's response, delta-RT). Only correct trials were considered in the analysis of RT. Considering that FER accuracy was equal across emotions in our pilot study without TMS stimulation, we then tested whether the delta-P and delta-RT differed significantly from zero, using 2-tailed 1-sample Student *t*-test with a significance threshold at $P = 0.05$ with Bonferroni correction. We predicted a significant change in FHR in the pre-SMA compared with the vertex condition resulting in a delta-P significantly different from zero for happiness but not for fear and anger.

To investigate the impact of TMS on mood, VAS ratings before and after the session were compared using a repeated-measures multivariate analysis of variance (MANOVA) with the within-subject factors session (pre vs. post stimulation) and TMS (pre-SMA vs. vertex), and items (the various aspects rated) as multiple dependent variable. Considering the risk of low statistical power because of the limited sample size, we therefore averaged the 16 items into an overall mood score and submitted this value to the repeated-measure analysis of variance (ANOVA) examining the impact of TMS and session only as a double-check.

To assess the adequacy of our crossover design (and rule-out any possible order/training effect), task performance in the first and second sessions (all emotions, morphings and TMS conditions collapsed) were compared using 2-tailed paired Student *t*-test. To quantify a possible training effect within each session, task performance for the first and the second series of each session (all emotions, morphings, and TMS conditions collapsed) were compared using 2-tailed paired Student *t*-test.

RESULTS

Effects of TMS on FER

Preliminary Considerations

No statistically significant difference was highlighted between the performance in the first session compared with the second, $t(17) = -0.04$, $P = 0.97$, and between the performance in the first compared with the second series of each session, $t(17) = -1.21$, $P = 0.24$. In the absence of order effect (i.e., no difference in FER performance between sessions 1 and 2), training effect (i.e., no difference in FER performance between series 1 and 2 of each session), and TMS effect on mood (i.e., no difference in VAS ratings before and after TMS), subsequent analyses examined the impact of TMS on FER data (pre-SMA – vertex) collapsed across series and TMS conditions, irrespective of stimulation sequence order (vertex – pre-SMA or pre-SMA – vertex). Although our study was not designed to test gender differences in FER, or in the effect of TMS on FER, exploratory (i.e., uncorrected) analyses revealed significant differences in FER between men ($n = 10$, mean = 54.73, SD = 5.75) and women ($N = 8$, mean = 63.04, SD = 8.04), $t(16) = 2.56$, $P = 0.021$, in line with previous studies (e.g. Montagne et al. 2005). Significant gender differences in FER were found for happiness and fear in the pre-SMA condition, and for fear in the vertex condition, but not for anger. Overall accuracy also differed between men and women, in both the vertex and the pre-SMA conditions (see Supplementary Table 1). Critically, however, there was no gender difference in the effect of TMS on FER when the pre-SMA data were subtracted from the vertex data (see Supplementary Table 2).

Effects of TMS on FER Performance

On average (i.e., all emotions and morphings collapsed), participants' performance was 57.62% (SD = 10.54%) in the pre-SMA condition and 59.24% (SD = 11.30%) in the vertex condition, a difference that was statistically significant, $t(17) = -2.20$, $P = 0.04$. As reported in Table 1 and illustrated in Figure 2, the delta-P for happiness differed significantly from zero, $t(17) = 2.95$, $P = 0.009$, whereas the delta-P for fear and anger did not, $t(17) = 0.56$, $P = 0.59$; $t(17) = 0.53$, $P = 0.60$, respectively.

As expected, subjects had more difficulty in identifying happiness in the pre-SMA TMS condition than in the vertex TMS condition, whereas fear and anger recognition were not significantly affected by TMS over the left pre-SMA compared with the TMS over the vertex.

Effects of TMS on RTs

RT data for each emotion and TMS condition (i.e., collapsed across all morphs), as well as the pre-SMA – vertex difference in RT (delta-RT) are summarized in Table 2. None of the delta-RT value differed significantly from zero, suggesting that TMS did not affect RTs.

Effects of TMS on Mood

We found no effect of TMS on mood. A repeated-measures MANOVA with the within-subject factors session (pre vs. post stimulation) and TMS (pre-SMA vs. vertex), and items as multiple dependent variable yielded a significant main effect of item ($F = 280$, $P < 0.001$). Importantly, however, there was no significant effect or interaction with the factors session and

Table 1
The mean score (expressed in percentage of correct responses) for the different emotions (happiness, fear, and anger, all morphings collapsed) in the vertex and pre-SMA conditions, delta-P (%; pre-SMA – vertex) and 2-tailed 1-sample Student *t*-test (*P* values; $n = 18$) all morphings collapsed. Only the delta-P for happiness differed significantly from zero ($P = 0.009$)

	Happiness		Fear		Anger	
	Mean	SD	Mean	SD	Mean	SD
Pre-SMA	58.93	11.26	56.20	9.93	57.74	10.18
Vertex	62.05	11.74	57.09	9.06	58.58	11.96
Delta-P	−3.12	4.49	−0.89	6.76	−0.84	6.75
Student *t*-test *P*-value	0.009		0.59		0.60	

Figure 2. Delta-P values (percentage of correct responses in the pre-SMA condition minus percentage of correct responses in the vertex condition) for each subject and each emotion (averaged across all morphings). The delta-P for happiness differed significantly from zero, whereas the delta-P for fear and anger did not (see text for statistics).

Table 2

Mean and SD for RT (ms) for correct trials for the different emotions (happiness, fear, and anger, all morphings collapsed) in the vertex and pre-SMA conditions, delta-RT (ms; pre-SMA – vertex), and 2-tailed 1-sample Student *t*-test (*P* values; $n = 18$). No statistical difference was highlighted

	Happiness		Fear		Anger	
	Mean	SD	Mean	SD	Mean	SD
Pre-SMA	413.69	161.43	613.87	204.19	548.67	144.18
Vertex	408.91	165.17	536.72	212.69	548.01	223.32
Delta-RT	−4.79	128.40	−77.15	198.08	−0.66	187.34
Student *t*-test *P* value	0.88		0.12		0.99	

TMS (all F's <1), suggesting that our TMS protocol did not significantly affect participants' mood. We note, however, that running this analysis with our limited sample size bears the risk of low statistical power. We therefore averaged the 16 items into an overall mood score and submitted this value to repeated-measure ANOVA examining the impact of TMS and session. This analysis showed very similar results; there were no significant main effect of TMS, and no TMS × session interaction (all *F*s <1). A marginal effect of session, $F = 3.47$, $P = 0.08$, suggested that mood varied between the beginning and the end of each session, probably due to fatigue. Critically though, this effect was not affected by the TMS condition. VAS ratings before and after each TMS session did not differ significantly (before pre-SMA: mean = 51.57, SD = 34.17; after pre-SMA: mean = 52.17, SD = 33.92; before vs. after pre-SMA: $t(15) = -0.44$, $P = 0.67$; before vertex: mean = 50.54, SD = 32.21; after vertex: mean = 51.68, SD = 33.99, before vs. after vertex: $t(15) = -1.14$, $P = 0.27$), suggesting that subjects' mood was not affected by TMS. There was no significant correlation between FER and mood (all *R*'s <0.34, *P*'s >0.17).

In summary, compared with TMS over the vertex, TMS over the pre-SMA impaired selectively the recognition of happy facial expressions, without affecting the recognition of anger and fear, and without affecting RTs and mood.

Discussion

The primary goal of the present study was to assess, using an interference technique (TMS), whether the pre-SMA is involved in FHR. We hypothesized that compared with TMS over the vertex, TMS over the left pre-SMA would specifically interfere with the recognition of happiness. As predicted, we showed that TMS over the left pre-SMA impaired the recognition of happy faces, without affecting the recognition of fearful and angry faces, and without affecting RT. There was no evidence that TMS pulses delivered during this study led to undesirable short- and long-term effects, and none of the subjects included in our study reported the adverse event. Moreover, we found no effect of TMS on mood, and no relationship between mood and FER. Hence, reduced happiness recognition following TMS stimulation of the left pre-SMA compared with the vertex, may be attributed to the perturbation of neural activity in the pre-SMA or in a broader neural network including this structure. Although the precise mechanism(s) by which the pre-SMA may be involved in the recognition of facial happiness remains unclear, our study provides the first evidence for a direct relationship between pre-SMA activity and recognition accuracy for happy faces in healthy subjects.

Previous studies examining the impact of rTMS of lateral prefrontal cortical areas (PFC) on mood suggest that the effects are opposed depending on the hemisphere stimulated (left vs. right) and on the frequency of stimulation [LF vs. high frequency (HF)]. In healthy volunteers, left PFC HF stimulation increases self-rated sadness (George et al. 1996; Pascual-Leone et al. 1996; Dearing et al. 1997), whereas HF stimulating of the right PFC increases self-rated happiness (e.g. George et al. 1996; Pascual-Leone et al. 1996), though negative results have also been reported (Mosimann et al. 2000). However, rTMS has been successfully used to treat depressive symptoms in patients with a major depressive disorder with 2 main approaches: HF rTMS of the left dorsolateral prefrontal cortex or LF rTMS of the right dorsolateral prefrontal cortex (George et al. 1999; Klein et al. 1999; Post et al. 1999; Eche et al. 2012). These therapeutic effects are confirmed by several large-scale clinical trials and a number of meta-analyses (see Padberg and George 2009; Fitzgerald 2011 for recent reviews). Interestingly, rTMS also has lateralized effects on facial expressions in depressed patients. In particular, the frequency of laughter was increased after stimulation of the left PFC and decreased following stimulation of the right PFC (Padberg et al. 2001). In sum, similar effects are found by either stimulating the left prefrontal cortex with HF or inhibiting the right prefrontal cortex with LFs, but opposite effects are found with the same stimulation protocol in depressed patients and healthy controls.

Here, we stimulated a different but connected region (the left pre-SMA) using 5 pulses of event-related TMS at 10 Hz (transient lesion) and found no effect on mood, making it unlikely that the TMS-induced perturbation of happiness recognition is an indirect consequence of the impact of TMS on mood. Although the disruption of activity in the left pre-SMA impaired the recognition of happiness without any short-term effect on mood, it is plausible that the modification in FER—in this case in happiness recognition—would affect mood in the long-term (e.g. with a prolonged rTMS treatment), similar to what is observed following antidepressants administration in both healthy volunteers (Harmer et al. 2004) and depressed patients (Harmer, O'Sullivan et al. 2009), in which changes in facial expression processing (especially fear and happiness recognition) are observed several days or weeks before changes in mood or depressive symptoms, and actually predicting these changes (Harmer et al. 2003, Hammer, Goodwin et al. 2009).

In addition to its effects on mood, rTMS of the dorsolateral PFC has been shown to affect attention and physiological responses in healthy volunteers (van Honk et al. 2003). LF rTMS of right prefrontal areas reduces attention to (unmasked) fearful faces (van Honk et al. 2002) and increases attention towards angry faces (d'Alfonso et al. 2000), whereas left rTMS diverts attention away from angry faces. However, the hemispheric lateralization of HF rTMS effects may depend on additional factors, such as the sex and the valence and/or motivational direction of the emotional expression (Brüne et al. 2006), though in this study the authors stimulated the left versus right temporal (not frontal) cortex and only included healthy female subjects. However, the transient modification of FHR by left pre-SMA TMS cannot be accounted for a general effect of TMS on attention for at least 2 reasons. First, the disruption was specific to happiness, and secondly, there were no differences in RTs between emotions and no

effect of TMS on RTs. Thus, we surmise that the decrease in FHR is caused by the impact of TMS on a selective mimicry-like mechanism involving the mirror properties of the preSMA, as discussed in more details here below. Our findings extend the current literature on the neurobiology of FER by showing that event-related TMS (as opposed to rTMS) of the left pre-SMA can impair the recognition of happiness selectively without any short-term modifications of mood and attention. Previous studies already suggested an implication of the somatosensory cortex in FER (Pourtois et al. 2004; Pitcher et al. 2007, 2008, 2009), and of the medial PFC in anger (Harmer et al. 2001).

Recent work (Mukamel et al. 2010) suggests that some neurons in the human pre-SMA show mirror properties—that is, discharging when executing a given motor act and when observing the same action being performed by someone else. An important element for understanding the selective impact of pre-SMA stimulation on happiness recognition is the motor aspect of facial emotional expressions. Facial expressions are differentiated on the basis of the activity of specific facial muscles (Ekman and Friesen 1978). In particular, anger is characterized by an increased activity of the Corrugator, producing frowning (Duchenne 1859). Similarly, fear is associated by an increased activity of the Orbicularis oculi (and/or frontalis) (Duchenne 1859) responsible for eyes-opening. Unlike these 2 expressions involving mainly the eyes region, happiness is easily recognizable via the contraction of the Zygomaticus characterizing smiles (Duchenne 1859). Happiness is also known to be particularly contagious (Dimberg et al. 2000). Passive viewing of happy faces induces contractions of the Zygomaticus (Hatfield et al. 1993), suggesting that this emotion is particularly keen to activate mirror neuron mechanisms. Importantly, the repertoire of the mirror neuron system indeed extends from hand actions to a wide range of body actions including facial actions (Buccino et al. 2001). Furthermore, the left SMA (SMA-proper and pre-SMA), but not the right, has a bilateral face representation essential in producing facial expressions (Fried et al. 1991). Facial happiness expression is intrinsically related to mouth movements, suggesting that pre-SMA mirror neurons may potentially discharge in relation to the mouth movement. Consistent with this idea, increasing the intensity of an emotional expression (i.e., morphing level) during passive viewing is associated with increases in both the evoked neural and the facial muscular activities involved in the expression of the perceived emotion (Achaibou et al. 2008). Thus, the observed effect of left pre-SMA stimulation on happiness recognition may be due to an impact of TMS on the activity of pre-SMA mirror neurons involved in the perception and production of mouth movements, or in their simulation. Just like mirror neurons located in the somatosensory cortex, mirror neurons in the pre-SMA may be involved in embodied cognition, and more specifically in the (motor) simulation mechanisms (e.g. facial mimicry) that are known to facilitate FER (Niedenthal 2007), and more particularly so for happiness (Oberman et al. 2007). The fact that a significant proportion of mirror neurons in the pre-SMA respond to communicative mouth movements (Mukamel et al. 2010) brings further support for this interpretation.

In our study, the 5 TMS pulses were applied over the left pre-SMA (50, 150, 250, 350, and 450 ms) after the offset of the facial stimulus (thus, between 100 and 500 ms after the stimulus onset). Our results are thus consistent with past electrophysiological studies showing a pre-SMA implication in FHR between 150 and 450 ms after the stimulus onset (Krolak-Salmon et al. 2006) or between 100 and 720 ms after the stimulus onset (Seitz et al. 2008). Current models (e.g. Adolphs 2002) suggest that the information sufficient to distinguish faces from other objects is encoded within 120 ms, whereas the construction of a detailed perceptual representation of a face requires ~170 ms, and the conceptual knowledge of the emotion signaled by the face, >300 ms. Furthermore, information sufficient to distinguish among different emotional expressions appears around 170 ms after the onset of the stimulus, suggesting that responses to emotional stimuli in visual cortices are modulated by a feedback from interconnected structures, such as the amygdala and orbitofrontal cortex (Adolphs 2002), where rapid responses to facial expressions have been recorded (Kawasaki et al. 2001; Krolak-Salmon et al. 2004). In line with this model, activity differentiating between specific emotional expressions can be recorded between 250 and 550 ms after the stimulus onset both intracranially (Krolak-Salmon et al. 2003, 2004) and on the scalp (Krolak-Salmon et al. 2001; Bediou et al. 2007) and even before over frontocentral electrodes (Bediou, Eimer et al. 2009).

Our results suggest a direct relationship between the activity of the left pre-SMA and FHR. The pre-SMA may react to happy faces very rapidly (within 100–450 ms), most likely via interactions with the orbitofrontal cortex, the amygdala, and occipitotemporal areas. The amygdala and orbitofrontal cortex may generate an emotional response in the subject, via thalamic connections to motor structures (e.g. the pre-SMA; Inase et al. 1996), hypothalamus, and brainstem nuclei, where components of an emotional response to the facial expression can be activated (Adolphs 2002). This mechanism may contribute to the generation of knowledge about another person's emotional state, via the process of simulation by motor mirror neurons, and would draw on somatosensory related cortices in the right hemisphere for representing the emotional changes in the perceiver (Adolphs 2001; Pitcher et al. 2008). Further studies are needed to uncover the dynamic functional connectivity of the pre-SMA with other brain areas involved in FHR. Double-pulses of TMS with 50 ms between pulses could be delivered at different times from the stimulus onset, in order to pinpoint the timing, and causality, of pre-SMA implication in FHR.

Because of our crossover TMS design, we were constrained in the number of trials per subject and thereby in the number of experimental conditions (i.e. emotions and morphing levels). Various arguments guided our choice of emotional expressions. First, fear, and anger differ from happiness on valence and motivational direction, 2 of the main underlying dimensions of emotion. Previous studies have found that the effects of TMS on FER depend on the valence or motivational categories of the emotions considered, and on the lateralization of the stimulation (d'Alfonso et al. 2000; Baeken et al. 2011). Considering that we were targeting the left pre-SMA to investigate its implication in happiness recognition (positive valence, approach motivation), our choice of fear (negative valence, avoidance motivation), and anger (negative valence, approach motivation) was motivated by the existence of the competing theories about the lateralization of emotions (Davidson 2004; Harmon-Jones 2004). Moreover, fear and

anger are known to attract strong attention, and together with happiness, are generally recognized easier than other negative emotions, such as disgust or sadness. Although sadness would have been the most intuitive emotion to oppose to happiness, this emotion tends to be poorly recognized in FER studies, especially when using morphed faces (Montagne et al. 2007). In addition, the neural circuitry underlying the perception and recognition of fear and anger is at least partly established, whereas the neurobiology of sadness recognition is much less clear. The neural basis of disgust recognition is also partly known, but when used with anger, the 2 emotions are less recognized. Thus, the fact that we observed a significant impairment in FHR following the disruption of the left pre-SMA activity is further consistent with an involvement of the left PFC in the recognition of a positive valence, and approach-related, emotional expression.

Our control condition (TMS over the vertex) may be subject of controversy. An appropriate sham should stimulate the ancillary aspects of TMS, such as scalp stimulation and acoustic artifacts, as closely as possible to experimental TMS, but should not result in cortical stimulation. Available sham coils fail to truly mimic the peripheral sensations associated with TMS easily, such that it becomes obvious to all subjects in a crossover protocol whether they are receiving the real or placebo stimulation. Furthermore, previous research has shown that the performance and RTs in a FER task were not affected by TMS over the vertex compared with a no-TMS condition (Pitcher et al. 2008). For these reasons, we used the same figure-8 coil over the vertex for our TMS-control condition. To our knowledge, the vertex is an appropriate control site for TMS stimulation in a FER task (Pitcher et al. 2008) in that it does not interfere with attentional processes, vision, and emotion recognition. Moreover, our VAS analysis showed that subjects' mood was not affected by TMS over the vertex. In the current study, none of the subjects was able to say whether he or she was stimulated on the vertex or pre-SMA. Thus, modifications of FHR performance can reliably be attributed to the functional TMS-induced perturbation of the targeted cortical area, which is the only parameter changing between the 2 sessions. As expected, TMS over the left pre-SMA resulted in lower performance for happiness recognition. Such an emotion-specific impairment is compatible with a selective involvement of the left pre-SMA in the processing of facial expressions of happiness (Krolak-Salmon et al. 2006).

In conclusion, we have demonstrated that the functional integrity of the left pre-SMA is indispensable for the recognition of happy but not angry and fearful faces. The present research provides new insights into the functions of this region and provides the first direct link between the activity of this region and the performance in a social cognitive task. Combined to works disclosing the selective pre-SMA reaction to happy faces, the present study supports the existence of mirror properties of pre-SMA neurons, which may represent a neural basis of embodied FER mechanisms that create a direct link between the sender and the receiver of a social message.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfourdjournals.org/.

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