1Hz rTMS over the right prefrontal cortex reduces vigilant attention to unmasked but not to masked fearful faces
Abstract

Recent repetitive transcranial magnetic stimulation (rTMS) research in healthy subjects suggests that the emotions anger and anxiety are lateralized in the prefrontal cortex. Low-frequency rTMS over the right prefrontal cortex (PFC) shifts the anterior asymmetry in brain activation to the left hemisphere and reduces anxiety. The same rTMS technique results in enhanced anger-related emotional processing, observed as elevations in attention for angry faces. The current study used low-frequency rTMS over the right PFC, and indexed selective attention to fearful faces, hypothesizing reduction in attention for fearful faces, i.e. a reversal of the latter effect. In a placebo-controlled design, 1Hz rTMS at 130% of the individual motor threshold (MT) was applied for twenty minutes continuously over the right PFC of eight healthy subjects. Effects on motivated attention were investigated by means of an emotional Stroop task, indexing selective attention to masked and unmasked fearful faces. Vigilant attention for masked and unmasked fearful faces was observed after placebo stimulation. As hypothesized, rTMS reduced the vigilant emotional response to the fearful face, but only in the unmasked task. These data provide further support for the lateralisation of the emotions anger and anxiety in the prefrontal cortex. In addition, the absence of an effect for masked fearful faces suggests that changes in emotional processing after a single session of rTMS predominantly involve the cortical affective pathways.
Introduction

In the human brain, emotion is regulated by a complex compound of cortical and subcortical circuits (Damasio et al., 2000; Panksepp, 1998). Gradually, neuroimaging studies are beginning to unravel the underlying dynamics of these affective processing pathways. In accordance with the approach and withdrawal dimensions of the valence hypothesis (Davidson, 1998), recent electroencephalographic (EEG) studies have found evidence for the lateralisation of the negative emotions anger and anxiety in the prefrontal cortex (PFC). The left PFC is evidently involved in anger proneness and the expression of the approach-related emotion anger (Coan, Allen, & Harmon-Jones, 1999; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001), whereas the right PFC is involved in fearful behavior and the expression of the withdrawal-related emotion fear (Coan et al., 1999; Kalin, Larson, Shelton, & Davidson, 1998).

The cerebral cortex, however, is not necessarily implicated in the processing of anger and fear. Functional neuroimaging studies have indicated that parallel to cortical routes, a primordial subcortical pathway to the amygdala might act as a neurobiological shortcut for fast activation of the arousal system. When presented briefly and backwardly masked, angry and fearful facial expressions are not consciously recognized, but nevertheless seem to be processed “unseen” by way of the thalamic nuclei (Morris, Öhman, & Dolan, 1999; Rauch et al., 2000). Based on this evidence, a simple model of human approach and withdrawal-related affective information processing has been constructed (Van Honk & De Haan, 2001). In this model, the left and right prefrontal cortices are respectively involved in consciously controlled (and thus more sophisticated forms) of behavioral approach and withdrawal (Davidson, 1998).

Furthermore, a subcortical affective shortcut, the thalamic-amygdaloid pathway subserves the more biologically prepared emotional response, not confounded by conscious control (Öhman, 1998; Ledoux, 1996). Conscious control is mediated by orbitofrontal and medial structures of the prefrontal cortex (OMPFC). These OMPFC affective control and relay stations have strong afferent and efferent connections with the
dorsolateral prefrontal cortices and the amygdala (Fuster, 1997). Since responses to masked and unmasked facial threat seem to provide insight in the difference between subcortical and cortical human affective information processing, facial threat might well be used to investigate a so-called attentional bias for threat, which characterizes emotional disorders (McNally, 1995; Rauch et al., 2000).

Recently, we set out to investigate the attentional bias for angry and fearful faces. An emotional Stroop task was used, comparing color-naming latencies of masked and unmasked neutral vs. angry or fearful faces. It is suggested that the angry facial expression plays an important role in regulating social interactions. Vigilant attention to the angry face would indicate an inclination to defend social status, that is face-to-face dominance (Mazur & Booth, 1998; Van Honk & De Haan, 2001). In agreement, subjects with high levels of the emotion anger or the hormone testosterone, both associated with interpersonal dominance, display vigilant attentional responses to angry faces in the Stroop task (Van Honk et al., 1999, 2001). In contrast, the fearful face serves as a danger call, indicating that threat is perceived by a member of the social group, which might readily apply to the observer. Anxiety is accompanied by a preoccupation for danger. Therefore, anxious individuals should display vigilant attention to fearful faces. In concordance, the more vigilant attentional response to the fearful face is related to physiological and self-reported indices of anxiety (Hermans et al., 1999). Notably, in the above line of research with the emotional Stroop task, the observed relations defy and sometimes even depend on backward masking (Hermans et al., 1999; Van Honk, Hermans, Putman, & Tuiten, 2000; Van Honk et al., 1998, 2001), suggesting that the subcortical pathway is importantly involved in these motivated aspects of attention (Morris et al., 1999; Rauch et al., 2000).

A technical innovation in neuroscience, repetitive transcranial magnetic stimulation (rTMS), is capable of establishing functional brain-behavior relationships by modulating brain activity in controlled designs (Pascual-Leone, Bartres-Faz, & Keenan, 1999). Moreover, recent studies suggest that rTMS is capable of influencing mood and motivated attention in
ways that can be functionally linked to the approach-withdrawal dimensions of behavior, that is anger and anxiety. Low-frequency rTMS (i.e., stimulation frequency $\leq 1$Hz) applied over the right dorsolateral PFC above the motor threshold (MT) for thumb movement (i.e., suprathreshold intensity) reduces anxiety and shifts the anterior asymmetry in brain activation to the left (Schutter et al., 2001). Furthermore, elevations in selective attention to unmasked angry faces were found after similar rTMS (D'Alfonso, Van Honk, Hermans, Postma, & De Haan, 2000), which are presumably anger-related and possibly left-prefrontally driven emotional responses (Coan et al., 1999; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001; Van Honk et al., 1999, 2001). Initially, this effect of low-frequency rTMS is induced by a transient neural inhibition of the targeted right PFC (Pascual-Leone et al., 1999). However, distant effects in anatomically interconnected brain areas have also been observed using neuroimaging techniques. For instance, low-frequency rTMS over the left or right PFC at the suprathreshold intensities produces contralateral excitation (Nahas et al., 2001; Schutter, Van Honk, D'Alfonso, Postma, & De Haan, 2001; Speer et al., 2000). This effect is possibly due to a reduction in transcallosal inhibition after the initial unilateral deactivation of the targeted area (Pascual-Leone et al., 1998; Schutter et al., 2001).

In sum, due to unilateral inhibition and/ or contralateral excitation, suprathreshold low-frequency rTMS over the right PFC seems to result in more left PFC dominant processing, reductions in anxiety (Schutter et al., 2001) and enhanced anger-related emotional processing (D'Alfonso et al., 2000). Taken together, these findings corroborate EEG evidence for the lateralisation of the approach-related emotion anger and withdrawal-related emotion anxiety. Moreover, effects on motivated attention were not observed in a lateralized suprathreshold low-frequency rTMS study over the PFC when angry faces were presented backwardly masked in the Stroop task (Van Honk & D'Alfonso, unpublished data). This suggests that transient changes in motivated attention induced by single-session rTMS predominantly take place on a cortical level.
The aim of the present rTMS study was to further investigate the anterior lateralisation of the emotion anxiety by using fearful faces in the Stroop task. In addition, it was investigated whether rTMS would again induce a selective effect when using a combined masked-unmasked Stroop paradigm (cf. D’Alfonso et al., 2000; Van Honk & D’Alfonso, unpublished data), since this would suggest that rTMS is capable of dissociating between conscious and preconscious affective processing. It was hypothesized that suprathreshold low-frequency rTMS over the right PFC would reduce selective attention to fearful faces in the unmasked task exclusively.

**Method**

**Participants**

Eight right-handed volunteers (four females) aged between 20 and 26 years participated in this single-blind, cross-over, counterbalanced, sham-controlled experiment. An informed consent was obtained, and subjects with a history of neurological or psychiatric disorder were excluded. All participants were naive of TMS and unaware of the aim of the study. The local ethical committee of the Faculty of Social Sciences approved the study.

**Procedure**

On separate days, 1Hz or placebo rTMS (Neopulse Magnetic Stimulator; Neotonus Inc., Atlanta) with an intensity of 130% of the MT for thumb movement was applied over the right PFC (position F4 according to the International 10-20 system) (see Figure 3.1a). For placebo stimulation, the coil position was tilted 90° (Schutter et al., 2001). 30 Minutes after stimulation or placebo, selective attention for masked and unmasked fearful faces was assessed using an emotional Stroop task comparing color-naming latencies for neutral and fearful faces. This 30-minute delay was used, because low-frequency rTMS research demonstrated delayed and extended effects in time on several indices of emotional processing (D’Alfonso et al., 1999; Schutter et al., 2001; Van Honk et al., 2001).
Emotional Stroop task

Masked and unmasked versions of an emotional Stroop task were employed to measure selective attention to fearful faces. This task requires participants to name as quickly as possible the color of pictures of fearful and neutral facial expressions (red, green, blue and yellow) presented on a 160Hz computer screen at a distance of 60 cm. The dependent measures in the emotional Stroop task are Attentional Bias scores (i.e., the mean individual color-naming latencies of fearful faces minus the individual mean color-naming latencies on neutral faces). Positive Attentional Bias scores, indicating slower color-naming responses to emotional compared to neutral stimuli, are interpreted as a vigilant response, whereas the negative Attentional Bias score, indicating faster color naming responses to emotional compared to neutral stimuli, is interpreted as an avoidant response. The stimuli were taken from Ekman and Friesen’s (1976) *Pictures of Facial Affect*. In the masked task, a fixation point was shown for 750 ms, followed by the target stimulus (a neutral or a fearful face) presented for 14 ms, before being replaced by a mask-
ing stimulus. Masking stimuli were randomly cut, reassembled and rephotographed pictures of faces. The presentation of the mask was terminated after vocal response initiation (see Figure 3.1b). In the unmasked task, the fixation point was also shown for 750 ms and followed by the target stimulus (a neutral or a fearful face) and target presentation was terminated after vocal response initiation (see Figure 3.1c). In both tasks, forty neutral and forty fearful faces were presented in random order with the restriction that the same color was never repeated more than twice consecutively. Stimulation and task condition assignments were fully randomized.

Subliminal thresholds were controlled for by both a subjective and an objective awareness check (i.e., a forced-choice emotional-neutral recognition check). Both checks were performed after the second session to ascertain that subjects remained unaware of the variable of interest in the Stroop task, during the course of the experiment. The subjective check was a simple interview asking subjects whether they had recognized the emotional valence of the faces that were displayed before the masks. The objective check was a two-alternative, forced-choice (2AFC) emotional-neutral recognition procedure. In this 2AFC, a random set of 30 masked faces was shown to the subjects. In advance, subjects were explicitly told that the set contained 15 neutral and 15 fearful faces, and were instructed to indicate (or guess), by pushing a button whether the presented picture was a neutral or an emotional expression (see Kemp-Wheeler & Hill (1988) for the rationale behind this instruction).

**Results**

There was no evidence of recognition of emotional valence during masked presentation, neither by subjective nor by objective checks. Subjects’ performance in the objective check did not differ from chance level, that is 15 correct identifications per subject in a two-alternative forced choice recognition check containing 30 stimuli. Of the total number of identifications (=240), 121 were correct (50.4 %). Individual upper limit was set at 19 correct scores. Non-parametric tests for devia-
tion from the expected value (cut-point=15) were not significant (n=8, p=1). Thus, masking was successful. Repeated MANOVAs were performed on the Attentional Bias scores, with Stim (F4 vs. placebo) and Exposure (unmasked vs. masked) as within-subject factors. Analyses showed a significant main effect for both Stim [ F(1,7) = 15.2: p < .01 ] and Exposure
[ F(1,7) = 16.1: p < .01 ]. There was, however, also a significant multivariate Stim X Exposure interaction [ F(1,7) = 23.3: p < .005 ], indicating different effects of stimulation in masked and unmasked exposure conditions. Separate analyses of unmasked and masked data showed no effect of Stim in the masked task [ F(1,7) = 0.3: n.s. ], but a highly significant effect in the unmasked task [ F (1.7) = 19.7: p < .004 ]. The pattern of results is shown in Figure 3.2.

![Figure 3.2](image)

**Figure 3.2.** Mean attentional bias scores and SEM in milliseconds for the masked and unmasked tasks in placebo and transcranial magnetic stimulation condition.

Additionally, two-tailed paired t-tests were performed to see whether the Attentional Bias scores differed significantly from zero (i.e., indicating no bias). In the placebo condition there was a significant positive Attentional Bias for the masked [ t(7) = 3.5: p < .01 ] and the unmasked task
In the F4 stimulation condition again, a positive Attentional Bias was observed for the masked task \( t(7) = 3.4; \ p < .015 \) but a negative Attentional Bias was found for the unmasked task \( t(7) = -3.1; \ p < .02 \).

**Discussion**

The present study investigated the effects of right PFC rTMS on attentional biases for masked and unmasked fearful faces. Vigilant attention for fearful faces was observed both in the masked and in the unmasked exposure condition after placebo stimulation. As hypothesized, rTMS significantly decreased vigilant attention for fearful faces in the unmasked, but not in the masked task. As previously suggested, this effect could have been induced by a more left-sided dominance in prefrontal processing. As noted, combined rTMS-neuroimaging studies did not only show focal changes in activation of the targeted areas, but also demonstrated distant effects in anatomically interconnected regions. Since these distant changes in activation are supervening on the initial focal effect, these are likely part of functionally connected (affective) networks or neurons in the brain. rTMS-neuroimaging studies might in fact reveal these functionally connected networks of neurons, and provide additional insight in the affective circuits of the human brain (cf. Fox et al., 1997; Paus et al., 1997). Moreover, the present findings in the Stroop task can functionally be linked to left PFC dominant processing as observed by EEG (Coan et al., 1999; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001). Furthermore, evidence from rTMS-EEG and rTMS-fMRI suggest that the present rTMS parameters (when applied over the right PFC) induce a left-sided dominance (Nahas et al., 2001; Schutter et al., 2001). Finally, elevations in attention for angry faces were demonstrated after suprathreshold low-frequency rTMS over the right PFC (D’Alfonso et al., 2000), in contrast to the current reductions in biased attention for fearful faces. Taken together, these findings seem to further support the involvement of the left PFC in the withdrawal-related emotion anger, and the right PFC in the approach-related emo-
tion fear (Coan et al., 1999; D’Alfonso et al., 2000; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001). In further support of this view, Figure 3.2 shows that biased attention for fearful faces was reversed after rTMS from positive to negative scores in the unmasked task, which indicates that the processing of the fearful faces was strongly inhibited. Disregarding a danger signal is a risky behavioral strategy and can most likely be observed in a low anxious, anger prone individuals, with a presumably left PFC-dominance (Coan et al., 1999; D’Alfonso et al., 2000; Fox, 1991; Hermans et al., 1999).

The current findings also show that the pattern of responding remains unchanged for the masked task after rTMS. This is likely due to the inability of the rTMS technique to directly modulate the emotional response when the emotional stimulus remains unconscious. As noted previously, the left and the right prefrontal cortices are respectively involved in conscious control of behavioral approach and withdrawal, whereas the thalamic-amygdaloid pathway subserves the rudimentary emotional response. The OMPFC contains the brain structures crucially involved in the modulation of emotion (Davidson, Putman, & Larson, 2000; Van Honk et al., 2000), but requires conscious monitoring for acting out its emotional control (Reiman, 1997). In agreement, neuroimaging studies have shown no activation in OMPFC regions when fearful and angry faces are presented masked (Morris et al., 1999; Rauch et al., 2000). Since the OMPFC can only operate when gaining conscious access to emotional value (Davidson et al., 2000; Reiman, 1997), the modulation of the emotional response to the masked fearful face arguably needs subcortical mediation (Van Honk et al., 2000; Van Honk & De Haan, 2001). It seems therefore justifiable to assume that the transient suppression of motivated attention in the present study was observed for the unmasked fearful face only, because the here applied rTMS technique induced functional changes in neural excitability of cortical affective circuits predominantly.

Finally, it may be noted that although rTMS did not induce an effect in the masked task, the present study fulfils all criteria for subliminal activation postulated by Dixon (1981). There was positive evidence for subliminal
activation (1) in both the placebo and rTMS condition, that is vigilant attention to masked fearful faces. An objective check of awareness was used, providing negative evidence of awareness (2) in the masked task. The crucial qualitative different effect for masked and unmasked stimuli (3) was also found, after real rTMS had been applied.

In conclusion, these data corroborate and extend the findings of our earlier reports (D’Alfonso et al., 2000; Schutter et al., 2001) and provide further support for the differential involvement of the PFC in the emotions anger and fear (Coan et al., 1999; Fox, 1991; Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001). In addition, the rTMS-induced effect for the unmasked, but not the masked task concurs with data from neuroimaging studies (Morris et al., 1999; Rauch et al., 2000), providing further evidence for a possible dissociation between cortical and subcortical affective circuits in the human brain.
References


