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Neurocognitive effects of HF-rTMS over the dorsolateral prefrontal cortex on the attentional processing of emotional information in healthy women: An event-related fMRI study

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ABSTRACT

Current evidence concerning the neurocircuitry underlying the interplay between attention and emotion is mainly correlational. We used high-frequency repetitive Transcranial Magnetic Stimulation (HF-rTMS) to experimentally manipulate activity within the right or left dorsolateral prefrontal cortex (DLPFC) of healthy women and examined changes in attentional processing of emotional information using an emotional modification of the exogenous cueing task during event-related fMRI. Right prefrontal HF-rTMS resulted in impaired disengagement from angry faces, associated with decreased activation within the right DLPFC, dorsal anterior cingulate cortex (dACC) and left superior parietal gyrus, combined with increased activity within the right amygdala. Left prefrontal HF-rTMS resulted in diminished attentional engagement by angry faces and was associated with increased activity within the right DLPFC, dACC, right superior parietal gyrus and left orbitofrontal cortex. The present observations are in line with reports of a functionally interactive network of cortical-limbic pathways that play a central role in emotion regulation.

Recent cognitive models of emotion processing in anxiety argue that selective attention to threat is determined by the relative signal strength from a pre-attentive threat evaluation mechanism versus that from top-down control mechanisms (Bishop, 2007). It has also been argued that dysfunctional top-down cognitive processes, such as those biasing attention to emotional information, may contribute to the onset and further development of depression (Dannlowski et al., 2009; De Raedt and Koster, 2010; Leppänen, 2006; Mayberg, 1997; Joormann et al., 2007).

Neuroimaging studies of healthy volunteers have provided support for a functionally interactive network of cortico-limbic pathways that play a central role in the top-down cognitive regulation of emotions (Seminowicz et al., 2004; Johnstone et al., 2007; Ochsner and Gross, 2005, 2008; Wager et al., 2008). This research has indicated that a functional balance between ventral (ventral anterior cingulate cortex, ACC) and dorsal compartments in the brain (dorsal ACC, dorsolateral prefrontal cortex-DLPFC) is necessary for maintaining homeostatic emotional control.

Emotional arousing stimuli activate the amygdala (Zald, 2003), which is connected to the ventral system. The anterior cingulate cortex (ACC) can be seen as a bridge between subcortical emotion processing and attentional control, integrating signals from the ventral ACC and the dorsal ACC (Bush et al., 2000). The dorsal ACC, implicated in conflict monitoring, signals to the DLPFC to alter the direction of attention or modify the distribution of processing resources (Hopfinger et al., 2000; MacDonald et al., 2000). According to the mediation hypothesis (Wager et al., 2008), prefrontal regions can send feedback signals to the subcortical system in order to suppress emotional processing, via connections with other frontal regions such as the orbitofrontal cortex (OFC) (Taylor and Fragopanagos, 2005). Indeed, a large number of studies suggest that the DLPFC initiates emotion regulation by causing inhibition of the amygdala (e.g., Siegle et al., 2007).

At the behavioural level, deficient regulation of negative affective states is associated with biases in the attentional processing of emotional information, more specific a difficulty to disengage attention away from threat (e.g. Koster et al., 2005; for a review, see De Raedt and Koster, 2010). These difficulties to disengage attention can be seen as a failure in the top-down control or down regulation of the amygdala. Fales and coworkers (Fales et al., 2008) showed

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that healthy control participants showed increased activity in right DLPFC (Brodmann areas 46/9) when ignoring fear related stimuli in an attention task, whereas depressed patients did not. Cognitive biases for threat are commonly related to right hemisphere regions implicated in anxiety such as prefrontal, orbital frontal, anterior cingulate and parietal cortices, as well as the amygdala (for a review, see Nitschke and Heller, 2005).

Although a lot of research has investigated the neural substrates of emotional attention processes, it has been mainly correlational. Experimentally induced manipulations of cortical processing in neurologically healthy individuals, using repetitive Transcranial Magnetic Stimulation (rTMS), may contribute to an in-depth mapping of the relevant interconnected brain systems (Sack and Linden, 2003; Schutter et al., 2004). rTMS involves using a repetitive alternating current at a specific frequency in a coil to induce magnetic fields that pass to the underlying brain area and induce electrical fields that depolarize neurons under the coil. A session of high frequency rTMS (>1 Hz) produces increases in brain activity that can last sufficiently long to allow measuring the effects during cognitive tasks after stimulation. It has been shown that rTMS over the DLPFC also indirectly affects connected areas that are related to attention and emotion processing (for a review, see Guse et al., 2010).

Recently, we have examined the interaction between attention and emotion by investigating the transient effects of HF-rTMS (10 Hz), applied over the left and right DLPFC, on the attentional processing of emotional information and on self-reported emotions in healthy volunteers (Leyman et al., 2009). In line with the existence of the abovementioned neurocircuitry of emotion regulation and the lateralization of emotional attention processes (see Nitschke and Heller, 2005), results indicated a specific involvement of the right (but not left) DLPFC in the attentional control of emotional information, evidenced by an instant impairment, following HF-rTMS, of the ability to inhibit negative information.

These interesting findings warrant further study into the neural structures involved in rTMS-induced modulation of emotional attention. Possibly, HF-rTMS to the DLPFC may cause a modulation of emotional attention through several neural mechanisms: (1) by inhibition of dorsal prefrontal and parietal areas that are important in top-down monitoring of attention, (2) by the indirect excitation of a set of more ventral and subcortical areas, (3) or by a combination of both (Sack and Linden, 2003).

Therefore, the aim of the present study was to investigate changes in attention towards threatening information (angry faces) in healthy volunteers, measured after HF-rTMS applied over the right and left DLPFC. To investigate attention towards emotional stimuli, we used a well-studied emotional modification of the exogenous cueing task (ECT), and administered this task during fMRI, before and after each HF-rTMS session. The ECT task allows to index multiple components (disengagement versus engagement) of emotional attention (Fox et al., 2001; Koster et al., 2005; Posner, 1980). Using event-related fMRI, we explored corresponding changes in activation patterns in a network of cortical-limbic brain regions involved in emotional attention.

The following hypotheses were tested with regard to the dependent measures involved (attention components as measured with the ECT and brain activity). Based on former research (Rounis et al., 2006), and in line with models of emotion lateralisation (e.g. Davidson and Irwin, 1999; Coan and Allen, 2004), one session of HF-rTMS over the right DLPFC was expected to induce deficiencies in attentional disengagement, with specific deficits in the attentional modulation of threatening information, whereas no changes in attentional performance were expected after one session of HF-rTMS over the left DLPFC (see Leyman et al., 2009). Second, comparing brain activity after versus before right sided HF-rTMS during the performance of the ECT attention task, we expected decreased activity in frontal compartments of the brain implicated in emotional control (DLPFC, ACC, OFC) and in the attention network (parietal gyri), and increased activity in the amygdala during difficulties to disengage from threatening information.

1. Method

1.1. Participants

Thirty-seven healthy, drug-free, right-handed female participants aged between 19 and 30 years (mean age of 22.6 years; *S.D.* = 2.6) were recruited to participate in this study. Only female participants were included for reasons of homogeneity and sex differences in brain activation patterns during the perception of facial affect (Killgore and Yurgelun-Todd, 2001). All participants received a complete description of the study procedure, which was approved by the institutional ethics committee of the University Hospital of the Free university of Brussels (VUB). All gave written informed consent. In order to meet safety criteria for HF-rTMS, participants were carefully screened by a trained psychiatrist prior to inclusion in the study. They underwent a thorough neurological (MRI) and psychiatric examination. Current and past psychiatric disorders were excluded on the basis of the MINI-international Neuropsychiatric Interview (MINI; Pinninti et al., 2003). In addition, the Beck Depression Inventory (BDI; Beck et al., 1961) was administered. All participants scored below 10, indicative of the absence of depressive symptoms ($M = 2$; *S.D.* = 2.35). Further exclusion criteria were a history of epilepsy and neurosurgical interventions, having a pacemaker or other metal or magnetic objects in the body and being pregnant. Finally, all participants had to be medication free. Only oral contraceptives were allowed. Handedness was assessed with the hand preference scale of Van Strien (2001). All participants were financially compensated.

1.2. Study design and procedure

The present study used a combination of a single-blind randomized crossover within-subjects design with a group receiving one session of HF-rTMS over the left DLPFC also receiving placebo (sham) stimulation ($n = 18$), and a between-subjects design with another group receiving one session of HF-rTMS of the right DLPFC ($n = 19$),[1] which was compared to the sham condition of the abovementioned left stimulation group. The participants receiving right sided stimulation were also involved in a single-blind within-subjects rTMS by sham randomised crossover design but they did not receive the fMRI/ECT procedure in the sham condition, which means that the only difference between left versus right stimulation groups was the absence of the fMRI/ECT scanning during their sham session (and this sham session could therefore not be used in the current study). We acknowledge this limitation, but due to the restricted availability of the scanner, we could not establish a complete sham/rTMS within-subjects design. The time interval between both sessions (sham/rTMS) was one week, to avoid carry over effects.

Before (T_{pre}) and thirty minutes after (T_{post30}) the end of active or sham stimulation, attentional processing of emotional facial expressions was measured using an emotional modification of the ECT, which was administered during event-related fMRI.

In order to evaluate temporary changes in perceived emotions before (T_{pre}), immediately after (T_{post}) and ±40 min after (T_{post40})

[1] Because the present study is part of a larger project investigating the influence of rTMS on different neuro-cognitive markers before and immediately after each rTMS (active/sham) session, additional cognitive tasks were also administered. However, these measurements were not used for the purposes of the present study. All measurements were presented in the same order for all participants.

the end of each rTMS (active/sham) session, emotion ratings were administered using five visual analogue scales providing measures of sadness, fatigue, tension, anger and vigour (McCormack et al., 1988). Participants were asked to describe how they felt "at that moment" by indicating on horizontal 10 centimetre lines whether they experienced the five abovementioned emotion states, from "totally not" to "very much".

1.2.1. Repetitive transcranial magnetic stimulation

For the application of rTMS we used a Magstim high-speed magnetic stimulator (Magstim Company Limited, Wales, UK) connected to a figure-eight-shaped coil. Before stimulation, the identification of the precise stimulation location of the left and right DLPFC (Brodmann area 9/46) was determined for each subject using Magnetic Resonance Imaging (MRI) non-stereotactic guidance. More specifically, to obtain individual anatomical information, all participants underwent a T1-weighted MRI of the brain (3D-TFE, voxel size 1 mm × 1 mm × 1 mm) using a 1.5T Intera MRI scanner (Philips, Best, The Netherlands). All post processing was done on a viewforum console from the same manufacturer. The DLPFC was located visually on the 3D surface rendering of the brain based on the subject's own gyral morphology, marking the middle part of the midfrontal gyrus as the centre of the left or right DLPFC, area 46/9 (MNI coordinates: −45, 30, 31) (Peleman et al., 2010). The corresponding coil position was marked by determining the perpendicular projection of this point on the scalp. Four reference points were marked on the 3D-reconstruction of the head – right ear, left ear, vertex and nose – which were connected by two reference axes: one from nose to atlas and one between the two ears. A fifth reference point, "top" (the projection of the DLPFC on the scalp), was determined by the crossing of these two axes. To visualize the coil position on the patient's head, these reference axes were marked on a cap by using the geodetic distance from nose to top, from right ear to top and from top to the coil position. This coil position was held fixed to this point on the scalp for each HF-rTMS session. Moreover, a stimulation intensity of 110% of the subject's motor threshold of the right abductor pollicis brevis muscle was determined using EMG.

During each high-frequency (10 Hz) stimulation session, participants received forty trains of 3.9 s duration, separated by an intertrain interval of 26.1 s (1560 pulses per session). Within the group receiving sham stimulation, the coil was placed at an angle of 90°, resting on the scalp with only one edge. During stimulation, all participants wore earplugs. Before and during stimulation participants were also blindfolded in order to ensure that the different orientation of the coil with respect to the scalp in the sham condition was effectively blinded. Safety guidelines based on recent available safety studies on rTMS were followed (Anand and Hotson, 2002; Wassermann, 1998; Rossi et al., 2009).

1.2.2. The exogenous cueing task (ECT)

At the beginning of the experiment, before entering the scanner, the ECT was fully explained to each participant (the instructions were also repeated on the computer screen). Participants were instructed to respond as quickly and accurately as possible to the appearance of a small black square on the left or right side of a screen positioned at 2 m of their feet, and viewed via a 45° mirror mounted on a head coil in the scanner. They were informed that a cue (picture of a face) preceded the presentation of the target and that this cue was not predictive for the target location. It was emphasized attention should be directed towards a fixation cross during each trial. The mirror was located at ±150 mm from the eyes of the participants. Responses were made using two response boxes, connected to a personal computer outside the scanner, that were held in the right and left hand during the experiment. Inquisit software (Millisecond Software, 2001, Version 1.33) was used to record response accuracy and latencies. The location of the picture cued the spatial location of the target in 2/3 of the trials (valid cue) and incorrectly cued the location of the target in the remaining 1/3 of the trials (invalid cue).

Each trial started with the presentation of 2 white frames (view in the mirror: 20 mm × 20 mm, visual angle 7.6° × 7.6°) located on both sides of a black background. These frames remained on the screen throughout the entire trial. The presentation duration of these frames was jittered over a range of intervals going from 100 ms up to 2000 ms, causing cues to occur in unpredictable sequences. That way, using post-processing deconvolutions, we were able to present a larger number of trials and improve statistical power of the event-related fMRI responses. Next, a fixation cross appeared in the middle of the screen for the remainder of the trial presentation. The middle of each of the white frames was at 40 mm distance (15.2° visual angle) from the fixation cross. Five hundred ms after presentation of the fixation cross, a picture of a neutral or angry face was projected for 200 ms on top of one of the 2 white frames. Next, after a mask of 50 ms, the target (3 mm × 3 mm; visual angle 1.1° × 1.1°) appeared for 1500 ms or until the subject responded. Fig. 1 provides an overview of a trial sequence.

The face pictures where selected at random, but neutral and angry faces appeared equally often on the left and right side of the screen. Also valid and invalid trails were presented randomly. Participants first completed 20 practice trials, followed by 189 test trials.

The pictures were taken from The Karolinska Directed Emotional Faces (KDEF) database (Lundqvist et al., 1998). All pictures were adjusted to exclude interference of background stimuli (hair, clothing) so that only the face of the person was presented. In addition, all coloured pictures were adjusted to the same size (326 × 326 pixels). A total of 20 neutral and 20 angry faces were selected based on a prior validation study of the KDEF picture set (Goeleven et al., 2008). Five neutral and 5 angry faces were used in the practice phase, the remaining pictures of 15 neutral and 15 angry faces were used in the test trials.

Comparing the speed of responding to valid and invalid emotional versus neutral trials, one can measure (a) facilitated attentional engagement, leading to response benefits in valid trials and (b) difficulties to disengage attention, leading to delayed responding to invalid trials.

1.3. Image acquisition

The study was carried out on a 1.5 Tesla scanner (Philips Intera, Best, The Netherlands). BOLD data were obtained using single shot T2-weighted EPI (echo planar imaging, TR/TE = 3000/35 ms, flip angle = 90°, reconstruction matrix = 128 × 128, field of view (FOV) = 250 mm, in-plane resolution 3.9 mm, 5 mm slice thickness with 1 mm gap, number of slices per volume = 18). The transverse slices covered most of the brain. Head movement was reduced by foam padding. A complete functional run consisted of 200 dynamic scans, and lasted 10 min 6 s. The start of the run was synchronized with that of the stimulus presentation. In addition to the functional data, anatomical images were acquired consisting of a transverse T1 weighted 3D data set (IR-TFE, TI/TR/TE = 566/20/4.6 ms, flip angle = 30°, reconstruction matrix = 512 × 512, FOV = 250 mm, slice thickness = 2 mm, number of slices = 100).

1.4. Data analysis

1.4.1. Perceived emotions

In order to analyze changes in subjective emotion ratings after HF-rTMS, two separate multivariate analyses of variance were conducted, with Stimulation as between subject factor (right vs.

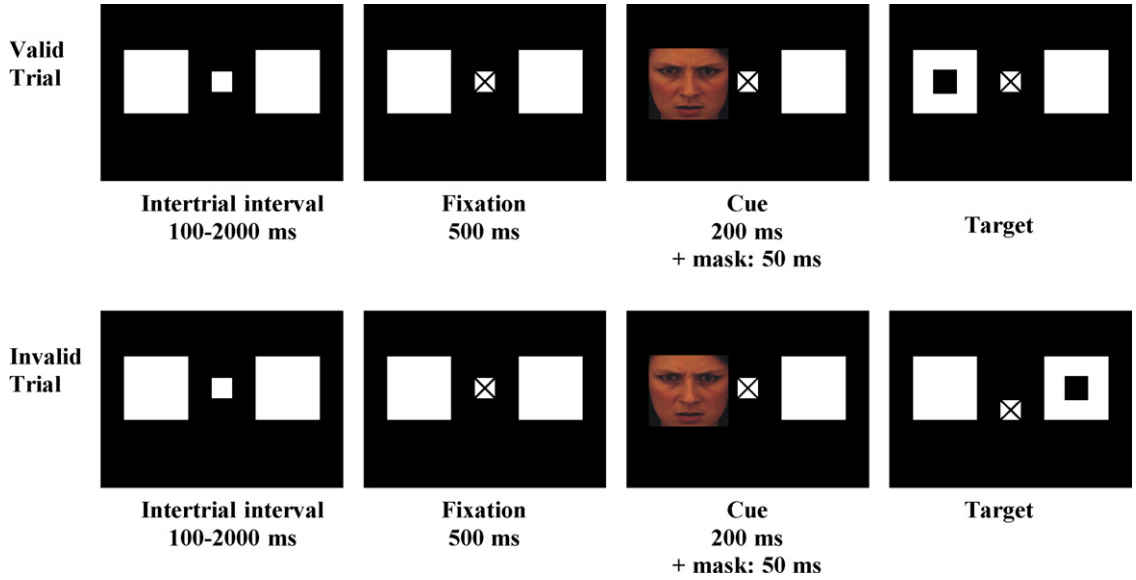

Fig. 1. The Exogenous cueing task: stimulus presentation on valid and invalid trials.

sham rTMS MANOVA) or within-subject factor (left vs. sham rTMS MANOVA), Time (T_{pre}, T_{post} and T_{post40}) as within-subjects factor and with the different VAS as multiple dependent variables.

1.4.2. Behavioural data

Before analysing response latencies of the ECT, 6.2% of the trials containing errors or responses shorter than 200 ms and longer than 750 ms – reflecting anticipatory or delayed responding respectively – were omitted. The outlier analysis was based on boxplots of the data, following Koster et al. (2005). Data analysis was performed on the remaining 93.8% of the data.

Two separate Analyses of variance, with Stimulation as between subject factor (right vs. sham rTMS ANOVA) or within-subject factor (left stimulation versus sham rTMS ANOVA), and Valence (angry vs. neutral facial cues), Cue Validity (valid vs. invalid trials) and Time (T_{pre} vs. T_{post}) as within-subject factors, were used to examine the behavioural reaction time (RT) data of the ECT. To further analyse interaction effects, scores for attentional engagement and disengagement were calculated using the following formulas: (1) Attentional Engagement: RT valid/neutral cue – RT valid/angry cue (a positive score indicates attentional capture by angry faces); (2) Attentional Disengagement: RT invalid/angry cue – RT invalid/neutral cue (a positive score indicates difficulties to disengage attention from angry faces). On these scores, *t*-tests were performed to examine differences within and between groups.

For the above analyses the significance level was set at an alpha level of.05. Estimates of effect size were also reported (partial eta squared: η_p^2 or Cohen's *d*). All procedures were two-tailed and analyses were conducted with SPSS 12.0.

1.4.3. Neuroimaging data

For the neuroimaging data, preprocessing and statistical analysis were conducted using the SPM5 software package (Wellcome Department of Cognitive Neurology, London, UK). All scans were realigned to the first one to correct for interscan movement, corrected for slice timing, spatially normalized to the standard EPI template in MNI-space (Montreal Neurological Institute) provided by SPM, and spatially smoothed with an 8 mm FWHM Gaussian kernel. A temporal high pass filter with a cut-off frequency set at 0.008 Hz was also applied. The effects of the stimuli (cues) on the response variable (target) were modeled as a linear combination of zero-duration events of four types, corresponding to valid and invalid trials for each of the two categories of faces (angry and neutral). This basic model was convolved with the standard canonical hemodynamic response function and corrected for serial correlations.

Next, fixed-effect analyses were undertaken for each subject separately. For each subject and for both time points (pre and post HF-rTMS stimulation), contrasts representing activation associated with engagement by angry faces (valid neutral–valid angry) and activation associated with the disengagement from angry faces (invalid angry–invalid neutral) were generated. The corresponding contrast images were entered into flexible factorial models including the within-subject factor time (T_{pre} vs. T_{post}), and stimulation as between subject factor (right stimulation vs. sham stimulation) or within-subject factor (left stimulation vs. sham stimulation). Thus, four factorial models were considered (engagement and disengagement, each comparing right vs. sham and left vs. sham). Given our hypotheses concerning the anatomical correlates of the observed behavioural effects, the analyses were restricted by means of the WFU pickatlas (Maldjian et al., 2003) to preselected regions of interest (ROI), comprising the stimulation area DLPFC (Brodmann's areas BA 9 and 46), ACC, the parietal gyri, OFC (comprising of the orbital parts of the inferior, middle and superior frontal gyri), and the amygdala. For the Brodmann areas, the definitions of the automated Talaraich atlas labels for functional brain mapping were used (Lancaster et al., 2000) and the automated anatomical atlas was used to define the ACC, parietal gyri and OFC (Tzourio-Mazoyer et al., 2002). Where group × time interactions were detected, the factor time (effect of stimulation) was additionally investigated in the corresponding groups separately to clarify the nature of the interaction. To control for multiple statistical testing, we maintained a cluster-level false-positive detection rate at $p < 0.05$ using a voxel threshold of $p < 0.005$ with a cluster (k) extent empirically determined by Monte Carlo simulations ($n = 1000$ iterations) for each ROI. This was performed by means of the AlphaSim procedure which accounted for spatial correlations between BOLD signal changes in neighbouring voxels (Forman et al., 1995), implemented in the REST toolbox (http://restfmri.net/forum/index.php). Empirically determined cluster thresholds were: DLPFC ($k = 17$), ACC ($k = 12$), OFC ($k = 14$), parietal gyri ($k = 18$), and amygdala ($k = 3$).

Table 1
Mean response times and standard deviations (in ms) for the ECT before (T_{pre}) and after(T_{post}) right versus placebo rTMS (a) and left versus placebo rTMS (b).

(a)					
Cue valence	Trial validity	Right rTMS (N = 19)		Placebo rTMS (N = 17)	
		T_{pre}	T_{post}	T_{pre}	T_{post}
Anger	Valid	327.94	317.25	342.26	309.70
		(33.33)	(29.78)	(48.34)	(33.94)
	Invalid	346.76	345.69	369.06	334.60
		(43.24)	(44.09)	(55.99)	(41.57)
Neutral	Valid	329.05	316.29	341.80	310.71
		(33.82)	(31.98)	(44.08)	(34.67)
	Invalid	349.18	336.33	374.96	335.39
		(45.04)	(37.40)	(58.75)	(44.33)

(b)					
Cue valence	Trial validity	Left rTMS (N = 16)		Placebo rTMS (N = 16)	
		T_{pre}	T_{post}	T_{pre}	T_{post}
Anger	Valid	332.59	316.82	349.10	312.55
		(42.01)	(39.82)	(45.59)	(34.51)
	Invalid	359.61	342.80	377.92	340.46
		(52.20)	(38.92)	(51.99)	(37.24)
Neutral	Valid	336.55	309.40	348.19	313.99
		(39.80)	(35.91)	(41.79)	(35.02)
	Invalid	368.82	338.66	385.10	341.14
		(54.17)	(42.85)	(53.19)	(42.00)

2. Results

2.1. Emotion ratings

2.1.1. Effects of right versus sham HF-rTMS

Due to missing values, one subject within the sham condition was removed from the analysis. Analyses revealed a significant main effect of Stimulation, $F(5, 30) = 2.58$, $p < .05$, $\eta_p^2 = .30$, with univariate tests revealing a significant difference between stimulation groups on reports of tension, $F(1, 34) = 11.96$, $p < .001$, $\eta_p^2 = .26$, but no significant differences between these groups on the remaining VAS, all Fs < 3.63, ps > .065. Analyses also revealed no significant overall effect of Time, $F < 1$, $p > .50$, and the crucial two-way interaction effect between Stimulation and Time was also not significant, $F < 1$, $p > .60$.

2.1.2. Effects of left versus sham HF-rTMS

Due to missing values, five participants were removed from analysis. Analyses revealed no significant overall effects of Time or Stimulation (all Fs < 1.1, ps > .40). The two-way interaction effect between Stimulation and Time was also not significant, $F(10, 3) = 3.81$, $p = .15$.[2]

2.2. Behavioural results

2.2.1. Effects of right versus sham HF-rTMS

Mean response times for the ECT are presented in Table 1a. Analysis revealed a significant main effect of Cue Validity, $F(1, 35) = 48.85$, $p < .001$, $\eta_p^2 = .58$, corresponding to a faster response on valid (mean = 324 ms) compared to invalid trials (mean = 349 ms). A significant main effect was also found for Time, $F(1, 35) = 25.16$, $p < .001$, $\eta_p^2 = .42$), with faster responses at post-testing (mean = 326 ms) compared to pre-testing (mean = 348 ms). We could also establish significant two-way interactions between Valence and Time, $F(1, 35) = 7.01$, $p < .05$, $\eta_p^2 = .17$; Valence and Stimulation, $F(1, 35) = 4.57$, $p < .05$, $\eta_p^2 = .12$; and Time by Stimulation, $F(1, 35) = 8.26$, $p < .01$, $\eta_p^2 = .19$. Finally, the three-way interaction between Valence, Time and Cue Validity was also significant, $F(1, 35) = 5.44$, $p < .05$, $\eta_p^2 = .14$). No other effects reached significance, all Fs < 3.2, ps > .08, $\eta_p^2 = .08$.

In order to further explore our a priori hypotheses, separate attentional engagement and disengagement indices for the angry facial expressions were calculated. When comparing engagement scores between and within groups before and after stimulation, none of the simple effects at all levels of group and stimulation, were significant, with all ts < 1.1, ps > .25.

Comparing disengagement scores between stimulation groups (sham versus real stimulation) before rTMS, no significant difference was found, $t < 1$, $p > .30$. However, a significant larger disengagement score was found after active stimulation of the right DLPFC (mean = 9.4 ms) compared to post-measures in the sham group (mean = −.8 ms); $t(35) = 2.13$, $p < .05$, $d = .87$ (Fig. 2A). Upon examining differences within stimulation groups, this disengagement score after active stimulation of the right DLPFC was found to be significantly larger than in the pre-measures (mean = −2.4 ms); $t(18) = 3.10$, $p < .01$, $d = .93$. The disengagement score for angry faces after active stimulation significantly differed from zero, $t(18) = 2.86$, $p < .05$, indicating retarded disengagement from negative material. These effects were not found within the group receiving sham stimulation, ts < 1.1, ps > .25.

2.2.2. Effects of left versus sham HF-rTMS

Mean response times for the ECT are presented in Table 1b. Due to a technical failure in the recording of response latencies, two participants were removed from analysis. Analyses revealed a significant main effect of Cue Validity: $F(1, 15) = 52.44$, $p < .001$, $\eta_p^2 = .78$, due to faster responding on valid (mean = 327 ms) compared to invalid trails (mean = 357 ms). A significant main effect was also found for Time, $F(1, 15) = 26.89$, $p < .001$, $\eta_p^2 = .64$, with faster responding at post-testing (mean = 327 ms) compared to pre-testing (mean = 357 ms). We could also establish a significant two-way interaction between Valence and Time: $F(1, 15) = 9.55$, $p < .01$, $\eta_p^2 = .39$. Finally, a significant three-way interaction between Valence, Time and Stimulation was found: $F(1, 15) = 5.52$, $p < .05$, $\eta_p^2 = .27$. All other effects did not reach significance, with all Fs < 2.5, ps > .13.

[2] We also made a direct comparison of our right versus left stimulation group using multivariate analyses of variance, with Stimulation as between subject factor (right vs. left rTMS), Time (T_{pre}, T_{post} and T_{post40}) as within-subjects factor and with the different VAS as multiple dependent variables. This MANOVA revealed no significant effects, Fs < 2.26, ps > .05.

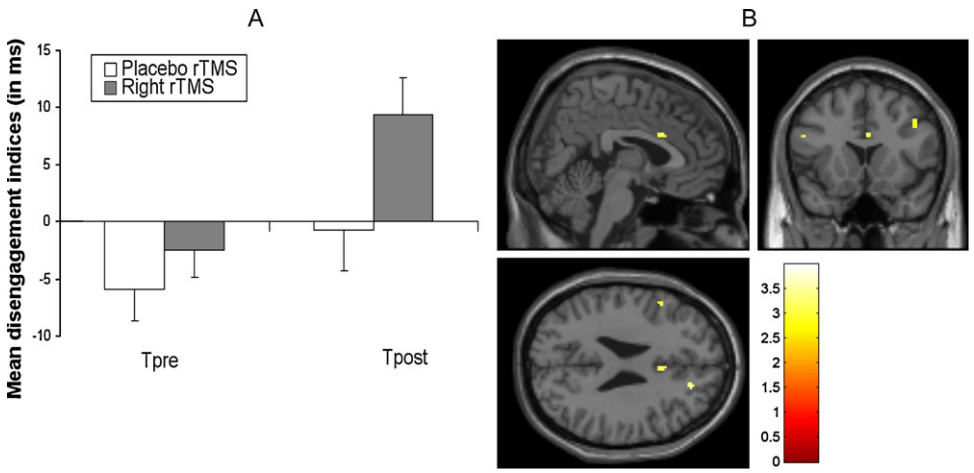

Fig. 2. Group (right stimulation vs. sham stimulation) × time (pre vs. post stimulation) interaction of (A) disengagement indices (RT invalid angry-RT invalid neutral cues) and, (B) brain activation associated with disengagement from angry faces.

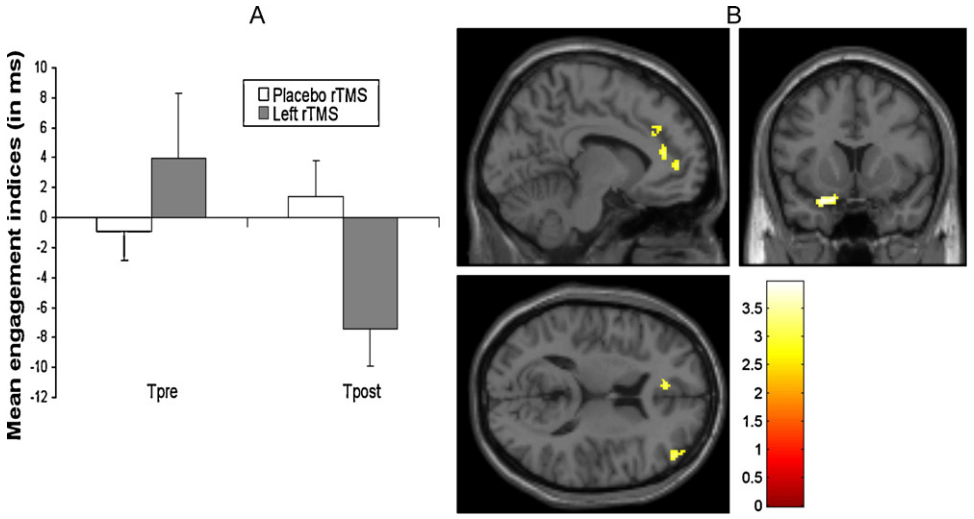

Fig. 3. Group (left stimulation vs. sham stimulation) × time (pre vs. post stimulation) interaction of (A) engagement indices (RT valid neutral-RT valid angry cues) and, (B) brain activation associated with engagement by angry faces.

We further tested our a priori hypotheses comparing engagement indices between the active and the sham condition. Before stimulation, no significant differences were found: $t < 1.1$, $p > .25$. However, comparing attentional engagement for angry facial expressions after stimulation, a significantly lower engagement score (Mean = −7.4 ms) was found within the active condition compared to the sham condition (Mean = 1.4 ms): $t(15) = 2.96$, $p = .01$, $d = .93$ (Fig. 3A). Moreover, this score was significantly different from zero, with $t(15) = 3.03$, $p < .01$, indicating a diminished attentional capture by negative material. Moreover, examining differences within both conditions, the engagement score after active stimulation of the left DLPFC (Mean = −7.4) was significantly lower compared to the pre-measures (Mean = 3.7 ms): $t(15) = 2.36$, $p < .05$, $d = .81$. These effects were not found within the sham condition: $t < 1$, $p > .40$.

Comparing disengagement between the active and the sham condition before and after stimulation, no significant differences were found: $ts < 1.2$, $p > .20$. Examining differences within both conditions, the disengagement score after active stimulation of the left DLPFC (Mean = 4.1 ms) was significantly larger compared to the pre-measures (Mean = −9.2 ms): $t(15) = 3.22$, $p < .01$, $d = .90$. However, this score did not significantly differ from zero: $t < 1.2$, $p > .20$. Also no significant effects were found within the group receiving sham stimulation condition: $t < 1.3$, $p > .20$.[3]

2.3. Neuroimaging results

2.3.1. Effects of right versus sham HF-rTMS

In the engagement contrast comparing the right stimulation group vs. sham stimulation group, group × time interactions were detected in the left OFC ($x = -16$, $y = 36$, $z = -14$, $k = 30$, $Z = 3.67$,

[3] We also compared left versus right stimulation groups using analysis of variance, with Stimulation as between subject factor (right vs. left rTMS), and Valence (angry vs. neutral facial cues), Cue Validity (valid vs. invalid trials) and Time (T_{pre} vs. T_{post}) as within-subject factors. As in both other analyses (left/right versus sham), we found a significant main effect of Cue Validity: $F(1, 33) = 49.75$, $p < .001$, $\eta_p^2 = .60$, due to faster responding on valid compared to invalid trails, and a significant main effect was also found for Time, $F(1, 33) = 14.57$, $p < .001$, $\eta_p^2 = .31$, with faster responding at post-testing compared to pre-testing. We could also establish a similar significant two-way interaction between Valence and Time: $F(1, 33) = 22.73$, $p < .001$, $\eta_p^2 = .41$. A three-way interaction between Valence, Time and Stimulation was only marginal significant, $F(1, 33) = 2.96$, $p < .095$, $\eta_p^2 = .08$. All other effects did not reach significance, with all $Fs < 2.5$, $ps > .12$.

$p = .0001$). The interaction in the engagement contrast was related to an increased activity in these regions in the right stimulation group compared with the sham group.

In the disengagement contrast comparing right stimulation group vs. sham stimulation group, robust group × time interactions were observed in the right DLPFC ($x = 20$, $y = 40$, $z = 26$, $k = 18$, $Z = 3.55$, $p = .0002$ and $x = 44$, $y = 14$, $z = 38$, $k = 22$, $Z = 2.94$, $p = .0016$), in the dorsal part of the ACC ($x = 6$, $y = 14$, $z = 26$, $k = 13$, $Z = 3.04$, $p = .0012$), and in the left superior parietal gyrus ($x = -40$, $y = -44$, $z = 60$, $k = 22$, $Z = 3.39$, $p = .0003$; Fig. 2B). The interaction was due to a decrease in activation associated with difficulty to disengage in the right stimulated group, whereas the sham stimulated group showed no changes. Additionally, employing a lowered threshold ($p = .05$, uncorrected), after right stimulation, an increase in right amygdala activation ($x = 26$, $y = 6$, $z = -16$, $k = 2$, $Z = 1.70$, $p = .047$) was also established.

2.3.2. Effects of left versus sham HF-rTMS

In the engagement contrast, comparing the left stimulation group vs. sham stimulation group, clusters of significant group × time interactions were detected in the left OFC ($x = -22$, $y = 10$, $z = -22$, $k = 117$, $Z = 3.66$, $p = .0001$), in the right DLPFC ($x = 46$, $y = 45$, $z = 18$, $k = 134$, $Z = 3.45$, $p = .0004$), in three clusters in the dorsal/pregenual ACC ($x = -6$, $y = 38$, $z = 16$, $k = 64$, $Z = 3.12$, $p = .0009$; $x = -6$, $y = 50$, $z = 4$, $k = 36$, $Z = 3.09$, $p = .001$; $x = -10$, $y = 36$, $z = 35$, $k = 23$, $Z = 2.89$, $p = .0019$) and in the right superior parietal gyrus ($x = 18$, $y = -50$, $z = 54$, $k = 22$, $Z = 3.40$, $p = .0003$; Fig. 3B). The interaction was caused by an increase in activation in the left stimulation group during the decreased engagement compared with sham group (Fig. 3B).

Finally, in the disengagement contrast, group × time interactions could be established in the left amygdala ($x = -24$, $y = 16$, $z = -24$, $k = 26$, $Z = 3.34$, $p = .0004$) and in the right OFC ($x = 40$, $y = 20$, $z = -12$, $k = 25$, $Z = 2.98$, $p = .0014$), explained by an increase of activity associated with difficulty to disengage in the left stimulation group.[4]

3. Discussion

At present, a wealth of neuroimaging data has indicated several brain regions to be implicated in emotion regulation (emotional attention processes). The aim of the present study was to further elucidate the role of the DLPFC within this cortico-limbic circuit, by manipulating cortical processing in neurologically healthy individuals using HF-rTMS.

Employing an emotional modification of the spatial cueing task that is thought to recruit the brain areas mentioned, we were able to demonstrate that HF-rTMS over the right DLPFC significantly delayed disengagement from angry faces and was associated with decreased activation within the right DLPFC, dACC and left superior parietal gyrus, and increased activation within the right amygdala (although this latter effect was only significant after introducing a lowered threshold of $p = .05$, uncorrected). When HF-rTMS was applied to the left DLPFC, attentional engagement toward these angry faces was diminished and associated with increased activation within the right DLPFC, right superior parietal gyrus, dACC and the left part of the OFC. These results were independent from changes in self-reported emotions, corresponding with previous reports of one session of HF-rTMS over the right or left DLPFC causing no immediate emotion changes in groups of healthy volunteers (Baeken et al., 2006, 2008). The fact that left HF-rTMS had contralateral effects is in line with the results of an interleaved online TMS/fMRI study (Nahas et al., 2001), showing that left sided stimulation (100% motor threshold) can spread over connected contralateral regions.

Although to date no research had specifically examined the above research question using a combined rTMS/fMRI offline design, the present findings agree well with several prior observations. Similar behavioural findings of biased attentional processing of negative information following HF-rTMS over the right DLPFC were also found when using a Negative Affective Priming task (Leyman et al., 2009). This decrease in attentional control after HF-rTMS over the right DLPFC was also reported during performance of a non-emotional cued visual choice reaction time task, in an event-related fMRI study of Rounis et al. (2006). We observed that difficulties in reorienting attention away from negative information following right prefrontal HF-rTMS were associated with decreased prefrontal activity – which was also reported by Rounis et al. in a non-emotional task variant (2006) – and diminished dorsal anterior cingulate brain activity. These brain regions were both found to be important in the evaluation and monitoring of cognitive conflict (Bush et al., 2000; MacDonald et al., 2000). A difficulty to disengage from angry faces was also associated with decreased parietal activation, specifically within the superior part of this region. The present result is in correspondence with recent findings of superior parietal cortices being involved in attentional orienting that is critical for normal performance in spatial cueing tasks (Corbetta et al., 1993; Fan et al., 2005).

A final activation pattern found to be associated with a deficient disengagement of attention from negative information following right prefrontal HF-rTMS was an enhanced right amygdala response. Although this was only obtained using a lowered threshold, this stronger increase in activation of the right amygdala was confirmed by our direct comparison between right and left stimulation groups (see footnote 4). In accordance with the present findings, previous research has indicated that amygdala activation is associated with reaction time costs to detect attentional targets preceded by negative cues (Wang et al., 2006) and increased amygdala activation has also been frequently reported during responses toward negative affective stimuli in depressed individuals (Fu et al., 2004; Sheline et al., 2001; Suslow et al., 2010). Although speculative, the established fronto-cingulate-parietal decrease and limbic increase after stimulation of the right DLPFC might be indicative of an induced imbalance between the dorsal and ventral parts of the emotion-attention regulation network, which is in line with findings from other correlational studies investigating the role of the DLPFC in the initiation of attentional control by causing inhibition of the amygdala (e.g. Siegle et al., 2007).

It is important to notice that the brain activity patterns we observed are not general increases or decreases following HF-rTMS, but activity patterns related to specific events, such as difficulties to disengage from angry faces.

While no behavioural effects were established, attentional engagement for angry faces following right HF-rTMS was also found to be associated with increased activation within the left OFC (and our direct comparison between right and left stimula-

[4] Additionally, effects of right stimulation vs. left stimulation were directly compared for the engagement and disengagement contrasts by means of a group (right vs. left) × time (pre vs. post stimulation). In the engagement contrast, clusters of significant group × time (pre vs. post stimulation) interactions were detected in the left OFC ($x = -18$, $y = 38$, $z = -12$, $k = 15$, $Z = 3.23$, $p = .0006$). The interaction was caused by a stronger increase in activation in the right stimulation group compared with the left stimulation group, which also demonstrated increase in activation but less than the right stimulation group. In the disengagement contrast, group × time interactions could be established in the bilateral OFC ($x = 38$, $y = 22$, $z = -14$, $k = 46$, $Z = 3.87$, $p = .0001$; $x = -20$, $y = 14$, $z = -18$, $k = 15$, $Z = 3.41$, $p = .0003$; $x = -52$, $y = 26$, $z = -8$, $k = 18$, $Z = 2.96$, $p = .0015$), explained by an stronger increase of activity associated with difficulty to disengage in the left stimulation group compared with the right stimulation group (which showed rather a non-significant decrease). Additionally, employing a lowered threshold ($p = .05$, uncorrected), after right stimulation, an increase in right amygdala activation ($x = 28$, $y = 6$, $z = -16$, $k = 4$, $Z = 1.90$, $p = .029$) was also established in comparison to the left stimulation group.

tion groups also showed a higher OFC response after right sided stimulation as compared to left sided stimulation, see footnote 4). Ideally positioned, the OFC has been found to function as a bridge between the amygdala and the higher cortical areas, sending information related to the affective value of a stimulus to the prefrontal cortices in order to efficiently modulate attention (e.g. Armony and Dolan, 2002; Carmichael and Price, 1995; Morecraft et al., 1992).

Contrary to the findings following right prefrontal stimulation, and to our hypothesis that no changes in attentional performance were expected after one session of HF-rTMS over the left DLPFC (Leyman et al., 2009; Rounis et al., 2006), stimulation of this brain area resulted into a significantly diminished attentional engagement by negative information. These behavioural results were associated with increased activation patterns within the right DLPFC, dACC and the left OFC. Although one session of HF-rTMS over the right DLPFC also resulted in increased left OFC activation during engagement toward angry facial expressions, these neural responses were not accompanied by a greater recruitment of right frontocingulate regions, possibly necessary to achieve the protective attentional processing bias mentioned (Killgore et al., 2007; Wagner et al., 2006). This may explain the absence of decreased engagement at the behavioural level following right sided stimulation. The present results correspond to recent reports showing that one session of left prefrontal HF-rTMS might have an instant top-down effect on the attentional processing (non-emotional) of both healthy and therapy-resistant depressive patients (Vanderhasselt et al., 2006, 2009). The finding of immediately improved spatial attentional processing (less engagement) of threatening information following one session of HF-rTMS applied over the left DLPFC might be especially germane in light of the therapeutic application of rTMS as a treatment for affective disorders. The present results indicate that left prefrontal HF-rTMS may increase the top-down regulatory effect of the prefrontal cortices thereby influencing subcortical systems implicated in affective processing, which in turn may lead to improved mood over time.

A limitation of the study is that, due to the small sample size and the requirement of an event-related design, the statistical power was limited and a ROI approach with pre-selected anatomical areas in separate left versus right stimulation models was necessary to maximize the sensitivity of the analyses. In our single model approach comparing left versus right stimulation directly, our lateralized effects only remained significant for the OFC (and the amygdala after a more lenient threshold). Moreover, participants receiving right sided stimulation were compared in a between-subjects design with the sham condition of the left stimulation group that was involved in a within-subjects design. In this way the procedure between both groups was not completely similar. Although the right stimulation group also received a sham session to obtain similar procedures, this was not accompanied by fMRI/ECT. Therefore, although the effects found in the right hemisphere stimulation condition were despite a less efficient between-subjects comparison, the hemispheric differences we found should be interpreted with caution.

In conclusion, the present study used HF-TMS to clarify the role of the DLPFC and the brain areas important during the attentional processing of emotional information. An important strength of this study was the unique combination of brain imaging, behavioural measures and rTMS to test the involvement of the DLPFC in emotion/cognition interactions.

In spite of the limitations of the study, the results suggest a specific involvement of the right DLPFC during spatial attentional processing of emotional information. They are indicative for a role of this brain area in down regulating subcortical areas, necessary to establish efficient emotion regulation.

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