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Laterality effects in selective attention to threat after repetitive transcranial magnetic stimulation at the prefrontal cortex in female subjects

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Abstract

Recently, several experiments have indicated that the left and right prefrontal cortex (PFC) are differently involved in emotional processing. The aim of this study was to investigate the role of the left and right PFC in selective attention to angry faces by using a pictorial emotional Stroop task. Slow repetitive transcranial magnetic stimulation (rTMS) was applied to the left and right PFC of 10 female subjects for 15 min on separate days. Results showed a significant effect of stimulation position: right PFC rTMS resulted in selective attention towards angry faces, whereas left PFC rTMS resulted in selective attention away from angry faces. This finding is in accordance with theoretical accounts of the neural implementation of approach and withdrawal systems.

Keywords: Transcranial magnetic stimulation; Prefrontal cortex; Selective attention; Threat

In recent years our knowledge of the processes involved in emotion and the different ways in which these processes might become disrupted in the human brain, has grown rapidly [2–4]. Studies using functional brain imaging techniques as fMRI and PET [6] have prompted us with detailed models of the anatomical structures involved in emotional perception and emotional responses. Specific neural circuits are involved in these processes, and consist of several interconnected areas as the orbitofrontal cortex, the dorsolateral prefrontal cortex (DLPFC), the cingulate cortex, the ventral striatum, the amygdala and the posterior parietal cortex [4,6]. There is evidence for two separate neural circuits involved in different forms of affect. In this paper we focus on two key elements of these circuits: the left and right prefrontal cortex (PFC). It has been suggested that the right prefrontal cortex mediates negative emotions (sadness, fear), whereas the left prefrontal cortex mediates positive emotions (happiness) [2–4]. This distinction is based on the concept that the DLPFC is involved in the representation of goal-directed behaviour. More specifically, two aspects of goal-directed behaviour, approach and withdrawal, are thought to be implemented in a neural circuit that involves the left DLPFC and right DLPFC, respectively [2–4]. Approach of a rewarding stimulus mediated by the left DLPFC would generate a positive emotion, whereas withdrawal from an aversive stimulus mediated by the right DLPFC would generate a negative emotion. An exception is the negative emotion anger, which is specifically associated with the approach system, since anger prepares individuals to fight or defend themselves aggressively [5,9].

An effective way to investigate an emotional goal-directed behaviour is by employing a motivational selective attention task. Most widely used is a modified version of the Stroop colour-naming task; the emotional Stroop task. In this task, subjects name the colour of threat words as quickly as possible, while the meaning of the words is ignored. The mean colour-naming latencies on threat words minus the mean colour-naming latencies on neutral words, the so-called interference scores are elevated in anxious individuals. Attention is suggested to be allocated towards the threat value of the word. Recently, motivational reactions towards angry faces have been demonstrated using a pictorial emotional Stroop task, comparing colour-naming latencies of neutral and angry faces. In these studies converging evidence was found for selective attention towards angry

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faces in subjects with high levels of self-reported anger and selective attention away from angry faces in subjects with high levels of cortisol [15,16]. High levels of cortisol and the emotion fear have been associated with relatively more right frontal brain activity [1,17], whereas the expression and the experience of the emotion anger have been associated with relatively more left frontal activity [8,13]. In conclusion, the left and right DLPFC might be differently involved in selective attention to angry faces.

A more direct way to examine the involvement of the left and right prefrontal cortex in selective attention to angry faces is by the use of repetitive transcranial magnetic stimulation (rTMS). This technique is capable of transiently disrupting local processing in neural networks in the brain. rTMS enhances the value of neuroimaging technique studies by adding information regarding the functional role of the targeted brain area [19]. Furthermore, rTMS appears capable of changing the cortical excitability of an underlying region resulting in a decrease or increase of cortical activity, and this effect can continue after stimulation offset [21]. A decrease or increase of cortical activity is dependent on stimulation parameters, such as frequency and intensity. For instance, fast rTMS (frequency >1 Hz) appears to produce facilitation of cortical excitability, while slow rTMS (frequency ≤ 1 Hz) appears to produce inhibition of cortical excitability [24]. Interestingly, in healthy subjects fast rTMS at the PFC has been shown to change mood after stimulation [10,20]. In addition, rTMS at the PFC has been shown to be a potential treatment for clinical depression [11].

In the present study, we used slow rTMS to examine selective attention to angry faces. It can be assumed that slow rTMS of the left PFC produces a decrease in activation of the PFC [21], resulting in the right PFC becoming relatively more activated and vice versa. It was hypothesised that there would be a significant difference between left and right PFC inactivation with increasing interference scores following right slow rTMS, but decreasing interference scores following left slow rTMS. In addition, a questionnaire was administered to investigate possible effects of rTMS on self-reported mood.

Ten healthy female subjects aged between 18 and 30 years participated in this experiment, all of whom provided written informed consent. Subjects with a neurological or psychiatric disorder where excluded from the study. The local ethics committee of the Faculty of Social Sciences approved the study. All subjects were naive for rTMS and unaware of the aim of the study. A Cadwell High Speed Magnetic Stimulator and a specially designed water-cooled 8-shaped coil (one loop has a diameter of 7 cm) was applied to stimulate the right and left PFC. Subjects were stimulated for 15 min on separate days at 130% of the Motor Threshold (MT) with a frequency of 0.6 Hz. MT was quantified using the method of visualisation of the left and right thumb movement [22]. The position of stimulation was 5 cm anterior to the area where the MT was determined [10,20]. This method was used to influence predominantly the right or left DLPFC. The coil was held tangentially to the stimulation point and the handle of the coil pointing posterior. A purpose-built coil holder was used to secure coil position during stimulation. After the stimulation the experimenter checked the position of the coil. The stimulation of position was randomised and counterbalanced across subjects.

Selective attention to angry faces was assessed using a pictorial emotional Stroop task following a rest period of 10 min after rTMS, comparing colour-naming latencies of neutral and angry faces. Stimuli were taken from Ekman & Friesen's Pictures of Facial Affect [7]. In the current experiment, pictures of ten different individuals were used, each displaying a neutral and angry expression. Duplications of each model were made and coloured transparent red, green, blue or yellow. An extra set of stimuli was prepared for practice trials. The stimuli were displayed on a computer monitor (refresh rate 160 Hz), with a viewing distance of 60 cm. One trial consisted of the presentation of a fixation point, which was shown for 1000 ms and was followed by the target picture (the coloured, neutral or angry face). A microphone connected to a voice level detector was placed in front of the subject. Initiation of vocal response was registered by the computer and subsequently terminated the target presentation. Forty neutral faces and 40 angry faces were presented in random order with the restriction that the same colour was never repeated more than twice. Subjects were instructed to ignore the content of the image and name the transparent colour (red, green, blue or yellow) as quickly as possible.

Subjects also completed the shortened 32-item version of the Profile of Mood States (POMS) [23] before and after rTMS. The sub-scales of the POMS provide measures of tension, depression, anger, fatigue and vigour. Mood scores were computed by adding up the scores on the relevant items of the different sub-scales.

Analysis of variance (ANOVA) for repeated measurements was used to analyze the results of the pictorial emotional Stroop task measured by attentional bias scores (the individual mean response latencies for angry faces minus the individual mean response latencies for neutral faces) with stimulation position (left vs. right) as within-subjects factor and order of stimulation position (left–right vs. right–left) as a between-subjects factor. Separate ANOVAs for repeated measurements were conducted using the different sub-scales of the POMS with stimulation position and time (before rTMS vs. after rTMS) as within-subjects factors and order of stimulation position (left–right vs. right–left) as a between-subjects factor. The significance level was set at $\alpha < 0.05$.

Responses with colour-naming errors (which are rare in emotional Stroop tasks) were eliminated, as well as outlayer latencies below 300 and above 3000 ms. In addition, latencies more than three standard deviations above each participant's mean were removed. Data of one subject were lost due to apparatus failure. Subjects reported no side effects.

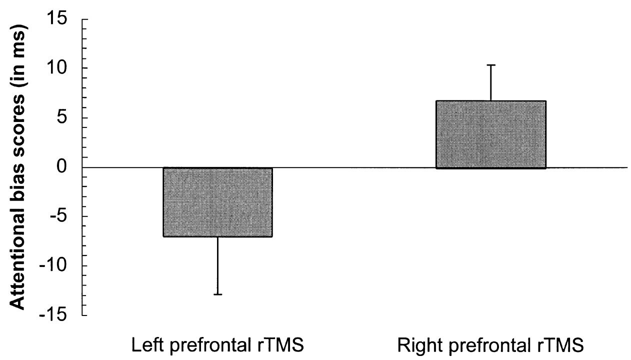

Fig. 1. Mean attentional bias scores (+ standard errors) on the emotional Stroop task after repetitive transcranial magnetic stimulation of the left and right prefrontal cortex.

There were no significant interactions concerning order of stimulation position. However, there was a crucial significant effect on stimulation position ($F(1,7) = 11.22$, $P = 0.012$). This effect is due to a difference in colour-naming neutral versus angry faces between left and right PFC inactivation. Fig. 1 shows the pattern of results on the basis of attentional bias scores.

As can be seen from Fig. 1, subjects showed positive attentional bias scores (i.e. approach) when the right PFC was inactivated and negative attentional bias scores (i.e. avoidance) when the left PFC was inactivated. On the POMS only tension showed a significant main effect on time ($F(1,7) = 21.61$, $P = 0.002$). This decrease in tension after rTMS might be explained by increased tension just before the rTMS procedure, which was novel for all subjects.

This study examined the effects of rTMS at the PFC on selective attention to angry faces. In accordance with our hypothesis we found a significant effect of left PFC stimulation compared with right PFC stimulation. That is, after stimulation of the right PFC subjects demonstrated selective attention towards angry faces most likely due to decreased right PFC activity. In contrast, after stimulation of left PFC subjects selectively attended away from angry faces due to decreased left PFC activity. Although rTMS evoked no clinically apparent and self-reported mood changes in subjects, except for the overall tension reduction, we assume that rTMS of the PFC changed the motivational stance or goal-directed behaviour by which a related emotion is generated. Inactivation of the right PFC caused predominantly left PFC-linked motivational (approach) behaviour, resulting in subjects automatically attending towards angry faces. Inactivation of the left PFC caused predominantly right PFC-linked motivational (withdrawal) behaviour, generating a fearful avoidance response in reaction to the angry facial expression. This suggestion is supported by research with Rhesus monkeys. Fearful monkeys had higher levels of cortisol and showed increased electroencephalogram (EEG) activity at the right frontal area, compared to monkeys with increased activity at the left prefrontal area that were less fearful [17]. Moreover, converging evidence has been found in human subjects. EEG alpha power showed more right frontal brain activity during the expression of the emotion fear and greater left prefrontal activity during the expression of emotion anger [1]. Finally, dispositional anger even so has been implicated with greater left- than right-frontal EEG alpha power activity [13]. As mentioned in the introduction, it was demonstrated in previous studies that human subjects with high baseline levels of cortisol selectively attended away from angry faces, whereas subjects with high levels of self reported anger attended towards angry faces. The present results are therefore in accordance with the hypothesis that the left prefrontal cortex is involved in a neural circuit implementing approach-related emotion and the right prefrontal cortex is involved in a neural circuit implementing withdrawal-related emotion [2–4].

On a more speculative note, our results might possible provide more insight in psychopathological disorders such as posttraumatic stress disorder (PTSD). Individuals with anxious tendencies or an anxiety disorders, who often show increased right hemisphere activity [3,14,15,17] avoid social threatening situations. Interestingly, there is support from studies with right frontal cortex slow rTMS stimulation in PTSD patients for improvement of PTSD symptoms [12,18], and also for improvement of the PTSD core symptom avoidance [18]. Our findings suggest that this might have been accomplished by suppressing the activity of the underlying right prefrontal cortex with slow rTMS, that is, decreasing the activity of the withdrawal system and its related emotions. This decrease in activity of the right frontal areas is in line with the results found in two patients who underwent positron emission tomography (PET) scans before and after rTMS of the right frontal cortex [18].

In conclusion, this rTMS study revealed a significant difference in attention to angry faces between the left and right PFC inactivation. Left slow rTMS induced selective attention to angry faces, whereas after right rTMS subjects attended away from angry faces. Our findings support theoretical proposals of an approach system and a withdrawal system implemented in a neural network that involves the left and right prefrontal cortex, respectively.

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