Effects of slow rTMS at the right dorsolateral prefrontal cortex on EEG asymmetry and mood

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In a sham-controlled design (n=12), slow repetitive Transcranial Magnetic Stimulation (rTMS) was applied to the right dorsolateral prefrontal cortex during a period of 20 minutes, and the subsequent effects on mood and the EEG spectrum were investigated. Analysis revealed a significant left hemisphere increase in EEG theta activity between 25 to 35 and 55 to 65 minutes after stimulation. In addition, participants reported significant decrease in anxiety immediately after stimulation, as well as 35 and 65 minutes after rTMS. These findings indicate that reductions in anxiety after slow rTMS at the right dorsolateral prefrontal cortex are associated with a contralateral increase in theta activity. *NeuroReport* 12:445-447.

Keywords: rTMS, dorsolateral prefrontal cortex, EEG power spectrum, mood

INTRODUCTION

There is now abundant evidence for the involvement of the prefrontal cortex in affective processes. According to the directional model of negative affect, the left anterior sector of the brain is involved in the approach-related emotion 'anger', whereas the right prefrontal sector is linked to the withdrawal-related emotion 'anxiety'[1,2]. Recently, D'Alfonso et al.[3] applied slow rTMS over the right dorsolateral prefrontal cortex. This method is commonly suggested to decrease neuronal activity in the stimulated area. Enhanced approach and reduced withdrawal-related motivation were found, as indexed by a motivational selective attention task. It was shown that right compared to left prefrontal stimulation induced vigilant attention for angry faces, in agreement with a line of findings in our laboratory in relation to low levels of social anxiety and high levels of anger[4].

Electrophysiologically, these hemispheric differences are commonly assessed on the alpha power band (8-13 Hz) in the electroencephalographic (EEG) spectrum, which is inversely related to cortical activity. Decreased activation of the right prefrontal cortex induced by slow rTMS should therefore result in a shift of the cerebral alpha asymmetry to the right prefrontal area, accompanied by reductions in anxiety and increases in anger. The present study was designed to investigate the latter hypotheses. RTMS was applied over the right dorsolateral prefrontal cortex, and its effects on self-reported mood (i.e. anger and anxiety) and the EEG frequency bands theta (4-7 Hz), alpha (8-12 Hz) and beta (13-30 Hz) were investigated.

MATERIAL AND METHODS

Participants

Twelve right-handed volunteers (four females) aged between 19 and 42 years (m=28.4; SD=8.9) participated in this single blind, cross-over, sham-controlled experiment. An informed consent was obtained, and subjects with a history of neurological or psychiatric disorder were excluded. All subjects were naïve of TMS, unaware of the aim of the study and were paid for participation. The local ethical committee of the Faculty of Social Sciences approved the study.

Apparatus and EEG recordings

A Neopulse Transcranial Magnetic Stimulator (Neotonus, Inc.) was used on separate days either to stimulate the right dorsolateral prefrontal cortex (F4) or to induce sham stimulation, with the coil positioned 90% tangential to the surface of the head. The target of rTMS was based on the International 10/20 System of EEG electrode positions. Subjects were stimulated for 20 minutes at 130% of the motor threshold (MT) with a frequency of 1 Hz. Stimulation and sham condition were randomised and counterbalanced across the participants. EEGs were recorded from the homologous F3 and F4 scalp positions, using an Electro-Cap with Ag/AgCl electrodes (Neurosoft, Inc.). EEG signals were referenced to an electrode placed behind the subject's right ear. For the purpose of artefact scoring, vertical (VEOG) and horizontal (HEOG) eye movements were recorded. Ag/AgCL electrode pairs (bipolar) were placed at the supra- and suborbit of the right eye and at the external canthi of each eye. ECI EEG Gel was used for both EEG and EOG and all electrode impendances were less than 5,000 Ohms. An acquisition amplifier (Ampligraph) was used to filter incoming signals (low-pass cut-off frequency 30 Hz; time constant 3 seconds). For the EEG recordings NeuroScan software was used. Amplification was set at 20,000 for both the EEG and EOG leads, and the sample rate was 250 Hz. The state anger and anxiety scales of the Spielberger State Trait Anger Scale (STAS)[5] and State Trait Anxiety Inventory (STAI)[6] were used in order to quantify self-reported changes in mood.

Procedure

First, all subjects completed the first of four STAS and STAI scales. Next, the Electro-Cap was positioned, and the subject was instructed to relax, without falling asleep in a dimly lit room. One of two randomly generated sequences of five 1-minute blocks of eyes-open relaxation and five 1-minute blocks of eyes-closed relaxation measurements were used during each recording and were counterbalanced within each session. After the first EEG recording, the F3 and F4 electrode sites were marked and the EEG cap was removed in order to start the rTMS procedure. At each first session, the MT was quantified, using the left thumb movement visualisation method[3]. Afterwards, slow rTMS at 130% MT with a frequency of 1 Hz during 20 minutes, or sham was applied at the F4 electrode position. A second version of the questionnaires was completed after rTMS. Next, the EEG cap was placed back on the subject's head, ensuring that the F3 and F4 electrodes sites were back on their previous positions and all electrode impendances were below 5,000 Ohms.

Ten minutes after rTMS, a second 10-minute EEG, 10 to 20 minutes post-rTMS was recorded. With a resting period of five minutes, a third EEG measurement, 25 to 35 minutes post-rTMS was completed followed by a third set of questionnaires. During 40 to 50 minutes post-rTMS a fourth EEG was recorded and a last EEG measurement was obtained 55 to 65 minutes after rTMS. The session was concluded by a final set of questionnaires.

Data reduction and analysis

Portions of each 1-minute EEG signal, containing eye movements, muscle movements, or other sources of artefact were rejected prior to further analysis. The designation of artefact in one of the two leads resulted in the removal of data in both channels to ensure that data preserved in both channels were derived from the identical time periods. After artefact rejection, EEG data were corrected for horizontal and vertical eye movements. Next, 1,024-s chunks of averaged artefact free EEG were used for spectral analysis. Epochs of artefact-free EEG were extracted through a Hamming window (length 10%) in order to reduce spurious estimates of spectral power. For each chunk, a Fast Fourier Transform method was used to derive estimates of spectral power (μV^2) in different 1 Hz frequency bins for each electrode site. Spectral power values were then averaged across all epochs within a single baseline.

Power values were then converted to power density values (μV²/Hz) for the standard frequency bands. Data were analysed, using MANOVAs and post-hoc paired t-tests. Significance level was set at $\alpha < .05$ (two-tailed).

RESULTS

Analysis of the EEG spectrum revealed no significant effects of stimulation, neither on the expected alpha band nor on the beta band. However, a Stimulation x Hemisphere interaction was found for theta power [$F(1,11)= 5.40$, $p=.04$] and post-hoc analysis revealed a significant increase in left prefrontal theta activity between 25 to 35 [$t(11)=2.28$, $p< .04$], and 55 to 65 minutes [$t(11)=2.59$, $p<.02$] after rTMS.

A MANOVA yielded an overall significant reduction of anxiety in the rTMS condition, compared to the sham condition [$F(1,11)=10.23$, $p=.008$]. Post-hoc analysis revealed that this reduction was significant immediately [$t(11)=2.93$, $p=.01$], following 35 minutes [$t(11)=2.22$, $p=.04$] and 65 minutes [$t(11)=2.32$, $p=.04$] after rTMS.

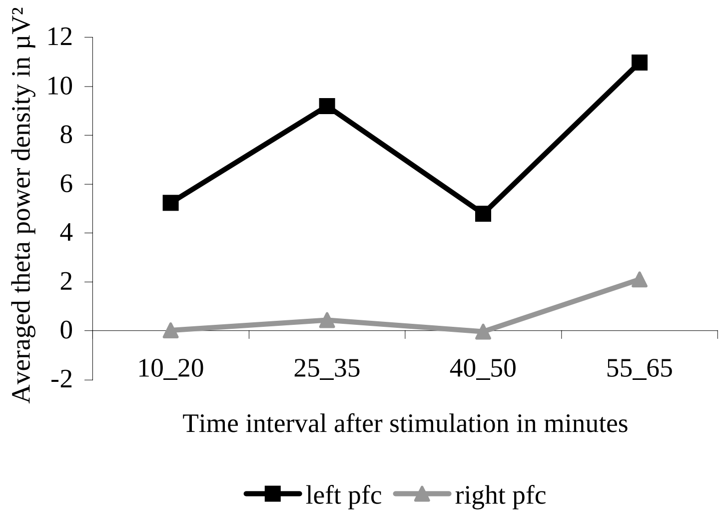

***Figure 1**. Sham corrected difference theta power densities for the left and right prefrontal cortex after slow rTMS.*

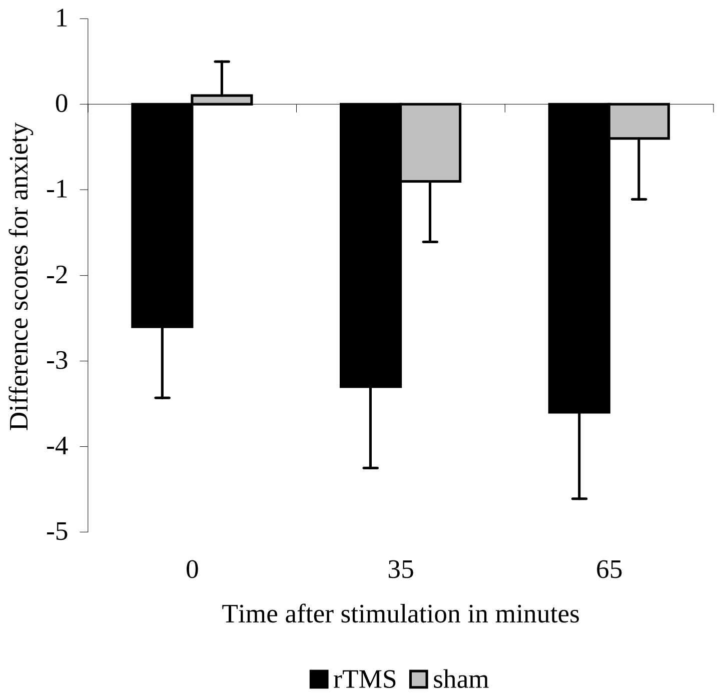

***Figure 2**. Baseline corrected mean scores and SEM for self-reported anxiety after slow rTMS and sham.*

DISCUSSION

In accordance with our hypothesis, slow rTMS resulted in a significant reduction in anxiety. Theoretically, inactivation of the right prefrontal area should be accompanied by reduced withdrawal-related negative affect. However, elevations in anger nor the hypothesized reductions in right prefrontal activation on any of the EEG frequency bands were observed. On the other hand, there was a significant contralateral increase in theta activity after slow rTMS. Interestingly, a recent rTMS-fMRI study also provides support for such contralateral effects of slow rTMS when stimulating at high intensities[7]. It this interleaved rTMS-fMRI study of Nahas et al., stimulation site was the left PFC and increases were found in right PFC activity. The authors speculated about the possibility of increased pain at high intensities resulting in activation in right-hemispheric biased pain circuits. The contralateral increases after slow rTMS observed in this study are, however, right-to-left, which refutes such an alternative explanation, and suggests that both the Nahas et al., and the present findings reflect real rTMS-induced effects on brain activation (Ziad Nahas, Personal communication). Furthermore, there is substantial evidence for the inverse relation between the behavioral and physiological effect, we observed after rTMS. Elevations in theta power have been linked to reductions in anxiety in several studies[8], and the present left-sided bias for theta power has been demonstrated in clinically anxious subjects[9], and in non-clinical subjects, when using anxiety questionnaires[10] and physiological indications of anxiety (i.e. cortisol levels)[11]. Finally, motivational aspects of attention are suggested to be specifically sensitive to the EEG theta rhythm[12] and in our earlier slow rTMS study[3], we also stimulated over the dorsolateral cortices with comparable stimulation parameters, and found significant changes in motivated attention

CONCLUSION

This study shows that slow rTMS at suprathreshold intensities over the right dorsolateral prefrontal cortex induces significant reductions in anxiety and instigates contralateral increases in EEG theta power. Increases in left prefrontal theta activity and reductions in anxiety, induced by slow rTMS fit in the anterior asymmetrical models of approach- and withdrawal-related emotion[1-2]. Furthermore, the contralateral increases in theta power after slow rTMS add to recent evidence demonstrating that local or distant effects of this technique may depend on the stimulation intensity used [7]. The anxiolytic mechanisms of action of rTMS are largely unknown. The converging evidence from literature for an inverse relationship between EEG theta and anxiety, suggests that the present findings provide a first initial insight in an anxiolytic mechanism of action of rTMS. It should however be noted that the physiological and behavioral changes likely depend on a cascade of effects of a highly complex nature, in which cause-effect relations elude a detailed understanding as of yet.

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