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Reductions in phenomenological, physiological and attentional indices of depression after 2Hz rTMS over the right parietal cortex

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Abstract

Research into emotion and emotional disorders by repetitive transcranial magnetic stimulation (rTMS) has largely been restricted to the prefrontal regions. There is however also evidence for the parietal cortex being implicated in emotional (dys-)functioning. Here we used rTMS to investigate a role of the right parietal cortex in depression. In a placebo-controlled design, 2Hz rTMS at 90% of the individual motor threshold (MT) was applied over the right parietal cortex of eight healthy subjects for 20 minutes continuously. Effects on mood, autonomic activity and motivated attention were investigated. Significant reductions in depressive mood were observed immediately following, and 30 minutes after stimulation. Moreover, these findings were objectified by a concurring pattern of autonomically-mediated changes in the attentional processing of angry facial expressions. These data suggest a role for the right parietal cortex in affective brain circuits regulating phenomenological, physiological and attentional aspects of depressive functioning.

Introduction

Human emotion is regulated by a complex compound of interacting brain circuits (Davidson, 1984). Repetitive transcranial magnetic stimulation (rTMS) may be capable of providing more insights into the workings of these affective circuits by modulating brain activity in controlled designs. Studies in clinically depressed populations show that treatment with high frequency rTMS (≥ 5 Hz) over the *left* prefrontal cortex (PFC) has antidepressant efficacy (Pascual-Leone, Rubio, Pallardo, & Catala, 1996a; George et al., 2000; Szuba et al., 2000; Daskalakis, Christensen, Fitzgerald, & Chen, 2002 for a review). Moreover, the same technique is even capable of improving mood in healthy subjects when applied in a single session (George et al., 1996; Pascual-Leone, Catala, & Pascual-Leone, 1996b). Although null-findings have also been reported (Mosimann, Rihs, Engeler, Fisch, & Schlaepfer, 2000; Jenkins, Shajahan, Lappin, & Ebmeier, 2002). Antidepressant and mood improving effects have been shown when applying low frequency rTMS (< 5Hz) over the *right* PFC (Klein et al., 1999; Schutter, Van Honk, D'Alfonso, Postma, & De Haan, 2001). Originally, it was suggested that the high frequencies produced neural excitation and the low frequencies neural inhibition of the target regions. But, recent research shows that low frequency rTMS at higher intensities produces contralateral excitation (Speer et al., 2000; Nahas et al., 2001; Schutter et al., 2001). Nevertheless, associations between relatively more left prefrontal activity and reduced depression support the valence hypothesis. Approach and withdrawal constitute the dimensions in the valence hypothesis. Imbalance may on the one hand result in anxiety or depression and on the other hand in aggression or psychopathy (Arnett, 1997; Harmon-Jones & Sigelman, 2001).

A methodological drawback in much rTMS-emotion research is the reliance on questionnaires of mood. Although consciously experienced mood constitutes an important output of the emotional system it provides little insight in the other constructs of emotion, physiology and motivational behavior (Buck, 1999). Emotionally generated physiological responses (e.g., heart rate, skin conductance) operate rather independ-

ently of verbal affective reports and provide for the opportunity to track psychological events in real time (Öhman, Hamm, & Kenneth, 2000). Motivational behavior can reliably be measured using motivated attention tasks, such as modified dot probe task or emotional Stroop tasks. These tasks index automatic behavioral tendencies towards or away from emotionally relevant stimuli (Van Honk, Tuiten, De Haan, Van den Hout, & Stam, 2001a). Using an emotional Stroop task, we showed that low-frequency rTMS over the right prefrontal cortex (PFC) induces vigilant attentional responses towards angry facial expressions, whereas left PFC rTMS induces avoidant responses (D'Alfonso, Van Honk, Hermans, Postma, & De Haan, 2000). The vigilant response to the angry face symbolizes the tendency for aggressive approach or social domination (Mazur & Booth, 1998; Van Honk et al., 2001a), while the avoidant response symbolizes submission or withdrawal (Van Honk et al., 1999; Öhman et al., 2000). Since low-frequency rTMS potentiates the contralaterally mediated emotion functions through unilateral inhibition and/or contralateral excitation, the above findings fit the valence hypothesis in terms of approach and withdrawal-related emotion. In further agreement, in the above study, elevations in cardiac sympathetic activity accompanied the vigilant responses after right PFC rTMS, whereas the avoidant responses after left PFC rTMS were accompanied by attenuated physiological responses (Van Honk et al., 2002). The former pattern suggesting preparation for approach-directed action and the latter characterizing conservation withdrawal (Van Honk et al., 1999, 2001a, 2001b; Nesse, 2001).

Research into emotion and emotional disorders by repetitive transcranial magnetic stimulation (rTMS) has largely been restricted to the prefrontal regions. There is however also evidence for the involvement of the parietal cortex in emotional (dys-)functioning (Davidson, 1984; Davidson & Henriques, 2000). Interestingly in this respect we recently showed an inverse relationship between baseline levels of cortisol, an endocrine marker for depression (Holsboer, 2000) and functional connectivity between the left PFC and right parietal cortex (Schutter, Van Honk, Koppeschaar, & Kahn, 2002). For these reasons in this study rTMS was

applied over the right parietal cortex in a placebo-controlled design, using the innovative frequency parameter setting of 2Hz at 90% of the individual motor threshold (MT) for 20 minutes continuously. Dependent measures were self-reported mood, physiology and motivated attention. rTMS was expected to induce reductions in depressive mood and more vigilant responses towards angry facial expressions (D'Alfonso et al., 2000) accompanied by elevations in cardiac activity during the motivated attention task (Van Honk et al., 2002).

Method

Participants

Eight right-handed volunteers (female-male ratio 4:4) aged between 20 and 28 years participated in this single blind, counterbalanced, cross-over, placebo-controlled design. 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.

Mood, physiological measures and motivated attention

Mood was established by the Profile of Mood States (POMS) using the subscales depression, anger and anxiety (Shacham, 1983). The subscales of the POMS seem to reveal changes in mood associated with changes in physiological functioning (Abplanalp, Donnelly, & Rose, 1979). Since slight but pertinent changes in mood in normal subjects are unlikely to be revealed by the conventional scale (Bond & Lader, 1974), visual analogue scales allowing responses ranging from 0 to 100 were used to enhance sensitivity (Van Honk et al., 1999). As physiological measures, heart rate and skin conductance were assessed. Heart rate was measured using a Finger Pulse Plethysmograph and skin conductance using a Self Balancing Skin Conductance Amplifier (Contact Precision Instruments, London, UK). Signals were sampled at 10Hz using analogue-digital converting devices and software for physiological measurements (Test-

point 2.3). Motivated attention was indexed using a dot probe task. Pairs of faces of the same actor appear 750 ms after presentation of a central fixation cross. One face is neutral and the other angry or happy. They are presented simultaneously to the left and right hemifield with 9 degrees of visual angle between the centers of the pictures. After 500 ms delay, the pictures are replaced by a target probe (the capital character A or O) in the position of one the faces and subjects are instructed to vocally identify this probe as fast as possible. Reaction times of vocal responses were recorded using a National Instruments data acquisition card (PC-TIO-10) connected to a Lafayette voice activated relais in an IBM-compatible PC running Testpoint software. We used 96 trials, depicting 8 female and 8 male actors displaying a neutral and an emotional face. After computer registration of voice response onset the probes would disappear and after 1500-2500 ms (quasi-random variation) a new trial would start. By subtracting the response latencies to probes appearing in the position of an emotional face from latencies to probes appearing in the position of the neutral face, one obtains an attentional bias score indicating vigilance for (bias score > 0) or avoidance of (bias score < 0) the emotional face.

Procedure

Before the experiment, on a separate day, individual MT was quantified using the left-thumb movement visualization method (Pridmore, Fernandes-Filho, Nahas, Liberatos, & George, 1998). Separate days were used for the placebo (coil angled 90%) and stimulation session. Order of sham and real stimulation were randomized and counterbalanced over subjects. In these sessions, subjects first completed the mood scales and physiological activity was measured continuously during the experiment. P4 electrode site, according to the International 10-20 EEG System was marked using an EEG cap and rTMS/placebo using a specially designed iron-core coil (Neopulse, Neotonus Inc., Atlanta) was applied at 90% MT with a frequency of 2Hz during 20 minutes. 5 Minutes after rTMS/placebo a second version of the mood scales was completed, followed by a final version 25 minutes later. Afterwards subjects performed the dot probe task. Each stimulation session was separated by at

least 24 hours. During the actual measurements the experimenter was in an adjacent control room, thereby minimizing the chance of a possible experimenter bias.

Results

The stimulations were well tolerated by all subjects. Analyses used related-sample (placebo vs. rTMS) Wilcoxon rank-order tests, with α set at .05, two-tailed.

Mood

There were no significant effects for the mood-scales anger and anxiety, however, there was a significant reduction in depressive mood just after [$Z = -2.06$: $p < 0.039$] and also 30 minutes after rTMS [$Z = -2.03$: $p < 0.042$]. See Figure 10.1.

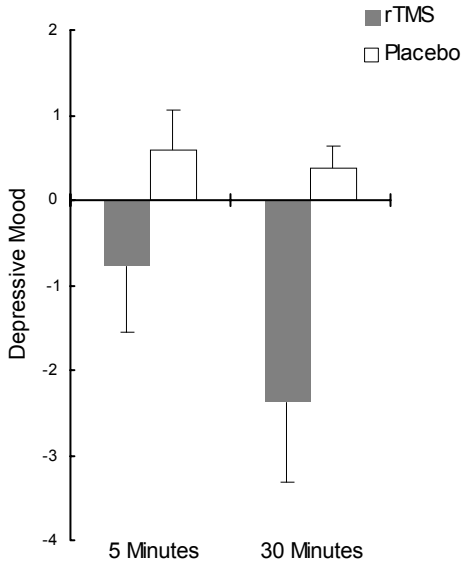

Figure 10.1. Mean (SEM) baseline-corrected changes in depressive mood 5 and 30 minutes after placebo and rTMS.

Motivated attention

There were no effects for happy faces, but rTMS resulted in a significant reduction in the avoidant response to the angry face (shown after placebo) when it appeared in the left-hemifield [$Z = -2.52$: $p < 0.012$]. See Figure 10.2.

Skin conductance and heart rate

No effects for skin conductance were observed. rTMS compared to placebo however showed significant elevations of heart rate during the performance of the dot probe task [$Z = 2.1$: $p < 0.036$], which is shown in Figure 10.2.

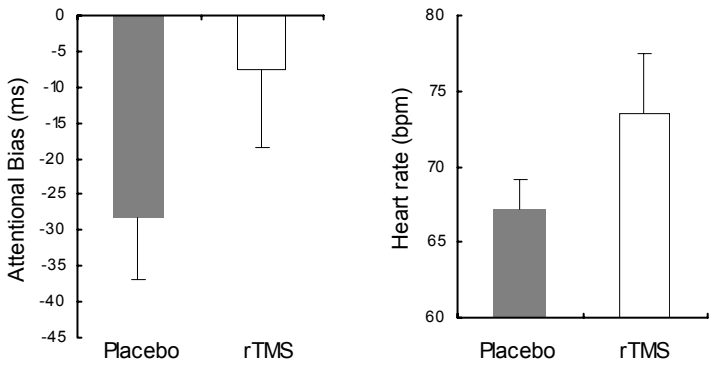

Figure 10.2. Mean (SEM) attentional biases for angry facial expressions in milliseconds (ms) in the left hemifield, and mean (SEM) heart rate in beats per minute (bpm) during performance of the motivated attention task after Placebo and rTMS.

Finally analyses were run to test for order effects of stimulation. The group who received rTMS on the first and sham on the second day was compared with the group who received sham on the first and rTMS on second day. No significant differences were found for the dependent measures (all Z's < 1.3, n.s.).

Discussion

To our knowledge this is the first rTMS study to investigate the role of the right parietal cortex in emotion. Compared to placebo, a single

session of rTMS induced slight, but significant reductions in depressive mood immediately after, and 30 minutes after stimulation. In addition, the avoidant pattern of responding to the angry face in the left hemifield (right hemispheric processing) was significantly reduced after rTMS, a reduction which was accompanied by a task-dependent elevation in heart rate, but not in skin conductance. Crucially, the role of the cardiac system in the modulation of motivated aspects of attention is well-documented (Öhman et al., 2000). As noted in the introduction, a converging elevation, in specifically, sympathetic, cardiac activity was shown after right PFC low-frequency rTMS during an emotional Stroop task, and was again accompanied by less avoidant emotional responses to the angry facial expression (D'Alfonso et al., 2000). Autonomic control over attention and emotion fits the polyvagal theory of Porges (1995), which in fact suggests that difficulties in autonomic control may lead to depressed mood. For all measures, self-report, motivated attention and physiology, the present effects constitute reductions in the outputs of low mood and depression (Van Honk et al., 1999, 2001a, 2001b; Nesse, 2001; Flinn, Baerwald, Decker, & England, 1998). It is argued that during social confrontations (i.e., when confronted with dominant figures displaying anger), the adaptive regulatory function of low mood and depression is to avoid injury and energy loss by securing for inhibited behavioral and physiological responses (Sapolsky, 1990). It seems justifiable to assume that the elevations in mood here induced by rTMS lead to a reduction of the tendency to avoid a socially threatening confrontation.

It should be acknowledged that the small sample size and the lack of a third control condition (e.g., left parietal cortex stimulation) somewhat limits this study. Sham controlled TMS designs have been a longstanding issue in TMS research, however in the present study subjects were not only naïve of TMS, but also unaware of the aim of the study and unfamiliar with the dependent measures. Additionally, as can be read in the Result section, there were no order effects for stimulation days.

When discussing these findings in relation to clinical rTMS research, where the left PFC is the main target region, the theoretical notion of dys-communication between the right parietal and left prefrontal cortex

in depression is notable (Van Honk et al., 2001b). Moreover as noted in the Introduction, higher baseline levels of the (depression-related) stress hormone cortisol, are in fact associated with reduced EEG coherence, i.e. functional connectivity in this left prefrontal-right parietal brain circuit (Schutter et al., 2002), and EEG coherence between these regions seems to be highly sensitive to rTMS (Jing & Takigawa, 2000). It might thus be suggested that one of the effects of 2Hz rTMS over the right parietal cortex is an increase in functional connectivity between the left prefrontal and right parietal cortex (Schutter, D'Alfonso, & Van Honk., 2003).

Finally, the present study adds to the methodology by exploring the large parameter range of rTMS (Sackheim, 2000). The reliability of rTMS effects seems to depend on the number of pulses applied, stabilizing at 1600 pulses (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000), and clinical studies show that the most pronounced anti-depressant effects also depend on pulse quantity (George & Epstein, unpublished data). To upgrade the quantity of pulses in the low frequency range the 2Hz frequency may be a promising parameter. A single session of 2400 pulses as reached here has not been reported in human research so far. Regarding the possible application of the present stimulation parameters in clinical studies it must mentioned that rTMS induced changes in mood in normal subjects and depressed patients not always point in the same direction. Nevertheless, given the relative safety of low frequency rTMS, the application of this parameter in clinical studies over both the left prefrontal and the right parietal cortex seems warranted. In sum, in the present sham-controlled design, 2Hz rTMS at 90% of the individual motor threshold (MT) was applied over the right parietal cortex of eight healthy subjects for 20 minutes continuously. Effects on mood, autonomic activity and motivated attention were investigated. Although all subjects scored at baseline in the lowest quartile on the scale measuring depressive mood, significant reductions in depressive mood were still observed immediately following, and 30 minutes after stimulation. Moreover, these findings were objectified by a concurring pattern of autonomically-mediated changes in the attentional processing of angry

facial expressions. These data suggest a role for the right parietal cortex in affective brain circuits regulating phenomenological, physiological and attentional aspects of depressive functioning.

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