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Increased sensitivity for angry faces in depressive disorder following 2 weeks of 2-Hz repetitive transcranial magnetic stimulation to the right parietal cortex

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Abstract
According to the cognitive neuropsychological hypothesis of antidepressant action, the onset of subjectively experienced therapeutic effects to treatment is preceded by favourable changes in psychological functioning that can be measured by implicit methods. The aim of this study was to examine additional data to explore this hypothesis in an intention-to-treat repetitive transcranial magnetic stimulation (rTMS) study targeting the right parietal cortex. Changes in depression scores from baseline and the sensitivity for recognizing emotional facial expressions were studied in 28 patients with depressive disorder receiving ten sessions of real (n = 14) or sham (n = 14) rTMS treatments in a double-blind, sham-controlled design. In the patient group results showed significantly higher sensitivity for recognizing angry facial expressions in response to receiving real compared to receiving sham rTMS treatment. Overall mood improvement was similar across real and sham rTMS treatments. However, the sensitivity for recognizing angry facial expressions was correlated to the percentage decrease in depression scores. These results provide the first preliminary support for the cognitive neuropsychological hypothesis of antidepressant action in rTMS treatment.

Received 8 February 2010; Reviewed 10 March 2010; Revised 17 May 2010; Accepted 19 May 2010; First published online 29 June 2010

Key words: Angry faces, antidepressant action, depressive disorder, parietal cortex, transcranial magnetic stimulation, treatment.

Introduction
According to the cognitive neuropsychological hypothesis of antidepressant action, the onset of therapeutic effects to treatment is preceded by changes in psychological functioning (Harmer et al. 2009a, Harmer, 2010). Changes in cognitive and emotive processes associated with the neurophysiological action of treatment are usually not consciously accessible to the patient or directly observable by others, but nonetheless they may reveal antidepressant action at an early stage of treatment. Single administrations of the antidepressant agents reboxetine and citalopram have, for instance, been shown to reduce biases for negative information and enhance the processing of positive information without an immediate effect on mood (Harmer et al. 2009b). Similar effects have been observed in non-invasive brain stimulation studies. Single administrations of 1-Hz slow-frequency repetitive transcranial magnetic stimulation (rTMS) have demonstrated decreased attentional
responses to fearful faces (van Honk et al. 2002), increased attentional responses to angry faces (d’Alfonso et al. 2000) and improved memory performance for happy faces (Schutter & van Honk, 2006). Notably, in all cases, no changes in mood were observed.

In the past 15 yr rTMS over the frontal cortex has been explored as an alternative way to treat depressive disorder. Recent meta-analytical studies indicate that rTMS reaches similar antidepressant efficacy as several registered antidepressant drugs (Demitrack & Thase, 2009; Schutter, 2009, 2010). Despite being equally effective as antidepressants, the clinical relevance of these effects appears to be moderate. Hence, the need for additional research exploring novel strategies to optimize therapeutic efficacy (Herrmann & Ebmeier, 2006; Schutter & van Honk, 2005).

Evidence for possible antidepressant working of rTMS applied to the right parietal cortex was found in a sham-controlled study by van Honk et al. (2003). In this study, a significantly increased vigilant response to facial anger accompanied decreases in self-reported depressive mood, following a single 20-min session of 2-Hz rTMS to the right parietal cortex in healthy volunteers. The combination of more vigilant responsiveness to facial anger and reduced depressive mood may indicate increased approach-related motivation (Depue & Iacono, 1989; Putman et al. 2004). These findings led us to perform a double-blind, sham-controlled study wherein, for the first time, we explored the antidepressant effects of 10 sessions of 2-Hz rTMS to the right parietal cortex in healthy volunteers.

In keeping with the cognitive neuropsychological hypothesis of antidepressant action in rTMS treatment, we did not find a main effect of treatment on the percentage change in depression scores measured with the 17-item Hamilton Depression Rating Scale (HAMD$_D$). However, we were able to collect and analyse additional behavioural data on the sensitivity for recognizing emotional facial expressions in a subset of 28 patients after the final treatment session, which allowed us to examine the cognitive neuropsychological hypothesis of antidepressant action in rTMS treatment.

Table 1. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>rTMS treatment characteristics</th>
<th>Real $(n = 14)$</th>
<th>Sham $(n = 14)$</th>
<th>$p$ value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± s.d., yr</td>
<td>44 ± 12</td>
<td>46 ± 13</td>
<td>0.69$^b$</td>
</tr>
<tr>
<td>Female/Male, n</td>
<td>10/4</td>
<td>6/8</td>
<td>0.25$^c$</td>
</tr>
<tr>
<td>Medication, n</td>
<td>10</td>
<td>9</td>
<td>1.00$^c$</td>
</tr>
<tr>
<td>Baseline HAMD$_D$$^d$, mean ± s.d.</td>
<td>21 ± 4</td>
<td>21 ± 5</td>
<td>0.93$^b$</td>
</tr>
</tbody>
</table>

$^a$ Two-tailed.

$^b$ Analysis of variance.

$^c$ Fisher’s exact probability test.

$^d$ 17-item Hamilton Depression Rating Scale.

**Methods**

**Participants**

Twenty-eight of the thirty-four in-patients and out-patients involved in clinical trial NTR1279 with a primary diagnosis of depressive disorder according to DSM-IV-TR criteria (APA, 2000) and a score of ≥15 on HAMD$_D$ were included in this follow-up analysis. Current depressive disorder was confirmed by the Structured Clinical Interview for DSM-IV, Research Version (SCID-I; First et al. 1996). Real $(n = 14)$ and sham $(n = 14)$ treatment groups did not differ in age, sex, medication and baseline HAMD$_D$ scores (Table 1).

History of seizures, neurological conditions, metal objects in or around the body that cannot be removed (i.e. cochlear implant, surgical clips, piercings and cardiac pacemaker), heart disease, pregnancy, drug and alcohol abuse were considered exclusion criteria. Antidepressant and hypnotic medication had been stable for at least 6 wk and 2 wk, respectively, prior to the study, and were kept constant during treatment. All participants received written and verbal information on the study and written informed consent was obtained. The study was in accordance with the Declaration of Helsinki and approved by the medical ethics committee of Free University Medical Center and St Lucas Andreas Hospital, Amsterdam, The Netherlands.

**Emotional facial recognition task**

The sensitivity for recognizing facial expressions was measured with a task adapted from Montagne et al. (2005) that used morphed images from neutral face (0% emotion) to full-blown expression (100% emotion). Stimuli were taken from four actors (two male, two female) who each posed a facial expression...
(i.e. neutral, anger, disgust, fear, happiness, sadness, surprise) in frontal view. These facial expressions were used to create short video clips that incrementally increase the degree of emotional expression in 10% steps (e.g. from neutral to anger). First, participants viewed the video clips running from neutral to 20% expression of all six emotional expressions by all four actors in random order. Next, the same procedure was applied for 30%, 40% and so on, until the final sequence of clips in which the neutral face changed into the full-blown expression (100%). There were 216 trials that were preceded by six practice trials. In each trial participants were required to make a forced choice, without time restriction, between one of six emotional expression labels that were shown on the computer screen. For each emotion, an average sensitivity score was computed on the basis of the minimum degree of emotional expression needed to correctly identify the emotional expression of the four actors with 100% accuracy.

Transcranial magnetic stimulation (TMS)

TMS was performed using a high-frequency Magpro Dantec magnetic stimulator with a MCF-B65 figure-of-eight coil (Medtronic, Denmark). At the start of the first session individual motor threshold (MT) of the right hemisphere was established using the visual twitch method to determine the fixed stimulation intensity (mean ± S.D.) (Pridmore et al. 1998), MT\textsubscript{real} [76.2 ± 16.5 dl/dt (A/s)] and MT\textsubscript{sham} [84.8 ± 17.7 dl/dt (A/s)]. Over the course of 2 wk patients received ten 20-min sessions of 2-Hz rTMS at 90% MT (i.e. 2400 pulses per session). Parameters were selected based on prior research showing that effects of rTMS on cortical excitability stabilize at 1600 pulses (Maeda et al. 2000) and clinical evidence indicating that the magnitude of the effects depends on the number of pulses (Touge et al. 2001). The rationale for applying rTMS at subthreshold intensity is based on previous findings of intensity-dependent increases of brain activity in local and distal sites (Speer et al. 2003). Here, we used low-intensity stimulation in an attempt to keep the effects restricted to the right parietal cortex. These parameter settings have proved successful in a related rTMS study in which reductions in phenomenological, physiological and attentional indices of depressive mood were found (van Honk et al. 2003).

Stimulation occurred over the P4 electrode site according to the International 10–20 EEG system targeting the right parietal cortex. The coil was held tangentially to the scalp with the handle pointing to the back and oriented away from the coil’s midline at 45°. For sham stimulation a specially designed figure-of-eight coil was used. This coil mimics the sensation and sound of real rTMS, but prevents the magnetic field from reaching the target tissue through interception by a built-in permalloy shield plate (MC-P-B70, Medtronic, Denmark). Contact between the physician applying rTMS and the patient was kept to a minimum. Stimulation parameters and procedure were in accordance with safety guidelines (Wassermann, 1998).

Procedure

Patients were randomly allocated to receive either real or sham rTMS treatment on 10 consecutive working days (i.e. 2 wk) via sealed envelopes opened immediately before the start of the first treatment by the clinician administering rTMS. Prior to entering the study the patient underwent standard clinical, psychiatric and laboratory tests and was screened for contraindications to rTMS. Clinical assessment was repeated after the final treatment session. Depression scores were acquired with HAMD\textsubscript{D} at baseline and after the final treatment session. The emotional facial recognition task was administered immediately after the final clinical assessment. Last, patients were asked to indicate whether they had received real or sham treatment. All ratings and tests were performed by trained researchers blind to the actual treatment.

Statistical analyses

A binomial test was performed to check that patients had remained blind to treatment. One-way analyses of variance (ANOVA) were performed to test the difference between real and sham rTMS treatments on percentage change from baseline on HAMD\textsubscript{D} scores and percentage sensitivity for the recognition of emotional facial expressions. A Pearson’s correlation was performed to examine the relationship between percentage change from baseline on the HAMD\textsubscript{D} scores and percentage sensitivity for the recognition of emotional facial expressions. For all tests, a two-tailed significance level of 0.05 (uncorrected) was applied.

Results

Treatment was well tolerated by the patients. A binomial test demonstrated that blinding of treatment condition was successful ($p>0.5$). The percentage reduction from baseline on HAMD\textsubscript{D} scores (mean ± S.E.M) did not differ between real (20.5 ± 8.8%) and sham (8 ± 7.9%) rTMS treatments ($F(1,27) = 1.00, p = 0.33$),
showing that 10 sessions of 2-Hz rTMS over the right parietal cortex did not yield significant improvements on depression severity (cf. Schutter et al. 2009) (Fig. 1).

In contrast, significant higher sensitivity (i.e. lower percentage) for the recognition of angry facial expressions was observed in the real (42.3 ± 4.2%), compared to the sham (60.7 ± 6.4%) rTMS treatments \([F(1, 27) = 5.76, p = 0.02]\). The difference between real (39.5 ± 5.8%), and sham (29.3 ± 2.2%) rTMS treatments for the sensitivity of happy facial expressions did not reach statistical significance \([F(1, 27) = 2.73, p = 0.11]\). Sensitivity for the other facial expressions was not statistically different between real and sham rTMS treatments (all \(p\) values > 0.35) (Fig. 2).

Finally, a significant correlation between percentage change from baseline on the HAMD\(_{17}\) scores and sensitivity for angry facial expressions was observed \([r(26) = 0.51, p = 0.005]\) (Fig. 3), indicating that the percentage reduction on HAMD\(_{17}\) scores from baseline was associated with increased sensitivity for recognition of angry facial expressions. Percentage reduction on HAMD\(_{17}\) scores did not correlate with the sensitivity for the other emotional facial expressions (all \(p\) values > 0.30).

Discussion

The aim of this study was to examine whether the neuropsychological hypothesis of antidepressant action has potential in rTMS treatment. This hypothesis states that prior to therapeutic onset positive effects of treatment can already be observed at the information processing level (Harmer et al. 2009a; Harmer, 2010).
Our results showed significantly higher sensitivity in recognizing angry facial expressions following 10 sessions of real vs. sham 2-Hz rTMS to the right parietal cortex. Despite observing an overall improvement in mood, no main effect of treatment was found. Furthermore, the sensitivity for recognizing angry facial expressions was correlated to the percentage decrease in HAMD<sub>17</sub> scores, indicating that the sensitivity for the angry face may capture aspects of antidepressant action. This latter finding would be in accord with a recent study in elderly depressed patients demonstrating improvements in mood and memory performance for angry facial expressions following antidepressant therapy with escitalopram (Savaskan et al. 2008). As mentioned earlier, heightened sensitivity for angry facial expressions has been interpreted as a behavioural sign of increased approach-related motivation (Putman et al. 2004), a condition which is typically reduced or absent in patients suffering from depressive disorder (Depue & Iacono, 1989). According to the integrative model of mood based on fear and anger traits by Lara et al. (2006), anger is conceptually related to appetitive impulsivity, drive, pleasure, aggressive behaviour, goal-directed behaviour, and dominance. Previous research has shown relationships between reduced cortical responses to anger-evoking events and diminished approach-related motivation as a possible vulnerability factor for depression symptoms (Harmon-Jones et al. 2002). In agreement, a functional magnetic resonance imaging study has shown reduced brain activation in response to angry facial expressions in major depressive disorder (MDD) patients (Lee et al. 2008). Interestingly, the processing of angry facial expressions has been linked to dopaminergic activity (Lawrence et al. 2007), providing an indirect neurochemical link between MDD and anger processing (Dunlop & Nemeroff, 2007). Finally, there is some evidence suggesting that antidepressant medication may have some anger-facilitating effects as paroxetine has been found to promote novelty-seeking in patients with social phobia (Allgulander et al. 1998).

Evidence for a role of the parietal cortex in the processing of angry facial expressions and possibly depression was found in an earlier study, which showed that vigilant attention for angry facial expressions was associated with reduced electrocortical activity recorded over the right parietal lobe (Schutter et al. 2001).

In agreement, as previously noted in a single-blind, sham-controlled study, we found significant increases in attention to facial anger accompanied decreases in self-reported depressive mood following 2-Hz rTMS to the right parietal cortex in healthy volunteers (van Honk et al. 2003). The subsequent intention-to-treat double-blind, sham-controlled study in depressed patient did not yield an overall difference in therapeutic response between 10 sessions of real and sham 2-Hz rTMS to the right parietal cortex (Schutter et al. 2009). According to some researchers, clinical improvement may not appear until several weeks following treatment onset (Harmer et al. 2009a; Frazer & Benmansour, 2002). In contrast, recent studies suggest that mood improvements can already be observed within 2 wk of starting of antidepressant treatment (Katz et al. 2010; Nakajima et al. 2010). The present data suggest that even though 2 wk of rTMS treatment may be too short to obtain robust and clinically relevant effects, the change in sensitivity for angry faces may, nonetheless, indicate onset of antidepressant action. Even though the precise relationship between the currently observed alteration in perceptual sensitivity and antidepressant action needs to be explored further, the increased sensitivity for angry facial expressions may indicate continuation of treatment.

Unfortunately, the hypothesized increase in the sensitivity for happy facial expressions did not reach significance and was not correlated to the baseline-corrected change in HAMD<sub>17</sub> scores. There was insufficient statistical power due to the relatively large between-subject variance in the sham condition and a ‘floor’ effect resulting from the fact that happy facial expressions are already recognized at very low intensities (see Fig. 2). In addition, small sample size and absence of a baseline measure on the recognition sensitivity of emotional facial expressions stress the preliminary nature of the present findings. Finally, despite the sham-controlled design, success of treatment blinding, the time delay between the final treatment and assessment, and the fact that the present findings are in good agreement with other electrophysiological and administration studies (Nakajima et al. 2010; Savaskan et al. 2008; Schutter et al. 2001), individual differences experienced in site pain or general discomfort as a function of stimulation intensity between real and sham rTMS conditions may have influenced the results. Finally, a general (subconvulsive) modulatory effect on the brain that is independent of the cortical site being targeted may provide another explanation for the present data (Schutter, 2010).

In conclusion, increased sensitivity of angry facial expressions after real compared to sham rTMS treatment together with the correlation between the sensitivity of angry facial expressions and percentage
change in HAMD_{17} scores is in agreement with previous studies and provides the first evidence in support of the cognitive neuropsychological hypothesis of antidepressant action in rTMS treatment.

Acknowledgements

Dr Dennis J. L. G. Schutter was supported by an Innovational Research Grant (452-07-012) from The Netherlands Organization for Scientific Research (NWO). Dr Jack van Honk was supported by a grant from the Hope for Depression Research Foundation (HDRF) and High Potential Grant from Utrecht University, the Netherlands. [The trial ‘Transcranial magnetic stimulation to the right parietal cortex in the treatment of depression’ is registered at The Netherlands Trial Register (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1279).]

Statement of Interest

None.

References


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