# Pre-treatment anterior cingulate activity as a predictor of antidepressant response to repetitive transcranial magnetic stimulation (rTMS)

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*Submitted: August 22, 2007* *Accepted: September 12, 2007*

*Key words:* **repetitive transcranial magnetic stimulation; major depression; predictor; functional imaging; single photon emission computed tomography; SPECT; treatment resistance**

Neuroendocrinol Lett 2007; **28**(5):633–638 **PMID:** 17984932 NEL280507A19 

## Abstract

**OBJECTIVES**: Repetitive transcranial magnetic stimulation (rTMS) is a brain stimulation technique which has received increasing attention as an antidepressant treatment. However available studies are characterized by a substantial variability in response. We hypothesized that individual patients' characteristics might contribute to such heterogeneity. Therefore we investigated whether either alterations of regional cerebral blood flow (rCBF) or clinical characteristics may predict antidepressant response to rTMS.

**DESIGN**: 24 patients with major depression and stable medication received high frequency (10 Hz) rTMS over the left dorsolateral prefrontal cortex (DLPFC) for two weeks as add-on treatment. ECD-Single photon emission computed tomographay (SPECT) imaging was performed 1 to 2 days before rTMS.

**SETTING**: Tertial referral center

**RESULTS**: After two weeks of rTMS a mean reduction of 30% of the initial Hamilton Depression Rating Score (HAMD) was observed. Using a multivariate regression model with simultaneous evaluation of the relative impact of a-priori chosen potential factors influencing treatment outcome, two variables, the pretreatment anterior cingulate rCBF and the former response to antidepressant agents proved significant. High pretreatment anterior cingulate activity and low treatment resistance to pharmacologic therapy were positive predictors for treatment response to rTMS.

**CONCLUSIONS**: Pretreatment anterior cingulate activity seems to be a useful prognostic marker of rTMS treatment response, which is in line with other treatment strategies, like sleep deprivation, electroconvulsive therapy or antidepressant medication.

ORIGINAL ARTICLE

## INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive tool that electrically modulates neuronal activity both locally in the cortex stimulated and transsynaptically in distant brain structures [1,2]. A growing number of studies have investigated effects of prefrontal high frequency rTMS effects in a large variety of psychiatric diseases [3–7]. Most studies investigated the use as an add-on treatment in major depression, in combination with antidepressant medication [8]. Recent meta-analyses of controlled trials [9–11] suggest that active rTMS compared with sham has a statistically significant effect on depressive symptoms. However, since treatment effects are characterized by a high variability, the identification of predictors of antidepressant response of rTMS seems of high importance. Clinical characteristics such as the presence of psychotic symptoms [12], older age [13,14] and treatment resistance [14,15] have been suggested to be linked to inferior rTMS outcome.

Recent studies investigated the influence of neurobiological markers on treatment outcome and identified reduced cerebral blood flow in the amygdala [16] and lower concentrations of glutamate in the DLPFC [17] as positive predictors for rTMS in depressive patients.

It has been demonstrated that rTMS impacts on perfusion and metabolism of the underlying brain regions [18,19]. There is also increasing evidence from a large variety of neuroimaging methods that rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) induces changes in deeper regions such as the anterior cingulate cortex or the basal ganglia [20–27].

Furthermore it has been shown that rTMS effects strongly depend on the pre-treatment activity of the stimulated area [17,28–32] and particularly for the treatment of depression of specific remote areas [20,33,34].

In the present pilot study we followed up on this notion by testing the hypothesis, whether pretreatment rCBF in specific frontal brain regions is a predictor for response to rTMS treatment in patients with major depression.

## PATIENTS AND METHODS

*Patients*

Twenty-four inpatients (18 women, 6 men, age 46.9±13.6 years) were included. Patients met DSM-IV criteria for either major unipolar depression or bipolar depression, depressive phase and had a score of at least 18 on the 21-item Hamilton depression rating scale (HAMD)[35]. The mean HDRS score was 27.1±8.9, the time since first diagnosis of depression was 13.3±10,2 years and the average duration of the current episode was 43.25±54.4 weeks. All participants provided informed written consent for the study which was approved by the ethics committee of the University of Regensburg and performed according to the declaration of Helsinki. Patients with an additional axis-I diagnosis, a history of seizures, organic brain disorder and patients with cardiac pacemakers, mobile metal implants or implanted medication pumps were not included. Pre-treatment with antidepressant medication was stable for at least 2 weeks prior to study entry and remained unchanged throughout the course of the study. Detailed clinical and demographic etails are given in Table 1.

*Administration of rTMS*

rTMS was administered with a figure-of-eight coil (outer diameter of each wing 90 mm) connected to a Magstim stimulator (Magstim Rapid, Magstim Company, Dyfed, UK) over the left DLPFC. Prior to stimulation the resting motor threshold (RMT) was determined over the motor cortex as the lowest stimulation intensity that evoked in at least four out of eight consecutive trials a magnetic evoked potential (MEP) of at least 50 μV in the resting right abductor pollicis brevis muscle (APB). The TMS coil was localized over the left DLPFC according to a standard algorithm by moving the coil from the optimal position for stimulation of the right APB 5 cm in anterior direction [36]. The coil was held with the junction of the two wings tangential to the skull and the handle pointing backwards and ~45° away from the midline. rTMS was applied over 10 days (all weekdays over 2 weeks), each session consisting of ten 5-s trains at 10 Hz with an intertrain interval of 25 s. The intensity was set at 110% of RMT. With 500 stimuli per session a total number of 5 000 stimuli was applied to each patient during the course of the treatment.

*Clinical Ratings*

The 21-item HAMD [35] was obtained at baseline and at the end of the treatment. The ratings were performed by certified psychiatrists tested for inter-rater reliability, who were not involved in rTMS treatment. Treatment response was defined as at least 50% reduction of the baseline HAMD score.

*SPECT imaging*

Single photon emission computed tomography (SPECT) imaging was performed 1 to 2 days before the beginning of rTMS treatment according to previously published protocols [37]. All subjects received an intravenous injection of 650 MBq of technetium-99 bicisate (ECD; Neurolite®, DuPont Pharma) and were in a quiet, dimmed room in a supine position with eyes closed and ears unplugged. SPECT images were obtained with a triple-headed camera (Siemens, Germany) equipped with low-energy ultra-high resolution parallel hole collimators. SPECT acquisition was initated about 60 min after tracer injection. Acquisition parameters were as follows: 128×128 matrix, non-circular orbit, step and shoot acquisition, 360° rotation with 120 single views (3°/view) and an acquisition time of 45 seconds/view. Oblique (along the orbito- meatal line), sagittal and coronal slices were reconstructed via filtered backprojection (Butterworth- filter, cut-off 0.4 of Nyquist, order 2). The

resolution of the system in air was 6.1 mm FWHM (Tc-99m, 20 % window). The images were finally displayed in a 128×128 matrix. Slice thickness was 1 pixel (3.2 mm).

*SPECT Data Analysis*

The SPECT images were analysed semiquantitatively by conventional region- of interest (ROI)- analysis using the manufacturers standard software package (Siemens ICON® – Software on a Macintosh – platform). ROIs for the orbital and lateral aspects of the prefrontal cortex as well as for the anterior cingulated cortex (Brodman area 24) were manually drawn by an investigator blinded for clinical data in the right hemisphere and mirrored to the left (oblique slices) with the help of a computed tomographic atlas [38]. For each cerebral area mean counts per pixel of the corresponding ROIs in three consecutive slices were averaged to minimize potential partial volume artefacts. A dimensionless, cardinally scaled rCBF- ratio R was calculated for each hemisphere region as a measure of functional equivalence to the cerebral activity in the corresponding regions using the averaged counts of the corresponding total slice for normalization.

**Table 1.** Clinical and demographic data.

| Patient | Gender | Age | Diagnosis | Years since first diagnosis of depression | Number of previous episodes | Duration of current episode (weeks) | Current medication | HAMD before rTMS | HAMD after rTMS |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 38 | unipolar | 3 | 1 | 105 | Amitryptilin, Lorazepam | 20 | 32 |
| 2 | F | 64 | unipolar | 34 | 3 | 30 | Imipramin, Lithium, Melperon | 19 | 2 |
| 3 | M | 26 | bipolar | 2 | 2 | 4 | Doxepin, Lithium Promethazine, Lorazepam | 44 | 14 |
| 4 | M | 67 | unipolar | 24 | 4 | 36 | Amitryptilin, Lithium, Olanzapine, Melperon | 19 | 22 |
| 5 | F | 38 | unipolar | 12 | 11 | 16 | Trimipramin | 42 | 35 |
| 6 | F | 40 | unipolar | 11 | 4 | 5 | Imipramin, Lithium, Olanzapine, Promethazine | 29 | 21 |
| 7 | F | 41 | bipolar | 12 | 15 | 22 | Citalopram, Doxepine | 23 | 20 |
| 8 | F | 24 | unipolar | 5 | 3 | 10 | Paroxetine, Mirtazapine, Lithium | 39 | 27 |
| 9 | M | 27 | bipolar | 8 | 3 | 200 | Sertralin, Trimipramin | 24 | 23 |
| 10 | F | 47 | unipolar | 25 | 4 | 150 | Mirtazapin, Promethazine | 18 | 17 |
| 11 | F | 60 | unipolar | 34 | | | Amitryptiiln, Promethazine | 22 | 11 |
| 12 | F | 38 | unipolar | 0 | 7 | 22 | Amitryptilin, Promethazine | 25 | 7 |
| 13 | F | 39 | unipolar | 13 | 1 | 56 | Fluoxetine, Haloperidol, Promethazine | 40 | 14 |
| 14 | M | 54 | bipolar | 10 | 3 | 3 | Amitryptilin | 23 | 21 |
| 15 | M | 62 | unipolar | 5 | 8 | 52 | Amitryptilin, Haloperidol, Promethazine | 23 | 10 |
| 16 | F | 56 | unipolar | 9 | 3 | 4 | Amitryptilin, Tranylcypromin | 24 | 11 |
| 17 | F | 36 | bipolar | 8 | 1 | 5 | Paroxetine, Diazepam | 32 | 5 |
| 18 | F | 60 | unipolar | 28 | 12 | 5 | Paroxetine, Doxepine, Promethazine | 21 | 11 |
| 19 | F | 54 | unipolar | 10 | 3 | 76 | Amitryptilin, Lithium | 21 | 27 |
| 20 | F | 64 | unipolar | 26 | 10 | 150 | Citalopram, Promethazine, Lorazepam | 31 | 29 |
| 21 | F | 46 | unipolar | 11 | 4 | 8 | Imipramine, Lithium, Promethazine | 19 | 20 |
| 22 | F | 28 | unipolar | 7 | 15 | 28 | Citalopram | 24 | 16 |
| 23 | M | 64 | unipolar | 1 | 2 | 24 | Doxepin, Haloperidol, Lorazepam | 48 | 46 |
| 24 | F | 52 | unipolar | 20 | 1 | 15 | Amitryptilin, Haldol | 21 | 10 |
| **MW** | | **46.9** | | **13.3** | **5.1** | **43.3** | | **27.1** | **18.7** |
| **SD** | | **13.6** | | **10.2** | **4.4** | **54.4** | | **8.9** | **10.3** |

*Statistical Analysis*

To evaluate the impact of multiple factors on treatment outcome a multivariate regression analysis with simultaneous estimation of a priori selected predictor variables was performed by correlating clinical outcome data with the following variables: age, gender, duration of illness, pre-HAMD score, number of previous episodes, prior response to antidepressants, activity of the cingulate cortex, activity of the orbitofrontal cortex, activity of the dorsolateral prefrontal cortex. p-values of Wald score tests greater than 0.05 were regarded as nonsignificant. Data in the text are given as mean±SD.

## RESULTS

*Clinical response*

During the course of 2 weeks rTMS, HDRS scores decreased by 31% from 27.1±8.9 to 18.8±10.3. Nine patients (37.5%) showed an improvement which met our clinical response criterium. Table 1 summarizes the results for all patients.

*Correlation analysis*

Pretreatment right anterior cingulate activity ($p=0.017$) as well as former response to antidepressant agents ($p<0.001$) showed a significant linear correlation with the treatment outcome. The positive correlation between pretreatment activity of the right anterior cingulate cortex and the reduction of Hamilton scores is illustrated in Figure1.

In the other investigated ROIs – the left anterior cingulate and both orbitofrontal and dorsolateral prefrontal cortices – there was no significant correlation between pretreatment activity and reduction of HAMD scores. The other investigated clinical characteristics like age, gender, baseline HAMD score, number of previous episodes and duration of illness did not show a significant correlation with treatment response.

## DISCUSSION

In the present study we aimed at identifying predictors for treatment response to rTMS as add-on treatment. Clinical improvement in this open study is similar to the average reduction of depressive symptoms of active rTMS in controlled studies [8–10]. The main finding was that pre-treatment rCBF in the right anterior cingulate and former response to antidepressants were significant predictors for treatment response to rTMS. In other words, patients with higher pretreatment activity in the right anterior cingulate and those with better response to pharmacological treatment had a higher benefit from rTMS.

This finding is in line with an earlier study which has shown that patients who responded well to rTMS had increased pre-treatment activity in the cingulate cortex [20]. Thus our result further underlines the relevance of the anterior cingulate cortex for antidepressant effects of rTMS treatment. The DLPFC, the target area of stimulation, is highly anatomically [39] and functionally [40] interconnected with the anterior cingulate. Accordingly it has been demonstrated that rTMS of the DLPFC modulates neuronal activity in the anterior cingulate [23]. Based on these findings one might speculate that rTMS exerts its antidepressant effects by modulating fronto-cingulate connectivity [41].

Our results are further in line with a large number of neuroimaging studies that have identified high anterior cingulate activity as a predictor for a wide variability of antidepressant treatment modalities, ranging from sleep deprivation [42] over fluoxetine [43] and tricyclics [44] to electroconvusive therapy [45].

Our results are discrepant to a recent study [33] which has demonstrated a negative correlation between treatment effects of rTMS in depressed patients and baseline rostral anterior cingulate activity. It has to be considered that the patients investigated in that study differed from

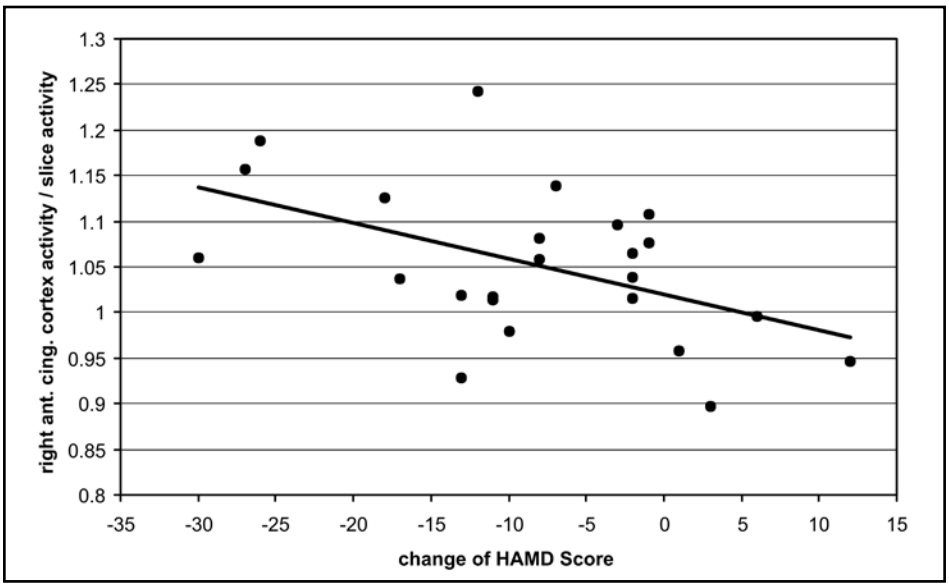


**Figure 1**. Correlation between activity in the right anterior cingulated cortex and reduction of Depression score during rTMS

those included in our study, as they had failed at least two medication trials and were tapered off their medication. As medication resistance is reflected by altered cingulate activity the discrepancy to our study is not surprising. It underscores the necessity to discriminate between different subgroups of depressed patients. In this context anterior cingulate activity could be a possible indicator. Beside pre-treatment cingulate activity, only previous positive response to antidepressant agents could predict a successful rTMS treatment outcome in our study. This finding is consistent with results of earlier studies that suggested less effectivity of severely medication-resistant patients [14,15,46] or depressive patients with psychotic sympoms [12]. With regard to psychotic symptoms our study may help to specify the role of this psychopathological symptom on the basis of biological evidence, pointing towards the fact, that not psychosis per se but poor adaptive potential as reflected by decreased anterior cingulate activity may be associated with treatment resistance to rTMS. This hypothesis is in line with results, demonstrating that therapeutic rTMS effects did not depend on the severity of clinical symptoms [32]. Moreover, positive response to antidepressant agents has been shown to depend on increased pretreatment anterior cingulate activity [43,44]. Therefore one could speculate taht previous successful response to pharmacological treatment, identified as clinical prognostic indicator in our study, might partially reflect previous increased pretreatment anterior cingulate activity in patients later benefitting from rTMS, too.

However, it has to be considered that the present study has several limitations. It is an open study without a placebo-treated control group. As it was shown, that cingulate activity is also linked to favourable outcome of placebo treatment [47] further placebo-controlled studies are necessary. As all patients were on antidepressant medication the data of our SPECT study are strictly related to rTMS as add-on therapy. Furthermore the low number of applied stimuli/day [8] and the relatively small sample size of 26 patients with its low statistical power have to be considered. Additional limitations include the relative rather than absolute nature of the data that SPECT imaging provides. Due to a poorer spatial resolution of SPECT imaging in comparison with positron emission tomography or functional magnetic resonance imaging, a SPECT camera must sum activity over discrete areas. Nevertheless, SPECT imaging has been proven to be a powerful and useful tool in mapping cerebral activity [20].

In spite of these limitations, the present study confirms previous findings of Teneback and co-workers [20] and gives further support for the hypothesis that rTMS of the DLPFC exerts its therapeutical effects by modulating fronto-cingulate circuits.

## ACKNOWLEDGEMENTS

We thank Helene Niebling, Sandra Pflügl and Walter Schindler for technical assistance with TMS application and Peter Maenner for assistance with SPECT data analysis.

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