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QEEG Theta Cordance in the Prediction of Treatment Outcome to Prefrontal Repetitive Transcranial Magnetic Stimulation or Venlafaxine ER in Patients With Major Depressive Disorder

Martin Bares[1,2], Martin Brunovsky[1,2], Tomas Novak[1,2], Miloslav Kopecek[1,2], Pavla Stopkova[1,2], Peter Sos[1,2], and Cyril Höschl[1,2]

Abstract

The aims of this double-blind study were to assess and compare the efficacy of quantitative electroencephalographic (QEEG) prefrontal theta band cordance in the prediction of response to 4-week, right, prefrontal, 1-Hz repetitive transcranial magnetic stimulation (rTMS) or venlafaxine ER in patients with major depressive disorder (MDD). Prefrontal QEEG cordance values of 50 inpatients (25 subjects in each group) completing 4 weeks of the study were obtained at baseline and after 1 week of treatment. Depressive symptoms were assessed using Montgomery-Åsberg Depression Rating Scale (MADRS) at baseline and at week 1 and 4. Treatment response was defined as a ≥50% reduction in baseline MADRS total score. All responders (n = 9) and 6 of 16 nonresponders in the rTMS group had reduced cordance at week 1 ($P < .01$). Reduction of theta cordance value at week 1 was detected in all responders (n = 10) to venlafaxine ER, but only in 4 of 15 nonresponders ($P = .005$). The comparison of the areas under the curve of cordance change for prediction of response between rTMS (0.75) and venlafaxine ER (0.89) treated groups yielded no significant difference ($P = .27$). Our study indicates that prefrontal QEEG cordance is a promising tool not only for predicting the response to certain antidepressants but also to rTMS treatment, with comparable predictive efficacy for both therapeutic interventions.

Keywords

major depressive disorder, prediction, quantitative electroencephalographic cordance, repetitive transcranial magnetic stimulation, venlafaxine ER

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Introduction

Despite recent progress in psychopharmacology, the treatment of resistant MDD remains a fundamental clinical problem, with approximately 30% of patients not responding to standard antidepressant treatment. rTMS for MDD is mostly provided at high-frequency (HF) stimulation (5-20 Hz) to the left dorsolateral prefrontal cortex (DLPFC) for 2 to 9 weeks, but low-frequency (LF, ˜1 Hz) stimulation over the right DLPFC and bilateral approach are also used with similar effect.[1]

Unfortunately, only limited clinical data are available for the prediction of rTMS outcome that address merely HF stimulation.[2-6] These findings show that only lower level of therapy resistance seems to be a robust predictor of response to rTMS. To date, only a very limited number of studies have examined the predictive potential of neurophysiological parameters (baseline prefrontal cordance, theta EEG power, event-related potential P 300, low-resolution brain electromagnetic tomography).[7,8]

In MDD, one of the best-documented neurophysiological biomarkers predicting response to antidepressants is the decrease of QEEG prefrontal cordance of theta.[9,10] Cordance is a QEEG method that combines information from absolute and relative power of EEG spectra.[11] It has been reported to have a stronger correlation with cerebral perfusion than standard spectral analysis and to be less influenced by age, gender, and severity of baseline depression than simple spectral power.[12-14]

[1]Prague Psychiatric Center and National Institute of Mental Health, Prague, Czech Republic
[2]The Department of Psychiatry and Medical Psychology of Third Medical Faculty, Charles University, Prague, Czech Republic

Corresponding Author:

Martin Bares, Prague Psychiatric Center, Ustavni 91, Prague 8–Bohnice, 181 00, Czech Republic.
Email: bares@pcp.lf3.cuni.cz
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Across the studies of depressed subjects treated with various antidepressants, decrease in prefrontal theta cordance after 1 week of treatment has consistently predicted response, with overall accuracy ranging from 72% to 88%.[9] Our group has demonstrated predictive value of cordance decrease for venlafaxine and bupropion in patients with resistant depression.[15,16] Although it is not completely understood what exactly cordance reflects,[17] it has been hypothesized that this measure could be within the same conceptual framework[18] as other functional neuroimaging studies demonstrating an abnormal pattern of metabolism, or perfusion, in the prefrontal cortex and anterior cingulate of depressed patients. Frontal electrical activity in theta has been associated with the function of these structures,[19] and previous research has linked higher pretreatment theta activity in anterior cingulate with clinical response to antidepressants.[20,21] Recent review demonstrates robust relationship between response to various antidepressive interventions and resting activity of rostral anterior cingulate.[22]

We were not aware of any head-to-head comparison of the predictive value of QEEG cordance between rTMS and antidepressants. Therefore, we conducted a 4-week, double-blind trial assessing and comparing the efficacy of 1-week decrease of theta prefrontal QEEG cordance in the prediction of response to 1-Hz, right prefrontal rTMS and venlafaxine ER (VNF) in resistant depression.

Materials and Methods

The Prague Psychiatric Centre Institutional Review Board approved this study, and a written informed consent to participate in the research was obtained from all subjects. The study was carried out in accordance with the latest version of the Declaration of Helsinki.

Subjects

We analyzed data from adults diagnosed with MDD (recurrent or single episode) without psychotic symptoms[23] who completed the single-center, 4-week, double-blind study comparing the treatment efficacy of rTMS and VNF.[24] In brief, all patients were hospitalized at Prague Psychiatric Centre from June 2005 to July 2008 and fulfilled at least stage I criteria for resistant depression (≥1 adequate antidepressant treatment in current episode) according to Thase and Rush.[25] We included subjects (18-65 years old) who reached a score of at least 20 on the MADRS.[26] We excluded subjects with suicidal risk, current psychiatric comorbidity, personality disorder, serious unstable medical illness, drug or alcohol abuse, head trauma, risk of seizure, and those using any treatment (including electroconvulsive therapy within 3 months before start of study), which can strongly affect EEG.

A total of 60 inpatients were randomly assigned to the treatment with rTMS + placebo (n = 29) and VNF + sham stimulation (n = 31) groups. Three patients treated with rTMS and 5 subjects from the VNF group discontinued treatment (worsening of clinical status, adverse events, patient's decision). The EEG recordings of 2 subjects (one from each group) were not available because of technical problems, and they were excluded from the analysis. The final sample comprised 50 patients (rTMS group, n = 25; VNF group, n = 25).

Treatment Trial and Clinical Assessment

Initial wash-out period ranged from 5 to 9 days. RTMS procedure and VNF treatment in the study were described in details previously.[24] In brief, rTMS (Magstim Super Rapid Stimulator, Magstim, Whitland, UK) was applied over the right DLPFC (1-Hz stimulation; 100% of motor threshold; 600 pulses per session) for 20 consecutive working days. Patients assigned to the VNF group received a daily dose of 75 mg of VNF on days 1-5. From day 6 onward, the dose was increased to 150 mg per day, and the dose could be subsequently increased to 375 mg per day according to the clinical judgment of the attending physician. The final average dose of VFN was 267 ± 48.8 mg per day. Placebo (sham) stimulation was delivered in the same anatomical location with identical stimulation parameters as real rTMS but with the lateral edge of the coil rotated 90° away from the scalp. Allowed concomitant medication for both groups included hydroxyzine (maximum 150 mg per day) for anxiety and zolpidem for insomnia. The continuation of benzodiazepine medication was allowed in unchanged dosage in patients who used them before the study. The patients were assessed with MADRS before a wash-out period, at baseline and after 1 and 4 weeks of treatment.

QEEG Techniques and Cordance Calculations

EEG data were recorded at baseline and after 1 week of treatment. We used a standard 32-channel digital EEG amplifier BrainScope (unimedis, Prague, Czech Republic) with 21 electrodes placed according to the International 10/20 System and referenced to the electrode FCz. The signals were sampled at 250 Hz and band-pass filtered from 0.15 to 70 Hz. The EEG was recorded for 10 minutes with the patients in a semirecumbent position, with eyes closed in a maximally alert state in a sound-attenuated room. Before the analysis of the data, artifact detection was performed visually to exclude all EEG segments containing obvious eye and head movements, muscle artifacts or decrease in alertness. In addition, split-half and test–retest reliability tests were conducted on the edited EEG data (NeuroGuide software; http://www.appliedneuroscience.com), and only records with >90% reliability were subjected to processing after digital filtering of 0.5 to 30 Hz. The EEG reviewer was blind to the subject's treatment condition and clinical status. Fast Fourier Transformation (FFT) with a Hamming window was used to calculate absolute and relative power spectra at each electrode in 4 frequency bands[27]: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-20 Hz). The values of theta power spectra from electrodes Fp1, Fp2, and Fz were averaged to yield the values of prefrontal absolute and relative theta power. Furthermore, to elucidate the changes in the EEG and to facilitate comparison with other studies, the values of FFT power spectra at electrode Fz were log transformed and then overlaid for baseline and week 1 for responders and nonresponders in both treatment groups (Figure 1).

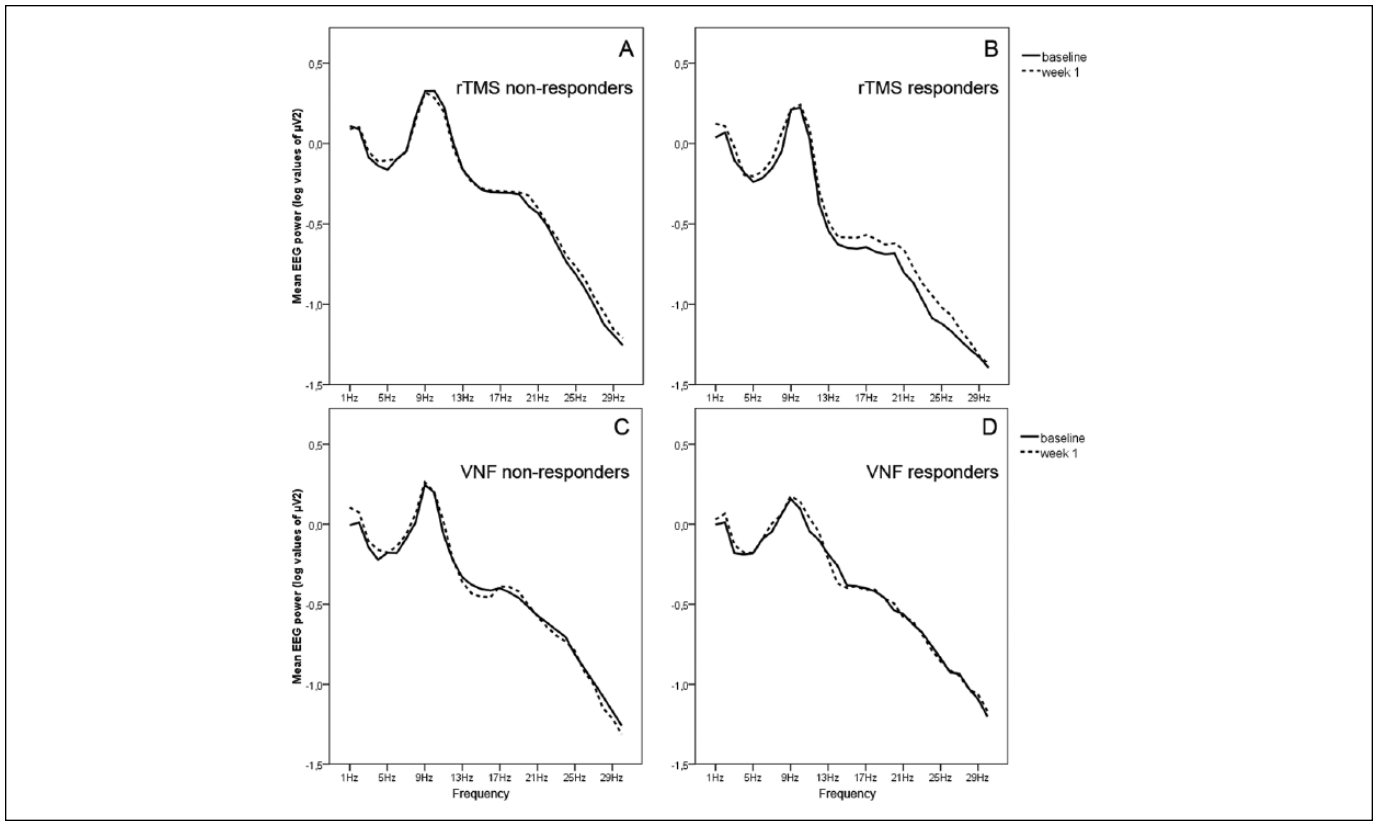

Figure 1. The EEG power spectrum at Fz for responders and nonresponders in treatment groups.
Abbreviations: rTMS, repetitive transcranial magnetic stimulation; VNF, venlafaxine ER.

QEEG cordance was calculated by our EEG software (WaveFinder v.1.70, unimedis, Prague, Czech Republic) using the algorithm that has been repeatedly described elsewhere in greater detail.[11,28] In brief, this algorithm normalizes power across both electrode sites and frequency bands in 3 consecutive steps: First, absolute power values are reattributed to each individual electrode by averaging power from all bipolar electrode pairs sharing that electrode. In the second step, the maximum absolute and relative power values ($AMAX_f$, $RMAX_f$) in each frequency band (f) are determined to obtain normalized absolute ($A_{NORM(s,f)}$) and normalized relative ($R_{NORM(s,f)}$) power values (absolute and relative power values at each electrode site (s) and for each frequency band (f) are divided by $AMAX_f$ and $RMAX_f$, respectively). In the third step, the cordance values at each electrode site (s) for each frequency band (f) are calculated by summing the A_{NORM} and R_{NORM} values, after a half-maximal values (0.5 on the normalized scale) are subtracted: $CORDANCE_{(s,f)} = (A_{NORM(s,f)} - 0.5) + (R_{NORM(s,f)} - 0.5)$. Average cordance values from 3 frontal electrodes (Fp1, Fp2, and Fz) in theta frequency band (4-8 Hz) were subjected to statistical analysis analogous to our previous studies.[15,16,29]

Statistical Methods and Data Analyses

The primary analysis was conducted to detect a difference between the number of responders and nonresponders in both treatment groups who decreased cordance (Fisher's exact test). Clinical response was defined as a reduction of more than 50% of the MADRS score.

The differences between responders and nonresponders in baseline clinical and demographic data, as well as in EEG power and prefrontal theta cordance, were assessed using Mann-Whitney U test in each treatment group. Within-group analyses of cordance values were performed using Wilcoxon sign rank test. Spearman's rank correlation coefficient was used to examine the relationship among various variables. All applied tests were 2-sided and the significance level of .05 was adopted. Positive predictive value (PPV), negative predictive value (NPV), number needed to diagnose (NND) with exact binomial 95% confidence intervals (95% CI), and post hoc effect size of cordance decrease were calculated for rTMS and VNF groups. To compare the predictive efficacy of cordance change after week 1, we determined the areas under curve (AUC) with exact binomial 95% CI of receiver operating characteristics (ROC) for both treatment modalities.

In our previous "cordance" study with venlafaxine,[15] the large effect size ($w = 0.59$) for response prediction was obtained. To detect a similar effect, 25 subjects in both groups was a sufficient sample size for a given power of 80% and α of 5%. Analyses were performed using SPSS version 13.

Table 1. Demographic, Neurophysiological, and Clinical Characteristics of Study Subjects by Treatment.[a]

	rTMS (n = 25)	Venlafaxine ER (n = 25)	*P* Value[b]
Age (years)	45.7 ± 12.0	44.4 ± 1 1.9	.75
Gender (female:male), n:n	20:5	19:6	1.0[c]
Illness duration (months)	85.8 ± 109.7	76.84 ± 89.5	.98
Number of previous episodes	2.0 ± 2.3	2.0 ± 1.7	.58
Duration of index episode before enrollment (weeks)	36.4 ± 50.3	33.4 ± 28.7	.67
Number of previous treatment trials of index episode	1.9 ± 1.2	1.6 ± 0.9	.51
Number of subjects taking BZD at baseline, n	18	15	.55[c]
Dose of BZD (diazepam equivalent, mg per day)	12.7 ± 12.5	14.2 ± 10.5	.60
Baseline cordance value	0.55 ± 0.3	0.53 ± 0.3	.58
Cordance value week 1	0.52 ± 0.2	0.51 ± 0.3	.89
Prefrontal baseline absolute theta power value (μV2)	4.16 ±1.3	4.05 ± 1.5	.64
Prefrontal baseline relative theta power value (%)	20.74 ± 7.3	21.1 ± 5.9	.66
Prefrontal absolute theta power value (μV2) week 1	4.45 ± 1.6	4.19 ± 1.7	.45
Prefrontal relative theta power (%) value week 1	21.24 ± 4.6	21.48 ± 6.1	.76
Change of prefrontal absolute theta power value (μV2) week 1	0.29 ± 1.1	0.14 ± 1.1	.44
Change of prefrontal relative theta power value (%) week 1	0.50 ± 2.0	0.37 ± 2.8	.46
Baseline MADRS score	27.4 ± 4.2	26.8 ± 4.3	.49
Final MADRS score	18.6 ± 8.1	17.2 ± 7.9	.54
Final reduction of MADRS score (%)	34.3 ± 22.3	36.7 ± 25.8	.80

Abbreviations: BZD, benzodiazepines; MADRS-Montgomery-Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation.
[a]Values are mean ± standard deviation unless stated otherwise.
[b]Mann-Whitney *U* test.
[c]Fisher's exact test.

Results

Demographic and Treatment Characteristics and Clinical Measures

Altogether, the data of 50 subjects (rTMS group, n = 25; VNF group, n = 25) were analyzed. The clinical response rate between treatment modalities was not different (rTMS = 36%, VNF = 40%, Fisher's exact test, $P = 1.0$). There were also no differences between treatment groups in terms of demographic, clinical, and cordance data (Table 1).

Predictive Value of Prefrontal Theta Cordance, Absolute and Relative Power

In the rTMS group, all responders (n = 9) and 6 of 16 nonresponders showed a decrease in prefrontal QEEG cordance after the first week of rTMS treatment (Fisher's exact test, $P = .003$). Using the decrease of prefrontal cordance value after 1 week of treatment as a predictor of response, PPV and NPV of this test yielded value of 0.6 (95% CI = 0.32-0.84) and 1.0 (95% CI = 0.69-1.0), respectively. NND for treatment response was 2 (95% CI = 1.6-6.6) with the effect size (*w*) of 0.62.

ROC analysis of cordance change after week 1 as a predictor of response showed AUC value of 0.75 (95% CI = 0.54-0.90). Detected optimal cutoff point of cordance change after week 1 for prediction was −0.02.

Analyzing cordance values as a continuous variable, we found significant differences between responders and nonresponders in baseline cordance value (Mann-Whitney *U* test, $U = 25$, $P < .01$) and change of cordance value after 1 week of treatment (Mann-Whitney *U* test, $U = 37$, $P < .05$). Furthermore, we detected significant change (decrease) of cordance value at week 1 in responders (Wilcoxon sign rank test, $Z = -2.67$, $P < .01$) but not in nonresponders (for numerical details see Table 2).

Additional ROC analysis of baseline cordance value as predictor of response yielded AUC of 0.82 (95%CI = 0.62-0.95). Optimal cutoff of baseline cordance for response prediction was 0.69. There was no significant difference between AUCs of baseline cordance value and cordance change for response prediction ($Z = 0.52$, $P = .6$).

Prefrontal absolute and relative theta power at baseline and week 1, as well as their changes, were not different between responders and nonresponders (Table 3). Figure 1A and B show averaged FFT power spectra at electrode Fz overlaid for baseline and week 1 for rTMS responders and nonresponders. Both groups did not differ in terms of Fz theta power at baseline (Mann-Whitney *U* test, $U = 44$, $P = .12$) and week 1 (Mann-Whitney *U* test, $U = 62$, $P = .6$). We also observed no correlations between final percentage MADRS score reduction and the values of absolute theta power (Fz) at baseline ($P = .1$) and week 1 ($P = .74$) in the whole group.

In the VNF group, all responders to VNF (n = 10) but only 4 out of 15 nonresponders decreased cordance value at week 1 (Fisher's exact test, $P = .005$). PPV and NPV of cordance reduction for prediction of response were 0.71 (95% CI = 0.42-0.92) and 1.0 (95% CI = 0.72-1.0), respectively. NND

Table 2. Prefrontal Cordance Values During the Study.[a]

	rTMS group (n = 25)			Venlafaxine ER group (n = 25)		
	Responders (n = 9)	Nonresponders (n = 16)	*P* Value[b]	Responders (n = 10)	Nonresponders (n = 15)	*P* Value[b]
Cordance value baseline	0.70 ± 0.1	0.47 ± 0.3	.007	0.62 ± 0.2	0.47 ± 0.3	.09
Cordance value week 1	0.56 ± 0.1	0.50 ± 0.3	.72	0.49 ± 0.2	0.51 ± 0.3	.50
Change of cordance value week 1	−0.13 ± 0.1	0.03 ± 0.3	.048	−0.13 ± 0.1	0.04 ± 0.1	<.001

[a]Values are mean ± standard deviation.
[b]Mann-Whitney *U* test.

Table 3. Prefrontal Absolute and Relative Theta Power Values During the Study.[a]

	rTMS group (n = 25)			Venlafaxine ER group (n = 25)		
	Responders (n = 9)	Nonresponders (n = 16)	*P* Value[b]	Responders (n = 10)	Nonresponders (n = 15)	*P* Value[b]
Absolute theta power value (μV2) baseline	4.04 ± 0.5	4.23 ± 1.3	.80	4.23 ± 1.9	3.94 ± 1.3	.85
Relative theta power value (%) baseline	20.85 ± 5.0	20.73 ± 4.0	.89	22.73 ± 6.8	20.02 ± 5.2	.22
Absolute theta power value (μV2) week 1	4.5 ± 1.7	4.42 ± 1.6	.72	4.44 ± 2.1	4.03 ± 1.4	.89
Relative theta power value (%) week 1	21.5 ± 6.0	21.1 ± 3.8	.76	22.74 ± 7.2	20.64 ± 5.4	.60
Change of absolute theta power value (μV2) week 1	0.46 ± 1.7	0.19 ± 0.7	.80	0.21 ± 1.6	0.05 ± 0.7	.68
Change of relative theta power value (%) week 1	0.8 ± 1.9	0.33 ± 2.0	.60	0.002 ± 3.5	0.62 ± 2.2	.22

[a]Values are mean ± standard deviation.
[b]Mann-Whitney *U* test.

for response was 2 (95% CI = 1.36-3.60) with the effect size (w) of 0.72. Calculated AUC of ROC analysis of cordance change at week 1 for response prediction was 0.89 (95% CI = 0.70-0.98); optimal predictive cutoff point of cordance change at week 1 for response prediction was −0.02, that is, the same value as for rTMS group. We also found significantly higher reduction of cordance change at week 1 in responders (Mann-Whitney U test, $U = 17.5$, $P < .001$) but not in baseline cordance value (Mann-Whitney U test, $U = 44.5$, $P = .09$). Similarly to rTMS group, there was significant decrease of cordance value at week 1 compared with baseline in responders (Wilcoxon sign rank test, $Z = -2.80$, $P < .01$) but not in nonresponders (for numerical details see Table 2).

We did not find a significant difference between responders and nonresponders in terms of prefrontal absolute and relative theta power at baseline and week 1, as well as in their changes (Table 3). FFT power spectrum (Fz), overlaid for baseline and week 1, for VNF responders and nonresponders is shown in Figure 1C and D. Similarly to rTMS group, there was no significant difference in absolute theta power between responders and nonresponders at both time points (Mann-Whitney U test, baseline: $U = 64$, $P = .57$; week 1: $U = 59$, $P = .4$), as well as no correlations between the values of theta power (Fz) and final percentage MADRS score change (baseline, $P = .47$; week 1, $P = .24$) in the whole group.

Comparison of the Efficacy of Prefrontal Theta Cordance in the Prediction of Response to rTMS and VNF. We did not find a significant difference in the predictive efficacy of cordance change after 1 week of treatment between rTMS and VNF groups (AUC rTMS = 0.75; AUC VNF = 0.89, $Z = -1.01$, $P = .27$)—see Figure 2. There was a similar pattern of results for analyses of cordance value as continuous variable for both treatment groups (reduction of cordance value after week 1 in responders and nonsignificant changes in nonresponders), with the exception of higher baseline value in responders in rTMS group (see Table 2).

Prefrontal Theta Cordance and Severity of Depressive Symptoms. Baseline cordance values in both groups did not correlate with baseline MADRS score, nor did change of cordance values with percentage change of MADRS score at week 1 in both groups, and in the whole sample. We observed significant correlations between percentage change of MADRS at the end of treatment and baseline cordance ($r_s = 0.42$, $P < .01$), as well as cordance change at week 1 ($r_s = -0.54$, $P < .001$) for the whole sample. Similar patterns were found in the rTMS group; that is, final percentage MADRS change correlated significantly with the baseline cordance ($r_s = 0.56$, $P < .01$) and cordance change at week 1 ($r_s = -0.41$, $P < .05$). There was also a significant relationship of final reduction in MADRS score with cordance change ($r_s = -0.64$, $P < .001$), but not with baseline cordance ($P = .13$) in the VNF group.

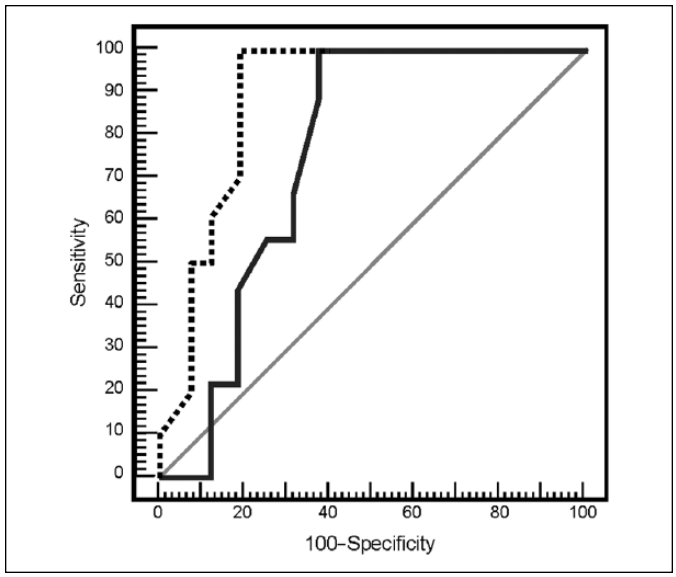

Figure 2. Receiver operating characteristics analyses of cordance change at week 1 for rTMS and VNF groups.
Dotted line (· · · ·): receiver operating characteristics curve of cordance change at week 1 in VNF group for prediction of response (AUC = 0.89). Solid line (—) receiver operating characteristics curve cordance change at week 1 in rTMS group for prediction of response (AUC = 0.75).

Discussion

As far as we know, this is the first study comparing the ability of prefrontal theta QEEG cordance to predict response to right-sided, prefrontal, LF rTMS, and VNF in the acute treatment of MDD.

The primary finding is that the decrease of cordance after 1 week of treatment predicts response to both treatment modalities in patients who failed to respond to previous antidepressant interventions and its predictive efficacy is comparable. Moreover, in comparison to baseline, theta cordance at week 1 was significantly decreased in responders, but not in nonresponders to rTMS and VNF. The relationship between cordance change and final MADRS score reduction was confirmed by a series of correlation analyses for both treatment groups and the whole sample.

Interestingly, the optimal cutoff point of cordance change at week 1 (ROC analysis; −0.02) for prediction of treatment outcome was the same for both treatments, and did not differ from the value detected by reanalysis of our older data for prediction of response to venlafaxine. [15]

The utility of prefrontal cordance in the prediction of response to various antidepressants in patients with MDD was repeatedly confirmed and independently replicated[15,16,28-31]; however, this is the first study demonstrating 1-week decrease of theta prefrontal cordance as a potential biomarker of treatment response to rTMS. Although the mechanism of antidepressant action of rTMS is not completely clear, there is some evidence for an association between basal metabolism and treatment-induced metabolic changes in anterior cingulate or DLPFC and the response to HF and LF rTMS.[22,32-36] Furthermore, a recent study has demonstrated that increased theta power in the subgenual anterior cingulate predicted response to HF rTMS in patients with vascular depression.[8] The observed decrease of theta prefrontal cordance may reflect early activity changes in anterior cingulate and prefrontal cortex linked to rTMS and antidepressant response. The changes of metabolic activity in anterior cingulate and adjacent orbital and prefrontal cortices were associated with response to treatment with chronic deep brain stimulation[37,38] and with antidepressants.[39]

Detected significantly higher baseline cordance value in responders to rTMS was not seen in several previous studies with antidepressants,[15,28,29] but it was found in our earlier study with bupropion.[16] It might be consistent with the results of studies linking higher baseline metabolism and higher theta activity to response to rTMS.[8,32,33]

We did not analyze cordance in other than theta since it was not the aim our study. However, a recent study has shown higher baseline values of prefrontal beta and delta cordance in responders to rTMS with no differences between groups in other frequency bands.[7]

The higher baseline theta cordance value might be clinically more useful and attractive than process predictor (mediator decrease of theta cordance)[40] because it is cheaper, faster, and can help identify patients that may benefit from rTMS treatment and those who are suitable for other antidepressive intervention. On the other hand, we are careful about predictive potential of higher baseline cordance because it was not our a priori hypothesis and should be replicated in another well-designed study. Based on our data, we hypothesize that both parameters (baseline cordance value and change of cordance after 1 week) closely interact and may be associated with change in depressive symptoms during rTMS treatment.

The results of the VNF-treated group are in accordance with our previous findings evaluating prefrontal cordance in the prediction of treatment outcome.[15,16,29]

The analyses of absolute and relative prefrontal theta power at baseline and week 1 did not reveal significant differences between responders and nonresponders in both treatment groups. Several previous studies showed a potential role of theta power in the prediction of response to antidepressant treatment or rTMS.[7,9,20,41-43] However, Cook et al.[28] did not find its usefulness when compared with cordance, and only a limited number of the aforementioned studies reported sensitivity and specificity for appropriate evaluation. Thus, we suppose that prefrontal theta cordance may be a more robust predictor of treatment outcome than theta power, but this should be determined by further metaanalyses or large-scale studies.

Contrary to other studies (rTMS, various antidepressants)[7,44] we did not find the relationship between pretreatment absolute theta power at electrode Fz and final change of depressive symptoms for both treatment groups, and similar results were observed also for theta power at week 1. This might be due to a different rTMS protocol and different antidepressants.

The limits of this treatment protocol were discussed in detail previously.[24] Briefly, the treatment duration of 4 weeks is likely adequate for rTMS treatment,[45,46] but might be too short to assess clinical response to an antidepressant. We did not include placebo control because Prague Psychiatric Center Institutional Review Board would not have approved a placebo-controlled study in the treatment of resistant patients. However, a previous study has demonstrated a different pattern of cordance changes in placebo responders (increase of cordance value) compared with medication responders after 4 weeks of treatment.[47]

The relatively small sample size could be a further limitation. Nevertheless, our sample size calculation was based on the results of our previous study.[15] The AUC of the change of cordance at week 1 observed in this study was 0.75, implying good, although not excellent, discriminative ability between responders and nonresponders to rTMS.

It should be noted that there is very limited literature on the effect of rTMS on QEEG parameters.[48-50]

Conclusion

Despite the limitations of this study, prefrontal QEEG cordance might be a promising tool, not only for predicting the response to certain antidepressants, but also for rTMS treatment of patients with MDD. The predictive efficacy of this measure seems to be comparable for both types of intervention.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Cyril Höschl: Clinical trials—coordinator of a multicentric study for Servier; consultant—advisory board member, Lilly and BMS; grant—Lilly; paid lectures for—Lilly, Janssen Cilag, BMS, Medicom, Nycomed, Krka, and Lupin; other—faculty member, Lundbeck International Neuroscience Foundation. Miloslav Kopecek: Advisory board member—BMS and Janssen Cilag; paid lectures for—Janssen Cilag and BMS.

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