Original article

Early reduction in prefrontal theta QEEG cordance value predicts response to venlafaxine treatment in patients with resistant depressive disorder

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Abstract

Introduction. — Previous studies of patients with unipolar depression have shown that early decrease of prefrontal EEG cordance in theta band can predict clinical response to various antidepressants. We have now examined whether decrease of prefrontal quantitative EEG (QEEG) cordance value after 1 week of venlafaxine treatment predicts clinical response to venlafaxine in resistant patients.

Method. — We analyzed 25 inpatients who finished 4-week venlafaxine treatment. EEG data were monitored at baseline and after 1 week of treatment. QEEG cordance was computed at three frontal electrodes in theta frequency band. Depressive symptoms and clinical status were assessed using Montgomery–Asberg Depression Rating Scale (MADRS), Beck Depression Inventory-Short Form (BDI-S) and Clinical Global Impression (CGI).

Results. — Eleven of 12 responders (reduction of MADRS ≥50%) and only 5 of 13 non-responders had decreased prefrontal QEEG cordance value after the first week of treatment (p = 0.01). The decrease of prefrontal cordance after week 1 in responders was significant (p = 0.03) and there was no significant change in non-responders. Positive and negative predictive values of cordance reduction for response were 0.7 and 0.9, respectively.

Conclusion. — The reduction of prefrontal theta QEEG cordance value after first week of treatment might be helpful in the prediction of response to venlafaxine.

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Keywords: Venlafaxine; Depressive disorder; Resistant depression; Cordance; QEEG; Response prediction

1. Introduction

A large percentage of patients (30–50%) fail to respond to an initial course of antidepressant treatment (for instance Refs. [16,52]). After 1 year of four consecutive antidepressant trials still around 25% and 33% of patients did not reach response or remission [44]. The average rate of response or remission to a given medication is well known but psychiatrists are not able to predict what therapy will be more effective in an individual patient. In clinical practice psychiatrists use the method of trial and error. There is a clear need for methods to select the right treatment for the right patient [50].

A considerable body of research supports the assertion that antidepressant medication effects are physiologically detectable in the EEG [20]. Use of the EEG in the prediction of antidepressant response is based on early studies, which identified various EEG parameters (left dominant pretreatment
alpha power value, significantly less pretreatment overall theta power, etc.) associated with response to treatment (for instance Refs. [6,21,22,53]). These studies provide the first evidence of capability of quantitative EEG to predict antidepressant response. According to Hunter et al., several lines of reasoning support the rationale for examining frontal EEG measurements in the theta band (4–8 Hz) in relation to an antidepressant response [20]. A consistent finding of neuroimaging studies is an abnormal pattern of metabolism or perfusion in the dorsolateral prefrontal cortex and/or the anterior cingulated cortex in depressed patients [14,28,29]. Both structures are connected neuroanatomically and functionally. Theta activity recorded in prefrontal channels may reflect both activity of the dorsolateral prefrontal cortex and projected rhythm generated in the anterior cingulate [2,35]. In addition, higher theta activity of the anterior cingulate before therapy (nortriptyline and citalopram) predicted response to treatment in depressed subjects [32,36].

Recent evidence suggests that change of QEEG cordance value might be useful in predicting antidepressant response [20]. Cordance is a new QEEG method which combines complementary information from absolute (the amount of power in a frequency band at a given electrode) and relative power (the percentage of power contained in a frequency band relative to the total spectrum) of EEG spectra [25]. Cordance combines these parameters to achieve a stronger association with cerebral perfusion than either measure alone. Of the three QEEG measures (absolute power, relative power, and cordance) examined, cordance had the strongest relationship with perfusion. Cordance and PET were equally effective in detecting lateralized activation associated with the motor task, while EEG power did not detect this activation [27].

The algorithm for cordance calculation yields two indicators for each electrode site in each frequency band: a categorical value (concordant or discordant state) and a numerical value [25,27]. Studies of Cook and Leuchter’s team have demonstrated that reduction of prefrontal QEEG theta cordance value after 1 or 2 weeks of treatment with selective serotonin reuptake inhibitors (SSRI) and selective serotonin–norepinephrine reuptake inhibitors (SNRI) can predict clinical response to 8-week treatment in non-resistant patients and these changes are different from those observed in placebo responders [8,10,26]. Our team replicated the predictive power of prefrontal theta cordance in a pilot study of 17 resistant inpatients on various antidepressants [4]. Positive predictive value (PPV) and negative predictive value (NPV) of reduction of frontal cordance in our study were estimated as 0.71 and 1.0, respectively. As far as we know, no study examining predictive value of QEEG cordance changes to antidepressant monotherapy in resistant subjects has been published. Venlafaxine was selected for our study because it is generally well tolerated and evidence about its efficacy in the treatment of resistant depression is relatively strong [3,16,37,43]. The aim of the present study was to examine whether the reduction of theta prefrontal QEEG cordance value after 1 week of venlafaxine administration is associated with response to 4-week treatment in patients, who failed to respond to at least one previous antidepressant trial.

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

2. Subjects and methods

2.1. Subjects

Our sample comprised 26 inpatients (8 men, 18 women, mean age 46.25 ± 10.1 years) with major depressive disorder (recurrent or single episode) diagnosed according to DSM IV criteria [1], confirmed using the Mini-International Neuropsychiatric Interview – M.I.N.I., Czech version 5.0.0 [46]. We included subjects who reached at least the total score of 20 in Montgomery–Åsberg Depression Rating Scale (MADRS) [31] and the score of four or more in the Clinical Global Impressions (CGI) [17]. Patients were rated by experienced clinical psychiatrists (M.B., T.N., M.K., P.S.). Inter-rater reliability was established (intraclass correlation > 0.80) for each clinician prior to conducting ratings [23]. All patients were hospitalized at Prague Psychiatric Centre between November 2004 and August 2007. They fulfilled at least Stage I criteria for resistant depression (≥1 adequate antidepressant treatment) according to Thase and Rush [49]. We excluded subjects with suicidal risk, current psychiatric comorbidity on axis I, serious unstable medical illness or neurologic disorder (e.g., epilepsy, head trauma with loss of consciousness) and patients using any treatment (including electroconvulsive therapy within 3 months before start of study) which can strongly affect EEG as well as patients who were resistant to venlafaxine during current or previous episodes. Response to treatment was defined as at least 50% reduction of MADRS score after 4 weeks of treatment.

2.2. Treatment trial

The length of venlafaxine treatment was 4 weeks. The dosage was flexible. The average daily dose was 150 mg ± 30.6 mg at the end of first week and 234 mg ± 45 mg at the end of the study. All patients took venlafaxine ER. In accord with other authors we supposed that higher dose of venlafaxine could maximize likelihood of response to treatment [40,48]. Depressive symptoms and clinical status were assessed before a wash-out period of 1–5 days, at baseline and after 1 and 4 weeks on venlafaxine using MADRS, Beck Depression Inventory-Short Form (BDI-S) [5] and CGI. Zolpidem and hydroxyzine were permitted as a concomitant treatment in case of severe insomnia or anxiety. The continuation of benzodiazepine anxiolytics was allowed in unchanged dosage in patients who used them before the study to avoid withdrawal effect and possible EEG changes.

2.3. QEEG techniques and cordance calculations

EEG data were recorded at baseline and after first week of treatment. We used a standard 32-channel digital EEG amplifier BrainScope (unimedis, Prague) with Ag/AgCl electrodes...
for the data acquisition. The EEG recording system acquires the data with a 16 bit depth and 7.63 nV/bit resolution (i.e., \(-130 \text{ bit}/\mu \text{V}\)) with the dynamic range of \(\pm 250 \mu \text{V}\). The data sampling rate was 250 Hz and the acquired signals were filtered with a band-pass filter of 0.15–70 Hz after the sampling. All the EEG recordings were performed with the 21 surface electrodes placed according to the international 10/20 system and referenced to the electrode situated between electrodes Fz and Cz in the midline (FCz). All electrode impedances were kept below 5 k\(\Omega\). The EEG was recorded with the patients in a semi-recumbent position, with eyes closed in a maximally alert state in a sound-attenuated room with subdued lighting. During the recording the alertness was controlled. If the patterns of drowsiness appeared in the EEG, the subjects were aroused by acoustic stimuli. The data, 30 min in duration, were collected with an on-line computer system and were stored for further computer off-line analysis. Before analysis of the data, artifact detection was performed visually to exclude all EEG segments containing obvious eye and head movements, muscle artifacts or a decrease in alertness. In each EEG, at least 30 s of artifact-free data were subjected to processing after digital filtering of 0.5–30 Hz and recomputing to average reference. Fast Fourier transform was used to calculate absolute and relative power in each of four non-overlapping frequency bands [34]: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–20 Hz). QEEG cordance was calculated by our EEG software (WaveFinder v.1.70, unimedis, Prague) using the algorithm available for research purposes. This algorithm normalizes power across both electrode sites and frequency bands in three consecutive steps: first, absolute power values are reattributed to each individual electrode by averaging power from all bipolar electrode pairs sharing that electrode. This electrode referencing method is similar to the Hjorth transformation [19] except that the current method averages power from neighboring electrode pairs and thus provides a stronger association between surface-measured EEG and perfusion of underlying brain tissue than either the linked-ears reference or the conventional Hjorth transformation [11]. Then the relative power values are calculated on the basis of dividing absolute power values by total power values for each electrode site in each frequency band. In the second step, the maximum absolute and relative power values (\(\text{AMAX}_f\) and \(\text{RMAX}_f\)) in each frequency band \((f)\) are determined to obtain normalized absolute \((\text{ANORM}_{N,N,f})\) and normalized relative \((\text{RNORM}_{N,N,f})\) power values (absolute and relative power values at each electrode site \((s)\) and for each frequency band \((f)\) are divided by \(\text{AMAX}_f\) and \(\text{RMAX}_f\), respectively). In the third step, the cordance values at each electrode site \((s)\) for each frequency band \((f)\) are calculated by summing the \(\text{ANORM}^{\prime}_f\) and \(\text{RNORM}^{\prime}_f\) values, after a half-maximal value (0.5 on the normalized scale) is subtracted:

\[
\text{CORDANCE}^{\prime}_{N,N,f} = (\text{ANORM}^{\prime}_{N,N,f} - 0.5) + (\text{RNORM}^{\prime}_{N,N,f} - 0.5).
\]

The exact algorithm of the cordance calculation has been published [25]. Average cordance values from three frontal electrodes (Fp1, Fp2 and Fz) in theta frequency band (4–8 Hz) were subjected to statistical analysis similar to previous studies [8,9,26]. EEG reviewer was blind to patients’ medication and the outcome of treatment.

2.4. Statistical methods and data analyses

Demographic and clinical characteristics are presented as median and interquartile range. Due to the small sample size and non-normal data distribution, nonparametric statistical tests were used to perform the within group (Wilcoxon sign rank test), between group (Mann–Whitney U test and Fisher exact test) and correlation analyses (Spearman’s Rho). All tests were two-sided and an exact significance level of 0.05 was adopted. No Bonferroni correction was applied. Analyses were performed using SPPS version 13. Positive predictive value (PPV) and negative predictive value (NPV) were also calculated.

3. Results

3.1. Clinical measures

We analyzed 25 patients who finished 4 weeks of treatment. One patient dropped out due to worsening of her clinical status. She was further treated by electroconvulsive therapy. Twelve (48%) out of 25 subjects responded to the treatment (reduction of MADRS \(\geq 50\%\)). No differences were found between responders and non-responders in age, gender, course of depression including number of previous treatments of index episode and in the dose of venlafaxine after 1 week of treatment and at the end of study (see Table 1). Groups of responders and non-responders were comparable in all rating scales at baseline. The scores of the clinical rating scales in both groups over time are summarized in Table 2. After the first week of treatment, we detected reduction of MADRS score in responders (\(Z = 2.44, p = 0.01\)) but not in non-responders. Also at this time point, we found intergroup difference in BDI-S score (\(U = 33, p = 0.01\)). However, we examined changes of MADRS and BDI-S scores between responders and non-responders after 1 week and did not find much difference (\(U = 45.5, p = 0.08\) and \(U = 48.5, p = 0.11\), respectively).

3.2. Cordance changes after first week and treatment outcome

We detected a decrease of prefrontal EEG cordance in responders (\(Z = -2.12, p = 0.03\)) and no significant change of cordance value in non-responders after first week (see Table 3). Furthermore, the responders and non-responders differed in prefrontal cordance changes at this time (\(U = 36, p = 0.02\)) — see Fig. 1. In absolute cordance values, no differences between responders and non-responders were detected at baseline and at first week. Examining correlation between MADRS score reduction from baseline to final visit and prefrontal cordance change after week 1 of treatment in the whole sample we found a significant relationship (\(r_s = -0.46; p = 0.02\)).
3.3. Predictive value of prefrontal cordance reduction

Eleven of 12 responders showed a decrease in prefrontal QEEG cordance after the first week of drug administration. In 13 non-responders, a decrease was found in five patients. A significant difference was detected between number of responders and non-responders who had decreased cordance value (Fisher exact test, \( p < 0.05 \)). Using the decrease of prefrontal cordance value after 1 week of treatment as an indicator of response to venlafaxine, PPV and NPV of this test were 0.69 (95% CI 0.45–0.86) and 0.89 (95% CI 0.67–0.98), respectively.

4. Discussion

As far as we know, this is the first study of the frontal theta band QEEG cordance as an early predictor of response to an antidepressant monotherapy in the treatment of resistant depression. After 1 week of antidepressant therapy the number of responders and non-responders who had decreased cordance value has been different. We demonstrated prefrontal cordance decrease in the responder group and not in non-responder group. We also found intergroup difference (responders vs non-responders) in cordance value changes at this time point. Using the decrease of prefrontal cordance value after 1 week of treatment as an indicator of response to venlafaxine, we were able to differentiate between responders and non-responders at the early phase of treatment.

Previous studies demonstrated predictive effect of a reduction of prefrontal cordance for fluoxetine and venlafaxine-treated, non-resistant outpatients [8,26] and for resistant patients, who were treated by various antidepressant interventions [4,9]. In the current study we examined the usefulness of prefrontal cordance changes for an antidepressant monotherapy (venlafaxine) in patients who failed to respond to at least one previous antidepressant treatment.

**Table 1**

Characteristics of subjects and clinical features of depression

<table>
<thead>
<tr>
<th></th>
<th>Responders ((n = 12))</th>
<th>Non-responders ((n = 13))</th>
<th>Statistical significance level(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46 (38–53)</td>
<td>43 (29–54)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (F:M)</td>
<td>8:4</td>
<td>9:4</td>
<td>NS(^b)</td>
</tr>
<tr>
<td>Duration of depressive disorder (months)</td>
<td>36 (21–180)</td>
<td>48 (29–60)</td>
<td>NS(^b)</td>
</tr>
<tr>
<td>Number of previous depressive episodes</td>
<td>1.5 (0.5–3)</td>
<td>2 (1–2)</td>
<td>NS(^b)</td>
</tr>
<tr>
<td>Duration of index episode before enrollment (weeks)</td>
<td>11 (5–28)</td>
<td>22 (12–43)</td>
<td>NS(^b)</td>
</tr>
<tr>
<td>Number of previous treatment trials of index episode</td>
<td>1 (1–2)</td>
<td>2 (1–2)</td>
<td>NS(^b)</td>
</tr>
<tr>
<td>Dose of venlafaxine after first week (mg/p.d.)</td>
<td>150 (150–150)</td>
<td>150 (150–150)</td>
<td>NS(^b)</td>
</tr>
<tr>
<td>Number of patients with concomitant benzodiazepines treatment</td>
<td>7</td>
<td>7</td>
<td>NS(^c)</td>
</tr>
<tr>
<td>Final dose of venlafaxine (mg/p.d.)</td>
<td>225 (187.5–262.5)</td>
<td>225 (225–225)</td>
<td>NS(^b)</td>
</tr>
</tbody>
</table>

IQR – interquartile range; NS – nonsignificant; and p.d. – per day.

\(^a\) \( p < 0.05 \).

\(^b\) Mann–Whitney U test.

\(^c\) Fisher exact test.

**Table 2**

Results of the clinical rating scales

<table>
<thead>
<tr>
<th></th>
<th>Responders ((n = 12))</th>
<th>Non-responders ((n = 13))</th>
<th>Statistical significance level(^a,b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS baseline</td>
<td>27.5 (25–28.5)</td>
<td>25 (23–33)</td>
<td>NS</td>
</tr>
<tr>
<td>MADRS week 1</td>
<td>22.5 (18–26.5)</td>
<td>26 (22–31)</td>
<td>NS</td>
</tr>
<tr>
<td>MADRS week 4</td>
<td>10.5 (7–12)</td>
<td>24 (18–28)</td>
<td>0.001</td>
</tr>
<tr>
<td>CGI baseline</td>
<td>4 (4–5)</td>
<td>4 (4–5)</td>
<td>NS</td>
</tr>
<tr>
<td>CGI week 1</td>
<td>4 (3.5–4)</td>
<td>4 (4–5)</td>
<td>NS</td>
</tr>
<tr>
<td>CGI week 4</td>
<td>2.5 (1.5–3)</td>
<td>4 (3–4)</td>
<td>0.002</td>
</tr>
<tr>
<td>BDI-S baseline</td>
<td>16.5 (13–21)</td>
<td>20 (16–26)</td>
<td>NS</td>
</tr>
<tr>
<td>BDI-S week 1</td>
<td>13 (12.5–18)</td>
<td>23 (19–29)</td>
<td>0.01</td>
</tr>
<tr>
<td>BDI-S week 4</td>
<td>10.5 (7–13.5)</td>
<td>18 (13–25)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

IQR – interquartile range; NS – nonsignificant; BDI-S – Beck Depression Inventory-Short Form; CGI – Clinical Global Impression; and MADRS – Montgomery–Åsberg Depression Rating Scale.

\(^a\) \( p < 0.05 \).

\(^b\) Mann–Whitney U test.

![Fig. 1. Prefrontal cordance value changes after week 1: the comparison of responders and non-responders.](image-url)
There are several caveats to our findings. First, the duration of 4 weeks might be too short to assess clinical treatment response. We cannot exclude the possibility of another clinical response emerging during longer treatment. However, in our opinion and in agreement with other authors, a period of 4 weeks of treatment without signs of response is sufficient to justify a change in the initial treatment strategy in common clinical practice [30,38,39,45,47]. Recent study demonstrates substantial improvement in depressive symptomatology (60% reduction on the MADRS) after 4 weeks of venlafaxine treatment [13]. Furthermore, two studies found that the change after the first 4 weeks of treatment predicted the outcome at 8 and 12 weeks [51].

Second, the raters were not blind to medication; however, they were blind to EEG results during the study. The third limitation is the relatively small sample size. Nevertheless, the effect size estimated from this sample (w = 0.59) is in the large range [7].

We used a short wash-out period to prevent potential side effects of rapid medication switching. Wash-out period is not essential for the detection of prefrontal cordance decrease in responders to antidepressant therapy [9].

Although we found a difference in BDI-S score between responders and non-responders after first week of venlafaxine administration, we do not suppose that an early reduction of BDI-S score could be useful predictor of response to treatment. We did not detect a significant group difference in the reduction of BDI-S scores at this time point. In accord with other authors, we assume that BDI-S could be less precise in evaluation of depressive symptoms than objective scales [12,41]. Also, discrepancies between objective and subjective scales depending on various demographic, clinical and personality variables were described [15]. In addition, it is not clear if there would be any cut-off of BDI-S score reduction for prediction of treatment response after 1 week of treatment. The detected decrease of MADRS score in responders after 1 week of treatment (20%) is not clinically meaningful [18] and the difference in the reduction of MADRS score between responders and non-responders was not significant.

Trivedi et al. differentiated clinical predictors on baseline and process predictors [50]. Baseline predictors are based on the information that is available to clinicians at the initiation of treatment, e.g., age, gender, personality, comorbidity and biological predictors. Baseline predictors are important because they could inform clinicians which treatment may be more effective than other treatments and can aid in the treatment choice. This type of predictors seldom proves useful in the clinical setting because of their modest to small effect size [42]. Trivedi et al., focused on process predictors that are based on information that becomes available to the clinician during the process of treatment. Examples of process predictors include timing and nature of change in the symptom severity, side effect burden, and patient adherence [50]. Research into these predictors is designed to determine whether continuation of the current therapy will produce response or remission, thus to identify effective treatment at the earliest time. Our study identifies QEEG prefrontal cordance changes as a process predictor. Recently we have presented two cases suggesting the possibility of sequential use of QEEG prefrontal cordance in the prediction of response to antidepressants [24].

PPV and NPV of reduction of prefrontal cordance value after 1 week of treatment are promising for predicting the treatment outcome in individual patients. According to our data we are able to predict non-response in 9 patients out of 10 after 1 week of venlafaxine treatment. In our opinion, this approach can help to decide whether to continue with a given antidepressant. To our best knowledge, prefrontal cordance is the only predictor whose validity was confirmed in more than two studies and whose results are not only statistically but also clinically significant.

5. Conclusion

Based on our results, the prefrontal QEEG cordance might be helpful in the early prediction of response to venlafaxine. Further evaluations of this test for other antidepressant interventions and clinical trials examining usefulness of QEEG prediction in sequential treatment are recommended.

Acknowledgements

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