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Changes in QEEG prefrontal cordance as a predictor of response to antidepressants in patients with treatment resistant depressive disorder: A pilot study

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Abstract

Introduction: Previous studies of patients with unipolar depression have shown that early decreases of EEG cordance (a new quantitative EEG method) can predict clinical response. We examined whether early QEEG decrease represents a phenomenon associated with response to treatment with different antidepressants in patients with treatment resistant depression.
Method: The subjects were 17 inpatients with treatment resistant depression. EEG data and response to treatment were monitored at baseline and after 1 and 4 weeks on an antidepressant treatment. QEEG cordance was computed at three frontal electrodes in theta frequency band. The prefrontal cordance combines complementary information from absolute and relative power of EEG spectra. Recent studies have shown that cordance correlates with cortical perfusion. Depressive symptoms were assessed using Montgomery–Åsberg Depression Rating Scale (MADRS).
Results: All 17 patients completed the 4-week study. All five responders showed decreases in prefrontal cordance after the first week of treatment. Only 2 of the 12 nonresponders showed early prefrontal cordance decrease. The decrease of prefrontal QEEG cordance after week 1 in responders as well as the increase in nonresponders were both statistically significant (p-value 0.03 and 0.01, respectively) and the changes of prefrontal cordance values were different between both groups (p-value 0.001).
Conclusion: Our results suggest that decrease in prefrontal cordance may indicate early changes of prefrontal activity in responders to antidepressants. QEEG cordance may become a useful tool in the prediction of response to antidepressants.

Keywords: Antidepressants; Treatment resistant depression; Cordance; QEEG; Response prediction

1. Introduction

Modern antidepressant drugs have response rates in the 65% range and response to treatment typically requires 2–6 weeks (Dodd and Berk, 2004). To date, no method is clinically proven to predict response to antidepressants. A method to predict response to antidepressants would be of a great value in the treatment of depressive disorder. Unsuccessful treatment means not only waste of resources and time, but increases the risk of worsening patient's clinical status and subsequent loss of cooperativeness.

Quantitative electroencephalography (QEEG) has been used as physiological measure in efforts to address the relationship of early physiological changes and eventual clinical outcome (Cook et al., 2002). EEG changes in healthy subjects immediately after the administration of an antidepressant have been demonstrated (for instance Saletu and Gruenberger, 1988; Herrmann et al., 1991), but their relationship to treatment response in depressed patients was unclear. Other work detected possible association of early changes in theta power with response to antidepressant

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treatment (Ulrich et al., 1988). Leuchter introduced cordance, a new QEEG method, which combines complementary information from absolute and relative power of EEG spectra to yield values that have stronger correlation with regional cerebral perfusion than either measure alone (Leuchter et al., 1999). This correlation provides a physiological basis for interpreting this measure (Cook et al., 2002). 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 (Leuchter et al., 1994, 1999). Frontal electrical activity in theta frequency band is associated mainly with the function of the anterior cingulate cortex which is involved in the pathophysiology of depression (Asada et al., 1999; Pizzagalli et al., 2003). Cook and his colleagues observed that subjects with concordant state in theta frequency band prior to fluoxetine treatment had better treatment outcomes than patients with discordant state (Cook et al., 1999).

Other studies of patients with depressive disorder which used numerical value of cordance for frontal electrodes have demonstrated that changes in prefrontal electrical activity 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 treatment after eight weeks (Cook and Leuchter, 2001; Cook et al., 2002, 2005) and these changes are different from those observed in placebo responders (Leuchter et al., 2002). The aim of our study was to examine whether an early decrease (after one week of treatment) of prefrontal QEEG cordance in theta frequency band is associated with response to treatment with antidepressive agents in patients with treatment resistant depressive disorder.

2. Materials and methods

2.1. Subjects

The sample consisted of 17 inpatients (8 men, 9 women, mean age 45.6 ± 13.2 years) with major depressive disorder (recurrent or single episode) diagnosed according to DSM IV criteria, confirmed using The Mini-International Neuropsychiatric Interview – M.I.N.I., Czech version 5.0.0. (Sheehan et al., 1998). We included subjects who reached at least the total score 25 in Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) and the score 4 or more in the Clinical Global Impression (CGI) (Guy, 1976). All patients were hospitalized at Prague Psychiatric Centre from November 2004 to August 2005 and fulfilled at least Stage I criteria for resistant depression (Thase and Rush, 1997). The subjects with concomitant anxiety were allowed to enroll provided they did not fulfill criteria for a DSM-IV anxiety disorder. We excluded subjects with suicidal risk, current psychiatric comorbidity, neurological abnormality (including history of skull trauma) and using any medication which can affect EEG. The Prague Psychiatric Centre Institutional Review Board reviewed and approved the protocol and 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.

2.2. Experimental procedures

2.2.1. Treatment trial

The length of study was four weeks (see Fig. 1). The depressive symptoms and clinical status were assessed before a wash-out period, at baseline and after one and four weeks on the new treatment using MADRS, Beck Depression Inventory – short form (BDI) (Beck et al., 1974; Beck and Beamesderfer, 1974) and CGI. Zolpidem and hydroxyzine were permitted as a concomitant treatment in case of severe insomnia or anxiety. The new antidepressant drugs (SSRI $n = 4$; SNRI $n = 8$; norepinephrine and dopamine reuptake inhibitors (NDRI) $n = 2$; tricyclic antidepressants $n = 2$; noradrenergic and specific serotonergic antidepressants $n = 1$) were prescribed according to clinical judgment of the attending psychiatrist and with regard to the history of previous treatment.

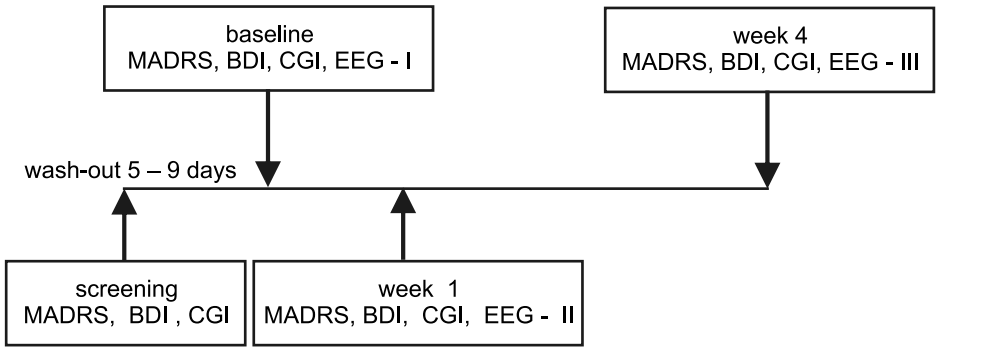

Fig. 1. Schedule of procedures.

2.3. QEEG techniques and cordance calculations

EEG data were recorded at baseline (after one week of wash-out period) and after one and four weeks of treatment. The 21 surface electrodes were placed according to the international 10/20 system, with all electrode impedances kept below 5 kΩ. We used the BrainScope 21-channel amplifier system (unimedis, Prague), with the reference electrode situated between electrodes Fz and Cz in the midline. 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. The data, 30 min in duration, were collected with an online computer system. All signals were sampled with a frequency of 250 Hz with 0.5–70 Hz filters and the data 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 or muscle artifacts. In each EEG, at least 30 s of vigilance controlled and artifact-free data were subjected to processing after digital filtering of 0.5–30 Hz and recomputing to average reference. A fast Fourier transform was used to calculate absolute and relative power in each of four non-overlapping frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–20 Hz).

QEEG cordance was calculated using the algorithm available for research purposes at the website www.cordance.com, which was implemented to our EEG software (WaveFinder v.1.70, unimedis, Prague). 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 (Hjorth, 1975) 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 (Cook et al., 1998). 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 ($AMAX_f$, $RMAX_f$) 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 value (0.5 on the normalized scale) are subtracted:

$$CORDANCE_{(s,f)} = (A_{NORM(s,f)} - 0.5) + (R_{NORM(s,f)} - 0.5).$$

The exact algorithm of the cordance calculation has been published before (Leuchter et al., 1994). According to previous studies (Cook et al., 2002, 2005; Leuchter et al., 2002), average cordance values from three frontal electrodes (Fp1, Fp2 and Fz) in theta frequency band (4–8 Hz) were subjected to statistical analysis. EEG reviewer was blind to patients' medication and the outcome of treatment.

2.4. Statistical methods and data analyses

Response to treatment was defined as equal to or more than 50% reduction of MADRS scores and remission as MADRS scores less than 12 points after four weeks of treatment. Due to the small sample size, nonparametric statistical tests were used to perform the within group (Wilcoxon Sign Rank Test) and between group (Mann–Whitney *U* Test and Fisher Exact Test) analyses and correlation analyses (Spearman's Rho). All analyses were computed at an exact significance level of 0.05. All tests were two-sided with the exception decrease of prefrontal cordance values in responders analyses where one-tailed test was used with regard to previous data about decrease of cordance value in responders (Cook et al., 2002). Analyses were performed using SPPS version 13.

3. Results

3.1. Clinical measures

All 17 patients completed the study. Five out of 17 (29%) subjects responded to the treatment after four weeks. Four patients achieved remission. No baseline differences were found between responders and nonresponders in age, gen-

Table 1
Characteristics of subjects and clinical features of depression

	Responders ($n = 5$) median (IQR)	Nonresponders ($n = 12$) median (IQR)	Statistical significance level $p < 0.05$
Age (years)	47 (33.5–57)	44.5 (43–55.5)	NS[a]
Gender (F:M)	3:2	6:6	NS[b]
Duration of depressive disorder (months)	72 (59.5–144)	60 (19–122)	NS[a]
Number of previous depressive episodes	2 (1–5.5)	2 (1–3)	NS[a]
Duration of index episode before enrollment (weeks)	28 (5.5–41)	29 (18–64)	NS[a]
Number of previous treatment trials of index episode	1 (1–2.5)	2 (1.7–4)	NS[a]

IQR, interquartile range; NS, nonsignificant.
[a] Mann–Whitney *U* test.
[b] Fischer Exact Test.

Table 2
Results of the clinical rating scales

	Responders ($n = 5$) median (IQR)	Nonresponders ($n = 12$) median (IQR)	Statistical significance level $p < 0.05$[a]
MADRS baseline	28 (26.5–32)	32.5 (26–35)	NS
MADRS week 1	24 (16–30)	25.5 (22.5–34.75)	NS
MADRS week 4	11 (6.5–13)	21.5 (19–28.75)	0.0003
CGI baseline	5 (4–5)	5 (4–5)	NS
CGI week 1	4 (3–5)	5 (4–5)	NS
CGI week 4	2 (1.5–3)	4 (3–4)	0.002
BDI baseline	19 (15–22)	24.5 (14.5–27)	NS
BDI week	17 (8.5–18.5)	23 (14.5–29.75)	NS
BDI week 4	9 (5.5–10)	19.5 (12.25–28)	0.01

IQR, interquartile range, NS, non-significant, BDI, Beck Depression Inventory, CGI, Clinical Global Impression, MADRS, Montgomery and Asberg Depression Rating Scale.
[a] Mann–Whitney *U* test.

Table 3
Prefrontal cordance values and changes during study

	Responders ($n = 5$) median (IQR)	Nonresponders ($n = 12$) median (IQR)	Statistical significance level $p < 0.05$[a]
Prefrontal cordance value baseline	0.60 (0.49–0.76)	0.47 (0.29–0.54)	NS
Prefrontal cordance value week 1	0.48 (0.36–0.61)	0.54 (0.44–0.65)	NS
Prefrontal cordance value week 4	0.37 (0.17–0.62)	0.59 (0.53–0.68)	NS
Change in prefrontal cordance week 1	−0.13 (−0.2–−0.08)	0.10 (0.01–0.17)	0.001
Change in prefrontal cordance week 4	−0.17 (−0.53–0.08)	0.15 (−0.003–0.2)	0.04

IQR, interquartile range; NS, nonsignificant.
[a] Mann–Whitney *U* test.

der and course of depression (see Table 1). The patients had previous unsuccessful medication trials (median was 2). The most recent medications before enrollment to the study were milnacipran + trazodone, escitalopram, chlorprothixene, venlafaxine in responders and paroxetine ($n = 2$), paroxetine + amisulpride, sertraline, citalopram, trazodone, tianeptine, bupropion, bupropion + olanzapine, mirtazapine, and fluoxetine + olanzapine ($n = 2$) in nonresponders.

The scores on the clinical mood rating scales over time in the group of responders and nonresponders are summarized in Table 2. In the responder group, there were two patients treated with venlafaxine, one with escitalopram, one with clomipramine and one with bupropion and in nonresponder group, there were five patients on venlafaxine, two on escitalopram and another were treated with mirtazapine, citalopram, bupropion, clomipramine and milnacipran.

3.2. Cordance changes after one week and treatment outcome

Prefrontal cordance values and changes during study are demonstrated in Table 3. At baseline, the responders had a

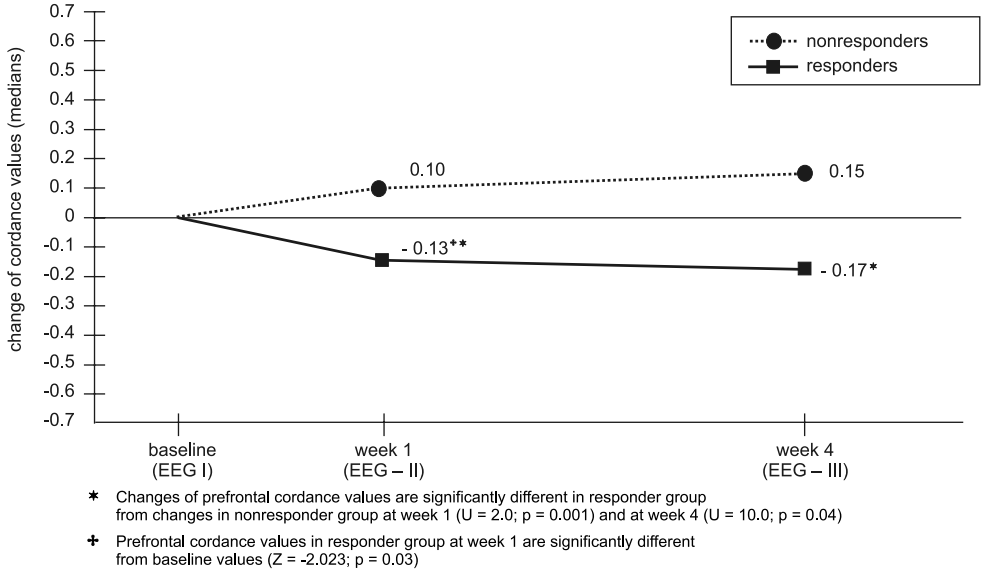

Fig. 2. The course of prefrontal cordance values changes.

numerically higher cordance values than the nonresponders, but the difference failed to reach the level of statistical significance ($U = 12$, $p = 0.06$). No differences in cordance values between responders and nonresponders were detected at weeks 1 and 4. However, the responders and nonresponders differed in prefrontal cordance *changes* both in week 1 and week 4 ($U = 2.0$; $p = 0.001$ resp. $U = 10.0$; $p = 0.04$, see Table 3 and Fig. 2).

All responders showed decrease in prefrontal QEEG cordance after the first week of drug administration. In 12 nonresponders, an increase of prefrontal cordance was detected in 10 patients and a decrease was found in two patients. We detected a decrease of prefrontal EEG cordance in responders using one-tailed test ($Z = -2.023$; $p = 0.03$) and an increase of prefrontal EEG cordance in nonresponders ($Z = -2.432$; $p = 0.01$) (Fig. 2).

Examining correlation between MADRS reduction from baseline to final visit and prefrontal cordance change after week one of treatment in whole sample we find significant relationship ($r_s = -0.535$; $p = 0.03$) and similar relationship exists between final MADRS scores and the change of prefrontal cordance ($r_s = -0.589$; $p = 0.01$) after one week. There were no relationships between baseline prefrontal cordance value and final MADRS respectively cordance value at week 1 and final MADRS ($r_s = -0.404$; $p = 0.11$, respectively $r_s = 0.282$; $p = 0.27$).

4. Discussion

We have demonstrated decreases of prefrontal cordance already after one week of antidepressant therapy in the responders group, although the level of symptom severity was not yet different between responders and nonresponders at that time point. These results are consistent with previous studies (Cook et al., 2002, 2005). The reduction of prefrontal cordance is thus an early neurobiological phenomenon, possibly a predictor of response at the time when no clinical changes are yet observable. A similar early change in decreased perfusion in the hippocampus after the first dose of risperidone predicted clinical effect after 6-weeks therapy in patients with schizophrenia (Ngan et al., 2002).

Cook's and Leuchter's studies demonstrated predictive effect of a reduction of prefrontal cordance only for fluoxetine and venlafaxine-treated non-resistant outpatients (Cook et al., 2002; Leuchter et al., 2002). Our study included hospitalized, treatment-resistant, depressive patients treated by a broader range of antidepressive agents (similarly Cook et al., 2005). After week 1, we found significant difference between cordance changes in responders and nonresponders. An increase of cordance was identified in nonresponders but a decrease was seen in responders. No significant difference was detected between 1st week prefrontal cordance values in responders and nonresponders. We suggest that the prediction of response is related to change of prefrontal cordance after week one rather than to cordance values. In addition, we find relationship between prefrontal cordance change after week one and final MADRS and not between cordance values (baseline and after week one) and final MADRS.

It is not clear which brain processes underlie decreases of theta prefrontal cordance. Cordance values in the theta frequency band were found to be positively correlated with cortical perfusion assessed simultaneously with PET (Leuchter et al., 1999). In rodents, theta rhythm has been linked to the hippocampal formation, as well as other regions, including the anterior cingulate cortex (ACC). Previous human studies suggest that theta band reflects the activity of anterior cingulate gyrus (Asada et al., 1999; Pizzagalli et al., 2003). The patients with better response to imipramine showed higher theta activity in the rostral anterior cingulate (Brodmann's area – BA 24/32) before imipramine therapy (Pizzagalli et al., 2001). Rostral anterior cingulate metabolism uniquely differentiated eventual treatment responders from nonresponders. Hypometabolism characterized nonresponders when compared with controls, in contrast to responders who were hypermetabolic (Mayberg et al., 1997). PET experiments have demonstrated decreased subgenual cingulate metabolism with successful antidepressant treatment (Mayberg et al., 2000). The subgenual or anterior cingulate decrease of ^{18}FDG PET uptake is seen not only with antidepressant medication, but also with response to ECT (Nobler et al., 2001) or sleep deprivation (Smith et al., 2002). Pilot study of deep brain stimulation of anterior cingulate (Cg25) showed antidepressive response in 4 from 6 pharmacoresistant depressive patients and, as documented by the PET scan studies, the hyperactivity of Cg25 decreased (Mayberg et al., 2005). The change of theta prefrontal cordance might thus be the main correlate of early activity changes in anterior cingulate. No published studies were focused on brain metabolism comparison between responders and nonresponders after 1st week of treatment.

We did not expect any cordance increase in nonresponders. The change we detected may be due to non-response to antidepressants or a consequence of the ongoing changes related to pathophysiological processes of depression.

We used a wash-out period analogous to Cook et al., 2002 in order to reduce psychopharmacological influences on EEG. However, Cook recently published a preliminary study demonstrating that a wash-out period is not essential for the detection of prefrontal cordance decrease in responders to antidepressant therapy (Cook et al., 2005). The elimination of a wash-out period would make an EEG prediction test more useful for clinical practice.

We did not instruct our patients to change their smoking and caffeine habits, so we cannot fully exclude their effects on the results. The outcomes of previous studies aimed at the effects of caffeine and nicotine on EEG parameters are conflicting (Pritchard et al., 1995; Gilbert et al., 2000).

There are several caveats to our findings.

First, we performed a four-week clinical trial. The duration of four weeks might be too short period to assess the treatment response in a clinical setting. However, recent

meta-analyses showed that only approximately 10% of responses occur after four weeks of treatment in 6-week clinical trials (Posternak and Zimmerman, 2005). We cannot exclude the possibility of another clinical response emerging during longer treatment, but in our opinion and with agreements to other authors, a period of four weeks of treatment without signs of response is in common clinical practice sufficient for a change in the treatment strategy (Pridmore and Turnier-Shea, 2004; Sackeim et al., 2005).

Second, the raters were not blind to medication, however, they were blind to EEG results during the study. Third, the responders had higher prefrontal cordance at baseline than the nonresponders. This difference, although not statistically significant, may have affected our results. The fourth limitation is the relatively small sample size.

The predictive value of the test such as QEEG cordance could significantly improve our clinical decisions. Positive predictive value (PPV) and negative predictive value (NPV) in our sample was estimated as 0.71 and 1.0, respectively. Adequate clinical trial of an antidepressant lasts at least between 4 and 6 weeks. In case of non-response to the first antidepressant the second choice therapy can be thus begun no earlier than after 4–6 weeks. Using QEEG cordance we could predict non-response already after the first week of new treatment. Thus the period of non-effective therapy could be reduced to only 1 week, with a consequent vast reduction of treatment costs. On the other hand, two QEEG assessments are required for this prediction procedure which makes its practical application somewhat demanding, especially in an outpatient setting.

5. Conclusion

Preliminary results suggest that QEEG cordance may be a promising tool in the early prediction of the response to antidepressants. Further evaluation of this test in a large sample of patients is recommended.

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