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Response to Pharmacological Treatment in Major Depression Predicted by Electroencephalographic Alpha Power – a Pilot Naturalistic Study

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Background: Pharmacological treatment of depression is currently led by the trial and error principle mainly because of lack of reliable biomarkers. Earlier findings suggest that baseline alpha power and asymmetry could differentiate between responders and non-responders to specific antidepressants.

Aim: The current study investigated quantitative electroencephalographic (QEEG) measures before and early in treatment as potential response predictors to various antidepressants in a naturalistic sample of depressed patients. We were aiming at developing markers for early prediction of treatment response based on different QEEG measures.

Materials and methods: EEG data from 25 depressed subjects were acquired at baseline and after one week of treatment. Mean and total alpha powers were calculated at eight electrode sites F3, F4, C3, C4, P3, P4, O1, O2. Response to treatment was defined as 50% decrease in MADRS score at week 4.

Results: Mean P3 alpha predicted response with sensitivity and specificity of 80%, positive and negative predictive values of 92.31% and 71.43%, respectively. The combined model of response prediction using mean baseline P3 alpha and mean week 1 C4 alpha values correctly identified 80% of the cases with sensitivity of 84.62%, and specificity of 71.43%.

Conclusions: Simple QEEG measures (alpha power) acquired before initiation of antidepressant treatment could be useful in outcome prediction with an overall accuracy of about 80%. These findings add to the growing body of evidence that alpha power might be developed as a reliable biomarker for the prediction of antidepressant response.

BACKGROUND

Depression is recognized as one of the most common and disabling psychiatric disorders. In addition to the suffering of the affected individuals and their families, there is a huge social and economic burden in terms of increased health-care costs, decreased productivity and absenteeism.¹ Due to lack of reliable biomarkers, current pharmacological treatment of depression is led mainly by the trial and error principle. Research in this area has been focused on examining several types of potential predictors such as early clinical improvement², genetic markers³, different electroencephalographic measures⁴,

and neuroimaging-derived markers.^{5,6}

The potential of several quantitative electroencephalographic (QEEG) measures for the prediction of antidepressant response has been investigated in the last few decades.⁷⁻⁹ The earliest studies found increased alpha power in responders compared to non-responders^{10,11} as well as greater alpha over the right compared to the left occipital sites.¹² Although some authors researching the predictive potential of the theta frequency band showed that higher absolute theta was associated with better response¹³, the majority of the studies found lower relative theta power in the groups of responders.^{11,14,15}

In several other QEEG studies, there was no pretreatment difference in alpha and theta powers between responders and non-responders to various antidepressants.¹⁶⁻²⁰ However, after the first week of treatment, a difference in a measure called cordance emerged between the two groups of patients. Those that were eventually (after 4 weeks) categorized as responders showed a decrease in theta cordance, something that was not seen in the group of the non-responders.¹⁸

Most of the alpha power studies were either placebo-controlled or open label on tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs), while some of the latest cordance studies implemented a naturalistic design and were thus closer to the clinical reality.

AIM

Based on these latest findings, the aim of our study was to investigate quantitative electroencephalography as a potential treatment-predictor in a naturalistic sample of patients with major depression before and during the early stages (on day 7) of their treatment with various antidepressants. We were aiming at developing markers for early prediction of treatment response based on different QEEG measures.

MATERIALS AND METHODS

SUBJECTS

A total of 29 patients with major depressive disorder were recruited in the study. All patients fulfilled the DSM-IV-TR criteria for this diagnosis, which was confirmed using the Mini-International Neuropsychiatric Interview.²¹ Subjects scoring more than 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and more than 4 on the Clinical Global Impression-Severity (CGI-S) were included in the study. Patients not included in the study were those who had an unstable medical condition or a neurological disorder (e.g. epilepsy, head trauma with loss of consciousness), high suicidal risk (Clinical Global Impression-Suicidality - CGI-SS > 2 and/or score on the 10th item of MADRS > 2), current psychiatric comorbidity, alcohol or substance abuse, electroconvulsive therapy (within 3 months before enrollment). A written informed consent was obtained from all subjects and the study protocol was reviewed and approved by the University's Ethics Committee. Three subjects dropped out after the first visit and one did not come for the last one thus bringing the number of patients in the final

dataset down to 25. Clinical response was defined as change in MADRS score from baseline to week 4 by at least 50%, and remission as total MADRS score below 12 at week 4.

EXPERIMENTAL PROCEDURE

The study started with a wash-out period of at least 1 day followed by a four week antidepressant treatment. The prescription of the particular antidepressants was left to the attending psychiatrist taking into account the subject's history, clinical status and general treatment guidelines (**Table 1**). Continuation of stable doses of benzodiazepines was allowed for those subjects who used them before the study. Patients were rated on MADRS, CGI-S and CGI-SS and filled out self-assessment scales on depression (Beck Depression Inventory – BDI) at study enrollment, on days 0, 7, and 28 of treatment.

EEG data were recorded before (baseline) and after one week of treatment with Neuron Spectrum 5 EEG amplifier (Neurosoft, Ivanovo, Russia) and a 19-channel electrode cap (Electro-Cap International, Eaton, Ohio, USA) using the 10/20 international electrode placement system. The EEG recordings were done in a quiet room with the patient in a comfortable seating position (with neck support), eyes closed in a maximally alerted state. The recording sessions were 20 minutes long with a sampling rate of 500 Hz. Low- and high-pass filters were applied to the data at 0.5 and 35 Hz, respectively. After visually inspecting the records for artifacts and periods of drowsiness or sleep, the best 30 sec. of vigilance were selected for further processing. Spectral analysis was performed by Fast-Fourier Transform (FFT) in the following frequency bands: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-20 Hz). For each subject the mean and total alpha powers (in μV^2), the alpha asymmetry (in %), the mean and total theta power (in μV^2) and the theta asymmetry (in %) were calculated at eight electrode sites (F3, F4, C3, C4, P3, P4, O1, O2) using the Neurosoft ω software v 1.6.4.3.

In each frequency band the mean power is calculated by averaging all amplitudes taken from the respective part of the power spectrum. The total power is calculated in a similar way but the amplitudes are summed instead. The percentage of asymmetry is defined as the power difference between the left and right electrodes divided by the higher of the two values or $A [\%] = 100 \times (L - R) / (\text{Max}(L, R))$, where A is the percentage of asymmetry, L and R are the powers registered by the

left and right electrodes and Max(L,R) is the higher of the two values.

STATISTICAL METHODS AND DATA ANALYSIS

Because of 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, Fisher's exact test) analyses and the regression and correlation analyses (Spearman's Rho). The significance level was set at 0.05 and all tests were two-sided. The software used for the statistical analysis was SPSS version 17 (IBM SPSS Statistics).

RESULTS

DEMOGRAPHIC CHARACTERISTICS AND CLINICAL MEASURES

A total of 25 subjects – 9 men and 16 women (median age 56 years, Interquartile range (IQR) 49-63 years) were included in the analysis. After 4 weeks of treatment 14 of them were classified as responders (MADRS decrease $\geq 50\%$) and 11 as non-responders. There was no significant difference in their baseline characteristics except for the duration of the current depressive episode which was longer in non-responders (**Table 1**).

Table 1. Descriptive statistics

	Responders (n=14) Median (IQR)	Non-responders (n=11) Median (IQR)	Statistical significance level
Age	56.5 (46.8-63)	56 (50-63)	0.77 ^a
Gender (M:F)	3:11	6:5	0.11 ^b
Duration of illness (months)	174 (45-342)	180 (28-252)	0.73 ^a
Duration of current episode (weeks)	8 (5.5-12)	28 (12-48)	*0.03 ^a
Treatment before enrollment	ESC – 3; SER – 2; VEN – 1; CLO -1; VEN + TRA – 1; ESC + TRA – 1; SER + PAR – 1 No treatment - 4	PAR -1; TRA – 3 VEN + QUE – 1, SER -1 No treatment - 5	
Treatment after enrollment	ESC – 2; SER – 1; VEN - 2; MIR – 1; DUL – 3; SER + MIR -1; SER + AGO -1; VEN + MIR -1 VEN + QUE – 1; VEN + TRA -1	ESC - 2; VEN - 4 TRA + QUE -2; DUL – 1 TRA + VEN -2	
N of subjects using BZD	9	7	1.00 ^b
Dose of BZD	5 (0-19)	10 (0-15)	0.94 ^a
MADRS baseline	32 (27-38)	35 (32-39)	0.50 ^a

IQR - Interquartile range, ^aMann-Whitney U test, ^bFisher's exact test, * $p < 0.05$, N - number, ESC - escitalopram, SER - sertraline, PAR - paroxetine, VEN - venlafaxine, MIR - mirtazapine, TRA - trazodone, DUL - duloxetine, QUE - quetiapine, CLO-clomipramine, AGO - agomelatine, BZD - benzodiazepine, MADRS - Montgomery-Åsberg Depression Rating Scale, BDI – Beck Depression Inventory.

BASELINE QEEG PARAMETERS

There were statistically significant differences between responders and non-responders in the total alpha averaged for all electrode sites, as well as in the mean and total alpha power at F3 and P3 sites with the responders showing greater baseline values (**Table 2**). The differences in the alpha asymmetry were not statistically significant. There were no differences between the groups regarding the theta power and asymmetry at baseline.

between the groups (**Table 1**). The influence of this factor was not statistically significant ($p=0.088$ for F3 alpha and $p=0.061$ for P3 alpha).

WEEK 1 QEEG PARAMETERS

After one week of treatment the responders had higher mean and total alpha power at C3 and C4 than the non-responders (**Table 3**). There were no significant differences between the two groups in alpha asymmetry, theta power and theta asymmetry

Table 2. Baseline QEEG parameters and antidepressant response

	Responders (n=14) Median (IQR)	Non-responders (n=11) Median (IQR)	Statistical significance Mann-Whitney U Test
F3 Mean Alpha Power - Baseline	3.0 (2.4-4.4)	1.4 (1.1-2.1)	0.03*
F4 Mean Alpha Power - Baseline	4.1 (2.5-5.0)	1.5 (1.1-2.7)	0.07
C3 Mean Alpha Power - Baseline	3.6 (1.3-6.0)	1.3 (1.1-2.2)	0.06
C4 Mean Alpha Power - Baseline	4.0 (2.6-7.7)	1.6 (1.1-2.8)	0.07
P3 Mean Alpha Power - Baseline	5.7 (3.0-8.5)	1.5 (1.0-2.3)	0.04*
P4 Mean Alpha Power - Baseline	5.7 (2.9-10.2)	2.0 (1.3-2.9)	0.10
O1 Mean Alpha Power - Baseline	5.8 (3.7-7.4)	2.3 (1.2-4.0)	0.15
O2 Mean Alpha Power - Baseline	4.7 (2.8-7.8)	2.4 (1.3-3.6)	0.24
Total Alpha Power - Baseline	3.9 (3.2-8.3)	1.8 (1.1-2.7)	0.05*

*statistically significant ($p<0.05$)

Logistic regression was applied to study the predictive value of baseline F3 and P3 mean alpha power and similar values were acquired for sensitivity – 80% (CI 51.91-95.67%) for F3 and 85.71% (CI 57.19-98.22%) for P3, specificity – 80% (CI 28.36-99.49%) for F3, 83.33% (CI 35.88-99.58%) for P3, positive predictive value (PPV) 92.31% (CI 63.97-99.81%) for both F3 and P3 and negative predictive value (NPV) 57.14 % (CI 18.41-90.10%) for F3 and 71.43% (CI 29.04-96.33%) for P3. Receiver operating characteristic (ROC) analysis of the predictive value of baseline mean P3 alpha gave an area under the curve (AUC) of 0.791 (**Fig. 1**). Choosing a cut-off value of 2.68 gives a sensitivity of 76.9% and specificity of 85.7%. Testing the mean F3 alpha power at baseline generates no higher AUC. In all analyses the duration of the current episode was added in order to be excluded as a confounding factor since it showed a significant difference

Figure 1. ROC curve of baseline P3 mean alpha power and response prediction (AUC=0.791).

Table 3. Week 1 QEEG parameters and antidepressant response

	Responders (n=14) Median (IQR)	Non-responders (n=11) Median (IQR)	Significance Mann-Whitney U Test
F3 Mean Alpha Power - Week 1	3.4 (1.5-4.8)	1.7 (1.4-2.4)	0.097
F4 Mean Alpha Power - Week 1	4.2 (1.8-5.2)	1.8 (1.3-2.7)	0.097
C3 Mean Alpha Power - Week 1	4.3 (2.5-5.0)	1.7 (1.1-2.0)	0.04*
C4 Mean Alpha Power - Week 1	4.7 (2.5-5.8)	1.9 (1.3-2.3)	0.05*
P3 Mean Alpha Power - Week 1	4.8 (2.7-8.5)	2.4 (1.4-3.6)	0.157
P4 Mean Alpha Power - Week 1	5.4 (2.7-9.2)	2.8 (1.6-4.7)	0.183
O1 Mean Alpha Power - Week 1	5.0 (2.4-7.3)	3.7 (2.4-5.0)	0.351
O2 Mean Alpha Power - Week 1	6.8 (2.2-10.6)	3.9 (2.0-5.7)	0.183
Total Alpha Power -Week 1	5.0 (2.5-7.5)	2.5 (1.6-3.5)	0.135

*statistically significant (p<0.05)

at week 1. Changes in the mean and total alpha and theta and the asymmetry were not significantly different between responders and non-responders. The C3 and C4 mean alpha powers at week 1 were capable of differentiating responders from non-responders with a sensitivity of 85.71% (CI 59.19-98.22%) and 84.62% (CI 54.55-98.08%), respectively and specificity of 83.33% (CI 35.88-99.58%) and 71.43 % (CI 29.04-96.33%) for C3 and C4, respectively. The duration of the current episode was not a significant confounding factor.

By means of logistic regression, the association between the treatment response and the QEEG parameters at baseline and at week 1 was investigated while controlling for the duration of the current episode. The combined model of response prediction based on baseline mean P3 alpha and mean C4 alpha power at week 1 was statistically significant $\chi^2(2) = 11.41$, $p < 0.05$. It explained 59.9% of the variance (Nagelkerke R^2) and correctly identified 80% of the cases. The sensitivity of the test was 84.62% (CI 54.55-98.08%), and the specificity – 71.43 % (CI 29.04-96.33%).

DISCUSSION

To the best of our knowledge, this is the first study to use QEEG alpha measures for the prediction of treatment response in a naturalistic sample of depressed patients. Our results demonstrate that before initiation of treatment the patients that were

ultimately classified as responders had greater total alpha power (across all electrodes) and mean alpha power in the frontal and parietal left sites (F3 and P3) as compared to the non-responders. After the first week of treatment this difference was no longer statistically significant but there emerged a difference at the central electrode sites (C3 and C4) where the responders showed again greater alpha power. The specific alpha measures showed substantial predictive capacity with overall accuracy around 80%. These findings and their significance are discussed below.

There is growing evidence that links resting EEG alpha with the so called Default Mode Network (DMN) that is activated during rest and deactivated during execution of tasks in functional magnetic resonance imaging (fMRI) studies.²² The DMN has been linked to self-referential processes and is found to be mostly hyperactivated in depressed patients although some authors report the opposite pattern and yet other studies demonstrate both hypo- and hyperactivation of different structures within the network.²³

Depressed subjects appear to have higher alpha power compared to healthy controls²⁴ and some of the first studies investigating the relation between EEG measures and treatment outcome^{10,11} found that responders had greater alpha compared to non-responders, which is generally in agreement with our results although this difference was more prominent at the occipital sites in the first study

and at the frontal sites in the second.

In addition, our findings on pretreatment alpha are consistent with some newer studies¹², where responders to fluoxetine had a tendency to demonstrate higher alpha power that did not reach statistical significance ($p=0.06$) although they had significantly more pronounced alpha asymmetry. Using different techniques for EEG analysis, Tenke et al.²⁵ reported higher alpha power in responders to SSRIs and SNRIs but found no difference in asymmetry. It is worth noting that based on previous results, most of the recent studies have focused only on posterior sites. Furthermore there are substantial differences in the EEG acquisition parameters (such as number of electrodes, montages) and subsequent analysis (absolute or relative power, current source density, independent component analysis) that could account for some of the inconsistencies of the findings.

Our results after the first week of treatment cannot be readily compared to other studies since most of them investigated the subjects for the second time at the end of the trial e.g. after several weeks of treatment. Studies that used the same design as ours with EEG recordings early in the treatment (on day 7) focused on a complex measure of absolute and relative theta power called cordance²⁶ and did not report on alpha measures.

The prediction of the treatment response based on the alpha measures before and after the first week of antidepressant treatment in our study showed similar values for sensitivity and specificity (around 80-85%) as did the combined model of prediction based on both pretreatment and week 1 alpha measures. This is to suggest that in further investigations baseline EEG might be sufficient for the development of potential response markers.

There are conflicting results about the significance, and more accurately, the direction of change in relative theta power in responders and non-responders. Most of the studies^{11,14,15} demonstrated that relative theta power was lower in responders compared to non-responders. More recently, Iosifescu et al.²⁷ found that the relative theta power was lower in responders to SSRI or venlafaxine. Contrary to their results, Spronk et al.¹³ reported that better treatment response of 25 depressed patients treated with SSRI and SNRI was associated with higher absolute theta power. In the present study no difference in theta power or asymmetry was found.

Limitations of this study are imposed by the small sample size and the lack of placebo controlled group. Because of the latter, we cannot overrule

the possibility that some of the results are related to placebo response. The naturalistic design has its weak and strong sides. It does not allow us to control for the type of medication but at the same time is much closer to the clinical reality, which could facilitate the implementation of alpha power as an early predictor of response to treatment.

CONCLUSIONS

Our results suggest that simple QEEG measures (alpha power) acquired before initiation of treatment with various antidepressants could be useful in predicting the outcome in a clinical sample of patients with major depressive disorder. The test shows a reasonable predictive value with an overall accuracy of about 80%.

The findings of this study add to the growing body of evidence that alpha power might be developed as a reliable biomarker for the prediction of antidepressant response in patients with major depression. Larger studies are needed in order to establish the reliability of this potential biomarker.

CONFLICT OF INTEREST

None.

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Ответ на фармакологическое лечение при большом депрессивном расстройстве, прогнозированном электроэнцефалографическими альфа-волнами – экспериментальное натурное исследование

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Введение: Фармакологическое лечение депрессивного расстройства в настоящее время руководствуется методом проб и ошибок в основном из-за отсутствия надёжных биомаркеров. В прошедших исследованиях утверждается, что базовые альфа-волны и асимметрия могут различаться у людей, реагирующих или не реагирующих на конкретные антидепрессанты.

Цель: Целью настоящей работы является исследование количественных электроэнцефалографических (КЭЭГ) измерений до и на ранних стадиях лечения в качестве потенциальных предикторов реакции на различные виды антидепрессантов в натурной группе пациентов в состоянии депрессивного расстройства. Нашей целью являлась разработка маркеров раннего прогнозирования ответа на лечение, базированного на различных КЭЭГ измерениях.

Методы: Были обработаны ЭЭГ данные 20 пациентов в состоянии депрессивного расстройства в начале и по истечении первой недели лечения. Средние и общие значения альфа-волн были установлены с восемью электродных позиций – F3, F4, C3, C4, P3, P4, O1, O2. Ответ на лечение был установлен как снижение на 50% показателя по шкале MADRS на четвёртой неделе лечения.

Результаты: Средние P3 альфа-волны прогнозируют ответ, чувствительность и специфичность которого составили 80%, положительные и отрицательные прогностические значения составили соответственно 92.31% и 71.43%. Комбинированная модель прогнозирования ответа, использующая средние P3 альфа значения в начале лечения и средние C4 альфа значения после первой недели лечения достоверно определила 80% случаев с чувствительностью 84.62% и специфичностью 71.43%.

Заключения: Стандартные КЭЭГ данные (альфа-волны), установленные до начала лечения антидепрессантами могут быть полезны при прогнозировании исхода терапии с общей точностью около 80 %. Эти данные дополняют уже солидную базу доказательств, что альфа-волны могут быть использованы в качестве надёжного биомаркера прогнозирования ответа на лечение антидепрессантами.