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Application of EEG Wavelet Power to Prediction of Antidepressant Treatment Response

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***Abstract*—**In clinical practice, the selection of an antidepressant often degrades to lengthy trial-and-error. In this work we employ a normalized wavelet power of alpha waves as a biomarker of antidepressant treatment response. This novel EEG metric takes into account both non-stationarity and intersubject variability of alpha waves. We recorded resting, 19-channel EEG (closed eyes) in 22 inpatients suffering from unipolar (UD, n=10) or bipolar (BD, n=12) depression. The EEG measurement was done at the end of the short washout period which followed previously unsuccessful pharmacotherapy. The normalized alpha wavelet power of 11 responders was markedly different than that of 11 nonresponders at several, mostly temporoparietal sites. Using the prediction of treatment response based on the normalized alpha wavelet power, we achieved 81.8% sensitivity and 81.8% specificity for channel T4.

***Keywords*—**Alpha waves, antidepressant, treatment outcome, wavelet.

I. Introduction

LOW remission rate and long response time are two fundamental difficulties associated with the pharmacotherapy of depression. For example, in the STAR*D study 47% of the 2876 major depressive disorder (MDD) outpatients responded to citalopram but only 28% achieved full remission [1]. Taking into account that clinical improvement may occur as long as 8 weeks after the onset of treatment [2], it is not surprising that the selection of an antidepressant is often based on lengthy trial-and-error. This difficulty has driven the search for treatment response biomarkers for several decades. Biomarkers rooted in electroencephalography (EEG) are particularly appealing since this technique is both cost effective and readily available in clinical practice [3], [4].

In the closed eyes condition, the prominent alpha wave spindles are the hallmark of the *non-stationarity* of EEG signals [5]. Nevertheless, the Fourier analysis, whose applicability requires the signal to be stationary, is predominantly used in quantitative EEG. In healthy individuals, the alpha power spectrum is usually stable but like other EEG traits must not be considered as unchangeable. However, intersubject differences are high which was demonstrated as early as in 1934 by Adrian and Matthews in front of the surprised members of Physiological Society gathered in Cambridge, England [6]. As long as the prediction of treatment response is based upon the changes in a patient's spectrum that are manifested shortly after the initiation of pharmacotherapy [7], [8], the intersubject variability is irrelevant. However, the effectiveness of any prediction algorithm based on a *single* EEG measurement may be degraded by the intersubject variability of alpha rhythm. In this work we test the hypothesis that the differences in alpha power topography between responders and nonresponders become much stronger when both non-stationarity and intersubject variability of alpha waves are properly taken into account.

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II. Methods

A. Subjects

The study comprised 33 depressive patients who were hospitalized at the Institute of Psychiatry and Neurology in Warsaw. The right-handed subjects aged between 18 and 75 years met International Classification of Diseases ICD-10 criteria (F31.3, F31.4, F33.0, F33.1, F33.2) of unipolar (UD) or bipolar depression (BD). Study protocol was approved by the Bioethical Commission of the Institute of Psychiatry and Neurology. All patients received written description of the protocol and signed the informed consent. Subjects were excluded if they met the criteria for substance abuse; were pregnant; had psychotic depression; organic brain pathology (confirmed by MRI or CT scan); a history of chronic benzodiazepine use; suffered from severe neurological (e.g. epilepsy, Alzheimer or Parkinson disease) or general medical conditions. In the group of patients suffering from bipolar depression, we enrolled only patients with a history of unchanged normothymic treatment during 4 weeks before the trial.

Reboxetine, venlafaxine, citalopram or bupropionemonotherapy was preceded by short washouts of an average length of 69 h ± 38 h and 80 h ± 23 h for bipolar and unipolar depression, respectively. Drug selection was based on initial psychiatric status, previous treatment history and patient preference. Doses of the antidepressants were consistent with official product characteristics (SPC). The study was scheduled for 4 weeks of active treatment. Out of 33 patients who entered the study, 22 (10 with unipolar and 12 with bipolar depression) reached completion, their

characteristics are presented in Table I. For the patients who completed the study the antidepressant selection was as follows. In the bipolar subgroup venlafaxine was chosen in 9 cases, bupropione in 2 and citalopram in one. In the unipolar depression subgroup 4 patients were treated with bupropione, 2 with venlafaxine, 2 with reboxetine, and 2 with citaloprame.

TABLE I
CHARACTERISTICS OF BD AND UD COHORTS

	Bipolar depression (n=12)	Unipolar depression (n=10)
Gender	F=10; M=2	F=5; M=5
Age (years)	46.8 ± 17.1	52.3 ± 19.2
MADRS pre-treatment	30.9 ± 7.7	26.2 ± 3.8
MADRS post-treatment	17.5 ± 11.2	16.1 ± 11.8
BDI pre-treatment	37.9 ± 10.6	32.1 ± 9.1
BDI post-treatment	21.9 ± 14.7	23.2 ± 17.2

TABLE II
ASSESSMENT OF DEPRESSIVE SYMPTOMS DURING THE TRIAL

	Responders (n=11)	Nonresponders (n=11)
Response in bipolar group (remission)	n=5 (4)	n=7
Response in unipolar group (remission)	n=6 (4)	n=4
MADRS pre-treatment	26.6 ± 5.5	31.0 ± 7.0
MADRS post-treatment	7.6 ± 4.7	28.0 ± 3.9
BDI pre-treatment	33.4 ± 12.1	37.2 ± 7.9
BDI post-treatment	10.8 ± 9.4	36.9 ± 6.6

B. Assessment of Depressive Symptoms

Depressive symptoms were quantified both by the Montgomery-Åsberg Depression Rating Scale (MADRS), administered by the attending physician, and the Beck Depression Inventory (BDI) which was completed by patients. The assessment of depressive symptoms was done at baseline and day 28 of the trial. Response to treatment was defined as the reduction of the final MADRS score by more than 50%. A final MADRS score less than or equal to 10 corresponded to remission.

C. EEG Recording

The EEG recording was done at baseline and day 28 of the trial. The 19 Ag/AgCl electrodes were placed according to the 10-20 international standard (impedances were below 5 kΩ). The reference and ground electrodes were mounted at the midsagittal line. The EEG was recorded through a Grass Telefactor Comet data acquisition system with the sampling frequency of 200 Hz and bandpass of 0.3–70 Hz. Subjects remained in supine position in a quiet room.

The measurement consisted of 4 five-minute intervals during which subjects had eyes alternatingly open and closed as shown in Fig. 1.

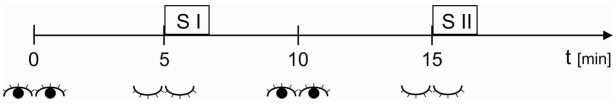

Fig. 1 The EEG protocol. The alpha wavelet power was calculated for two, artifact free, 2 min segments (SI and SII) under closed-eye conditions

D. Data Analysis

We selected 2min artifact-free data segments from the second and fourth measurement intervals. Hereafter, we refer to these segments as SI and SII. For these segments, we calculated the continuous wavelet transform $W_s(f_a, t_0)$ using the complex Morlet

$$\Psi(t) = \frac{1}{\sqrt{\pi f_b}} e^{i2\pi f_c t} e^{-t^2/f_b} \quad (1)$$

as a mother function (with parameters fc=1 and f_b=1.8). We used time averaged wavelet power

$$w(f) = \left\langle \left| W_s(f_a, t_0) \right|^2 \right\rangle_{t_0} \quad (2)$$

to investigate topography of alpha waves. Consequently, the calculations were performed for the pseudo-frequency f_a=10 Hz (value close to the average frequency of alpha waves in healthy adult subjects). For this choice of the complex Morlet parameters and pseudo-frequency f_a=10 Hz the wavelet power is just the weighted average of power in the entire alpha band (8-13 Hz). In other words, wavelet smooths out the alpha band spectrum as illustrated by Fig. 2.

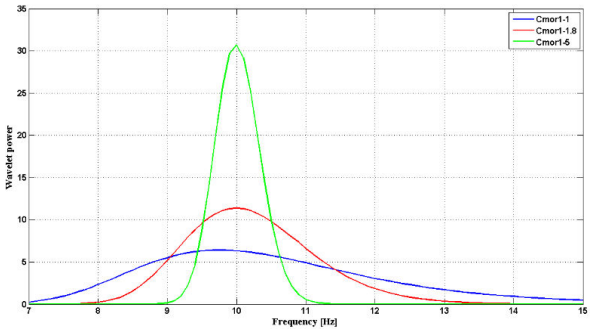

Fig. 2 The wavelet power of the monochromatic signal (10Hz) for three choices (1,1.8, 5) of bandwidth parameter f_b of complex Morlet mother function

Finally, the averaged wavelet power in each channel was normalized by the total averaged wavelet power from all 19 channels.

$$n(f;i) = \frac{w(f;i)}{\sum_{i=1}^{19} w(f;i)}. \quad (3)$$

Consequently, the normalized wavelet power is independent of the subject's EEG amplitude. The use of a just single pseudo-frequency to characterize the power in the alpha range is not by all means obvious. Even if the average alpha frequency of the subject is different that the chosen value of 10 Hz; the wavelet power is approximately proportionally reduced in all channels preserving the topography of the

normalized wavelet power.

The Mann–Whitney U test was used to assess the statistical significance of differences in normalized wavelet power n(10 Hz) between responders and nonresponders. We chose the paired, two-sided Wilcoxon signed-rank test to compare n(10 Hz) for segments SI and SII. In all cases the traditional p=0.05 was chosen as the threshold of statistical significance.

From the mathematical point of view prediction of treatment response is equivalent to binary classification based upon a single criterion (normalized alpha wavelet power). The area under the receiver operating characteristic curve (AUROC) [9] was used to quantify the performance of the binary classifier based on the normalized wavelet power. In addition, for channels for which classification was feasible we calculated the optimal threshold value (cut-off point) of the wavelet power as well as the sensitivity and specificity.

III. Results

A. Normalized Alpha Wavelet Power

The two-sided, paired Wilcoxon signed rank test showed no statistically significant differences in normalized alpha wavelet power for segments SI and SII of the first EEG monitoring. Consequently, we analyse the wavelet power averaged over these two segments (SI + SII). Averaging significantly improved the prediction of treatment response.

The topography of group averaged normalized wavelet power for responders and nonresponders are presented in Fig. 3.

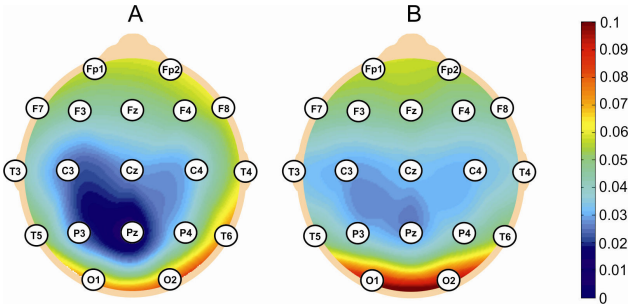

Fig. 3 Group averaged normalized alpha wavelet power for: (A) responders, (B) nonresponders

The differences between responders and nonresponders were significant at six, mostly temporoparietal, sites: T4, T6, T3, C3, P3, and Pz. The lowest p-value was found for channel T4 (p=0.001). The group averaged values for responders, nonresponders and controls were: nR(10Hz;T4) =0.07 ± 0.01, nN(10Hz;T4) =0.04 ± 0.02, nC(10Hz;T4) =0.03 ± 0.02, respectively. At the prefrontal, right frontal sites the wavelet power of responders is significantly greater.

The topography of the area under the receiver operating characteristic curve (AUROC) is presented in Fig. 4 for: the binary classification of responders and nonresponders. AUROC equal to 1 corresponds to perfect classification. When the outcome of classification is statistically indistinguishable from guessing the AUROC takes on the value of 0.5.

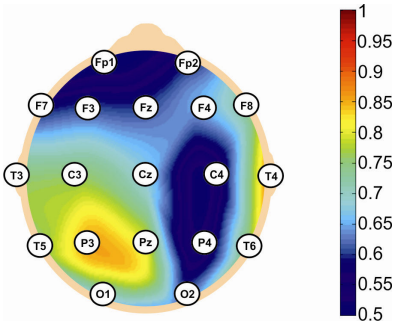

Fig. 4 AUROC for the binary classification of: responders and nonresponders. The classification was based on the normalized alpha wavelet power

The largest value (0.91) of the AUROC was observed in channel T4. Using the optimal cut-off point 0.058 we were able to correctly predict the outcome of treatment in 18 out of 22 patients (81.8% sensitivity and 81.8% specificity). For the prediction of treatment response, there were 7 channels for which the AUROC was significantly greater than 0.5. The qualitative description of the binary classification for these channels is presented in Table III. For convenience, in this table we inserted a row with the p-value of the Mann-Whitney U-test. We can see that the classification is statistically meaningful for channel T5 even though the p=0.07 exceeds the traditionally adopted threshold of 0.05.

TABLE III
THE OUTCOME OF BINARY CLASSIFICATION (PREDICTION OF TREATMENT RESPONSE) BASED ON NORMALIZED ALPHA WAVELET POWER

Channel	T4	T6	T3	T5	C3	P3	Pz
AUC	0.91	0.83	0.76	0.74	0.77	0.84	0.81
Test U	0.001	0.009	0.045	0.066	0.035	0.007	0.015
Cut-off point	0.058	0.078	0.038	0.050	0.023	0.032	0.020
Sensitivity [%]	81.8	72.7	63.6	90.9	72.7	90.9	72.7
Specificity [%]	81.8	90.9	81.8	63.6	90.9	72.7	90.9

IV. Discussion

Using the prediction of treatment response based on the normalized alpha wavelet power, we achieved 81.8% sensitivity and 81.8% specificity for channel T4. Bruder et al. using the logarithm of alpha power obtained 72.7% sensitivity and 57.5% specificity [10]. By combing two metrics: asymmetry and power of alpha waves, they improved the classification performance to 83.3% sensitivity and 67.7% specificity. In this study, the forecasting of response to an antidepressant is possible at seven, mostly temporoparietal sites (*cf.* Table III). The fact that the alpha wavelet power is equally effective as a response predictor in patients with unipolar and bipolar depression is an important result of this investigation. To our knowledge this is only the second study which explores the possibility of forecasting response to antidepressant intervention in bipolar affective disorder. In the recent work Bares et al. [11] found that the treatment response

in BD patients is associated with the reduction of prefrontal theta cordance after one week following administration of a new antidepressant, such reduction was first observed in UD [12]–[19].

The previous attempts to employ alpha waves for predicting the outcome of pharmacotherapy have met with limited success. Nevertheless, the properties of this EEG band have been incorporated into the Antidepressant Treatment Response Index (ATR) that combines *prefrontal* EEG theta and alpha power from baseline and after a week of pharmacotherapy [7], [8]. In their recent study Leuchter et al. [8] forecast response to escitalopram with 58% sensitivity and 91% specificity.

It is worth emphasizing that the presented approach is intrinsically different from the prediction based on the changes in prefrontal EEG induced by pharmacotherapy over a given time (usually a week) and quantified either by ATR index [7], [8], [20] or theta band cordance [12]–[19]. The fact that normalized alpha wavelet power does not change even after 4 weeks of active treatment is in agreement with the finding of [10]. Thus, the question arises as to the nature of persistence of the distinct properties of alpha waves observed in responders. Some argue that these properties reflect endophenotypic vulnerability to depression [10], [21] while others support the hypothesis of time-dependent susceptibility of depressive patients to pharmacotherapy. Either of two hypotheses can be ultimately verified only with a QEEG metric that proves highly successful in the prediction of antidepressant treatment response. We strongly believe that any such metric should take into account at least two fundamental features of human EEG time series: non-stationarity and intersubject variability. Herein we pointed to the mathematical framework of continuous wavelet transform as a possible source of such metrics. The limitations of this and similar studies [3] are related to open, nonrandomized treatment with a variety of medications. There is no doubt that the rigorous testing of the presented approach to prediction of antidepressant treatment response on a much larger cohort of depressive patients is required before a definitive assessment of its applicability can be made.

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