Research article

Neurobiological parameters in quantitative prediction of treatment outcome in schizophrenic patients

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Abstract

The aim of this study was to reveal the set of neurobiological parameters informative for individual quantitative prediction of therapeutic response in schizophrenic subjects. Correlation and regression analyses of quantitative Positive And Negative Syndromes Scale clinical scores, together with background electroencephalographic spectral power values and four immunological parameters: enzymatic activity of leukocyte elastase and of alpha-1 proteinase inhibitor, as well as serum levels of autoantibodies to common myelin protein and to nerve growth factor, were performed for 50 female subjects with hallucinatory-delusional disorders such as attack-like paranoid schizophrenia. Background neurobiological data obtained before the beginning of a syndrome based treatment course were matched with Positive And Negative Syndromes Scale clinical scores of the same subjects after a treatment course to the stage of establishment of remission. The multiple linear regression equations were created which were described by only three or four (from an initial 80) background electroencephalographic parameters and one of four immunological parameters. These mathematical models allowed prediction of 65–76% of Positive and Negative Syndromes Scale score variance after a treatment course. The data obtained may be useful for elaboration of methods for individual quantitative prediction of treatment outcome for schizophrenic subjects.

Keywords

Quantitative electroencephalography; immunological parameters; paranoid schizophrenia; hallucinatory-delusional disorders; mathematical modeling; prediction of treatment outcome

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1. Introduction

The problem of optimization of the treatment of schizophrenia is highly siginificant. It is due to a wide spread and chronic illness with a course typically involving multiple relapses, serious disturbances of cognitive functions (memory, attention, perception, thinking, decision-making) and behavior of subjects, and by a rather high percentage (up to 30%) of non-responders [1]. All these factors lead to serious social problems including decreased ability to work, impairment of educational and family adaptation to those who suffer from it, and results in very unfavorable economic and social-psychologic consequences.

The reality of the problem and the lack of useful clinical indicators for prediction of therapeutic response in schizophrenia [1] determine the need of further clinical-biological studies aimed to search for possible neurobiological predictors of individual efficiency of treatment, with a final goal of treatment optimization for this severe and socially significant mental disorder.

One of the possible ways forward for treatment optimization is a search for objective neurobiological parameters (biomarkers), which would serve as predictors of individual treatment outcome before completion of a course of treatment (that takes up to 6–12 weeks), best of all – just before prior to the beginning of treatment [2–4].

Among such biomarkers, electroencephalographic (EEG) ones are the most widely used because of the relatively low cost of EEG technology and its wide availability in clinical practice. However, the great majority of studies are devoted to the search for EEG predictors of treatment outcome in depressive subjects suffering from a major depressive disorder or from some depressive phase of a bipolar disorder [5, 6]. Design of these studies is similar: the subject's cohort is divided into responders and non-responders by the conventional criterion of 50% decrease of clinical rating scale (Hamilton's Depression Rating Scale – HDRS, or Montgomery-Asberg Depression Rating Scale, or Beck's Depression Inventory) scores after a course of treatment, or the difference between subgroup mean values of certain statistically assessed EEG parameters.

The majority of these studies use only one particular EEG parameter. Thus, Ulrich *et al.* [7, 8], Knott *et al.* [9], and Bruder *et al.* [10] explored alpha and/or theta spectral power. Knott *et al.* [11] measured beta spectral power, Iosifescu *et al.* [12] – relative theta power. Debener *et al.* [13] and Bruder *et al.* [14] used alpha and/or theta hemispheric asymmetry, Suffin & Emory [15] – EEG coherence, Tenke *et al.* [16] – alpha current source density. Bruder *et*

al. [17] and Kalayam & Alexopoulos [18] assessed amplitude and/or peak latency of the P300 wave of auditory event-related potentials.

Only a few studies used combinations of alpha and theta spectral power [12], or of absolute and related theta power – "cordance" [19–21], or even more EEG variables [15, 22].

One part of these studies used only one background value of an EEG parameter. Another dealt with changes of EEG parameters after several days [4, 8, 12, 21], or even after several hours [22] from the beginning of a treatment course, that required at least double EEG recordings.

Few studies deal with EEG predictors of treatment outcome in schizophrenia. Some of them have explored single EEG parameters as possible predictors: entire alpha (8–13 Hz) spectral power [23], alpha-1 (8–9 Hz) spectral power [24], or EEG coherence [25]. While others have investigated wide-band EEG: "EEG profiles" [22], or so called "referenced EEG" combining both EEG frequency band spectral power and its coherence [15].

Most of these studies demonstrated rather high accuracy: sensitivity and specificity were as great as 70–80%, in other studies [21] as high as 100 %. But a common limitation of all studies listed above is that prediction of treatment outcome in terms of "responder/non-responder" determines only the fact that the subject's condition after a course of treatment improves, but does not quantify the degree of any such improvement.

Several recent studies [26–28], using several different approaches have been employed by this group to search for EEG predictors of treatment outcome in affective disorders and schizophrenia. They have been directed towards quantitative prediction of treatment outcome by using the values of clinical rating scale scores. For this goal, correlation coefficients were calculated between background EEG parameters (recorded before the beginning of a course of treatment) and quantitative clinical assessments obtained after treatment at establishment of remission. EEG data comprising absolute spectral power values in eight narrow frequency bands: delta (2–4 Hz), theta-1 (4–6 Hz), theta-2 (6–8 Hz), alpha-1 (8–9 Hz), alpha-2 (9–11 Hz), alpha-3 (11– 13 Hz), beta-1 (13–20 Hz), and beta-2 (20–30 Hz), proved to be informative in assessment of brain functional states of subjects in previous studies. Clinical assessments were HDRS scores in depressive subjects, Young Mania Rating Scale scores in subjects with mania, and Positive And Negative Syndromes Scale (PANSS) scores in schizophrenic subjects. Values of these correlation coefficients then were then topographically mapped for better visibility using "BrainSys" software [29].

In depressive subjects increased EEG beta-1 (13–20 Hz) and beta-2 (20–30 Hz) spectral power values in temporal regions and of alpha-1 (8–9 Hz) all over the scalp were associated with relatively worse treatment outcome [26–28]. In subjects with mania, it was increased beta-1 (13–20 Hz) and beta-2 (20–30 Hz) spectral power in frontal regions, and decreased spectral power in 2–13 Hz frequency range all over the scalp [26]. In schizophrenic subjects, it was mainly increased EEG delta (2–4 Hz) spectral power in anterior (frontal-central-temporal) regions [26].

Based in the data obtained, it was suggested that sets of background neurophysiological parameters would be more informative for prediction of treatment outcome than single parameters, and the discovery of such sets has been attempted, so as to provide quantitative prediction of treatment outcomes.

Contemporary data emphasize the role of processes of neuroplasticity and neuroinflammation in pathogenesis of endogenous mental disorders, including schizophrenia [30–33]. In particular, it has been shown that high activity of leukocyte elastase (LE) and alpha-1 proteinase inhibitor ($\alpha - 1 - PI$) has been associated with exacerbation of endogenous mental disorders, while in remission their activity decreased [33, 34]. Moreover, these immunological parameters not only reflected the acuity of illness, but also may precede the clinical signs of relapse [33]. Appearance of autoantibodies to neuroantigenes (to common myelin protein–AAB_CMP and nerve growth factor–AAB_NGF – S100B protein) in serum is associated with the most severe and highly aggressive forms of mental disorders reflecting nonreversible changes in brain tissue [33]. Some positive correlations between quantitative clinical assessments and the levels of autoantibodies to AAB_CMP and AAB_NGF were identified in subjects with depressive-delusional and manic-delusional disorders such as attack-like paranoid schizophrenia [26, 35]. Thus, together with the requisite EEG parameters, those immunological parameters that may have predictive value could be combined to form sets of potentially informative neurobiological variables.

In a pilot study, using appropriate mathematical modelling methods [36], the possibility of rather accurate quantitative prediction of treatment outcome (in PANSS scores) was shown for subjects with manic-delusional disorders such as attack-like paranoid schizophrenia [35].

The goal of the present study was to reveal the sets of neurobiological parameters (including both EEG and immunological variables) informative for quantitative prediction of treatment outcome in another group of schizophrenic subjects that suffered from hallucinatory-delusional disorders such as attack -like paranoid schizophrenia.

2. Materials and methods

The present multidisciplinary clinical, neurophysiological, and neuroimmunological study was carried out at the Laboratory of Neurophysiology, Laboratory of Neuroimmunology, and Department of Endogenous Mental Disorders and Affective Conditions of the Mental Health Research Center, and followed contemporary ethical norms and rules for biomedical research in accordance with the World Medical Association's 1964 Helsinki Agreement. All subjects signed an informed consent prior to participation in the study.

2.1. *Subjects*

Subjects comprised 50 in-patients from the Clinic of Mental Health Research Center (Moscow, Russia) who had been diagnosed with hallucinatory-delusional disorders such as attack-like paranoid schizophrenia (meeting the criteria of F20.0 by ICD-10 or 295.3 by DSM-IV-R) were enrolled in the study as a learning sample. All subjects were right-handed females, age 21–50 years (mean age 32.9 $\pm$ 10.8), and received standard syndrome based psychopharmacological treatment with atypical antipsychotics.

Quantitative clinical assessments were recorded, and neurophysiological (resting EEG), and immunological parameters were both measured twice in all subjects, before beginning the treatment course (visit one), and after the course of treatment following pronounced clinical improvement when remission was established (visit two).

2.2. *Clinical assessment*

The number of psychopathological signs were assessed quantitatively using PANSS scores for schizophrenia [37], in which higher

score values correspond to more severe symptoms. The total sum of PANSS scores (PANSS-sum), as well as sums of scores of the Positive And Negative Syndrome Subscales (PANSS-pos and PANSS-neg, respectively) were also determined.

2.3. Neurophysiological (EEG) study

Multichannel recording of the background EEG was acquired prior to the course of treatment by using "Neuro-KM" EEG topographic mapping hardware ("Statokin", Russia) and "BrainSys" software [28]. The subject sat in a comfortable chair in a state of quiet wakefulness with eyes closed. Monopolar EEGs were recorded from 16 Ag/AgCl electrodes (impedance $< 10k\Omega$) according to the International 10-20 system: F7, F3, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2 with ipsilateral ear-lobe references A1 and A2, and the ground electrode placed between Fz and Fpz. The EEG was acquired with a 35 Hz bandpass filter, 0.1 time constant, an additional 50 Hz notch filter, and was recorded to computer hard disc with a 200 Hz sample rate. Duration of EEG recordings was greater than 3 minutes.

Artefact rejection was performed automatically using a"BrainSys" software option (amplitude threshold 4 SD). Low-amplitude artefacts from slow eye movements were rejected manually accounting for their specific frontal-posterior amplitude gradient.

Fast Fourier Transform based spectral analysis of artefact-free EEG fragments (more than 30 epochs, 4-second duration) was employed using "BrainSys" software. Absolute spectral power values (in μV^2) were calculated for eight narrow frequency EEG sub-bands: delta Δ(2–4 Hz), theta-1 $\theta 1$ (4–6 Hz), theta-2 $\theta 2$ (6–8 Hz), alpha-1 $\alpha 1$ (8–9 Hz), alpha-2 $\alpha 2$ (9–11 Hz), alpha-3 $\alpha 3$ (11–13 Hz), beta-1 $\beta 1$ (13–20 Hz), and beta-2 $\beta 2$ (20–30 Hz) from frontal (F3, F4), central (C3, C4), temporal (T3, T4), parietal (P3, P4), and occipital (O1, O2) EEG leads.

2.4. Immunological study

Peripheral blood samples were taken from each subject as part of their clinical assessment and EEG recording. Four immunological parameters were measured: the enzymatic activity of LE and of α-1-PI as biomarkers of neuroinflammation, as well as serum levels of autoantibodies to AAB_CMP and AAB_NGF as biomarkers of neuroplasticity processes. The measurements were performed using a standard solid-phase Enzyme-Linked ImmunoSorbent Assay (ELISA) method [38] such as "Neuro-Immuno-Test" laboratory technology [39]. Measurement of these immunological parameters is relatively simple and low cost in comparison to other neuroinflammation and neuroplasticity markers.

2.5. Data analysis

Mathematical analysis of the obtained set of clinical and neurobiological parameters was performed using the statistical package of the "BrainSys" software, and computational facilities of the Department of Computational Mathematics, M.V. Lomonosov Moscow State University (R-package). In accordance with the main goal of the study, neurobiological data recorded during visit one and were matched with quantitative clinical assessments of the same subjects obtained after their course of treatment following pronounced clinical improvement at the stage when remission was established during visit two.

Spectral analysis of EEG data obtained during visit one gave 80 variables for each subject (values of absolute spectral power for eight narrow frequency bands in 10 EEG leads). Immunological study during visit one gave four variables for each subject: values for LE and α-1-PI enzymatic activity, and values of serum levels for AAB_CMP and AAB_NGF. Quantitative clinical assessments (by PANSS scale) during visit two gave three variables for each subject: sum of scores of Positive Syndromes Subscale (PANSS-2-pos), sum of scores of the Negative Syndromes Subscale (PANSS-2-neg), and the total sum of PANSS scores (PANSS-2-sum).

Correlation coefficients were calculated between all 84 neurobiological parameters recorded during visit one and all three clinical parameters obtained during visit two. Correlation coefficients between clinical and EEG parameters were topographically mapped for better visibility (Fig 1–3) using the "BrainSys" software.

Further, multiple linear regression equations were created for each of three clinical parameters obtained during visit two (PANSS-2-pos, PANSS-2-neg, and PANSS-2-sum) using the least squares method. The goal was to identify the most informative set of neurobiological parameters for quantitative prediction of treatment outcome:

$$y2 = ax_1 + bx_2 + \cdots + nx_i + C$$

Dependent variables $(y2)$ were the quantitative clinical assessments (by PANSS scale) during visit two (PANSS-2-pos, PANSS-2-neg, and PANSS-2-sum). Independent variables $(x_1, x_2, \ldots, x_i)$ were the neurobiological parameters of the first visit most closely correlated with the corresponding clinical parameter of the second visit. $a, b, \ldots, n$ were coefficients of the independent variables, and C ws a free term of the equation.

The efficiency of these mathematical models (multiple linear regression equations) was assessed using three criteria: the R-square criterion indicated the extent of dependent variable variance explained by the model, a corrected R-square criterion used for comparison of models with different numbers of independent variables, and a variance inflation factor (VIF = $1/1 - R^2$) enabled detection of the presence of multicolinearity in the model. The model considered the most efficient explained the highest percent of dependent variable variance, had the highest value of corrected R-square criterion, and was free from multicolinearity (VIF < 4).

The accuracy such models for quantitative prediction of treatment outcome was tested in a group of subjects (control sample, $n = 10$) with the same diagnosis, treated with the same antipsychotics, but not included in the learning sample.

3. Results

3.1. Clinical assessments of treatment outcome

Statistical analysis of the dynamics of quantitative clinical parameters in the treatment course revealed a significant decrease of group mean values of PANSS scores that confirmed pronounced improvement of subject's clinical conditions after the course of treatment. Scores of PANSS-pos decreased from 27.04 ± 6.03 to 12.04 ± 3.18 ($p < 0.001$), scores of PANSS-neg decreased from 25.08 ± 6.09 to 16.84 ± 4.52 ($p < 0.001$), and scores of PANSS-sum decreased from 106.76 ± 21.82 to 58.76 ± 12.63 ($p < 0.001$).

3.2. Correlation analysis of clinical and neurobiological data

For better visibility, results of the correlation analysis of clinical and EEG data are presented in Fig. 1–Fig. 3 as topographical maps.

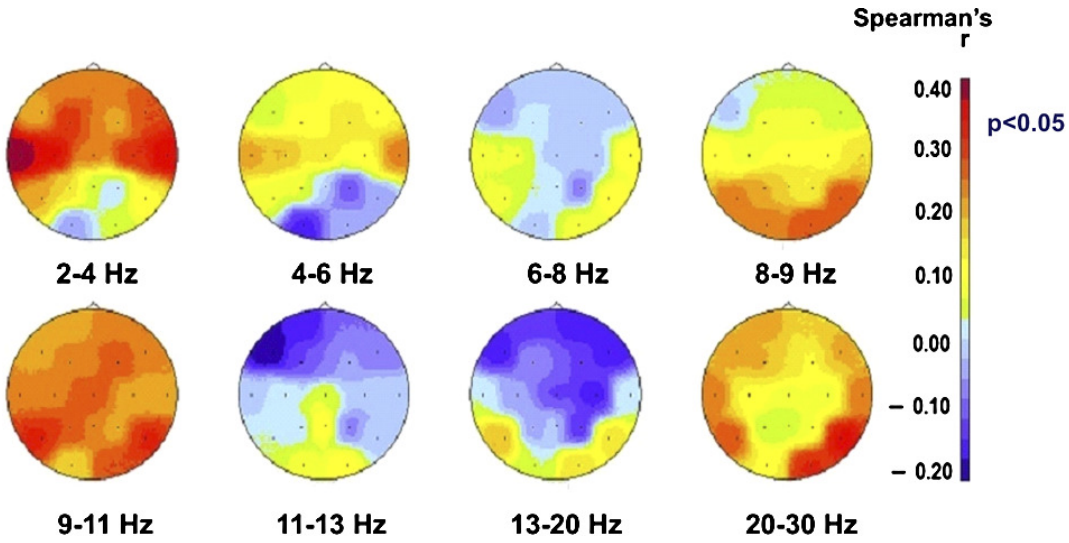

Fig. 1. Topographic maps of distribution of values of Spearman's correlation coefficients (r) between the PANSS-2-pos scores at the stage remission was established (visit two) and spectral power values of eight narrow frequency bands of background resting EEG (visit one) in subjects with paranoid schizophrenia and hallucinatory-delusional disorders. Color scale at right – in values of Spearman's r.

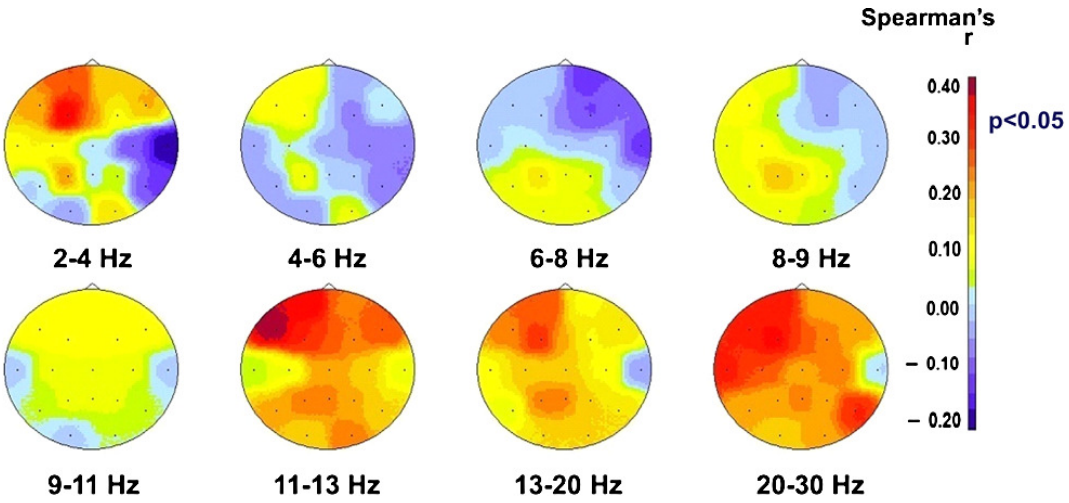

Fig. 2. Topographic maps of distribution of values of Spearman's correlation coefficients (r) between the PANSS-2-neg scores at the stage remission was established (visit two) and spectral power values of eight narrow frequency bands of background resting EEG (visit one) in subjects with paranoid schizophrenia and hallucinatory-delusional disorders. Color scale at right – in values of Spearman's r.

The maps show the spatial distribution of correlation coefficients between background values of absolute EEG spectral power in eight narrow frequency sub-bands (visit one) and the outcome of clinical assessments (visit two) – sum of scores of PANSS-2-pos, sum of scores of PANSS-2-neg, and PANSS-2-sum.

Fig. 1 shows the spatial distribution of correlation coefficients between background values of absolute EEG spectral power in eight narrow frequency sub-bands (obtained visit one) and outcome sum of scores of PANSS-2-pos (visit two). It is seen that values of absolute EEG delta spectral power in the left temporal lead (T3) correlates positively ($r = 0.364$, $p < 0.05$) with PANSS-2-pos scores. Correlation coefficients between other background EEG parameters and outcome PANSS-2-pos scores did not reach the level of statistical significance.

Fig. 2 shows the spatial distribution of correlation coefficients between background values of absolute EEG spectral power in eight narrow frequency sub-bands (visit 1) and outcome sum of scores of PANSS-2-neg (visit two). It is seen that values of absolute EEG spectral power correlate positively with PANSS-2-neg scores in delta ($r = 0.357$, $p < 0.05$) and in alpha-3 ($r = 0.411$, $p < 0.05$) bands in the left frontal lead (F3). Correlation coefficients between other background EEG parameters and outcome PANSS-2-neg scores did not reach the level of statistical significance.

Fig. 3 shows the spatial distribution of correlation coefficients between background values of absolute EEG spectral power in eight narrow frequency sub-bands (visit one) and PANSS-2-sum (visit two). It is seen that values of absolute EEG spectral power in delta band correlates positively with PANSS-2-sum scores in left frontal lead (F3) ($r = 0.456$, $p < 0.01$) and in right frontal lead (F4) ($r =$

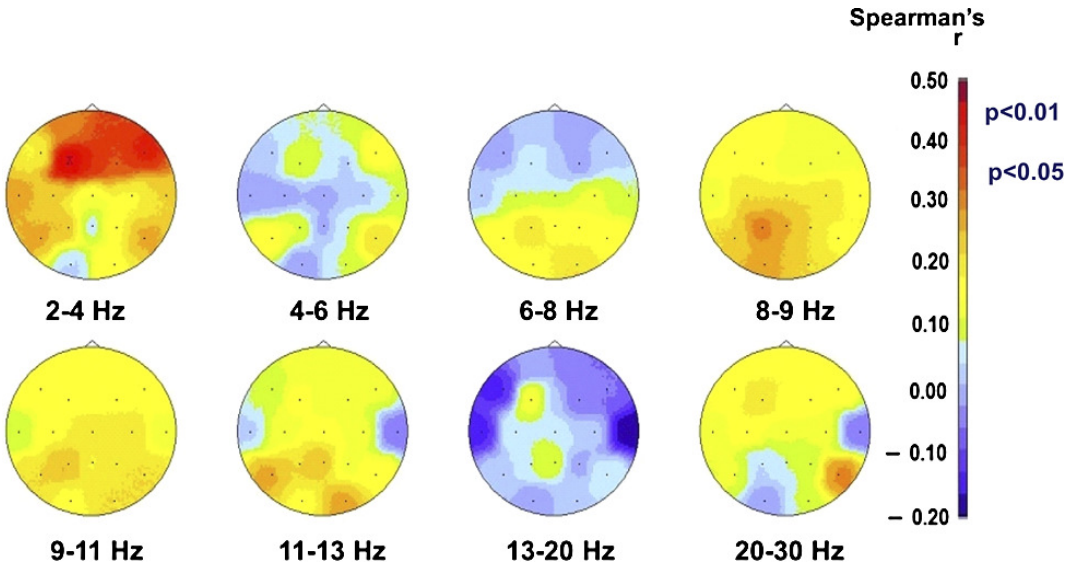

Fig. 3. Topographic maps of distribution of values of Spearman's correlation coefficients (r) between the PANSS-2-sum scores at the stage remission was established (visit two) and spectral power values in eight narrow frequency bands of background resting EEG (visit one) in subjects with paranoid schizophrenia and hallucinatory-delusional disorders Color scale at right – in values of Spearman's r.

Table 1. Correlation coefficients between outcome clinical assessments (visit two) and background immunological parameters (visit one) in subjects of the learning sample ($n = 50$).

Outcome PANSS scores	LE	α 1-PI	AAT_CMP	AAT_NGF
PANSS-2 positive	−0.155	0.233	0.354*	0.113
PANSS-2 negative	−0.227	0.049	0.201	0.146
PANSS-2 sum	−0.212	0.073	0.195	0.365*

PANSS-2-positive – the sum of scores of the positive syndromes PANSS subscale assessed after treatment course at the stage of remission establishment (visit two)
PANSS-2-negative – the sum of scores of the negative syndromes PANSS subscale assessed after treatment course at the stage of remission establishment (visit two)
PANSS-2-sum – total sum of PANSS scores assessed after treatment course at the stage of remission establishment (visit two) LE – enzymatic activity of LE (visit one)
α 1-PI – enzymatic activity of α 1-proteinase inhibitor before the beginning of treatment course (visit one)
AAT_CMP – level of autoantibodies to common myelin protein before the beginning of treatment course (visit one)
AAT_NGF – level of autoantibodies to nerve growth factor before the beginning of treatment course (visit one)
*$p < 0.05$.

0.384, $p < 0.05$). Correlation coefficients between other background EEG parameters and outcome PANSS-2-neg scores did not reach the level of statistical significance.

Results of correlation analysis of clinical and neuroimmunological data are presented in Table 1.

Table 1 shows that only two of four background immunological parameters (AAB_CMP and AAB_NGF) correlated significantly ($p < 0.05$) with outcome quantitative clinical assessments obtained during visit two. They were correlation of the level of autoantibodies to AAB_CMP with PANSS-2-pos ($r = 0.354$, $p < 0.05$), and correlation of level of autoantibodies to AAB_NGF withPANSS-2-sum ($r = 0.365$, $p < 0.05$). Other correlations did not reach the level of statistical significance.

3.3. *Mathematical models for quantitative prediction of treatment outcome*

Mathematical models for quantitative prediction of PANSS score values in subjects with hallucinatory-delusional disorders such as attack-like paranoid schizophrenia were created as multiple linear regression equations. Dependent variables were quantitative clinical assessments (by PANSS scale) obtained during visit two (PANSS-2-pos, PANSS-2-neg, and PANSS-2-sum) The independent variables were those of the neurobiological parameters of the first visit which most closely correlated with the corresponding clinical parameters of the second visit.

The mathematical models obtained contained only three or four (from the initial 80) background EEG parameters, one of four immunological parameters, and a free term in the equation. The models were as follows:

$$\text{Model I: PANSS-2-pos} = 0.999 \times \Delta\_T3 + 0.139 \times \alpha 2\_P3 - 0.847 \times \theta 1\_O1 + 7.624 \times \text{AAB\_CMP} + 15.854$$

$$\text{Model II: PANSS-2-neg} = 1.969 \times \Delta\_F3 + 1.467 \times \alpha 3\_F3 + 0.886 \times \beta 2\_C3 - 0.548 \times \theta 1\_O1 + 9.869$$

Table 2. An example of testing of mathematical models for quantitative prediction of clinical outcome. Subject I., Female, age 30 (control group). D-s: attack-like paranoid schizophrenia with hallucinatory-delusional disorders (F20.0 by ICD-10; 295.3 by DSM-IV-R).

PANSS scores	Actual score after treatment	Predicted score after treatment	Deviation predicted vs. Actual scores	Permitted deviation ($p <$ 0.001)
PANSS-2 positive	16	14	12.5%	± 38%
PANSS-2 negative	19	17.5	8%	± 24%
PANSS-2 sum	76	71.4	6%	± 36%

PANSS-2-positive – the sum of scores of the positive syndromes PANSS subscale(visit two)
PANSS-2-negative – the sum of scores of the negative syndromes PANSS subscale (visit two)
PANSS-2-sum – total sum of PANSS scores (visit two)

Table 3. An example of testing of mathematical models for quantitative prediction of clinical outcome. Subject B., Female, age 32 (control group). D-s: attack-like paranoid schizophrenia with hallucinatory-delusional disorders (F20.0 by ICD-10; 295.3 by DSM-IV-R).

PANSS scores	Actual score after treatment	Predicted score after treatment	Deviation predicted vs. Actual scores	Permitted deviation ($p <$ 0.001)
PANSS-2 positive	10	11	10%	± 38%
PANSS-2 negative	16	17	5%	± 24%
PANSS-2 sum	60	74	24%	± 36%

PANSS-2-positive – the sum of scores of the positive syndromes PANSS subscale (visit two)
PANSS-2-negative – the sum of scores of the negative syndromes PANSS subscale (visit two)
PANSS-2-sum – total sum of PANSS scores (visit two)

$$\text{Model III: PANSS-2-sum} = 3.671 \times 1\Delta\_F3 + 0.478 \times \alpha 1\_P3 - 2.137 \times \beta 1\_C3 + 19.694 \times \text{AAB\_NGF} + 28.885$$

Model I explains 62% of PANSS-2-pos variance ($p < 0.00006$), Model II explains 76% of PANSS-2-neg variance ($p < 0.000006$), and Model III explains 64% of PANSS-2-sum variance ($p < 0.00004$), where: PANSS-2-pos – sum of scores of Positive syndromes subscale after the course of treatment; PANSS-2-neg – sum of scores of Negative syndromes subscale after the course of treatment; PANSS-2-sum – total sum of PANSS scores after the course of treatment; Δ_F3 – delta (2–4 Hz) spectral power (in μV^2) in left EEG lead ($F3$); Δ_T3 – delta (2–4 Hz) spectral power (in μV^2) in left temporal EEG lead ($T3$); $\theta 1\_O1$ – theta-1 (4–6 Hz) spectral power (in μV^2) in left occipital EEG lead; (O1) $\alpha 1\_P3$ – alpha-1 (8–9 Hz) spectral power (in μV^2) in left parietal EEG lead (P3); $\alpha 2\_P3$ – alpha-2 (9–11 Hz) spectral power (in μV^2) in left parietal EEG lead (P 3); $\alpha 3\_F3$ – alpha-3 (11–13 Hz) spectral power (in μV^2) in left frontal EEG lead (F3); $\beta 1\_C3$ – beta-1 (13–20 Hz) spectral power (in μV^2) in left central EEG lead ($C3$); $\beta 2\_C3$ – beta-2 (20–30 Hz) spectral power (in μV^2) in left central EEG lead ($C3$); AAB_CMP – level of autoantibodies to common myelin protein (in optical density units, OD); AAB_NGF – level of autoantibodies to nerve growth factor (in optical density units, OD).

3.4. *Testing of the mathematical models that were developed*

The validity of mathematical models obtained were tested in a control group of subjects ($n = 10$) with the same diagnosis, treated with the same antipsychotics, but not included in the learning sample. The values of corresponding background EEG and neuroimmunological variables (visit one) were inserted into the equations obtained, and the results were compared with PANSS scores obtained by clinicians (visit two). Two examples of such testing are presented below in Table 2 and Table 3.

Table 2 and Table 3 show that prediction accuracy was rather high. Deviation of predicted PANSS score values of the control group from PANSS values (visit two) varied from 5% for PANSS-2-neg (permitted deviation 24%, $p < 0.001$) to 24% for PANSS-2-sum (permitted deviation 36%, $p < 0.001$).

4. Discussion

This study shows for the first time the possibility of predicting treatment outcome, not only qualitatively (in terms: responder/non-responder), but also with quantitative accuracy (as values of the PANSS rating scale scores). Moreover, such prediction appeared to be possible not only for total sum of PANSS scores, but also for the separate sums of scores of PANSS-2-pos and PANSS-2-neg.

While the result of such prediction is not dichotomic (in terms: responder/non-responder), but quantitative, it may be a characterizion only by accuracy, not by sensitivity and specificity. Deviation of predicted PANSS scores values in subjects of the control group from their clinically determined values obtained during visit two varied from 5% to 24% for different PANSS scales, and was significantly lower than the expected deviation. It should be noted that prediction accuracy was somewhat higher for PANSS-2-neg than PANSS-2-pos or PANSS-2-sum scores. The corresponding equation explains 76% of PANSS-2-neg variance, and deviation of predicted PANSS-neg values vs. the clinically determined values obtained during visit two was less than 10%.

Prediction is based entirely on the set of a few background neurobiological parameters obtained prior to the beginning of a course of treatment, and does not use any background clinical assessment. Thus, such an approach has some benefits in comparison with other methods of assessment such as a subject being either a responder or non-responder that must obtain clinical ratings at least twice.

According to the set of neurobiological variables included in the equations, and the signs (positive or negative) of their coefficients, the EEG signs for predicting a poorer outcome for a subject

with hallucinatory-delusional disorders such as attack-like paranoid schizophrenia are increased amounts of left frontal delta activity (2–4 Hz EEG lead F3, for PANSS-2-neg and for PANSS- 2-sum) and in left temporal (EEG lead T3, for PANSS-2-pos) brain regions, reflecting decreased functional state of anterior (frontal-central-temporal) brain areas – hypofrontality. Moreover, five other EEG spectral power variables included in the equations are also located in the left hemisphere: theta-1 in left occipital EEG lead (O1), alpha-1 and alpha-2 in left parietal EEG lead (P3), alpha-3 in left frontal EEG lead (F3), beta-1 and beta-2 in left central EEG lead (C3).

From a neurophysiologic perspective, the left hemispheric location of these EEG signs, informative for outcome prediction, emphasizes a role for the left hemisphere in pathogenesis of schizophrenia that is in good concordance with the literature. It was shown that schizophrenic subjects with activation dominance of the left hemisphere demonstrated a prevalence of positive symptoms, while subjects with the opposite asymmetry, i.e. with more active right hemisphere and/or decreased functional state of the left hemisphere, demonstrate a prevalence of negative symptoms [40, 41].

As well, the poorer clinical outcome associated with higher levels of autoantibodies to AAB_CMP, for PANSS-2-pos, and of autoantibodies to AAB_NGF, for PANSS-2-sum, reflect activation of destructive neuroplasticity processes that disturb the normal integrative activity of the brain [33].

In contrast with earlier studies on EEG prediction of treatment outcome in schizophrenic subjects using EEG alpha parameters [23, 24], in this study EEG parameters played the main role in delta prediction. This discrepancy may relate to sampling differences, and/or choice of only one EEG parameter as a predictor, and/or assessment of subjects as responders/non-responders in the above-cited studies.

The limitations of the present study (as well as of many similar studies – see [5]) are related to its open, non-randomized design, and the polypharmacy treatment with a variety of medications. Expansion of the described approach to larger cohorts of schizophrenic subjects with different syndrome structures of illness, and inclusion of male subjects are the subject of ongoing studies.

It is suggested that the approach described here may help in the prediction of individual effects of standard syndrome-based psychopharmacological treatment for schizophrenic subjects with sufficient accuracy, both on general treatment outcome and on decrease of positive and negative symptoms separately. If a subject responds insufficiently (in general or in relation to positive or negative symptoms), the clinician may pay special attention to them, perform additional diagnostic procedures to justify their condition and diagnosis, may change or correct medications from the very beginning of treatment, and do not need to wait for several days for clinically marked treatment effects.

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Conflict of Interest

All authors declare no conflicts of interest.

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