

The new method of assessing EEG synchrony is the best instrument for identifying interindividual and intergroup differences

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Abstract

The principal errors of spectral and coherent analysis are discussed, and the mathematics of these methods is not related to EEG nature. In this regard, in 2011, the new method was developed for evaluating EEG synchrony by the correlation of envelopes, which has a direct and fundamental physiological meaning. The basics of this method and the methodology of subsequent multilateral statistical analysis are considered. The effective use of the method for identifying individual and intergroup differences in the norm and several types of schizophrenia, depressive diseases, five stages of sleep, and similar functional states are presented.

Objective

Unfortunately, in the field of computational or quantitative EEG (qEEG), metrological criteria, assessments and standards have not been formed globally for several of reasons [1]. As evidenced by the content of the special fundamental monograph [2] and many journal publications on qEEG, metrological issues almost do not attract the attention of EEG researchers. The new proposed mathematical methods are not compared with analogs; their effectiveness in solving typical physiological problems is not evaluated, is not compared and is not statistically verified. Traditional methods are not critically examined and rethought. Periodically, attempts are made to introduce completely exotic and unrelated brain physiology methods from the theories of chaos, information, and entropy, fractals, attractors, automatic regulation, nonlinear dynamics, wavelets, etc.

One way or another, but scientific research of EEG mainly followed in the wake of physical and technical applications of mathematical methods of signal analysis which were often directly and uncritically transferred by involved engineering and physical specialists without due consideration of a) the fundamental non-stationarity of biosignals; b) the inharmonic nature of their sources; c) the presence of amplitude modulation. Indeed, there is not a single well-known a pure or applied mathematician who has contributed

to the development of special methods of EEG analysis. As a result, many methods that were inadequate in this field were transferred, which, in the absence of metrological criticism, leads to incompatibility and inconsistency of the results and conclusions obtained by different researchers. And such a situation can in no way be recognized as the scientific one.

It is no exaggeration to say that the main means of qEEG are [2] spectral estimates of EEG amplitude in frequency domains and estimates of synchrony between pairs of derivations using the coherence function.

EEG amplitude estimates

During the pre-computer era, EEG amplitude was estimated by direct measurements (DM) of EEG waves. After the FFT algorithm appearance in 1965, EEG amplitude was indirectly estimated (IdE) from the amplitude and power spectra. There is no doubt that DM acts as an indisputable standard, and IdM may differ from them in the resulting values. The corresponding comparison was carried out in the special metrological study [3], and it showed the following differences:

1. the three studied in [3] DM indicators give almost equivalent estimates that highly significantly differ from IdE;
2. DM demonstrate the smooth dynamics of their value change at successive epochs, whereas IdE are subject to

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drastic and casual fluctuations;

3. IdE, unlike DM, don't possess the property of additivity, which is inherent for statistical averaging, its values depending on the number and length of averaged epochs can differ in 3 or more times;
4. IdE on simulated signals with known amplitude ratio give estimates by 1.4–1.55 times different from true value whereas DM proper correlations of average amplitudes;
5. IdE depending on the shape of spectrum amplitude distribution, may vary in its ratio to a variety of subjects more than five times while DM show the same relation of values which differ from IdE in 1.38–3.7 times;
6. the largest errors were found for the power spectrum.

These conclusions do not allow metrologically qualify IdE as the analytical tools adequate to the nature and specifics of EEG potentials. Their use may lead to the incompatibility of results obtained by different researchers.

In addition, the spectra have an extremely distant relation to EEG nature since, unlike sound and electromagnetic signals, EEG is not the sum of harmonics. EEG is the sum of postsynaptic potentials under the electrode whose short-time changes take the form of asymmetric bell-shaped functions. Therefore, individual spectral harmonics have no physiological meaning. They change arbitrarily both when the length of the analysis epoch changes, as well as on neighboring epochs.

Coherence

The poorly known history of EEG coherence is a vivid example of the mass spread of pseudoscientific misconception. The coherence function was formulated in 1930 by Norbert Wiener [4], implementing the idea previously expressed by David Hilbert that it would be good to have something similar to Pearson correlation in the spectral region. Wiener intended this function for problems of quantum mechanics and nonlinear optics, which are obviously extremely far from EEG studies. Subsequently, coherence became widespread in the analysis of physical signals but as a purely auxiliary indicator for assessing the significance of other cross-spectral characteristics [5].

Many years have passed when in 1963, the newly minted young Ph.D. [6], without any reference to sources and predecessors, proposed coherence as the main indicator of EEG synchrony. This Ph.D. published 2–3 more articles on this topic, after which he lost interest in it. But the growing snowball of coherency rolled around the world, capturing the minds of many thousands of followers like a mass pandemic.

The special metrological analysis of the weaknesses and errors of coherence was carried out in the study [7], which gave the following results:

1. the coherence mainly evaluates the degree of phase instability of the cross-spectrum of two EEG signals, which to an even greater extent than spectral harmonics has no physiological meaning;
2. at the same time, the coherence also changes depending on the ratio of the values of the cross-spectrum vectors at neighboring epochs¹, and such a dual sensitivity is unacceptable for a measuring instrument;
3. the coherence dependence on phase instability has a highly

nonlinear snake-like character, which is unacceptable for accurate measurements;

4. the coherence values are strongly influenced by choice of four setting parameters which is also unacceptable for a measuring instrument;
5. different EEG analyzers secretly use different settings of these parameters, so the obtained coherence values are incompatible.

Thus, coherence evaluates unknown what, unknown how, and unknown why, being an example of pseudoscientific anachronism. As the literature reviews, performed in the three main areas of scientific and medical research, show [9–11], the use of coherence leads to a total incompatibility of results on the localization of inter-individual and intergroup differences. Thus these numerous publications do not belong to the field of science, which is designed to search for and finds objective laws in natural phenomena, but to the category of random noise or pseudoscientific garbage.

Correlation of EEG envelopes

In connection with the numerous and fundamental errors of coherence considered, another and adequate assessment of EEG synchrony was proposed in 2011 [8] by calculating the Pearson correlation coefficient between the envelopes of two EEG derivations. Unlike coherence, this assessment has a direct and fundamental physiological meaning. Indeed, since the envelope represents a change in EEG amplitude modulation (Figure. 1)², it increases with increasing synchrony in the change of postsynaptic potentials under the electrode. Therefore, the envelopes correlation evaluates the degree of synchrony in the dynamics of postsynaptic synchrony between two EEG derivations.

It was found that in more than 42% of cases, there are high correlations between the envelopes of closely located (neighboring) derivations from 0.6 to 0.99 at the median = 0.42, while for more distant derivations, 98.5% of the envelope correlations do not exceed 0.6 at the median = 0.17. At the same time, highly correlated connections between the envelopes form distinct topographic patterns on the scalp, which are largely preserved in neighboring EEG frequency domains.

This allows us to reduce the amount of significant information, limiting ourselves only to the grid of connections between nearby pairs of derivations; for the 10–20% scheme, such pairs will be 43 (Figure. 2a). The use of such a standard grid, in particular, contributes to the comparability of the results obtained by different researchers. Within the framework of such a grid, it is easy to visualize highly correlated connections between envelopes (Figure. 2a–c), obtaining well-visually detectable topographic patterns.

The sequence of correlation coefficients between EEG envelopes for pairs of derivations in their ordered sequence in such a standard grid is called the profile of synchrony (PS) of the subject. It is convenient to depict PS in the form of a bar chart (Figure. 2d), which provides the researcher with an additional visual pattern. It is precisely such profiles that are the source material for the further areas of analysis.

In the case of a group of subjects, we will have a PS matrix

² Mathematically, the envelope is a module of an analytical (complex-valued) signal, the real part of which is equal to the signal itself, and the imaginary part is obtained from the signal by the Hilbert transform. In turn, Hilbert transform is equivalent to the double Fourier transform, when before the reverse transformation, all spectral harmonics are shifted in phase by 90°.

¹ As the difference in values of vectors increases, the coherence increases, which is directly opposite to the Pearson correlation property. Thus, Wiener, in his algorithm, distorted Hilbert's original idea.

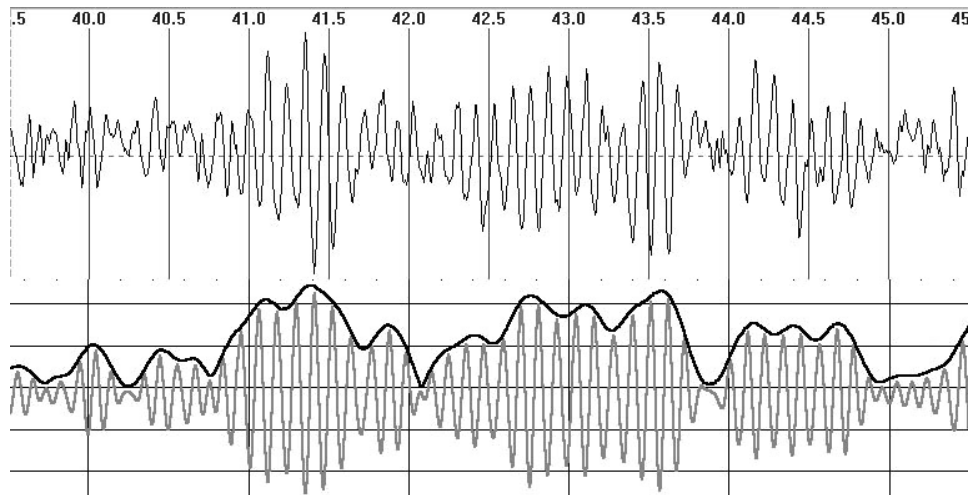


Figure 1. Example of an envelope: above – EEG with a high content of alpha rhythm; below – the result of filtering in alpha domain³ with an overlay of the envelope.

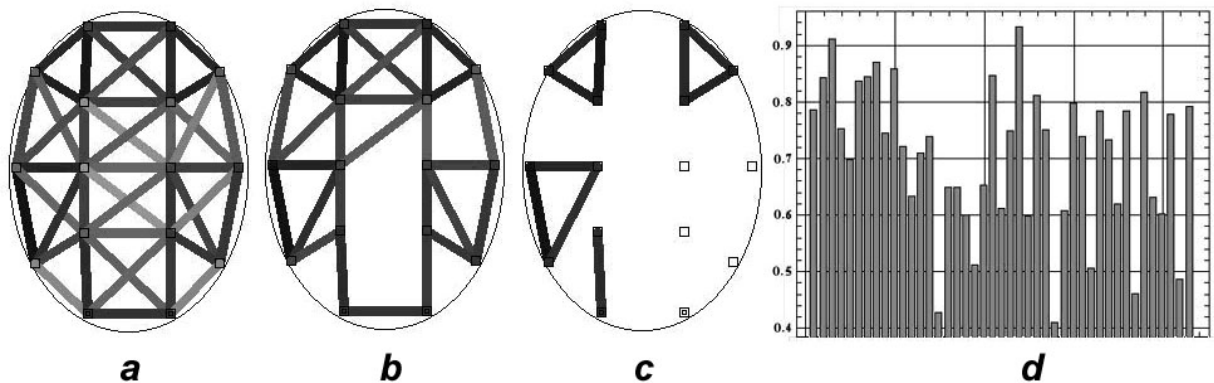


Figure 2. The three topograms of EEG synchrony of chosen subject for standard grid of channels depending on correlation value r_{xy} : a – $r_{xy} > 0.2$; b – $r_{xy} > 0.6$; c – $r_{xy} > 0.8$; d – profile of synchrony for chosen subject: vertical axis – correlation values; horizontal axis – the nearby pairs of derivations ordered from left to right and from top to down according to its arrangement on a scalp.

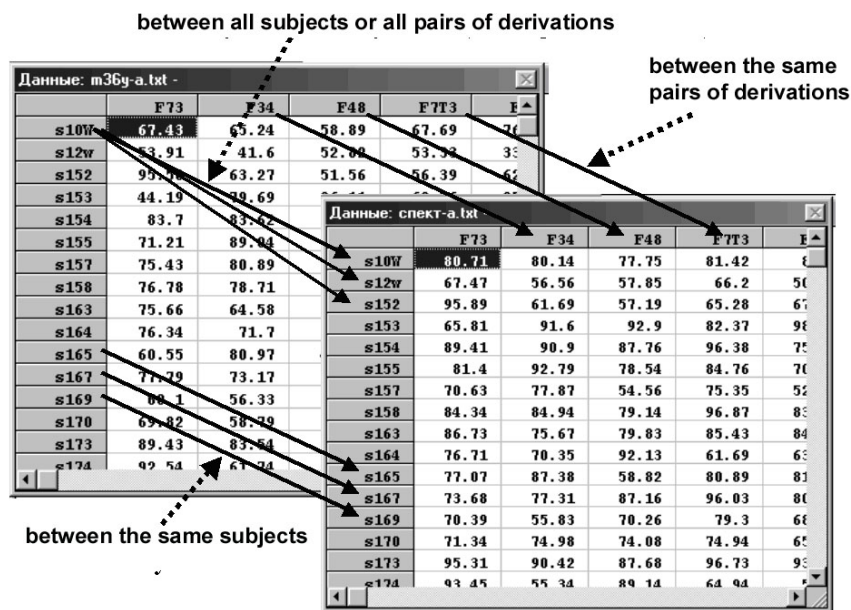


Figure 3. The example of two matrices with profiles of synchrony for two groups of subjects and three variants of its comparison.

3 Preliminary filtering of the signal in the selected frequency domain is preferably performed by the double FFT method, characterized by minimal amplitude and phase distortions compared to classical filters.

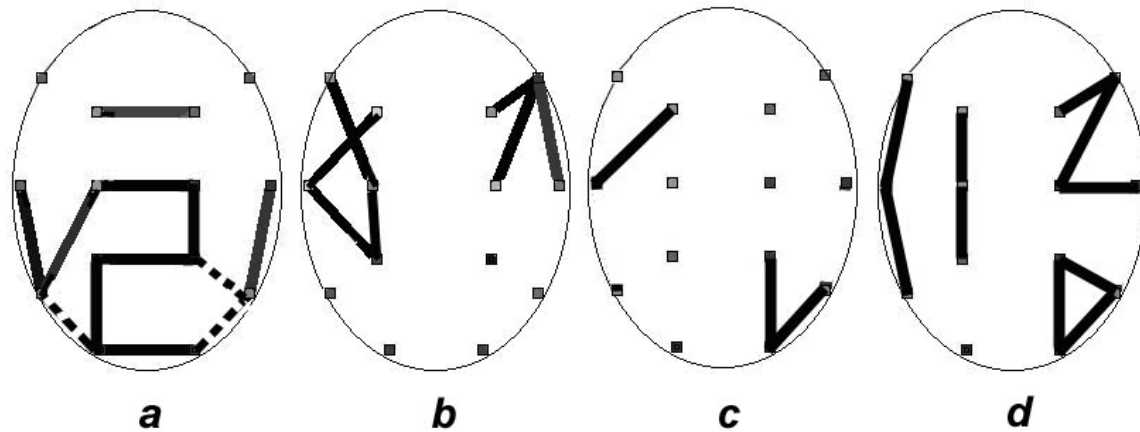


Figure 4. Differences in EEG synchrony of alpha domain among two groups of examinees: a — the differences between pairs of EEG-channels on significance level $p < 0.05$ (solid lines — more EEG-synchrony in the norm group, dotted lines — more EEG-synchrony in the schizophrenia group); b — statistically undistinguished pairs of EEG-channels on significance level $p > 0.6$; c — the differences between symmetric pairs of EEG channels (dominating pairs are shown) in norm group; d — the differences between symmetric pairs of EEG-channels in the schizophrenia group.

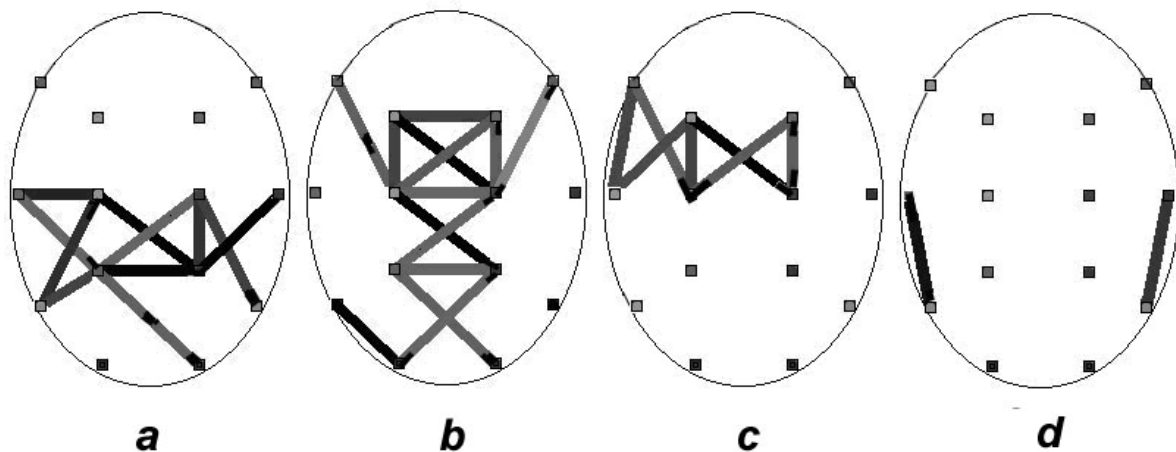


Figure 5. The pairs of EEG derivations which PS has preferential projections on the first (a, b) and second (c, d) of main factors for the norm (a, c) and schizophrenia (b, d) groups.

(Figure. 3): columns are pairs of derivations from the standard grid, rows are the subjects. Such matrices can be obtained: 1) for different time intervals of the same functional state; 2) for different functional states; 3) for different frequency ranges; 4) for different groups of subjects that differ in certain characteristics, etc. And such matrices in further directions of analysis can be compared in pairs (Figure. 3): 1) by the same pairs of derivations (by columns); 2) by the same subjects (by rows); 3) for all subjects, each with each; 4) for pairs of derivations each with each.

Methodology of the subsequent analysis

After calculating PS of two or more groups of subjects, it is necessary to identify and reliably statistically justify the existence of differences of interest to the researcher [8]. For individual pairwise comparisons, there are several options (Figure. 3). The similarity of the compared pairs is estimated by the correlation coefficients of Pearson, Spearman, Kendall, etc., and the differences are estimated by the parametric and nonparametric criteria of Student, Fisher, Wilcoxon, signs, Ansari Bradley, Klotz, Kolmogorov–Smirnov, etc. Thus, it is possible to identify completely different PS patterns characteristic of pathology

and norm groups (Figure. 4). Simultaneously, it should be remembered that with several paired comparisons at the same time, it is necessary to adjust the critical level of significance of null hypotheses using the Bonferroni correction.

Further, it is possible to study the difference and similarity of PS of each subject in different frequency domains and at different time intervals to assess the stability of the functional state. Here, according to the correlation coefficients r_{jj} between PS of each j -th subject in two adjacent frequency domains or on neighboring time intervals (Figure. 3), it is possible to make inter-individual comparisons and ranking of the subjects.

The next direction is the use of multidimensional statistical methods to identify intergroup differences. The differences of the matrices in the average PS values are estimated using the 2-ways ANOVA method.

The next step may be to use factor analysis for each matrix to identify PS, mainly projected on the principal factor axes. As follows from Fig. 5, these projections are fundamentally different for the norm and pathology groups. To quantify the differences, it is possible to calculate correlations between the factor loadings of PS for each factor performed between the

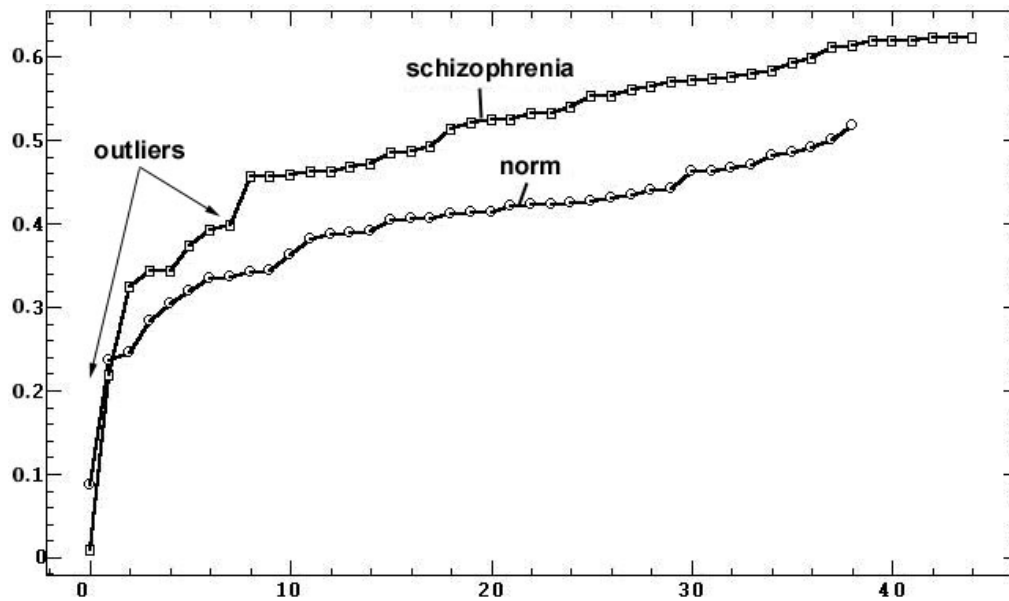


Figure 6. The diagram of the distribution of average correlation between PS of alpha domain in two groups of subjects: vertical axis — correlation values; horizontal axis — the subjects ordered on increase of average correlation.

two groups of subjects. As a result, the correlations for the three principal factors are obtained at a minimum of 0.106–0.328, which indicates a fundamental difference in factor structures and intergroup differences.

One of the most important methods is to use the discriminant analysis, which allows us to construct a classifying function for a statistically reliable and stable division of subjects into two analyzed groups. Such a function can be practically used to assign new individuals to a particular group, that is, as a means of preliminary medical or functional diagnostics.

Identification of highly consistency groups of subjects

One of the important statistical tasks is the identification and processing of outliers and the selection of homogeneous groups of subjects, which, unfortunately, are almost not taken into account in EEG studies. Such outliers are the result of the action of extraneous and accidental causes that can mask really existing patterns. Inattention to these issues may lead to the identification of pseudo-significant or pseudo-not-significant individual and intergroup differences.

Since in the method under consideration, we do not have samples of variable values, but PS are the sets of measurements, so we do not apply the usual method of detecting outliers by large deviations from the average value. Therefore, a special method of averaged correlations of PS was developed [8]. In this case, for each group, paired correlations r_{jk} between PS of all j, k -subjects are calculated at a given time interval. Then we get a square correlation matrix $|r_{jk}|$ by which the average value $Mj(r_{jk})$ from its correlation with all other k -th subjects is determined for each j -th subject. Then, using the obtained $Mj(r_{jk})$, variation series or Quetelet graphs are constructed (Figure. 6), on which subjects with low consistency or outliers are distinguished. They may be the result of uncontrolled features of current functional and mental state or errors in diagnosis. Therefore, they should be removed from further analysis.

Fig. 6 also shows a higher value of average consistency in pathology group $Mj(r_{jk})=0.505\pm 0.12$ in comparison with norm group $Mj(r_{jk})=0.397\pm 0.084$ with their significant difference at the significance level $p<0.00005$. This confirms a well-known rule: «every healthy person is healthy in his own way, but all the "sick" persons are sick in the same way». This is a real confirmation of the effectiveness and adequacy of the envelope correlations method.

Results of the method application

The described method of envelope correlations (MEC) was used to assess various mental diseases and functional states. EEG recordings were carried out in a state of relaxation with closed eyes according to 10–20% system of derivations.

Schizophrenia [8]

The material included adolescents aged 10–14 years: 39 schoolchildren without mental disorders (the control or norm group) and 45 patients with schizophrenic disorders in categories F20, F21, F25 according to ICD-10.

The following significant results were obtained: 1) numerous topographic patterns that are far from a random distribution (Figures. 2 and 5); 2) proximity of topographic patterns in neighboring frequency ranges (Figures. 7 and 8); 3) higher stability of functional state over time in the norm group; 4) higher interindividual consistency of pathology group (Figure. 6); 5) difference of pairs of derivations with high synchrony in the two groups of subjects (Fig. 8); 6) higher synchrony in the norm group (Figure. 7); 7) a consistent decrease in synchrony from the frontal interhemispheric connections to the occipital ones in both groups (Figure. 7); 8) a difference in topography of hemispheric dominance with its wider spatial representation in pathology group (Figure. 8); 9) a strong factor structure of PS in both groups with the predominance of four main factors; 10) a qualitative and quantitative difference in the factors acting in two groups (Figure. 5).

Further, the MEC results were compared with five other well-

known synchrony estimates in the literature: coherence [7], inter-segment synchrony [12], correlations between the frequency parts of amplitude and phase spectra [13] and between filtered EEG. According to the indicators of descriptive statistics, MEC differed favorably from other methods in terms of centering and uniformity of its values distribution in 0–1 region.

The discriminant classification gave the best results in θ , α , β_1 domains with 2–3% errors for each group compared to 5.5–28.2% errors when using other methods [14–17]. Statistical modeling showed that the resulting small percentage of MEC errors differs significantly from the random one at the significance level $p < 0.005$. Then, EEG measurements of amplitudes in derivations were added to the PS matrices, which led to 100% reliable, error-free classification.

To substantiate the practical significance of the results obtained, a control check was carried out. To do this, the pathology group was randomly divided into two ones in a ratio of 3:2 – the learning and classified samples. The discriminating function was calculated from learning sample, which was then used to assign to a particular group of classified subjects. Using of α domain and consistent subgroups of subjects gave the best result: 1.5% of errors in learning classification and 6.2% of errors in control classification. It should be noted that such important control checks have never been carried out anywhere and by anyone.

Schizophrenia [9]

The material included three groups of 8–15 years adolescents: 36 schoolboys without mental disorders (the norm N group), the group of 45 patients with the diagnosis of F20 schizophrenia, and the group of 80 patients with the diagnosis of F21 schizotypal disorder.

The results of the performed complex analysis reveal the complicated picture of regional, interhemispheric differences in EEG synchrony between two schizophrenic disorders and the norm. In particular, most of the patterns listed at the beginning of Section "Schizophrenia [8]" were confirmed.

It is necessary to emphasize, that in this study not only the usual problem of differentiation of norm and pathology was considered, but at the same time also the non-depicted earlier in literature more complex task of detection of subtle differences between the two close nosologies. The significant differences between F20 and F21 groups appear mainly in frontal and occipital areas in certain frequency domains. Besides, in occiput, interhemispheric and intrahemispheric synchrony for schizophrenia (F20) in some cases was closer to normal. In contrast, for schizotypal disorder (F21), intrahemispheric synchrony is higher than normal, but interhemispheric synchrony is below than normal. Certain relationships of this kind are also observed in parietal, temporal, and central areas.

One the distinctive and stable component of mental disorders in comparison with the norm is the presence of the vast areas of low synchrony separating isolated frontal and occipital intrahemispheric areas with synchrony near to normal level (Figure. 8). The presence of such a reduction and detection of right-sided asymmetry can indicate a substantial violations of interhemispheric and frontal-occipital relationships for the schizophrenic and schizotypal disorder, which fits into the framework of the well-known theory of disintegration of cortical electrical activity.

The intergroup comparison reveals the crosswise area of the sharp decrease in synchrony of pathology groups ("downfall") in

comparison with the norm, including sagittal-interhemispheric and axial-central segments (Figure. 8). It's possible that this indicates significant violations of interhemispheric and frontal-occipital relationships at disorders of the schizophrenic spectrum. When comparing of two pathology groups (F20–F21), in many frequency domains we also observe distinctive regional and interhemispheric areas of increase-decrease of synchrony.

Four psychometric tests were performed on all patients: volume of direct reproduction defined by the technique of memorization of 10 words under verbal presentation; volumes of simple and difficult paired associates; runtime of Schulte tables execution. Indeed, violation of cognitive functions is one of the main consequences of schizophrenia. Several high correlations between psychometric indicators and local estimates of synchrony for each of F20 and F21 groups were revealed.

The main results of discriminant classification are the following: 1) θ domain provides the lowest percentage of classification errors; 2) β_2 domain is the next one by its discriminant sensitivity; 3) association of PS of these two frequency domains gives the exact classification of three groups without any errors. The obtained results favorably differ from several alternative approaches using other indicators and more sophisticated methods – see in Section 7.1. It should also be emphasized, that the efficiency for classification of θ domain was also found in the previous study.

Numerous confirmations of the results of the previous study in different groups of patients indicate the stability and effectiveness of MEC compared to the above-mentioned randomness of the coherent analysis results.

Depression [10]

The material included two groups of older adults aged 49–82 years: 1) 11 men and 40 women with the psychogenically provoked depressive reaction of bereavement: category F43.21 according to ICD-10, HDRS=22±5.09 on Hamilton scale; 2) a control group of 18 men and 11 women without depressive disorders.

The results of the analysis revealed a complex picture of regional and interhemispheric differences in EEG synchrony between the norm and depressive deviations, including different ratios of greater-less or the same synchrony in activity of different cortical zones.

One of the principal features of the obtained integral picture is the presence of extended zones of sharply reduced synchrony of neurophysiological activation processes in depression, covering the entire premedial region in the forehead-occipital direction, including interhemispheric connections, as well as lateral fronto-temporal connections in both hemispheres. In the same time, a single topographic picture of changes in EEG synchrony during depression is reproduced in general terms in all frequency domains. This indicates a deep deprivation in depressions of frontal-occipital, frontal-temporal and interhemispheric interactions throughout in sagittal direction.

There is a general decrease in sagittal directions with signs of left-sided asymmetry. This indicates that greater activation of right hemisphere, which causes the predominance of negative emotions in depression, maybe enhanced with a greater discoordination of processes in the right hemisphere.

In addition, an increase in synchrony was revealed in several axially directed intrahemispheric pairs of derivations primarily in temporo-central and temporo-parietal ones. This

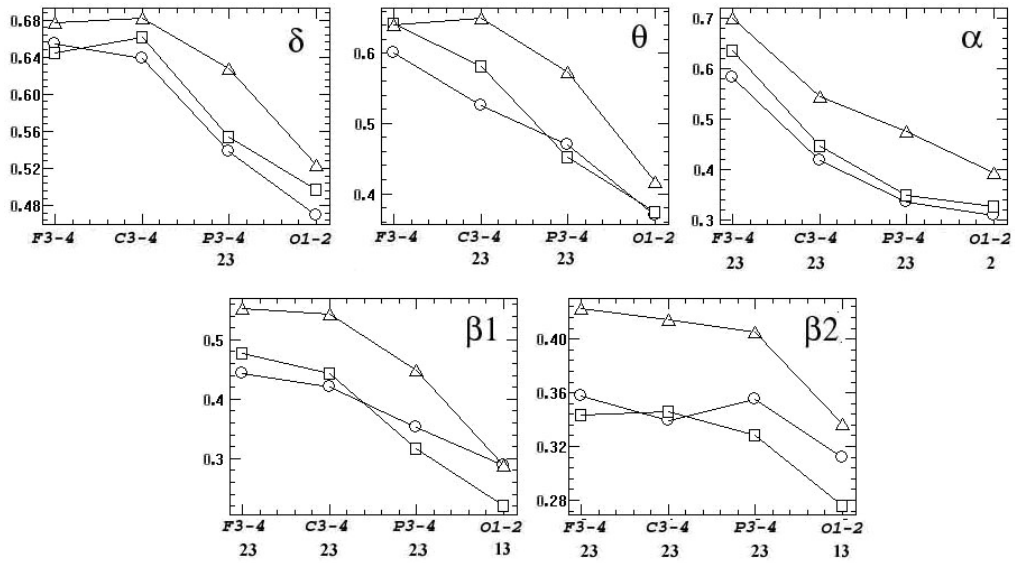


Figure 7. Differences in interhemispheric synchrony for five frequency domains ($p=0.04-0.0004$). The values averaged for each group, synchrony (vertical axes) are shown for derivation pairs: F3–F4, C3–C4, P3–P4, O1–O2 (horizontal axes). Group markers: circles – F20, squares – F21, triangles – N. Below graphics, the designation of reliable intergroup differences is shown in number notation: 1 – F20–F21, 2 – F20–N, 3 – F21–N

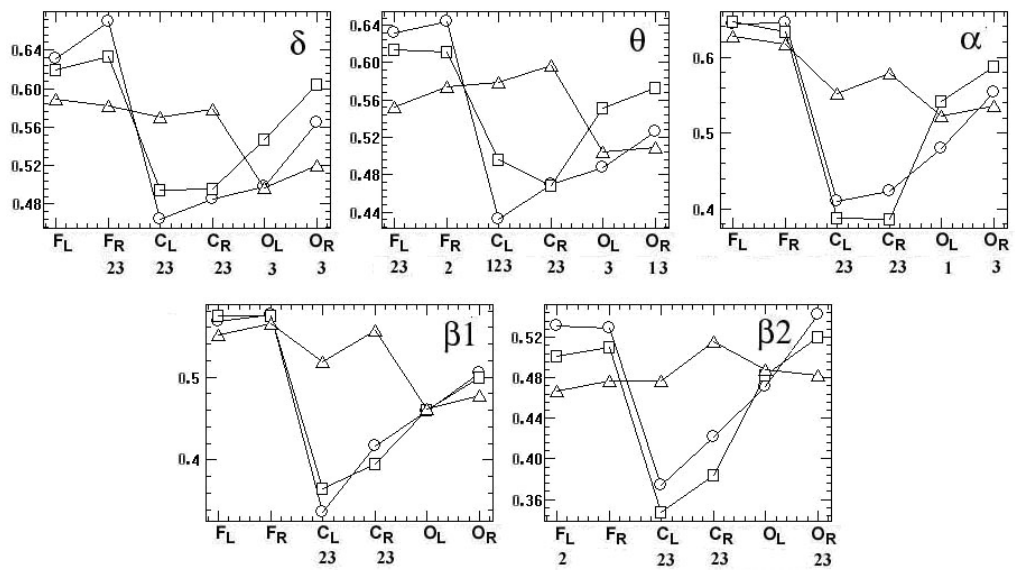


Figure 8. Regional intrahemispheric differences in frequency domains ($p=0.033*10^{-8}$). The averaged values of synchrony for each group (vertical) in order of regions (horizontal): FL, FR (frontal left and right), CL, CR (central left and right), OL, OR (occipital left, right)¹, other notations are similar to Figure. 7.

may indicate an increase in systemic coordination between auditory and somatosensory sensitivity in the primary projection areas and in the associative posterior temporal and parietal zones. On the other hand, a decrease in synchrony in sagittal anterior-posterior-temporal and central-parietal pairs of derivations may indicate a deprivation of systemic coordination between the processes in the areas of primary projection of the auditory and tactile analyzers and the associative processes of integrated perception of corresponding sensations. About the primary and associative visual areas, such synchronization-

desynchronization phenomena are not observed.

It should be particularly noted that a similar picture of differences in norm and pathology was also revealed in the study of schizophrenia, where there was also an extended interhemispheric and premedial-sagittal zone of decreased synchrony from the forehead to the back of the head with a compensatory increase in correlation synchrony in axially conjugated pairs of derivations. This indicates the similarity of changes in synchrony of neurophysiological activation processes in these two types of mental disorders.

⁴ e.g., FL region comprising the synchrony values between F7, F3, T3, C3 derivations; CL, region including synchrony between T3, C3, T5, P3; OL region including synchrony between T5, P3, O1, etc.

This similarity of changes looks even more convincing considering that the topography of correlation synchrony distribution in the group of healthy adolescents had significant differences from the group of healthy older adults. This suggests that MEC detects similar changes in different forms of pathology and in different age groups. This stability compares favorably with the heterogeneity of the results obtained when using coherence function in studies of depression and schizophrenia.

In discriminant classification, the use of δ , θ , β_2 frequency domains allows to accurately separate the records of two studied groups without any errors. Recall that θ , β_2 domains were also the best ones for classification of schizophrenia, which once again confirms the stability of MEC results. The only alternative classification of norm and depression using estimates of spectral power and coherence [18] was accompanied by 8.7% of errors.

Sleep stages [11]

The material included many hours of sleep recordings for 15 right-handed men aged 18–34. Seventy-five 20-second fragments were visually selected for each of 5 sleep stages W, 1, 2, 3/4, REM according to Rechtschaffen—Kale criteria. The five PS matrices calculated from these fragments were the source material for subsequent cross-analysis.

In addition to numerous particular regularities, the following significant results were obtained: 1) left-hemisphere dominance in all stages of sleep, which is natural for right-handed subjects and indicates the effectiveness of MEC; 2) the dominance of the frontal regions over the occipital ones; 3) differences in the synchrony ratios for sleep stages in different frequency domains; 4) differences in the patterns of synchrony changes in interhemispheric connections from the forehead to the occipital ones; 5) topographic features of localization of highly synchronous connections by sleep stages and frequency domains; 6) significant topographic difference of W stage from other stages; 7) close topography is observed: in θ domain for all stages; as well as in stages 2 and 3/4 for all frequency domains.

Discriminant classification with expanded data matrices, when amplitude indicators were added to PS matrices, revealed an average of 11% errors, and classification errors of individual stages were in the range of 3–20%. This is significantly better than the results of four similar publications using other methods, where the classification errors of various stages were 5–42% [19–22].

Additionally, a control check was performed when the records of each sleep stage were divided into two groups in the ratio of 80 to 20% – a learning and a classified sample. The number of classification errors of the learning sample was 7%, and the attribution errors of the classified sample were 18.3%. This seems to be a completely acceptable result, which is absent in other publications.

Conclusion

The results presented exhaustively and comprehensively substantiate the thesis formulated in the title of the article.

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