J Exp Integr Med 2013; 3(4):x-x **ISSN: 1309-4572**

GESDAV

Journal of Experimental and Integrative Medicine

available at www.scopemed.org

Original Article

Differentiation of norm and disorders of schizophrenic spectrum by analysis of EEG correlation synchrony

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Received May 7, 2013
Accepted July 6, 2013

Published Online September 18, 2013

DOI 10.5455/jeim.060713.or.081

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Key Words
Discriminant classification;
Electroencephalography;
Envelope correlation;
Schizophrenia;
Schizotypal disorder

Abstract
Objectives: Experimental work was designed to find the integrated differences in electroencephalography (EEG) synchrony between normal people and patients with disorders of schizophrenic spectrum.
Methods: In this study EEG recording have been performed in a state of quiet wakefulness with eyes closed for three groups of 8-15 years old adolescents: normal group and two groups of mental disorders in nosological categories F20 and F21 according to International Classification of Diseases (ICD)-10. We have used the alternative method for EEG synchrony estimating based on correlation between envelopes of EEG signals. This method was previously proven as a highly sensitive tool of differentiation of psychopathological and functional states.
Results: As a result of research, the complex picture of significant topographical, inter-hemispheric, regional and age distinctions was revealed, in which many of fragmentary results previously received by other researchers found their confirmation. One of the basic features of the received integrated picture of pathology is existence of extended zones of sharply lowered EEG synchrony dividing local and isolated areas in frontal and occipital regions mainly of normal or sometimes increased EEG synchrony. The received results completely fit into the framework of the theory of disintegration of cortical electric activity in cases of disorders of schizophrenic spectrum.
Conclusion: The used method provides close to 100% reliability of tripartite classification of norm and two pathology groups separately, it allows revelation of many authentic correlations between EEG synchrony estimations and psychometric indices, its results are consistently reproducible for different groups of patients and examinees, which opens up opportunities and prospects for its use as an auxiliary quantitative differential indicator.

INTRODUCTION

Among numerous papers devoted to electroencephalography (EEG) differences between norm and schizophrenia, relatively few studies relate to differences in EEG synchrony in a state of quiet wakefulness as it follows from the special review [1]. However, classificatory sensitivity of EEG synchrony estimations is significantly higher compared with amplitude spectrum [2-4], power spectrum [1] and some other measures [4]. To a large extent this is determined by the fact that estimates of EEG synchrony have a significantly lower intra-individual variability, which according to our data obtained at different experimental material and estimated by variation coefficient is 8-12 against 23-41% for average amplitude spectrum and against 86-95% for power spectrum. So by EEG synchrony estimations it is possible to receive reliability of comparable distinctions at smaller sample volumes and reliability of smaller distinctions under comparable sample volumes.

Results obtained by different researchers are rather fragmentary and contradictory, that was noted in the discussion [5]. Some researchers have found that compared with the norm at schizophrenia a coherence is lower, namely: ***(a)*** intra- and inter-hemispheric coherence in all domains [6]; ***(b)*** violated left hemispheric *F-T* connections [7]; ***(c)*** a coherence in delta (δ) and theta (θ) domains at *Fp1-F7* derivations and in alpha (α) domain at *F7-F8* [8]; ***(d)*** a coherence in δ domain in temporal lobe [9]. Other studies on the contrary have shown that for schizophrenia compared with the norm a coherence is higher, namely: ***(a)*** intra- and inter-hemispheric one in θ domain and intra-hemispheric one in α domain [10]; ***(b)*** inter-hemispheric one in δ and beta (β) domains at *O1-O2* and in δ domain at *T5-T6* [11]; ***(c)*** intra-hemispheric one in general [12] or only in δ domain [13]. It is significant that most of the cited works were published about ten and more years ago. Probably, such a situation is caused by the fact that coherence function is unstable indicator of EEG synchrony [14-17]. The observed inconsistency of results makes it actual to use alternative approaches for the evaluation of EEG synchrony in this field.

MATERIALS AND METHODS

EEG recording was carried out in a state of quiet wakefulness with eyes closed. The electrodes were placed according to 10-20% system in 16 cortex areas (*O1, O2, P3, P4, C3, C4, F3, F4, T5, T6, T3, T4, F7 and F8*); united ears electrodes were used as referents (*A1+A2*); the bandwidth was 0.5-35 Hz; sampling rate was 200 Hz. For the analysis we selected the fragments free of artifacts with a duration of 41 seconds (8196 discrete time slots). The analysis was carried out in five standard frequency domains: δ 0.5-4 Hz, θ 4-8 Hz, α 8-13 Hz, β-1 13-20 Hz, β-2 20-32 Hz.

The group of patients with disorders of schizophrenic spectrum was diagnosed according to International Classification of Diseases (ICD)-10 in Mental Health Research Center, Moscow and it consisted of 125 boys (8-15 years old). For 45 of them (age 11.5 ± 2.2 years), the diagnosis made was schizophrenia, childish type (F20), and for 80 adolescents (age 11.9 ± 2.5 years) schizotypal disorder (F21). Control group (N, norm) included 36 pupils from Moscow's schools without documented mental deviations (age 12.2 ± 2 years). Parents of all examinees gave the written permission for carrying out researches and publication of their results.

In this study we used the alternative approach to similarity estimation between bioelectric activity of different cerebral areas: the analysis of EEG correlation synchrony (ACS) was proposed and detailed previously [4]. It estimates the degree of EEG synchrony by correlation coefficient between envelopes of EEG records preliminary filtered in a given frequency range. Here it is appropriate to emphasize that as an envelope representing a change of EEG amplitude modulation, the synchrony estimation constructed on its basis has the direct and important physiological sense (unlike coherence). Indeed, the EEG amplitude increases with increase of synchrony of postsynaptic potentials, so the correlation of EEG envelopes estimates the degree of synchrony in change of such intra-neuronal synchronism.

An ordered sequence of such correlations between nearby derivations (in our case, between 36 EEG derivation pairs) have been named 'profile of synchrony' (PS) and such profiles as topographic patterns of EEG synchrony (for group of subjects we have an array or a matrix of profiles) are the source material for the further analysis. This method has already demonstrated its high efficiency for a similar problem [4] as well as for differentiation of night sleep stages, *i.e.* functional states [3].

Below for evaluation of pairwise sample differences we use the nonparametric Wilcoxon test since a large part of sample distributions differs from normal law. For evaluation of group differences we also apply the two-way analysis of variance (ANOVA) with repeated measures design (number of repeated measures is equal to number of subjects in compared groups). We also use the designations of groups: F20, F21, N and the designation of frequency domains: δ, θ, α, β-1, β-2.

RESULTS

Analysis of records on consistency

In any statistical sample due to influence of casual, uncontrolled in experiment factors there are outliers, and also among measurements there are more consistent and less consistent ones. For reliable separation of prevailing parities it is desirable preliminary to clear samples from outliers as well as from less consistent measurements. In our case, a role of random factors can be acted by: ***(1)*** instrumental factors such as differences in position of electrodes concerning anatomic cortex structures, changes in inter-electrode resistance, *etc*; ***(2)*** personal factors such as differences in individual EEG characteristics, differences in current physiological and psychological state, *etc*; ***(3)*** classifying factors such as patients belonging to nosology not differentiated or not clearly differentiated in ICD-10 [18], subjective judgments of psychiatrists, *etc*. Therefore, in each of two groups of patients it is desirable to get rid of influence of such extraneous casual factors by extracting among each of groups a central compact "kernel" of highly consistent measurements. In connection with the representative statistical volume of available samples, such selection of compact "kernel" is considered to be possible to perform.

For this purpose we used the method, which was proposed previously [4] and showed its effectiveness for a similar task as well as for differentiation of

 DOI 10.5455/jeim.060713.or.081

functional states [3]. Its essence is calculation of the average correlation of PS of each subject with profiles of synchrony of all other subjects. This average correlation estimates the average personal consistency of topographic distribution of EEG synchrony on scalp. As a result, a growing sequence of such estimates (rank-ordered sample) is formed. Using this chart we select subjects, averaged correlations of which exceed 0.4-0.5 and number of which is not less than 50% of original sample.

Since our analysis is carried out in 5 frequency domains, in order to perform the abovementioned selection, the estimates should be used that averaged over 5 domains. In the variational series for F20 and F21 groups (Fig.1a) we can see the presence of outliers and of several subgroups of different degree of consistency. Fig.1b presents variational series of highly consistency subgroups of F20, F21 and N subjects. The fact draws the attention that N subgroup is characterized by less averaged consistency (0.5) compared with F20 and F21 subgroups (0.52 and 0.55, respeptively). This confirms the conclusion [15] that a sample from a less representative general population related to a particular type of pathology turns out to be more consistent than a sample from a much larger population related to psychological norm, or in other words according to winged expression: every "healthy" man is healthy in its own way but every "sick" one is sick alike.

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 nosology. Such a formulation of the task proves advisability and necessity for the following analysis of use of the highly consistent EEG records (Fig.1b): ***(1)*** F20 subgroup included 23 patients in age of 11.2 ± 2.1; ***(2)*** F21 subgroup included 41 patients, in age of 12.2 ± 2. As anyone can see, the selected subgroups reproduce the age ratio of initial groups in a well-balanced way, and on this basis they are also quite suitable for the further analysis.

In a case of larger volume of experimental data the second stage could be completed of the source material purification, which consists in removal of records, synchrony profiles of which contain two or more values exceeding three standard deviations. A simple statistical calculation shows that probability of occurrence of such a "complex" outlier among 36 variables of synchrony profile is 0.054.

Discriminant classification

The results of some our researches, in particular [3, 4], have shown that linear discriminant classification of groups of subjects corresponding to different nosology, therapeutic treatment, functional states, social, age and sexual categories is the effective primary indicator of prospectivity of a further research. If such a classification of originally specified groups gives a significant number of errors (over 20-30%), then such groups are slightly differing by their EEG indicators or are strongly internally heterogeneous, and if so further detailed analysis of their differences is as a rule unproductive.

The results of the classification are given in Table 1. Let us note the following: ***(1)*** θ domain provides the lowest (on average) percentage of classification errors, which confirms the previous results [4]; ***(2)*** β-2 domain is the next one by its discriminant sensitivity; ***(3)*** association of indicators of these two frequency domains gives the exact classification of three groups; ***(4)*** presence of small errors of classification shows that: ***(a)*** the performed selection of subjects assured sufficient consistency of each pathology group; ***(b)*** a detailed analysis of intergroup differences promises fruitful results.

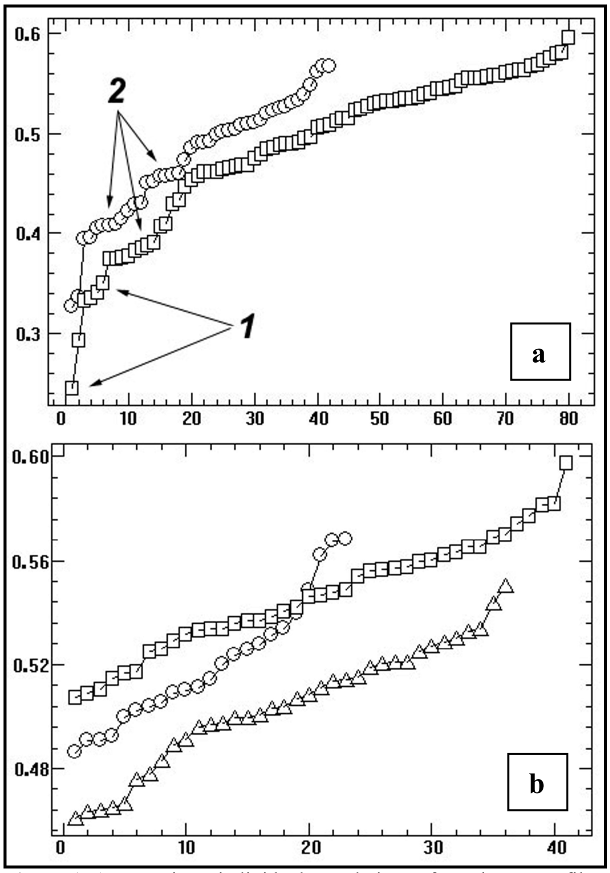

Figure 1. Average inter-individual correlations of synchrony profiles of EEG records **(vertical)** in its ascending order **(horizontal)**: **(a)** all records of F20 and F21 groups; circles, F20 group; squares, F21 group; **(b)** highly consistent records of F20 and F21 groups, and all records; triangles, N group; ***(1)*** outliers, ***(2)*** less harmonized subgroups.

Table 1. Errors of discriminant classification (in percentage) between the norm and the pathology (F20 + F21 ↔ N) and between two pathology categories (F20 ↔ F21) depending on a frequency domain

Frequency domain	$F20_m + F21_m \leftrightarrow N_m$	$F20_m \leftrightarrow F21_m$	Mean value
δ	4	7	5.5
θ	4	3	3.5
α	2	10	6
β-1	3	10	6.5
β-2	1	9	5
θ + β-2	0	0	0
Mean value	2.3	6.5	

The obtained results favorably differ from a number of alternative approaches using other indicators and more sophisticated methods for classification by normal and schizophrenic patterns of EEG, where the number of errors makes: 23% [19], 12.5% [20], 5.5-13.5% [21], 25-28.2% [22], 18.6% [23]. Only in the study by Kaplan *et al* [24] the accuracy of classification has been achieved close to 100%, however, the revealed there set of rules was able to achieve a unidirectional separation of schizophrenia from the norm, but not vice versa.

It is also interesting to compare these results with discrimination by usage of spectral estimations. Let's restrict ourselves to θ domain which is the best one for minimizing errors. The usage of spectrum amplitude averaged in frequency domain [mcV] gives **'(9 + 25) / 2 = 17%'** classification errors in average (9%, 25% and 17% correspond to three columns of Table 1); a usage of averaged power estimates [mcV^2] gives **'(15 + 29) / 2 = 22%'** errors; the logarithm of power [$2\log(mcV^2)$] often used in studies gives **'(10 + 22) / 2 = 16%'** errors. This once again confirms the above given conclusion on the higher discriminating sensitivity of EEG synchrony estimates.

Local relations of synchrony

In order to determine directions and prospects for further analysis it is necessary, first of all, to examine the overall detailed picture of relations of EEG synchrony between normal and pathological groups. For each of three groups we compute the average values of synchrony in each derivation pair and scrutinize intergroup ratios of greater/lesser synchrony (Figs.2&3)

At the topograms in Figs.2&3, first of all, our attention is drawn to the crosswise area of sharp decrease in synchrony of pathology groups ("downfall") in comparison with the norm, including sagittal inter-hemispheric and axial-central segments. It's possible that this indicates significant violations of inter-

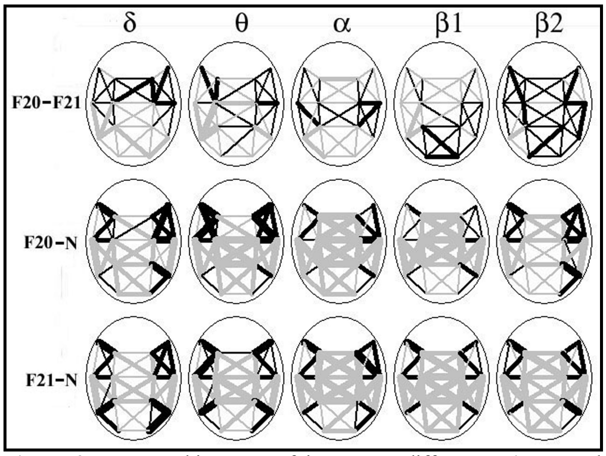

Figure 2. Topographic maps of intergroup differences (compared groups are designated at the left) in averaged synchrony for all derivation pairs in 5 frequency domains (specified at top). **Black lines** specify the more high synchrony in the first of two compared groups; **gray lines**, the smaller synchrony; **three gradation of lines thickness** specify the absolute difference in averaged synchrony (ΔS) between two compared groups as it increases: $\Delta S < 0.05$; $\Delta S < 0.1$; $\Delta S > 0.1$.

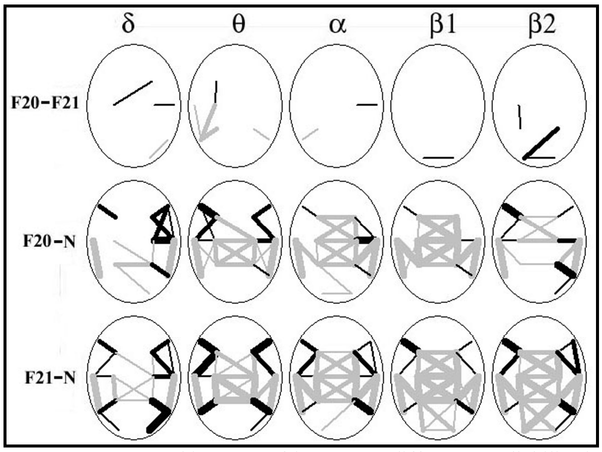

Figure 3. Topographic maps of intergroup differences reliability in averaged synchrony for derivation pairs in 5 frequency domains. **Three gradation of lines thickness** specify the significant level of null hypothesis: $0.01 < P < 0.05$; $P < 0.01$; $P < 0.001$. Other notations are similar to Fig.2.

hemispheric and frontal-occipital relationships at disorders of schizophrenic spectrum. At comparison of two pathology groups (F20-F21), in many frequency domains, we also observe distinctive regional and inter-hemispheric areas of increase/decrease of synchrony.

Due to observed regional structure of intergroup synchrony relations with a purpose of identification of statistically significant patterns it is more appropriate now to consider separately inter-hemispheric and averaged regional intra-hemispheric ratios.

Interhemispheric synchrony

For each group and each frequency domain there were calculated average values of synchrony between

 DOI 10.5455/jeim.060713.or.081

derivations *F3-F4, C3-C4, P3-P4* and *O1-O2*. The results are presented in Fig.4. From comparison of the charts and the statistical distinctions, first of all, it should be noted that;

(1) In most cases, there can be observed a reduction of synchrony in **'center → vertex → occiput'** direction. Jonckhreere test, which takes an orientation of factor effect into account, reveals the existence of such trends at P = 0.03-10^{-7} for all groups and domains (except for F20 group in β-2 domain). The reduction of synchrony in **'front → center'** direction is observed for all groups in α domain (P = 0.0002-10^{-7}) and for pathology groups also in θ domain (P = 0.016-0.0012). This conclusion coincides with the results of Borisov *et al* [5].

(2) In most cases (68% from 40 comparisons, P = 0.04-0.0004) there is observed the higher synchrony in N group in relation to F20 and F21 groups, and in 23% cases this ratio is manifested in a form of trend of mean values. This conclusion coincides with the results of Borisov *et al* [5] and Strelets *et al* [6] being opposite to some fragmentary conclusions [10, 11]; the latter ones however are distinguished by statistically small volumes of samples included 8 and 11 patients.

(3) Local differences between F20 and F21groups are observed only in *O1-O2* occipital pair in β-1 (ð = 0.04) and β-2 (ð = 0.03) domains, and in both cases, the synchrony values for F20 group do not differ from the norm (ð = 0.46), but for F21 group these values are significantly lower (P = 0.043).

(4) However, in Fig.4 for F20 and F21 groups in sagittal neighboring derivation pairs we see systematic differences between them that the analysis of variance allows to reveal when the second factor is regional one (2 factor gradations): ***(a)*** increase of synchrony in F21 group (with the convergence to the norm) in *F-C* region in θ domain (P = 0.00005); ***(b)*** increase of synchrony in F20 group (with the convergence to the norm) in *F-C* region in β-1 (P = 0.00001) and β-2 (P = 0.004) domains.

(5) For differences between front-occiput regional synchrony (*F-O*) there is only one distinction between F20 and F21 groups in β-1 domain (P = 0.01)

Regional intra-hemispheric differences

For each group and for each frequency domain there were calculated average values of synchrony for six regions: for the left and right frontal regions (F_L and F_R, respectively) comprising the values of synchrony between *F7*, *F3*, *T3*, *C3* and *F8*, *F4*, *C4*, *T4* derivations; for the left and right central ones (C_L and C_R) including synchrony between *T3*, *C3*, *T5*, *P3* and *C4*, *T4*, *P4*, *T6* derivations; for left and right occipital ones (O_L and O_R) including synchrony between *T5*, *P3*, *O1* and *P4*, *T6*, *O2* derivations. The results are presented in Fig.5.

From comparison of the charts and shown statistical differences, first of all, it should be noted that;

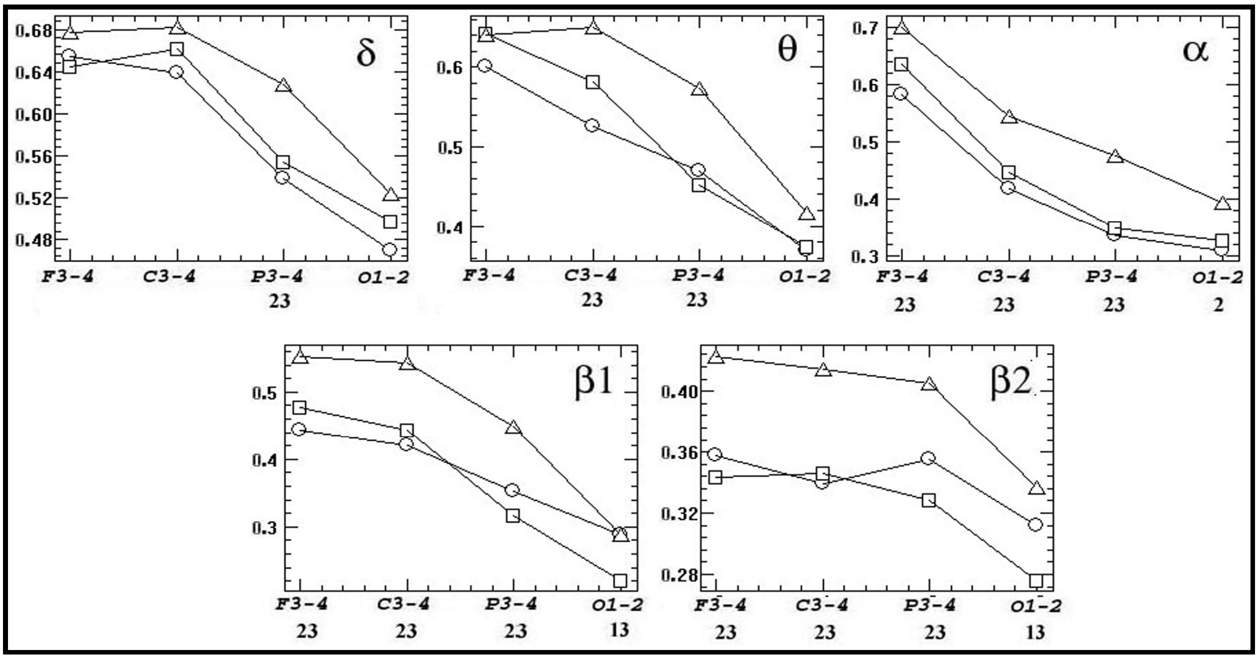

Figure 4. Differences in inter-hemispheric synchrony for 5 frequency domains (P = 0.04-0.0004). The values averaged for each group synchrony (vertical axes) are shown for derivation pairs: *F3-F4, C3-C4, P3-P4* and *O1-O2* (horizontal axes). **Group markers**: **circles**, F20; **squares**, F21; **triangles**, N. **Below graphics**, the designation of reliable intergroup differences is shown in number notation: **1**, F20-F21; **2**, F20-N; **3**, F21-N.

(1) In N group there is observed: ***(a)*** approximate equality of synchrony in frontal-central F_L, F_R, C_L, C_R regions (except its decrease in α domain, P = 0.02-0.0007); ***(b)*** reduction of synchrony in the occipital O_L, O_R area ($P = 0.048\text{-}10^{-5}$, except β-2 domain).

(2) In F20 and F21 groups it is observed a sharp decrease of synchrony in central region compared with frontal and occipital ones. In most cases the differences between F_L-C_L, F_R-C_R, C_L-O_L, C_R-O_R manifest itself with high confidence (76% reliable differences from 50 comparisons, $P = 0.033\text{-}10^{-8}$).

(3) Synchrony in N group compared with F20 and F21 groups is as follows: ***(a)*** it is significantly higher in central region (95% reliable differences from 20 comparisons, $P = 0.01\text{-}10^{-7}$), which coincides with the results of Borisov *et al* [5], Strelets *et al* [6] and Winterer *et al* [9]; ***(b)*** in some cases it is lower in frontal and occipital regions (30% reliable differences from 40 comparisons, P = 0.049-0.001), which partially coincides with the results of Mann *et al* [12], Merrin *et al* [10], Strelets *et al* [6] and Wada *et al* [13].

(4) Local intraregional differences between F20 and F21 groups are detected in C_L and O_R regions in θ domain (P = 0.04) and in O_L region in α domain (P = 0.047). Additionally, in Fig.5, the macro regional intergroup differences (for both hemispheres) are also observed, and analysis of variance allows to reveal those differences in case that as a second factor we use left and right regions: ***(a)*** reduction of synchrony in F20 group in occipital O_L-O_R area in δ (P = 0.007), θ ($P = 10^{-6}$) and α (P = 0.0002) domains with its convergence to the norm and increase of synchrony in central C_L-C_R area in β-2 domain (P = 0.008); ***(b)*** reduction of synchrony in F21 group in frontal F_L-F_R area in β-2 domain (P = 0.004) with its convergence to the norm.

(5) Comparing of the difference between frontal synchrony and occipital one reveals differences between F20 and F21 groups in δ domain for F_R-O_R remainder (P = 0.03) and for remainders between F_L-O_L (P = 0.02) and F_R-O_R (P = 0.03) regions in θ domain.

Regional asymmetry

Visually, in Fig.5 we can note some signs of right-sided asymmetry; most distinctly they appeared in F20 and F21 groups. Statistical comparison of mean values for left and right regions reveals the presence of right-sided asymmetry (P = 0.048-0.007) in occipital O_L-O_R area for F20 group in δ, α and β-2 domains and for F21 group in α, β-1 and β-2 domains, and also in central C_L-C_R area for F20 and N groups in β-1 domain. Differences in asymmetry coefficient calculated by the formula **'(L x R) / (L + R)'** are detected in central C_L-C_R area in θ domain (P = 0.035-0.018) between F20 and N groups and between F20 and F21 groups.

On the one hand, these asymmetries are not that numerous so to indicate a general pattern; on the other hand, no case of asymmetry is revealed in N group.

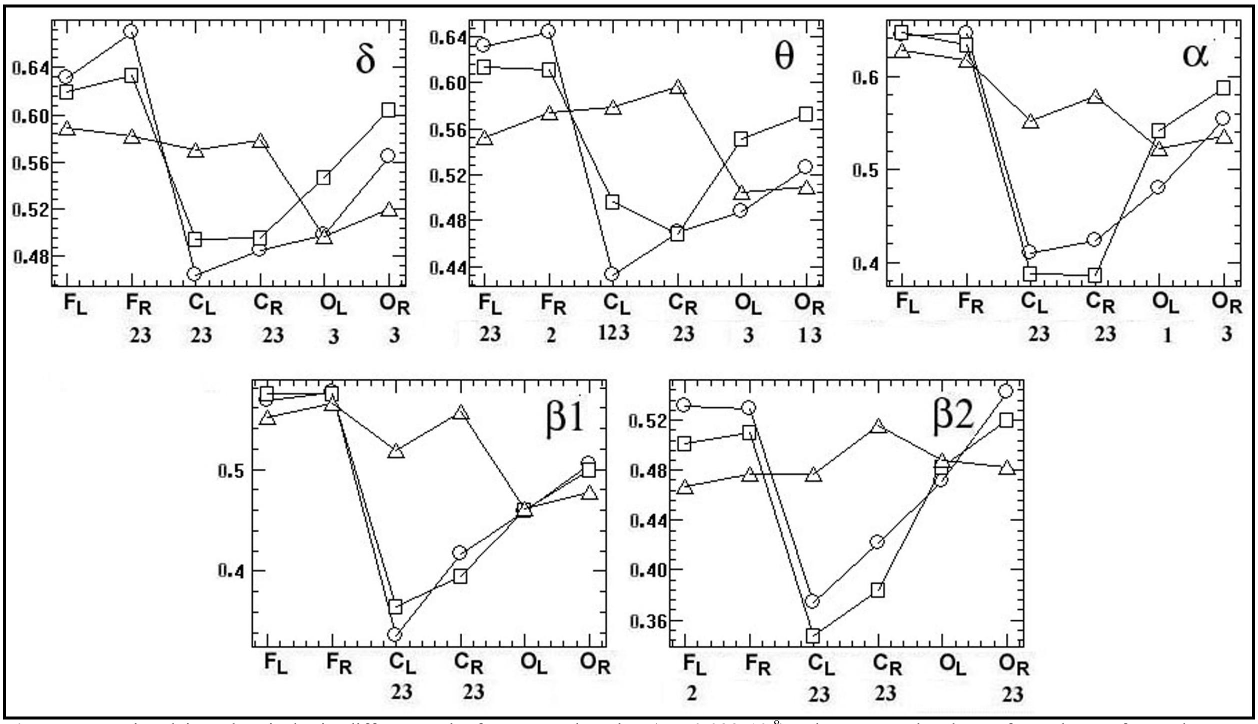

Figure 5. Regional intra-hemispheric differences in frequency domains ($P = 0.033\text{-}10^{-8}$). The averaged values of synchrony for each group (vertical) in order of regions (horizontal): F_L, F_R (frontal left and right), C_L, C_R (central left and right), C_L, C_R (occipital left, right); other notations are similar to Fig.4.

 DOI 10.5455/jeim.060713.or.081

Age and sex differences

In order to identify age-related differences we divide each group into two subgroups in age ranges of 8-11 and 12-15 years (the respective number of subgroups is 16 and 7 boys for F20 category, 16 and 20 boys for F21, category and 22 and 19 boys for N category). Now let's make a comparison of these subgroups. The results are presented in Table 2, from a consideration of which we can make the following conclusions:

(1) In all detected cases, the differences are associated with an increase in synchrony with age, and this indicates a presence of systematic tendency;

(2) Intraregional changes of synchrony are most representative in N group and intra-hemispheric ones in F20 group;

(3) In a case of the pair comparison of three N, F20, F21 groups, the most of changes in synchrony topographically do not coincide, except for following cases: in α domain in F_R region for N, F21 groups, in β-1 and β-2 domains in C_L region for N, F20 groups, in α domains for *C3-C4* derivation pair for F20, F21 groups and for *P3-P4* derivation pair for N, F20 groups;

(4) If we compare the results of Table 2 with the charts at Figs.4&5, then the convergence of EEG synchrony with the age to the norm is observed in pathology groups in inter-hemispheric connections predominantly in α domain, whereas as for relative intra-hemispheric relations, the situation is reversed: in C_R region differences increase and in F_L, F_R, O_R regions the higher synchrony observations are leveled in pathology groups in relation to norm.

Revealed age differences may indicate an identification feasibility of the differences between norm and pathology within specific age categories in a case of presence of much more voluminous experimental material.

The scope of this article do not allow to consider our available results of analysis of female adolescents, topography of distribution of EEG synchrony of which in control and pathology groups has a number of significant local differences and yet maintains the marked phenomenon of cross–shaped "downfall" in EEG synchrony at pathology. However, it certainly indicates that such studies should be performed with taking the gender into account.

Comparison with psychometric measures

For assessment of cognitive functions of patients, violation of which is one of the main consequences of schizophrenia, the following four psychometric indices were used:

Volume of direct reproduction (VDR); defined by the technique of memorization of 10 words under verbal presentation (developed by A.R. Luria in 1962). This technique is intended to assess the status of voluntary verbal memory, fatigue, activity of attention, storing, preservation, reproduction, voluntary attention, *etc*.

Volume of simple and difficult paired associates (VSA, VDA)/paired-associates learning (PAL); this technique is intended to study the memory and memory processes;

Runtime of Schulte tables execution (TS); this technique is applied to research a rate of sensorimotor reactions and characteristics of attention, level of intellectual working capacity.

Table 2. Authentic age changes in intra-hemispheric and inter-hemispheric EEG synchrony in frequency domains δ, θ, α, β-1 and β-2. Remainders are represented between average values of synchrony in subgroups of 8-11 and 12-15 years old; the significance values are shown in brackets.

Group	Localization	δ	θ	α	β-1	β-2
F20	F_R				0.13 (0.01)	0.14 (0.01)
F21	F_L			0.1 (0.005)		
F21	C_R			0.07 (0.01)		
N	F_L	0.09 (0.02)	0.11 (0.001)	0.09 (0.02)		
N	F_R	0.1 (0.01)	0.1 (0.004)	0.12 (0.001)	0.05 (0.04)	0.07 (0.01)
N	C_R	0.1 (0.01)	0.07 (0.02)	0.09 (0.03)	0.06 (0.02)	0.08 (0.01)
N	O_R	0.1 (0.006)			0.09 (0.002)	0.08 (0.01)
F20	*F3-F4*				0.13 (0.03)	0.1 (0.01)
F20	*C3-C4*			0.15 (0.047)		0.08 (0.04)
F20	*P3-P4*		0.1 (0.04)	0.17 (0.02)		
F20	*O1-O2*	0.16 (0.02)				
F21	*F3-F4*			0.1 (0.01)		
F21	*C3-C4*			0.11 (0.04)		
F21	*O1-O2*			0.12 (0.006)		
N	*P3-P4*			0.1 (0.01)		

Between these indices for both groups of patients there were found no significant correlations (except VDA and TS, P = 0.49), which indicates that there is no strong functional dependencies between those indices for analyzed samples of patients.

The proximity of estimates of EEG synchrony to psychometric indices was assessed by Pearson correlation coefficient *r* critical value of which for those samples is $r_{cr} < 0.31$ at P = 0.05. Fig.6 shows the identified significant correlations with local estimates of EEG synchrony between derivation pairs in the range of average and above average correlation values ($r = 0.45$-0.75, P = 0.03-0.008). In addition, it is interesting to calculate correlations with the average estimates of regional intra-hemispheric synchronities as well as of differences between them that characterize the magnitude of decrease of EEG synchrony in C_L, C_R regions in relation to neighboring F_L, F_R, O_R, O_L regions. These correlations are presented in Table 3. The received results allow making the following conclusions:

(1) The greatest number of significant correlations with the psychometric indices is revealed for F20 group (25 *vs* 9 for F21 group); it is quite consistent with the fact that for schizophrenia category (F20) the violations of cognitive processes estimated by these psychometric indices are more expressed.

(2) The greatest number of significant correlations belongs to "downfall" of synchrony for pathology groups in central axial area and to its remainders with with neighboring regions: 19 significant correlations against 11 for other areas and derivation pairs.

(3) In rank-order of total numbers of significant correlations, the frequency domains are ranked as follows: β-2 = 11, θ = 9, α = 9, δ = 4 and β-1 = 4 correlations. With respect to local correlations (Fig.6) β-2 and θ domains have the obvious advantage as well as in a case of discriminant classification; the leading place of β-2 domain can be determined by its greater relationship with cognitive activity.

(4) In rank-order of significant correlations, the psychometric indicators are ranged as follows: VDA = 13, VSA = 11, TS = 10 and VDR = 8 correlations. According to average value of correlations, the TS index has a considerable advantage ($r = 0.7$) in comparison with VDR (0.49), VSA (0.48) and VDA (0.5). The last would seem to indicate that in F20 group (which shows the most number of correlation), the features of attention and mental performance are more vulnerable compared with the capabilities of memorizing and reminiscence

(5) Signs of correlations for VDA, VSA are opposite to ones for TS, which corresponds to their psychometric ratio.

(6) In high-frequency domains (β-1, β-2) compared with mid-frequency domains (θ, α), in most cases there are inversion of signs of correlations, which can be a result of opposite relationship between the activity of these domains and the cognitive abilities.

Let us note that in recent years we can see an increasing interest of researchers to comparison of different estimates of EEG synchrony on one hand and psychometric and syndromic indicators of schizophrenic spectrum disorders on the other hand. These studies reveal the following significant correlations: 0.36-0.52 [25], 0.27-0.39 [26], 0.37-0.82 [27] for a small group of 14 patients, 0.37-0.55 [28], 0.38-0.49 [29]. In this comparison, the numerous received by us significant correlations between EEG synchrony estimates and psychometric indices in a range of 0.45-0.75 look rather perspective.

Reproducibility of results

In order to test the stability of our results obtained on the basis of the here stated methodology, we analyzed another EEG data which has been recorded in 2001-2004 and discussed earlier [5]. Two groups of male adolescents 10-12 years old include: F20 group of 18 patients (in age range of 12.1 ± 0.93) and control group of 25 pupils (in age range of 12.1 ± 0.53). The results turned out to be similar to Figs.4&5; they are shown in

Table 3. Correlations between psychometric measures with intra-hemispheric regional synchrony and with remainders between regional synchrony for frequency domains δ, θ, α, β-1 and β-2.

Indice	δ	θ	α	β-1	β-2
VDR		-0.41 F_R-C_R	-0.53 F_R -0.50 F_R-C_R		
VSA			-0.50 F_R-C_R		
VDA	-0.47 O_L-C_L	-0.43 F_R-C_R		-0.54 O_L-C_L	-0.47 O_R-C_R
TS	-0.56 C_L -0.47 C_R		-0.52 F_R -0.57 C_L -0.49 C_R +0.48 O_R-C_R		

 DOI 10.5455/jeim.060713.or.081

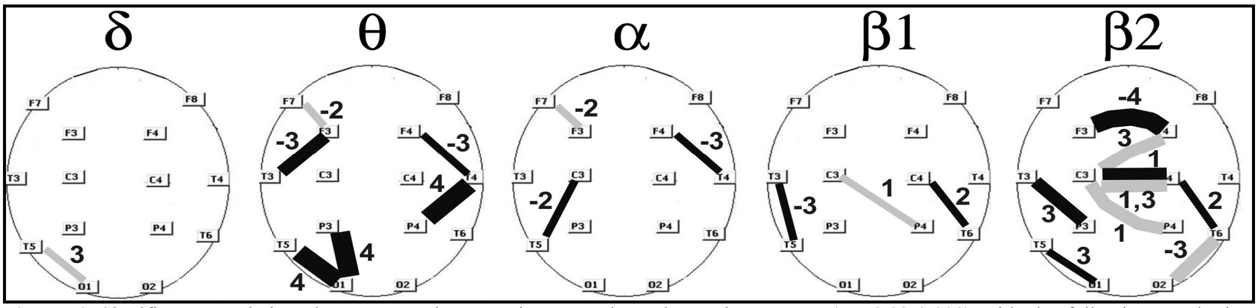

Figure 6. Significant correlations between synchrony estimates and psychometric measure (P = 0.03-0.008) with the following numbering notation: **(1)** volume of direct reproduction by technique of memorization of 10 words under verbal presentation; **(2)** volume of simple binary associations; **(3)** volume of complex binary associations; **(4)** runtime of Schulte tables execution. Color of lines indicates the group of patients: **black** F20, **gray** F21; **three grades of lines thickness** indicate the absolute value of correlations: 0.45-0.49, 0.5-0.59, 0.6-0.75. The figures at lines indicate the numbering notation of psychometric measure; **minus** indicates a negative correlation.

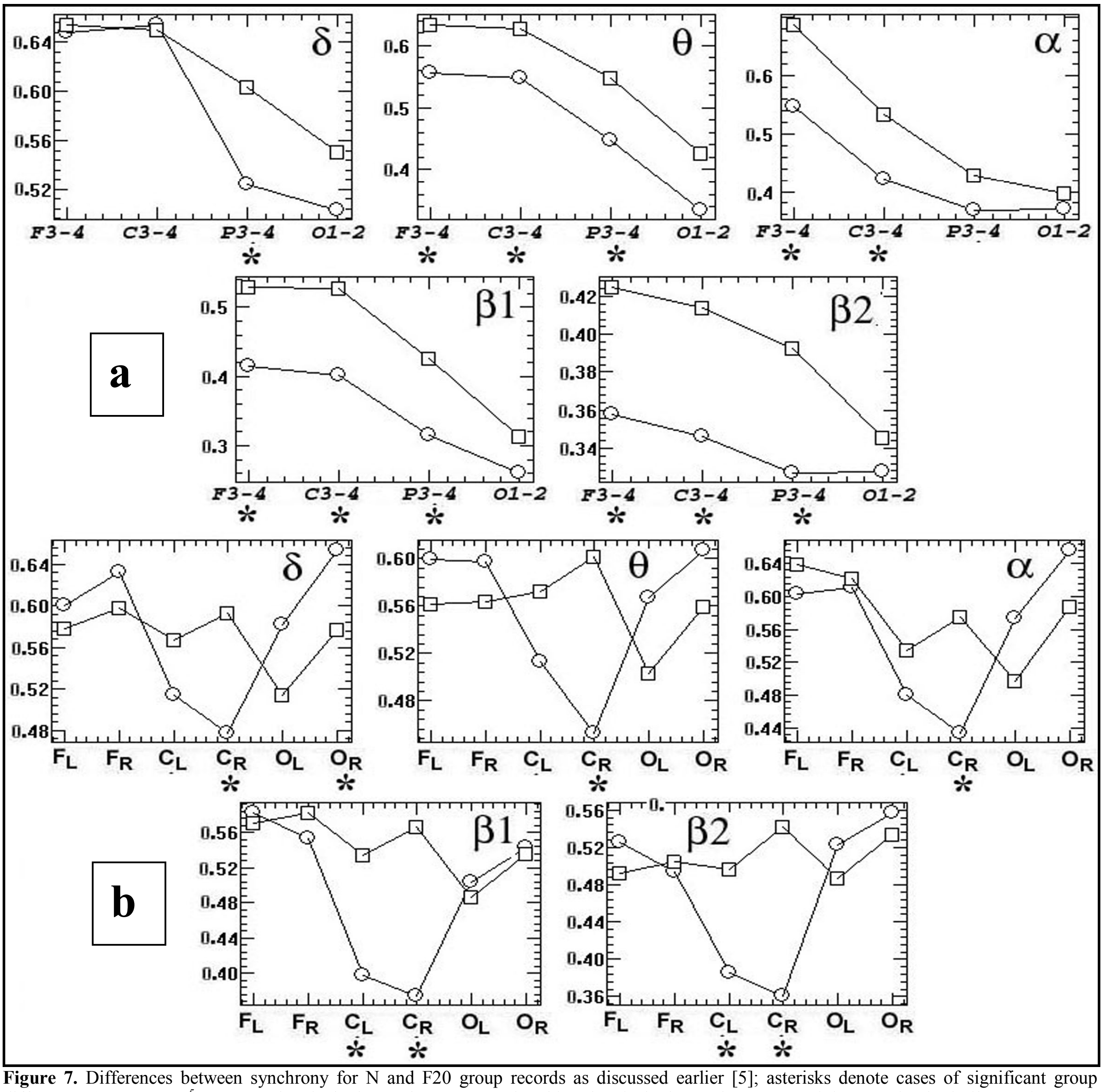

Figure 7. Differences between synchrony for N and F20 group records as discussed earlier [5]; asterisks denote cases of significant group differences (P = 0.47-10^{-5}). **(a)** Inter-hemispheric synchrony, **(b)** regional intrahemispheric synchrony. Remaining notation is similar to Figs.4&5.

Fig.7 (identified significant differences showed $P = 0.047\text{-}10^{-5}$). As you can see, these charts are in good agreement with Figs.4&5 with the exact reproduction of the phenomenon of cross-shaped “downfall” in EEG synchrony for F20 group. The separate and not numerous distinctions can be a consequence of narrower age range of the used groups. The discriminant classification gives an unmistakable separation of normal and pathological groups in all frequency domains. Thereby, the ACS-method possesses sufficient accuracy and stability, yielding almost identical results on various groups of examinees and patients.

DISCUSSION

The results of our complex analysis reveal the complicated picture of regional, inter-hemispheric and age differences in EEG synchrony between two disorders of schizophrenic spectrum and the norm, including interchanging cortical areas with oppositely directed ratios of higher, lesser or equal synchrony. Apparently, this is caused the apparent inconsistency of fragmentary results obtained by other researchers as noted in the introduction. Disclose of complete picture of EEG synchrony relations in these studies could be prevented by: ***(a)*** uncertainties of coherent analysis [15]; ***(b)*** small volume of experimental data [10, 11, 27]; ***(c)*** absence of selection of EEG records on consistency; ***(d)*** absence of separation of groups according to nosological type, age and sex. However, many of particular conclusions of other researchers find their counterparts in the considered complex picture: local cases of increase of intra-hemispheric coherence in schizophrenics [6, 10, 12, 13], its decline in central region [5, 9], reduced inter-hemispheric synchrony [5, 6], a violation of frontal-temporal relationships [7].

One of distinctive and stable components of above considered picture of mental disorders in comparison with the norm is the presence of the vast areas of low synchrony separating isolated intra-hemispheric (frontal and occipital) areas with synchrony near to normal level. The presence of such a reduction and detection of right-sided asymmetry can indicate a substantial violations of inter-hemispheric and frontal-occipital relationships for schizophrenic and schizotypal disorder, which fits into framework of the well-known theory of disintegration of cortical electrical activity [30, 31] ascending to Bleuler’s studies (1911, 1913). Apparently, in schizophrenic process, a tendency to disintegration comprises cortical neuronal substrate at different levels, *i.e.* from local neuronal ensembles to spatially separated neural networks, which causes serious disturbances in their interaction [5]. It is considered that one of direct consequences of this disintegration is represented by observed violations of cognitive and behavioral functions at patients with schizophrenic disorders.

Our additional task of differentiation of two closely related F20 and F21 categories among the block of disorders of schizophrenic spectrum is especially complicated because among experts there is still no consensus on a safe separation criteria for schizophrenia and schizotypal disorder [18]. The significant differences between F20 and F21 groups appear mainly in frontal and occipital areas in certain frequency domains. With this in occiput an inter- and intra-hemispheric synchrony for schizophrenia (F20) in some cases was closer to normal, whereas for schizotypal disorder (F21) intra-hemispheric synchrony is higher than normal, but inter-hemispheric synchrony is below than normal. Certain relationships of this kind are also observed in parietal, temporal and central areas. Apparently, this is due to the fact that criteria of schizotypal disorder includes, in particular, the presence of unusual phenomena of perception including somatosensory, auditory and visual illusions or hallucinations, and as a result there can be more drastic deviations of EEG synchrony from the norm in areas of primary projection of corresponding analyzers.

On the other hand, in frontal and some central cortex areas in F20 group there are observed greater deviations of inter-hemispheric and intra-hemispheric synchrony estimates from the norm than in the case of schizotypal disorder. This is consistent with concept of greater safety of frontal cortex at patients of F21 categories [18]. It is significant that most such deviations in intra-hemispheric synchrony manifest themselves in β-2 domain, whose activity is directly related to cognitive activity, and namely violations of cognitive processes are most typical just for schizophrenia pathology [18].

We note also that most of patterns on charts like Figs.2-5 also appear when we analyze full amount of data (125 patients), but the performed selection of highly consistency subgroups (64 patients) improved considerably the reliability of conclusions about observed differences. Moreover, re-calculating of previous EEG records [5] by the here used methodology confirms all the above mentioned inter-hemispheric and regional relationships with high numerical accuracy. That proves the stable reproducibility of results in different groups of patients by the use of ACS-method.

These results demonstrate the high efficiency of ACS-method in differentiation of normal examinees from patients of different mental disorders by EEC and according to its classifying efficiency θ and β-2 frequency domains have noticeable advantage. It should also be emphasized that the efficiency for classification of θ domain was found in our previous

 DOI 10.5455/jeim.060713.or.081

paper [4]; in the same paper there was shown an advantage of ACS-method in comparison with other methods of classification and with other EEG indices.

The present study also showed that for the reliable differentiation on EEG of various subcategories within such the complex and multidimensional nosology as psychiatric disorders of schizophrenic spectrum, it is necessary to use: ***(1)*** a bigger volume of experimental data than it takes place in most cited studies: ***(2)*** separate study of different nosology, age categories and sexual groups; ***(3)*** preliminary extraction of highly consistent EEG records for elimination of extraneous factors influence.

Apparently the real progress towards development and implementation of efficient numerical methods for differentiation of norm and various forms of mental pathology by EEG is possible upon condition of international cooperation and coordination of researches. It also requires a formation of an integrated bank of EEG records from the data of various research and clinical centers differentiated by separate nosology, functional states, sex, age and other characteristics. One of possible mechanisms for this integration may be obligation to upload EEG records in standard European Data Format (EDF) in such a bank and do it for all articles published in leading scientific journals. In addition, such publicly-accessible bank will make the results and theoretical conclusions of EEG studies to be the falsifiable in sense of Karl Popper. For the purification of such a bank from influence of extraneous random factors a technique can be used similar to above discussed extraction of highly consistent EEG records.

Considered multidimensional results on distinctions of the norm and two groups of deviations of schizophrenic spectrum confirms in particular; ***(a)*** the revealed numerous significant correlations of EEG synchrony estimates with psychometric indices, ***(b)*** the high classifying sensibility of the used ACS-method, near 100% reliability, and ***(c)*** the reproducibility of results for different groups of patients and examinees. All this shows that EEG correlation synchrony measures can be perspective for the use as auxiliary quantitative estimates (in addition to ranking expert estimates) at diagnostics of mental deviations of schizophrenic spectrum.

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 DOI 10.5455/jeim.060713.or.081