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Analysis of EEG Structural Synchrony in Adolescents with Schizophrenic Disorders

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Abstract—A total of 39 healthy adolescents and 45 adolescents with schizophrenic disorders (mean age 12.3 years) were examined to study the EEG structural synchrony as reflecting temporal synchronization of the operational activity of neuronal networks. A significant decrease in the EEG structural synchrony was observed in the adolescents with schizophrenic disorders as compared to the healthy adolescents. The decrease was detected predominantly in the interhemispheric pairs of EEG derivations, as well as in the pairs related to the frontal, temporal (predominantly on the left), and right parietocentral regions. The findings provide evidence in favor of Friston's hypothesis of disintegration of cortical electrical activity in schizophrenia and extend the hypothesis in that it is the operational synchrony of cortical activity that might suffer first in schizophrenia.

Schizophrenia falls into the small category of diseases that impair the total psychic activity rather than particular brain systems and functions. It is not surprising that researchers have long been interested in the integrative activity of the human brain in schizophrenia. They have reported considerable data on histological and physiological changes in the human brain, providing evidence for disturbance of interrelationships and functional association between different parts of the brain at different stages of schizophrenia [1–3]. The most conspicuous data have been obtained for the brain electrical activity [4–10]. Based on these data, a hypothesis of disintegration of cortical functions (the disconnection hypothesis) has been advanced [11] to explain the schizophrenic disorders [11–13].

In EEG studies, spectral and correlation analyses are a common method for investigating the integrative activity of the human brain, yielding evidence for the impairment of local and distant synchronies of neuronal networks in schizophrenia [4, 5, 7, 8, 14]. However, a number of limitations typical of spectral methods, specifically, of the coherence function [7, 15–17], have motivated the development of new techniques to examine the interdependences of EEG paired time series data in schizophrenia, including nonlinear interdependence [9], mutual information transmission measure [18], and phase locking [10], which reflect nonlinear and, in the last case, also in-phase components of the interdependence of cortical electrical processes.

The results of the above studies are also in line with Friston's hypothesis of disintegration of neuronal networks in schizophrenia [11].

Yet, cortical bioelectrical processes associated with ontological nonstationarity of the EEG signal [19–21] are not covered by the traditional or new methods of quantitative analysis of EEG spatiotemporal correlations.

EEG nonstationarity implies that the EEG signal consists of quasi-stationary segments that reflect the changes in metastable states of the brain on different time scales [20, 21], from microstates, with a duration of no more than several seconds [15, 22], to macrostates, with a duration of tens or hundreds of minutes [23]. This concept of EEG nonstationarity provides a means for obtaining new insights into the cooperation of cortical structures. For this purpose, it is possible to estimate the EEG structural synchrony [15], i.e., the temporal synchronization of intersegmentary transitions between different EEG channels. Estimation of the spatiotemporal synchronization of local metastable states of neuronal networks appears to be a new measure of the integrative activity of the human brain.

The functional importance of the EEG structural synchrony and segment characteristics has been described in a series of our works performed in several laboratories and with several cognitive and pharmacological paradigms [24–27]. In our previous work [28], changes in quasi-stationary segments of the EEG α activity were detected in adolescents with schizophrenic disorders.

The objective of the present work was to analyze the disease-related changes in structural synchrony of the EEG α activity in adolescents with schizophrenic disorders.

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METHODS

The study involved 45 boys with schizophrenic disorders (infant schizophrenia and schizotypical and schizoaffective disorders (F20, F21, and F25 according to the ICD-10)) with similar symptoms. The diagnoses of all patients were confirmed by specialists of the Mental Health Research Center (MHRC). None of the enrolled patients received chemotherapy during the examination at the MHRC. The age of the patients varied from 10 years and 8 months to 14 years. The control group included 39 healthy schoolboys aged from 11 years to 13 years and 9 months. The mean age in both groups was 12 years and 3 months.

The EEG was recorded in wakeful relaxed adolescents with the eyes closed from 16 electrodes, which were placed according to the international 10–20 system at O_1, O_2, P_3, P_4, Pz, T_5, T_6, C_3, C_4, Cz, T_3, T_4, F_3, F_4, F_7, and F_8 and monopolarly referenced to coupled ear electrodes. The EEG recordings were analyzed with a sampling rate of 128 samples per second, and only artifact-free EEG segments were used for analysis.

Analyzing the EEG structural synchrony, we used the SECTION 0.1 technology [24, 29] to perform EEG adaptive segmentation in order to identify quasi-stationary segments of the α activity. Thereafter, the index of structural synchrony (ISS) of the EEG [15, 29] was calculated using the JUMPSYN 0.1 technology as

$$\mathrm{ISS} = \frac{Pe - Pt}{m},$$

where Pt is the theoretically predicted frequency of coincidences of segment boundaries between two EEG derivations provided that the derivations are independent, Pe is the observed frequency of coincidences of segment boundaries between the two EEG derivations, and m is the mean error of Pt.

As can be seen from the formula, the ISS shows the extent of synchrony of the boundaries of quasi-stationary segments, free from random coincidences, for a given pair of derivations.

The quasi-stationary segments of the EEG α activity are supposed to reflect changes in local cortical neuronal ensembles [24, 25]; therefore, the ISS shows the extent of temporal synchronization of integration or disintegration events in local neuronal ensembles for pairs of different EEG derivations.

For the 120 possible combinations of the 16 EEG derivations, 120 ISS values were calculated. To determine the ISS confidence interval (the stochastic level) giving an error probability of no more than 5% for the conclusion of a nonrandom nature of the structural synchrony for a given pair of derivations, a numerical experiment according to the Monte Carlo technique was performed with 500 iterations.

The ISS values calculated for each pair of derivations were averaged for each group. The total synchrony, i.e., the mean ISS for all derivations, and the group synchrony for certain sets of derivation pairs, including left hemispheric (O_1, P_3, Pz, T_5, T_3, C_3, Cz, F_3, and F_7), right hemispheric (O_2, P_4, Pz, T_6, T_4, C_4, Cz, F_4, and F_8), frontal (F_3, F_4, F_7, and F_8), central (T_3, T_4, C_3, Cz, and C_4), parietocentral (P_3, P_4, Pz, T_5, T_6, T_3, T_4, C_3, C_4, and Cz), posterior (O_1, O_2, P_3, P_4, Pz, T_5, and T_6), and symmetrical bilateral (pairs O_1–O_2, P_3–P_4, T_5–T_6, T_3–T_4, C_3–C_4, F_3–F_4, and F_7–F_8) derivations, were calculated separately for the control and test groups.

The paired Wilcoxon *t*-test was used to estimate the significance of differences in the total and group synchronies between the control and test groups.

Along with the group synchrony analysis, a detailed analysis of the ISS values was performed with regard to the ISS stochastic level and the distance between the electrodes for a given pair of derivations. The Mann–Whitney *U*-test was used to compare ISS values exceeding the stochastic level in at least one of the groups under study.

RESULTS

Comparison of the ISS values averaged for the 120 pairs for the control and test groups showed that this index was significantly lower in the adolescents with schizophrenic disorders (control group, 2.03 ± 0.19; test group, 1.67 ± 0.17 ($M \pm m$)).

Analysis of the group synchrony, i.e., ISS values averaged for various sets of EEG derivations, revealed a decrease in this parameter for most sets of EEG derivation pairs (left hemispheric, right hemispheric, parietocentral, posterior, and bilateral) in the test group (Fig. 1). The differences in the ISS were nonsignificant only for the frontal and central pairs of the EEG derivations, although they showed a trend common to all groups of derivations.

We concluded that the level of EEG structural synchrony in the adolescents with schizophrenic disorders was generally lower than in the healthy subjects.

The question arises as to whether a decrease in the ISS for the above pairs of derivations in the test group is indicative of a regular trend equally typical of each derivation pair or the ISS demonstrates different disease-related trends for different pairs of derivations. To answer this question, we analyzed in detail the ISS values for each pair of EEG derivations.

The topographic patterns of the ISS calculated for each of the 120 derivation pairs with regard to the stochastic level and for both the control and the test groups are given in Fig. 2. The ISS considerably exceeded the stochastic level in many pairs of EEG derivations, thereby evidencing a nonrandom character of coincidences of intersegment transitions in the corresponding pairs of EEG derivations.

When analyzing the differences in ISS between the control and the test groups, we were interested in comparing the above pairs, in particular, the topographic distribution of these pairs in each group.

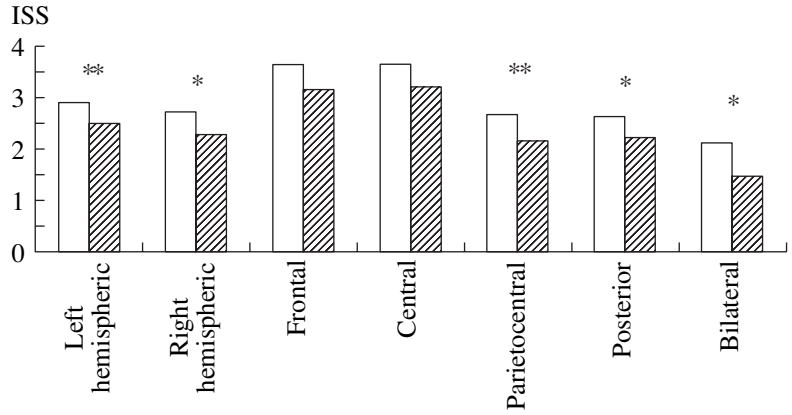

Fig. 1. ISS values averaged for different pairs of derivations in the control (light columns) and test (dark columns) groups. Abscissa, pairs of derivations. Differences in group synchrony indices were significant at (*) $P < 0.05$ and (**) $P < 0.001$.

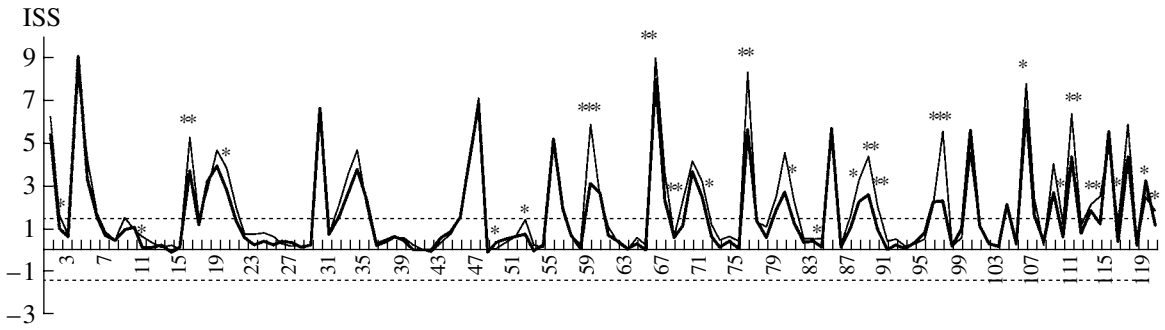

Fig. 2. Topographic patterns of the ISS (for each of the 120 pairs of EEG derivations) with the ISS stochastic level for the control and test groups. Because the ISS stochastic level was virtually the same in both groups, it is given only for the control group. Abscissa, ordinal numbers of the derivation pairs; ordinate, ISS. Thick line, ISS in the test group; thin line, ISS in the control group; dashed line, experimentally determined maximum and minimum stochastic levels of the ISS. Asterisks indicate the pairs of leads in which the differences in ISS between the control and the test groups were significant (the Mann–Whitney *U*-test) at (*) $P < 0.05$, (**) $P < 0.01$, and (***) $P < 0.001$.

The topographic distribution of the derivation pairs with the ISS exceeding the stochastic level was analyzed for three ranges of interelectrode distance (0.48–0.67, 0.79–0.95, and 1.14–1.39) in both the control and the test groups (Figs. 3a–3c, respectively). The interelectrode distances were calculated using three-dimensional coordinates for each of the derivations [30, 31].

As can be seen from Fig. 3, the ISS exceeded the stochastic level in the same derivation pairs for the control group as for the test group. However, there were another ten pairs in which the ISS exceeded the stochastic level in the control but not in the test group.

It was found that, in the control group, the pairs of EEG derivations with the above-threshold ISS were mostly observed for a large interelectrode distance (Fig. 3c) and rarely for the minimum interelectrode distance (Fig. 3a).

Analysis of the percentage of these pairs in both the control and the test groups (table) showed that the pairs of EEG channels with the above-threshold ISS in the test group, when compared to those in the control group, demonstrated a trend towards a distance-dependent redistribution so that the percentage of such pairs increased in the case of minimum interelectrode distances and decreased in the case of maximum interelectrode distances. Compared with the control group, the test group demonstrated a decrease predominantly in distant structural synchrony. This was true mainly for

Percentage of the pairs of derivations (for different ranges of interelectrode distance) with the ISS exceeding the stochastic level in the control and test groups

Group	Range of interelectrode distance			Total pairs
	0.48–0.67	0.79–0.95	1.14–1.39	
Healthy adolescents	50.0%	30.8%	19.2%	52
Schizophrenic adolescents	57.1%	31.0%	11.9%	42

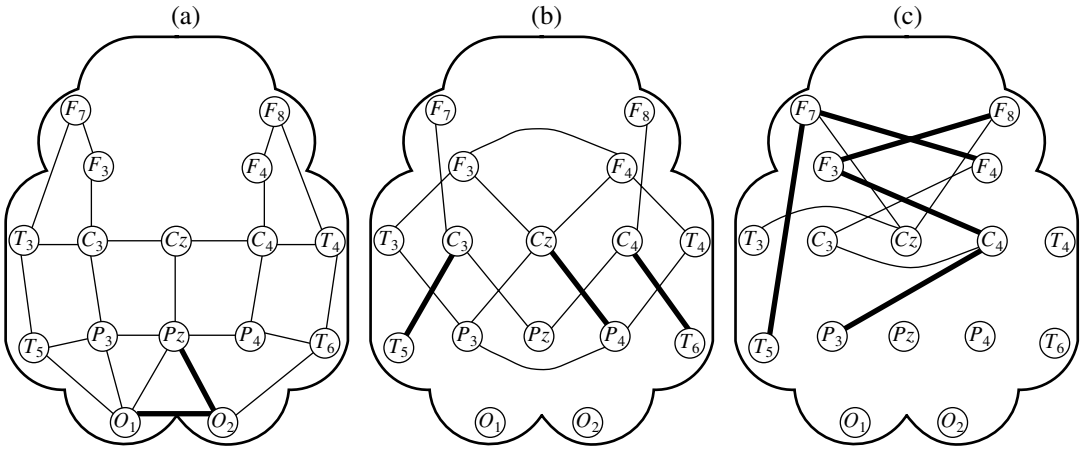

Fig. 3. Topographic distribution of the pairs of derivations with interelectrode distances in the ranges (a) 0.48–0.67, (b) 0.79–0.95, and (c) 1.14–1.39 and the ISS exceeding the stochastic level. Thick line, pairs of derivations with the ISS exceeding the stochastic level only in the control group; thin line, pairs of derivations with the ISS exceeding the stochastic level in both groups.

the left fronto–temporal diagonal and bilateral asymmetrical connections (Fig. 3).

Along with the topographic analysis of the derivation pairs with ISS values exceeding the threshold in both the control and the test groups, we compared the ISSs of individual pairs between the groups. The ISSs were compared only for the derivation pairs in which the value exceeded the threshold in at least one of the two groups. The pairs of derivations with significant differences in the ISS between the control and the test groups are represented in Fig. 4.

The ISS was lower in the test group for almost all such pairs of derivations (except O_2–T_6). In addition to the pairs represented in Fig. 2, this was true for bilateral symmetrical (O_1–O_2, P_3–P_4, C_3–C_4, and F_3–F_4), predominantly right parietocentral (Pz–P_4, Pz–C_4, P_4–C_4, Cz–C_4, and C_3–P_4), predominantly left temporal (T_3–T_5, T_3–C_3, and T_4–T_6), and left prefrontal (F_3–Cz) pairs of EEG derivations.

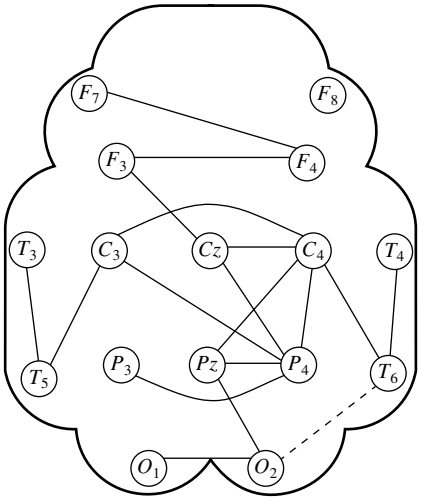

Fig. 4. Topographic distribution of the pairs of derivations in which the differences in the ISS between the control and the test groups were significant ($P < 0.05$, $P < 0.01$, and $P < 0.01$). Solid line: the ISS is higher in the control group; dotted line: the ISS is higher in the test group.

DISCUSSION

The results of spectral and correlation analyses of the interaction between different parts of the brain in schizophrenia may lead to conflicting conclusions. Some researchers have reported an increase in EEG coherence in schizophrenia at rest [6, 32–34] and during solving cognitive tasks [14]. In other studies involving the same frequency ranges and functional states, either quite opposite effects were observed [7, 8, 35, 36] or virtually no significant differences in EEG coherence were found between patients and control subjects [37].

Conceivably, such a variety of estimations of EEG coherence in schizophrenia might be caused by the lack of uniform standards for the organization of such studies with respect to test paradigms, EEG frequencies, and stages of the schizophrenic process [7, 38].

Application of new techniques for studying corticocortical interactions also contributes to the variety of conclusions. One such example is [17], where coherence analysis and analysis of coincidences of peak frequencies in pairs of EEG derivations were performed with the same samples of healthy subjects and schizophrenics. It was found that the topography and the changes in correlations between EEG parameters depend not only on the method applied but also on whether positive or negative symptoms are observed in schizophrenics [39], as well as on the frequency ranges and particular pairs of EEG derivations used in the test procedures [39]. Entropic analysis of the EEG (mutual information analysis), which reports the mutual orderliness of distributions of temporal series, showed a vari-

ety of changes in information transmission between different cortical areas in schizophrenics [18]. Detection of specific nonlinear interdependences through mutual prediction [40] led to the conclusion that the difference between healthy and schizophrenic subjects concerns the topography of interactions between different cortical areas rather than the direction of changes in EEG synchronization or their dependence on particular pairs of derivations [9].

Summarizing the above data, we may argue that schizophrenia is associated with a variety of changes in types of mutual determination in pairs of different EEG derivations.

In this work, we were the first to obtain data on the changes in EEG structural synchrony in schizophrenic disorders. The specific feature of the method we used for estimating cortical integration is that it describes the EEG patterns represented by quasi-stationary segments rather than particular peaks or waves of the EEG signal [20, 21].

Our results are generally consistent with the data on considerable changes in corticocortical interrelationships in schizophrenia that were reported in other studies.

The topographic analysis of the derivation pairs with a decreased structural synchrony in the test group compared to the control group and of the pairs with the ISS exceeding the threshold only in the control group revealed a decrease in structural synchrony between the hemispheres (the O_1–O_2, P_3–P_4, and C_3–C_4, F_3–F_4 pairs of bilateral symmetrical derivations and the P_3–C_4, C_3–P_4, F_3–C_4, F_3–F_8, and F_7–F_4 pairs); in the temporal regions of both hemispheres, predominantly on the left (T_5–T_3, T_5–C_3, T_5–F_7, T_6–T_4, and T_6–C_4); in the frontal regions, predominantly on the left (F_3–F_8, F_7–F_4, F_3–F_4, F_3–Cz, F_3–C_4, and T_5–F_7); and in the right parietocentral region (Pz–P_4, Pz–C_4, Cz–P_4, P_4–C_4, and Cz–C_4).

Interestingly, the largest number of derivation pairs with the ISS lower than the stochastic level in the test group and higher than this level in the control group were observed for the pairs with the maximum distance between the electrodes. This suggests a disruption of functional interdependence between rather distant regions in the test group, although the percentage of such interdependences in adjacent regions was even higher than in the control group.

Our findings concerning the topographic distribution of the derivation pairs with structural synchrony lower in the test than in the control group are consistent to some extent with data obtained using other techniques for EEG synchrony in different regions of the brain in schizophrenic patients.

Thus, a decrease in the functional hemispheric interdependence in schizophrenia was revealed by the analysis of EEG coherence and β-range synchronization [8] and EEG cross-correlation analysis [41]. A decrease in EEG synchronization in the frontal and central regions, predominantly on the left, was also reported for schizophrenics [41]. A decrease in coherence in the Δ, θ, and α ranges was detected in the left frontal region [7].

Analysis of nonlinear interdependences showed that the EEG difference between schizophrenics and healthy subjects is most pronounced in the left intrahemispheric regions [9]. Auto mutual information analysis and mutual information transmission measure (CMI analysis) of the EEG in schizophrenic patients revealed a functional deficit of the left temporal lobe and increased interhemispheric information transmission in the temporal lobe [18].

Topographically, our findings on a decrease in EEG structural synchrony in the adolescents with schizophrenic disorders are consistent to some extent with published data on the changes in functional interdependences between different regions of the brain in schizophrenia. However, fundamental differences in the methods used for estimating EEG spatial synchrony can produce unequal results; therefore, one must be careful when comparing these results either with each other or with our findings.

What is the physiological significance of the detected decrease in EEG structural synchrony in adolescents with schizophrenic disorders? The phasic structure of the EEG, specifically, of the α range, reflects the dynamic changes in cortical neuronal ensembles [24, 25], while the ISS is used to estimate the temporal synchrony of cortical activity of different regions of the brain with regard to the dynamic changes in local neuronal ensembles. A significant simultaneous integration (or disintegration) of such assemblies in distant cortical regions may be regarded as spatiotemporal synchronization of local cortical processes [20, 21, 42].

Thus, the decrease in the ISS detected for many pairs of derivations in the schizophrenic adolescents may provide evidence for disintegration of operational cortical activity.

In our previous study [28], we examined EEG segments of α activity in the same adolescents. According to our results, the EEG α activity in adolescents with schizophrenic disorders significantly differs from that in healthy adolescents. In our opinion, these differences point to lesser integration of cortical neurons via local synchronization of their activity in adolescents with schizophrenic disorders as compared to control subjects. Even when such synchronization occurs, it is of a lesser duration and is less stable. On the strength of these data, we assumed that a disintegration trend is typical of the whole neuronal substrate at all levels from local neuronal ensembles to spatially distant neuronal networks, causing serious disturbance of interdependences in schizophrenia.

The results of this study support the above assumption and show that this disease is associated not only with alteration of local synchronization mechanisms but also with dramatic impairment of intercortical connections, spatiotemporal disintegration being greater between distant regions.

The results of this work are generally consistent with Friston's hypothesis of disintegration of cortical electrical activity in schizophrenia [11], although they extend the hypothesis in that it is the operational synchrony of cortical functions that might suffer first in schizophrenia.

CONCLUSIONS

(1) The EEG structural synchrony may be used as an additional index for detecting schizophrenic disorders in adolescents.

(2) Unlike healthy adolescents, those with schizophrenic disorders show a decrease in the ISS, predominantly, in interhemispheric, left frontal and temporal, and right parietocentral pairs of derivations.

(3) The results of analysis of EEG structural synchrony in adolescents with schizophrenic disorders support the hypothesis of disintegration of functional interdependences between different parts of the brain in schizophrenia.

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