# INTERICTAL EEG AS A PHYSIOLOGICAL ADAPTATION
## Part II: Topographic variability of composition of brain oscillations in interictal EEG

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**Abstract:** *Objective:* In the present experimental study, we examined topographic variability of composition of brain oscillations and their temporal behavior in frequencies from 0.5 to 30 Hz of interictal EEG without epileptiform abnormalities and healthy EEG. *Methods:* Spatio-temporal variability of brain oscillations (indexed by short-term EEG spectral patterns (SPs)) was assessed by the probability-classification analysis of SPs. As a result, multi-dimensional SP-vector for each analysis EEG epoch was obtained. *Results:* It was demonstrated that interictal EEG was characterized (a) by a significant decrease of spatio-temporal variability of brain oscillations, (b) by longer periods of temporal stabilization for operational modules which comprise larger number of cortical areas, and (c) by significantly more intermittent recurrence when compared with EEG of control subjects. Generally it was shown that EEG channels display different states of coordination independently on their correlation and coherence using brain oscillations at multiple frequencies. *Conclusion:* Results of this study suggested that EEG correlate of chronic epileptogenesis in the brain is a particular metastable state of biopotential field which can be estimated by SP-vector. The fact that all results were significantly different from surrogate EEGs reflects a non-occasional and thus, most likely, an adaptive nature of spatio-temporal reorganization in interictal EEG. *Significance:* Parameters of spatio-temporal organization of interictal EEG without the signs of epileptiform activity can be considered as additional information in premorbid diagnostics of status epilepticus, and may also provide insights into basic laws that govern brain oscillations in general.

*Keywords***:** Epilepsy; Interictal electroencephalogram (EEG); Multiple brain oscillations; Short-term spectral patterns; Spatio-temporal variability; Topographic variability; Metastability.

## 1. Introduction

In our previous study (Fingelkurts et al., 2005a) we reported considerable changes in the local dynamics of the epileptic brain in interictal period. Thus, it was demonstrated that interictal EEG without signs of epileptiform abnormalities during chronic epilepsy had a number of differences (from EEG of healthy subjects) which constitute EEG microstructural reorganization, and reflect a disorganization of neurodynamics in the epileptic brain (for details, see Fingelkurts et al., 2005a). These findings supported the assumption of Lopes da Silva et al., (2003) that in the epileptic brain, neuronal networks can display several different kinds of states with oscillations at different frequencies with specific dynamics. However, the analysis in our previous study (Fingelkurts et al., 2005a) was performed for each EEG channel separately, thus reflecting local dynamics. At the same time, recent research emphasizes that the majority of brain disorders and psychiatric problems are accompanied by disruption in the temporal structure of *integrative* brain activity (Dawson, 2004), where this spatio-temporal structure could be either more irregular (uncorrelated randomness) or more regular (excessive order) than normal (Glass, 2001; Buchman, 2002; for the recent review, see Fingelkurts et al., 2005d). From this perspective, such disruption is viewed as a disorder of the metastable balance between large-scale integration and independent processing in the brain, in favor of either independent or hyper-ordered processing (Bressler, 2003). Metastability is a brain condition where global integrative and local segregative tendencies coexist (Kelso, 1995; Friston, 1997; Kaplan, 1998). More precisely, in the metastable regime of brain functioning, the individual parts of the brain exhibit tendencies to function autonomously at the same time as they exhibit tendencies for coordinated activity (Bressler and Kelso, 2001; for the recent reviews on metastability in the brain, see also Fingelkurts and Fingelkurts, 2001; 2004). The synchronized operations of distributed neuronal assemblies are metastable spatial-temporal patterns because intrinsic differences in activity between the neuronal assemblies are sufficiently large that they do their own job, while still retaining a tendency to be coordinated together (Fingelkurts and Fingelkurts, 2005). The disruption in brain metastability and temporal dynamic is suggested as a contributing factor to the disorganization syndrome in many psychiatric and brain diseases (Haig et al., 2000; Dawson, 2004).

In Fingelkurts et al., (2005a) we have suggested that chronic epilepsy may be conceptualized as a new metastable state around altered homeostatic levels in the brain. Such a metastable state is viewed as an adaptation which is manifested as a semi-permanent self-

reorganization of the system. In this context, it is important to study how chronic epilepsy alters the temporal structure and metastable regimen of brain activity. Here, the methods of analysis of coordination of many EEG channels are of special interest. Such methods permit researchers to study the integrated organization of cortical bioelectrical field.

Currently, a number of EEG/MEG measures of integrative brain activity indexed by functional connectivity are available. They are the following: (1) correlation and coherence coefficients (for the reviews, see Thatcher and Krause, 1986; Nunez et al., 1997) as well as partial directed coherence (Baccala and Sameshima, 2001); (2) dynamic imaging of coherent sources (Gross et al., 2001), and phase synchrony based on wavelet (Lachaux et al., 1999) or Hilbert (Tass, 1999) transforms; (3) indices of mutual information (Xu et al., 1997); (4) "geometric" estimations of joint coordination of local EEGs calculated with the help of factor analysis (Manmaru and Matsuura, 1989; Lazarev, 1997) and multivariate linear regression (Wada et al., 1996; Lehmann et al., 1995) of the primary EEG characteristics; (5) chaotic dynamics of an EEG vector composed of simultaneous momentary counts of local EEGs (Matousek et al., 1995); (5) spectro-correlative characteristics of local EEGs (Ivanitski et al., 1990; Sviderskaya and Korol'kova, 1997); and (6) spatially oriented segmentation of cortical potentials proposed by Lehmann (Lehmann, 1971, 1987).

Even though, many of these approaches have proved to be useful for characterization of integrative activity in EEG during epilepsy (Franaszczuk and Bergey, 1999; Sackellares, et al., 1999; Bhattacharya, 2000, 2001; Jing and Takigawa, 2000; Mormann et al., 2003), all of them have one or more drawbacks and limitations (for the critical and detailed discussion, see Fingelkurts et al., 2005c, Fingelkurts and Fingelkurts, 2005) from the following list: Such methods (1) are designed predominantly for EEG analysis only in pairs of derivations, (2) do not take into consideration the nonstationary nature of the signal, (3) indicate only the linear statistical link between time-series curves in a frequency band, (4) require long time epochs of analysis, (5) can be applied only to homogeneous medium, which is an unrealistic assumption for the brain, (6) borrow complex methodologies and conceptual frameworks from physics, mathematics, and engineering, but use them loosely when applying to the analysis of physiological signal, (7) as very averaged indices they lose a substantial part of their diagnostic value for studying discrete functional states of the brain, (8) local EEGs participate in the formation of the resulting dipole vector far from equally, what is unjustified from the viewpoint of indubitable neurobiological equivalence of cortical areas, (9) the measures used to characterize the EEG are often difficult to interpret in terms of their

physiological correlate, (10) all existed measures of brain functional connectivity do not directly estimate metastability in the brain (Fingelkurts and Fingelkurts, 2004).

Additionally, lack of initial "attachment" of the majority of the abovementioned measures to brain oscillations makes results ontologically unpromising and consigns them to the status of phenomenological description. At the same time, different frequencies of brain oscillations reflect functionally different components of information processing acting on various spatial scales (Klimesch et al., 2005). It is supposed that brain pathological process alters neuronal networks which are based on short- and long-range interactions between neuronal assembles which oscillate at multiple frequencies (Jing and Takigawa, 2000; Bhattacharya, 2001) which are coherent and specific and thus capable of resonance – functional communication (Basar et al., 2001). Hence, brain disease involves a disturbance of oscillation frequencies, and of the communications associated with them.

Therefore, it was proposed to combine the advantages of the temporal and frequency approaches for the analysis of segment-to-segment organization of the cortical biopotential field (Kaplan et al., 1999). In such a way, this approach results in the topographic map of the EEG spectral patterns (SP) and thus, enables researches to study spatio-temporal variability of brain oscillations (indexed by short-term spectral descriptions) in multichannel EEG. It was demonstrated that the dynamics of spatio-temporal variability of resting EEG short-term spectral patterns (SPs) was characterized by alteration of relatively stable periods, the duration of which were significantly different from the respective characteristics of a stochastic process (Kaplan et al., 1999). Authors demonstrated that using this approach it is possible to detect periods with more or less generalized stabilization in the dynamics of the spatial mosaic of different types of SPs in the cortical EEG. Thus, analysis of topographic SP variability may permit researches to trace episodes of the metastable cortical inter-area cooperations independently on partial correlation and/or coherency between the local EEGs.

Hence, the aim of this study was to investigate the episodes of the metastablity in the dynamics of the spatial mosaic of different brain oscillations (indexed by SP types) in a broad frequency range (0.5-30 Hz) in interictal EEG without epileptiform abnormalities during resting conditions. Considering that chronic epilepsy may be conceptualized as a metastable state around new homeostatic levels of the brain (Fingelkurts et. al., 2005a), we hypothesize that interictal EEG without signs of epileptiform abnormalities would have episodes of the metastablity of a different lifespan and size (the number of EEG channels involved) when compared with EEG of healthy subjects.

**2. Methods**

*2.1. Subjects*

Six medication-free right-handed patients with idiopathic generalized epilepsy (aged 17-40, 3 females) were selected for the study. There were clear evidences for the absence of brain lesions (computer tomography and neurological tests) and a clear defined syndrome of juvenile myoclonic epilepsy characterized by myoclonic jerks, generalized tonic-clonic seizures, and sometimes absence seizures. The scalp-recorded ictal EEG pattern revealed a typical generalized, but anterior-predominant, discharges which were bisynchronous and symmetrical. Inclusion criteria for patients were (a) the persistence of epilepsy more than one year and (b) the absence of any neurological condition other than epilepsy, or any acute or chronic medical illness at the time of the EEG registration. Inclusion criterion for EEG analysis was the absence of any epileptiform activity in the interictal EEG: generally, interictal EEG was characterized by epileptiform discharges (spikes, spike-and-waves and polyspike-and-waves), but only those portions of EEG recordings were taken in the study which did not have any signs of epileptiform activity. Interictal epileptiform activity was identified via visual inspection according to the criteria laid down by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN, 1999). All patients were in good physical health, determined by a physical examination and laboratory evaluation including a complete blood count, glucose, and hepatic enzymes, renal and thyroid analyses. Patients could have taken medication for extended periods but not during the final two weeks prior to the study.

Seven sex- and age-matched healthy control subjects (aged 19-35, 3 females) participated in the study. Before inclusion, the control subjects underwent a medical examination and were also screened for EEG epileptiform activity. All control subjects had epileptiform-free EEGs.

All the subjects studied gave informed written consent before enrolling in the study and institutional ethical committee approval was obtained.

*2.2. Procedure and data acquisition*

Five 16-channel 1-min EEGs were recorded for each subject during resting condition (closed eyes). Such ongoing EEG activity during resting condition reflects the current

functional state of neuronal masses rather than a random process (Livanov, 1984; Fingelkuts et al., 2003b). Sixteen Ag/AgCl electrodes were placed bilaterally on the subject's scalp using the 10/20 system of electrode placement at $O_{1/2}$, $P_{3/4}$, $C_{3/4}$, Cz, $T_{3/4}$, $T_{5/6}$, $F_{3/4}$, Fz, $F_{7/8}$. Vertical and horizontal electro-oculograms were recorded. All electrodes were referred to linked ears. Raw EEG signals were amplified and bandpass-filtered in the 0.5-30 Hz frequency range and digitized at a sampling rate of 128 Hz by a 12-bit analog-to-digital converter. This frequency range was chosen because approximately 98% of spectral power lies within these limits (Thatcher, 2001). The impedance of the recording electrodes was always below 5 kΩ. The presence of an adequate EEG signal was determined by visual inspection of the raw signal on the computer screen.

Instructions designed to minimize movement and relax jaw muscles resulted in suppressing the myogram class of artifact to the extent that the high-frequency spectrum was not significantly affected. Cardiac interference at low frequencies was also found to be minimal, with no spectral peak detection at the heartbeat frequency of around 1 Hz, or its harmonics. A subject was instructed also to look straight in front of him/her (even though the eyes were closed) and to avoid unnecessary eye movements. Constant visual EEG monitoring allowed for selection of only those artifact-free EEG recordings for analysis.

Alertness of the patients and control subjects during the EEG recording was determined by the design of the study: five separate one-minute EEGs were recorded in well-lighted room with a short break in-between to assume a comfortable position. Such design should keep the patients and control subjects awake. Vigilance of the patients and control subjects was controlled by visual detection of the presence of sleep spindles which naturally appear during drowsiness (Rechtschaffen and Kales, 1968). None of the patients and control subjects demonstrated sleep spindles in the recorded EEGs.

To examine the actual composition of brain oscillations and their temporal behavior in EEG, a total of 18 (3 minutes for each patient) and 14 (2 minutes for each control subject) artifact-free one-minute EEGs were selected in this study.


*2.3. Data processing*

Since EEG is widely referred to as a nonstationary signal with varying characteristics (Kaplan and Shishkin, 2000; see also Fingelkurts and Fingelkurts, 2001), brain oscillations are expected to be dynamic in nature. In order to capture such changing dynamics, the data series were divided into overlapping windows. Brain oscillations were quantified by

calculation of individual short-term SP. Individual power spectra were calculated in the range of 0.5–30 Hz with 0.5-Hz resolution (61 values), using FFT with a 2-sec Hanning window shifted by 50 samples (0.39-sec) for each channel of one-minute EEG. According to previous studies, these values proved the most effective for revealing oscillatory patterns from the signal (Levy, 1987; Kaplan, 1998). According to the work of Kaplan (1998) in which the author studied the effect of window shift on disclosing oscillatory patterns from the signal using shifts from 1 to 256 samples, the window shift in 50 samples was the most effective. Additionally, such shift permitted us to obtain relatively large number of SPs. Such approach is justified because 2-sec EEG epochs for SP's calculation may be taken in any place of EEG, not only in the fixed positions. Sliding spectral analysis compensated for the effects of windowing, preventing us from losing information due to residual activity, and improving the statistical confidence in the results due to relatively large number of SPs.

As a result, the total number of individual SPs for each channel of 1-min EEG was 149 (Fig. 1). These SPs formed the multitude of the objects for further analysis. In short, this analysis was undertaken in two stages (Fig. 1). During the first stage, the compositions of brain oscillations (in terms of EEG SPs) were estimated with the help of a probability-classification analysis of the short-term EEG SPs (SCAN, suggested by A.Ya. Kaplan, Moscow State University). Considering that detail description of this analysis was published elsewhere (Fingelkurts et al., 2003a, 2005a,b), here we are highlighting only the most important aspects. Sequential single EEG SPs were adaptively classified in each channel of 1-min EEG using a set of standard SPs. Standard SPs were generated from the data itself. The set of standard SPs was formed automatically using heuristic procedures and Pearson's correlation coefficients (CC): A pool of SPs ($n = 14\,016$) was built from all the SPs of the entire EEG signal (all locations) for all subjects. From this pool, all identical SPs with peaks in the same frequencies were counted. The set of identical SPs with the highest count was the most likely candidates to form the "set of standard SPs." Only those SPs with minimum cross-CC were selected. Thus, the standard set included 32 SPs. Basic procedure of adaptive classification was performed in three steps. During the first step, the initial matrix of cross-correlations between standard and current individual SPs of analyzed EEG was calculated for each channel separately. On the basis of CC which were obtained at the first step, the current SPs were sorted: all current SPs that their CC passed the acceptance criteria of $r \geq 0.71$ were attributed to their respective standard classes. During the second step, the current SPs which were included in a particular class were averaged within this class. The same procedure was performed for all classes separately for each EEG channel. On the back of this, the standard

spectra were reconstructed but this time taking into account the peculiarities of the spectral description of concrete channel of the particular EEG. In this way an "actualization" of the initial standard SP set was performed. In other words, they were converted into so-called actual spectral patterns. This actual SP set was in turn used for the third step - the final classification of the current SPs. As a result of this classification, each current SP was labeled according to the index of the class to which it belongs. Hence, each EEG signal was reduced to a sequence of individually classified SPs (Fig. 1).
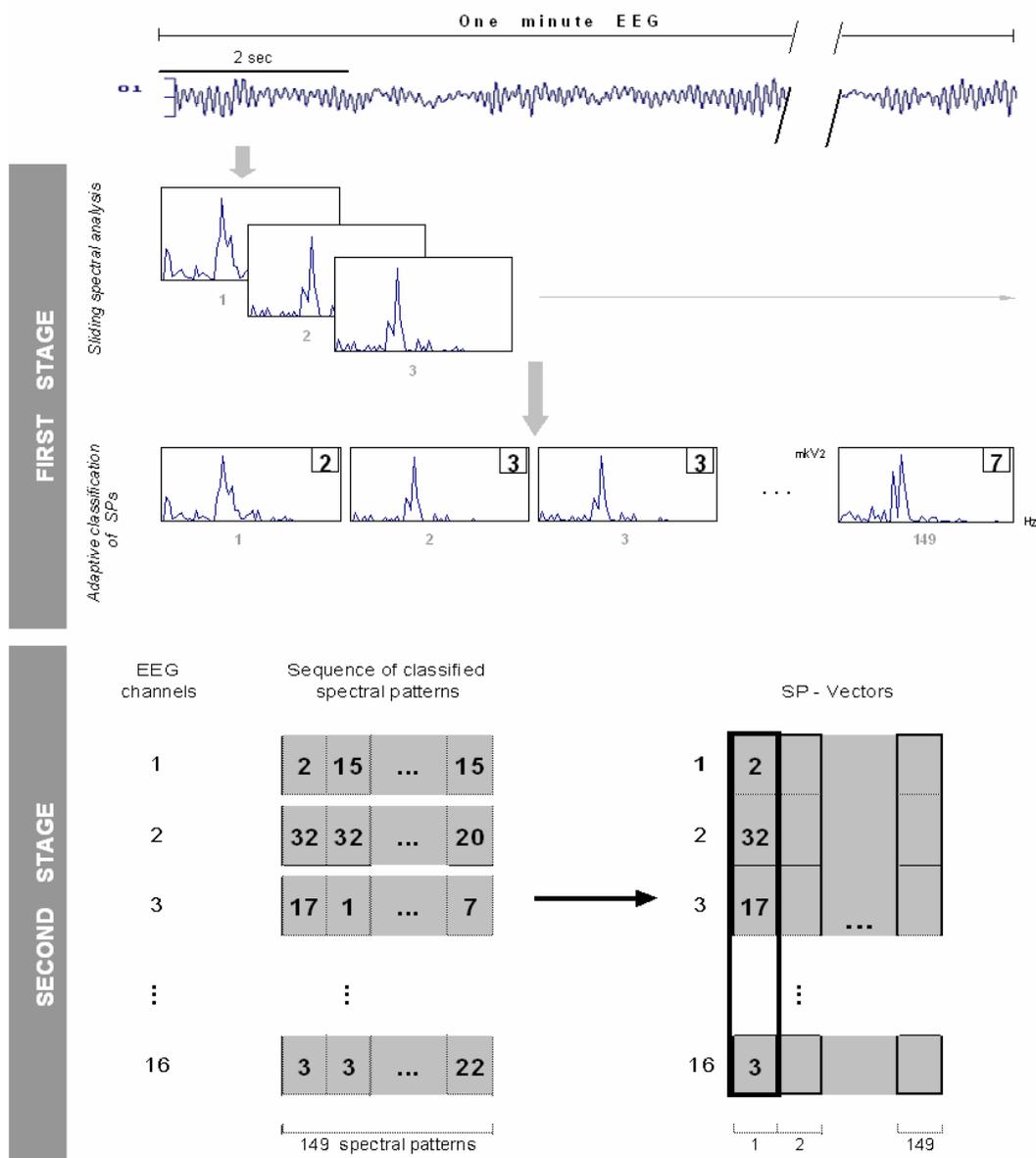
**Figure 1. The scheme of the data processing.** First stage: Sliding spectral analysis and adaptive classification of short-term spectral patterns (SP) were done separately for each subject and each channel of 1-min EEG. $O_1$ = Left occipital EEG channel. Gray small numbers under each SP represent the running numbers from 1 to 149. The number in the square represents the class to which a given SP was assigned during classification procedure. Second stage: Spatio-temporal variability was assessed by constructing a 16-dimentional SP-vector – the set of 16 classified SPs from each of sixteen EEG channels for a particular analysis epoch. 1-16 = EEG channels. The numbers in the sequence represent the classes to which SPs were assigned during classification procedure. Black frame outlines individual SP-vector for the first analysis epoch.

At the second stage, a set of 16 classified SPs in each EEG channel was presented as a 16-dimensional vector (SP-vector) for each analysis epoch. Each component of this 16-dimensional vector corresponds to one SP from one EEG channel and can vary in the range of 0-32 in accordance with its classification number from the standard SP set (zero represents a polyrhythmic SPs) (Fig. 1). Thus, each minute of multichannel EEG was reduced to a sequence of 149 SP-vectors by the number of elementary analysis epochs of the EEG signal.

Each SP-vector represents the overall state of brain electromagnetic field. As it has been suggested, the evolution of SP-vector is governed by the state transition (Kaplan et al., 1999). In order to estimate parameters of topographic variability of EEG SPs, comparison of sequential SP-vectors is of particular interest. The degree of mismatch between two consecutive SP-vectors from this sequence was scored by the number of components distinguishing them (from 0 to 16). The peak values of SP-vector mismatch estimation indicate the moments of substantial transformation of the spatial organization of the spectral descriptions of 16-channel EEG. On the contrary, low mismatch estimations for a series of sequential SP-vectors reflect the periods of relative stabilization of cortical relations between the EEG SPs. Thus, it is possible to trace the periods with more or less spatially variable EEG SPs by the index of the mismatch between sequential SP-vectors. If to specify the threshold of the SP-vector mismatch, it is possible to assess the periods of relative stability of the SPs within which the SP type change at transition from one analysis epoch to another would occur only in a limited number of cortical areas.

Cross-comparisons of all SP-vectors may be represented by a spatial SP map. A spatial SP map is constructed as comparison matrix of all SP-vectors ($n$ = 149). In this matrix the axes refer to the SP-vectors which are ordered temporally, horizontally from left to right, and vertically downwards. Each cell represents the mismatch between any two SP-vectors. The degree of mismatch between two SP-vectors was scored by the number of components

distinguishing them (from 0 to 16, see above). Dark cells in this matrix are associated with low values of the mismatch between these SP-vectors, while lighter cells represent high values.

## *2.4. Statistics*

Surrogate data were used to control for the neural origin of spatio-temporal dynamics of SPs, which is commonly applied as direct probing a signal for a non-random spatio-temporal structure (Ivanov et al., 1996). Surrogate signals have identical parameters with the original signals but do not have spatio-temporal correlations. We used two types of surrogate data which determine "floor" and "ceiling" for spatio-temporal interactions of SPs (Fig. 2).
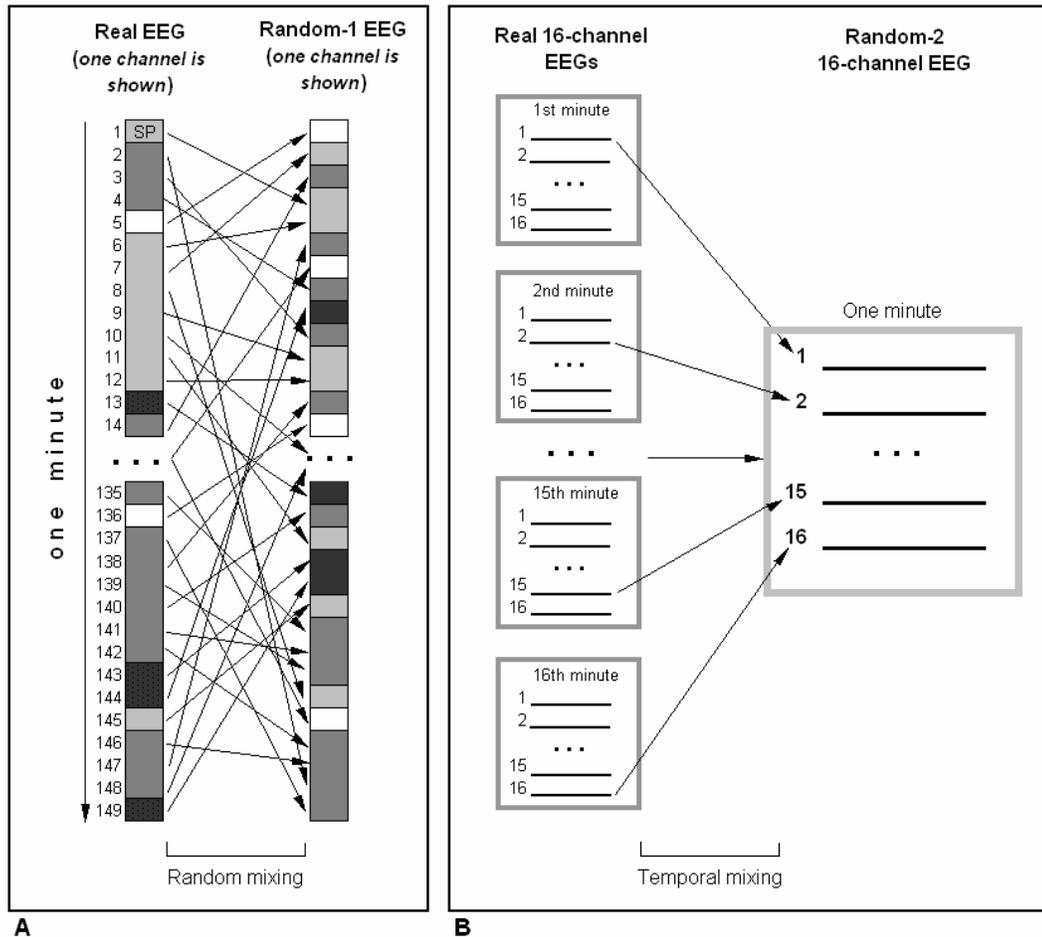


**Figure 2. Construction of surrogate data: (A) Random-1 EEG and (B) Random-2 EEG**. For (A): Different spectral pattern (SP) types are marked in different colors (the same SP types have the same color). Numbers indicate 149 SPs calculated on 2-sec EEG epochs with 50 points shift (0.39-sec). For (B): only one channel of each Real 16-channel EEG (one

minute) was mixed into a separate channel of the Random-2 16-channel EEG (one minute). Thus, mixing of the Real EEG channels was done in such a way that each channel was recorded in a different time.

Construction of surrogate data I (floor). Each channel of the actual EEG was subjected to a randomized mixing of SPs. In such a way, the natural dynamics of SP sequence within each EEG channel was completely destroyed, but the percentage ratio between different types of SPs remained the same. This modified EEG was described as "Random-1" (Fig. 2 A).

Construction of surrogate data II (ceiling). In order to simulate a situation with full temporal mismatch, 16 channels of the initial one-minute EEGs were mixed in such a way that in each of the newly constructed 16-channel one-minute EEG there was no pair of channels recorded at the same time. In such a way, the natural time relations between channels in EEG were completely destroyed, however, the natural dynamics of SP sequence and the ratio between different types of SPs within each EEG channel remained the same. This modified EEG was described as "Random-2" (Fig. 2 B).

In order to reveal statistically significant differences between epileptics, control subjects, and surrogate data the Wilcoxon test was used. Chi-square test for equality of distributions was used when appropriate. Statistical significance was assumed when $P < 0.05$ (only statistically significant values are displayed).

## 3. Results

### 3.1. Dynamics of topographic stabilization of spectral patterns in interictal EEG

Let us consider the total SP dynamics over all EEG channels. In a single analysis epoch SP-vector for epileptics has in average smaller percent of the SP types from their total number in the standard set of SPs than SP-vector for controls ($P < 7E-26$) (Table 1). The mean estimation of the mismatch between the successive SP-vectors of the interictal EEG was also smaller than of the control EEG ($P < 2E-11$) (Table 1). At the same time, the mean estimation of the mismatch between the successive SP-vectors in both interictal EEG of epileptics and in EEG of control subjects significantly differed ($P < 2E-26$) from a Random-1 EEG (EEG where the natural dynamics of SP sequence within each EEG channel was completely destroyed).

**Table 1.** Estimation of the SP type variability for SP-Vector in average for one EEG epoch (*n* = 149).

|        | Control  | Epileptics | Random-1 |
|--------|----------|------------|----------|
| M(D)   | 32±1.2   | 25±1.3     | 32±1.2   |
| M(ME)  | 7.4±0.9  | 6.6±0.8    | 13±0.6   |

M(D) - is a mean value of the estimation of the diversity of SP types in SP-Vector (in % from the total number of SPs in standard SP set); M(ME) - is a mean value of the mismatch estimation between the SP-Vectors for neighboring epochs; ± - Standard deviation; Random-1 EEG - EEG where the natural dynamics of SP sequence within each EEG channel was completely destroyed, but the percentage ratio between different types of SPs remained the same.

This signifies that at the shift of the neighboring vectors by 50 counts, i.e., by 20% of the analysis epoch duration (2 sec corresponds to 256 counts), the SP type changes, in average, in 6.6 (for epileptics), in 7.4 (for controls), and in 13 (for Random-1 EEG) of 16 local EEGs. At longer shifts between the compared EEG analysis epochs, the mismatch estimation increases and reaches its maximum at the shift of 400 counts (for epileptics), at the shift of 300 counts (for controls), and at the shift of 50 counts (for Random-1 EEG) (Table 2). Maximum value characterizes a stochastic level of the SP type change incidence.

**Table 2.** Average mismatch estimation between the SP-Vectors for sequential EEG analysis epochs at different time shift between them.

| Shift      | 50        | 100      | 150       | 200       | 250       | 300           | 350       | 400           | 450       | 500       | 550       |
|------------|-----------|----------|-----------|-----------|-----------|---------------|-----------|---------------|-----------|-----------|-----------|
| Control    | 7.43±0.9  | 9.69±0.8 | 10.84±0.8 | 11.61±0.7 | 11.97±0.7 | **12.10±0.6** | 12.19±0.6 | 12.28±0.6     | 12.23±0.6 | 12.27±0.6 | 12.25±0.6 |
| Epileptics | 6.56±0.8  | 8.75±0.8 | 9.84±0.8  | 10.53±0.9 | 10.89±0.6 | 10.97±0.6     | 10.99±0.8 | **11.03±0.7** | 11.08±0.6 | 11.07±0.6 | 11.11±0.5 |
| Random-1   | **13.31±0.6** | 12.9±0.6 | 13.14±0.5 | 13.19±0.6 | 13.29±0.5 | 13.33±0.6     | 13.33±0.6 | 13.4±0.5      | 13.37±0.5 | 13.3±0.5  | 13.38±0.5 |

Shift designates the number of counts of a digitized EEG signal between the initial moments of the neighboring analysis epochs; "Random-1" = EEG which natural sequence of spectral pattern types has been completely removed in each individual channel. ± - Mean error; Bold indicates the critical shift which characterizes a stochastic level of the SP type change incidence.

Notice, that interictal EEG had significantly smaller values of this mismatch estimation than control EEG for all shifts (*P* < 0.02, Table 2). At the same time, both interictal EEG of epileptics and EEG of control subjects differed statistically significant from a Random-1 EEG (*P* < 0.001). Thus, deterministic influence of the SPs in SP-vectors of the neighboring analysis epochs on each other was absent for Random-1 EEG, was medium for EEG of control subjects, and was maximal for interictal EEG of epileptics.

On closer examination, these observations turn out to be the direct result of parameters of SP variability for the neighboring epochs in each individual EEG channel (see Fingelkurts

et al., 2005a). In fact, if the relative SP change rate at the transition from one epoch to another in each EEG channel is in average equal – as an example – to 0.46 and 0.76 for inter-epoch shifts of 50 and 300 counts respectively (see Table 3, Controls, in Fingelkurts et al., 2005a, in press), and if the SP change in one channel is scored as 1, then the total mismatch estimation for 16 EEG channels should be in average 1 x 0.46 x 16 = 7.36 or 1 x 0.76 x 16 = 12.16, which fits experimental data (Table 1, 2, present study). Therefore, these estimations do not contain information about cooperative properties of the spatial dynamics of SPs. At the same time, such information is represented by parameters of the distribution of individual values of the SP-vector mismatch estimation. If there is no inter-channel synchronization of the SP type change at transition from one analysis epoch to another, then the distribution of the SP-vector mismatch estimations should apparently adhere to normal distribution.

In order to examine the SP-vector mismatch estimations in a situation with full temporal mismatch, a Random-2 EEG (EEG where the natural time relations between channels were completely destroyed, however, the natural dynamics of SP sequence and the ratio between different types of SPs within each EEG channel remained the same) was used.
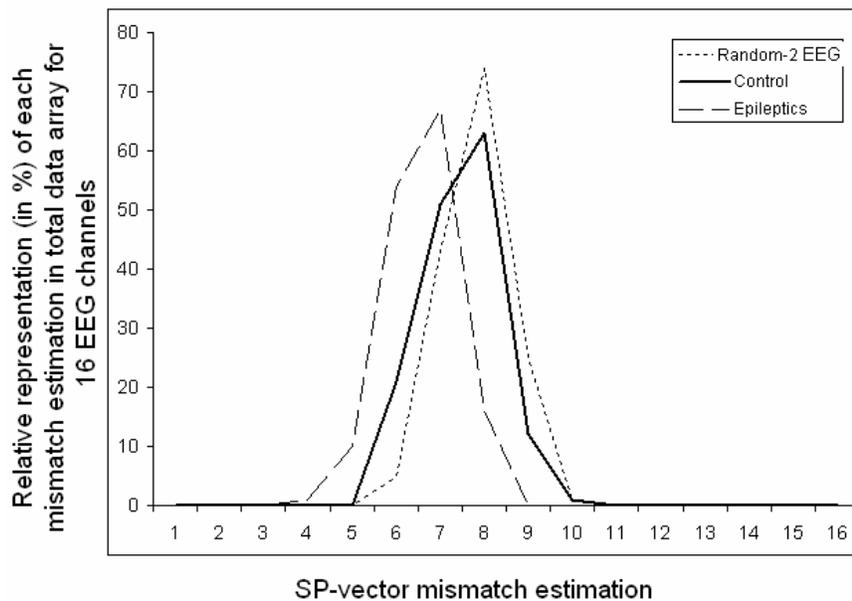


**Figure 3. Distribution of SP-vector mismatch estimations** for real (interictal and control) EEGs, and for Random-2 EEG, in which all the channels were completely mismatched in time. *X*-axis: SP-vector mismatch estimation from 0 (fully identical SP-vectors) to 16 (full mismatch between SP-vectors). *Y*-axis: relative representation (in %) of each mismatch estimation in total data array for 16 EEG channels.

The distributions of the mismatch estimations between the neighboring SP-vectors for the real (epileptics and controls) and Random-2 EEG are presented in Figure 3. As can be seen, this distribution for the Random-2 EEG approaches the standard distribution, what indicates that there is no any inter-channel cooperation of the SP type change at transition from one analysis epoch to another. At the same time, distribution for the real EEG (both epileptics and controls) is markedly different from the standard distribution ($P < 0.05$-$P < 1E-16$, Fig. 3). Thus, about 50-60% of these estimates for EEG of control subjects were grouped in the range from 7 to 8, and about 10-20% were evenly distributed in the range from 6 to 9. Whereas, interictal EEG of epileptics was characterized by a shift of distribution peak to the value 7: about 54-67% of these estimates were grouped in the range from 6 to 7, and about 10-16% were distributed in the range from 5 to 8 ($P < 2E-6$, Fig. 3). These findings appear to conform to the dynamic range of SP-vector variability, which contains estimations of the functional lability of spatial dynamics of SPs.

Thus, with the specified parameters of spectral analysis and EEG acquisition, the characteristics of topographic SP variability fall within a rather wide dynamic range for neighboring analysis epochs which are overlapped by about 80% (see Methods). Such conditions make it possible to estimate temporal dynamics of SP-vector with sufficiently good temporal resolution in 50 counts, i.e., 0.39 sec. In particular, it is possible to trace the periods with more or less spatially variable EEG SPs by the index of the mismatch between sequential SP-vectors.

What was the mean duration of the relative stabilization of SP-vector in interictal EEG?

*3.2. Temporal dynamics of SP-vector in interictal EEG*

If to specify the threshold of the SP-vector mismatch, it is possible to assess the periods of relative stability of the SPs. Within these periods, the SP type change at transition from one analysis epoch to another would occur only in a limited number of cortical areas. The mean duration of the period of the relative SP-vector stabilization as a function of a specified threshold of SP-vector mismatch estimation is presented in Figure 4.

Firstly, let us consider the EEG of control subjects. It is evident that the period of relative SP-vector stabilization increases almost 22 times from 2.9 to 64.1 sequential epochs (i.e., from 2.8 to 26.6 sec) with the increase in the threshold level of difference from 8 to 13, and at the next step of threshold change the stabilization period already occupies almost whole EEG, i.e., 108.2 epochs (43.8 sec) (Fig. 4).
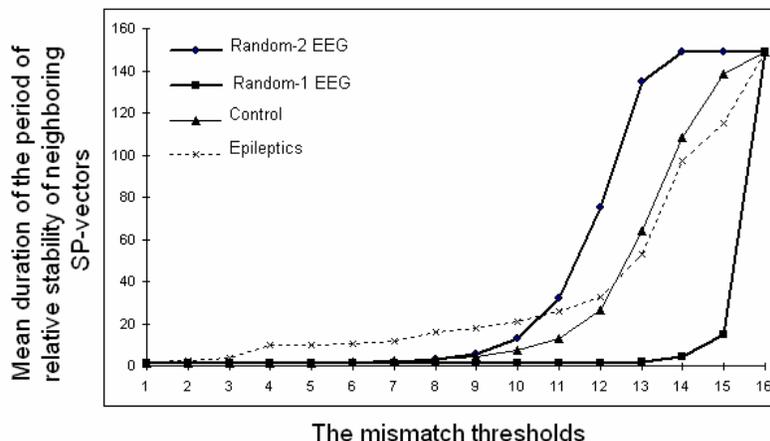
**Figure 4. Dependence of the SP-vector stabilization period on the threshold (specified) of the SP-vector mismatch** for the real (interictal and control) EEGs, and surrogate data: Random-1 EEG – EEG where the natural dynamics of SP sequence within each EEG channel was completely destroyed, but the percentage ratio between different types of SPs remained the same, and Random-2 EEG - EEG where the natural time relations between channels were completely destroyed, however, the natural dynamics of SP sequence and the ratio between different types of SPs within each EEG channel remained the same. *X*-axis: the mismatch thresholds; *Y*-axis: mean duration (for 16 channels) of the period of relative stability of neighboring SP-vectors (at the shift of 50 counts) corresponding to a given mismatch threshold.

To what extent do these estimations reflect the functional cortical inter-regional cooperation? It is obvious, that even in the absence of any interrelation between the EEG channels there should be a certain stochastic level of SP-vector stabilization, which would reflect merely occasional combinations of SP types in different channels. The duration of periods of such occasional stabilization of inter-area relations would probably be substantially lower than in the presence of functional interaction between the areas of EEG derivations.

Figure 4 depicts the mean duration of SP-vector stabilization periods for the Random-2 EEG, in which the inter-channel correlation is completely absent whereas the regularities of SP sequence within each channel remain unchanged. It is evident that, in the range of threshold mismatch between the SP-vectors from 10 to 15, the Random-2 EEG had substantially larger periods of relative SP-vector stabilization than real EEG ($P < 0.001$). The above assumption about longer periods of SP-vector stabilization in the real EEG was not confirmed (possible reasons for that see in Kaplan et al., 1999). It turned out that, in a rather wide range of threshold differences between the SP-vectors, the native EEGs were characterized by notably shorter periods of SP-vector stabilization than the corresponding

estimations for the Random-2 EEG (Fig. 4). At the same time, these estimations did not approach the possible minimum ($P < 0.0001$) determined by the EEG with a fully destroyed natural sequence of the SP types in each individual channel (Random-1 EEG).

Thus, the position of estimation of the mean period of SP-vector stabilization of real EEG in "coordinates" of factors of inter- and intra-channel coordination of the SP sequence enables this EEG to be characterized from the viewpoint of more or less general coordination between its short-term local spectral descriptions.

Estimations of the mean period of SP-vector stabilization in interictal EEG of epileptics differed significantly from such estimations for control EEG for different threshold mismatch between the SP-vectors ($P < 0.001$) (Fig. 4). At the same time, interictal EEG differed significantly from both Random-1 ($P < 0.00006$) and Random-2 ($P < 0.001$) EEGs. Note, that interictal EEG was characterized by increased periods of relative SP-vector stabilization for lower levels of threshold mismatch between the SP-vectors (from 4 to 10) when compared with control and surrogate EEGs ($P < 0.002 – P < 0.0005$) (Fig. 4).

*3.3. Temporal heterogeneity of the spatial SP map for interictal EEG*

Figure 5 illustrates spatial SP maps for interictal EEG of epileptics and EEG of control subjects. Both spatial SP maps are characterized by non-uniformity, which is indicative of nonstationarity (temporal dynamics of topographic variability of SPs). At the same time, interictal EEG had larger periods of temporal SP-vector stabilization (marked by areas of the same color) with involvement of more brain areas (labeled by darker color) than control EEG (Fig. 5). These periods of temporal SP-vector stabilization represent periods of metastability in brain activity. The intermittent recurrence of shading along a horizontal and/or vertical axis is associated with recurrence of the metastability. It can be seen that interictal EEG was considerably more recurrent than control EEG.

**4. Discussion**

Results obtained in the present study confirm our hypothesis that interictal EEG without signs of epileptiform abnormalities would have episodes of the metastablity of different lifespan and size (the number of EEG channels involved) when compared with EEG of healthy subjects. In spite of the fact that interictal EEG had not any visible signs of epileptiform abnormalities, observed results permitted us to outline some peculiarities of the

formation of steady cortex inter-area cooperations (independently on their correlation and coherence) during epilepsy in comparison with EEG of healthy subjects.
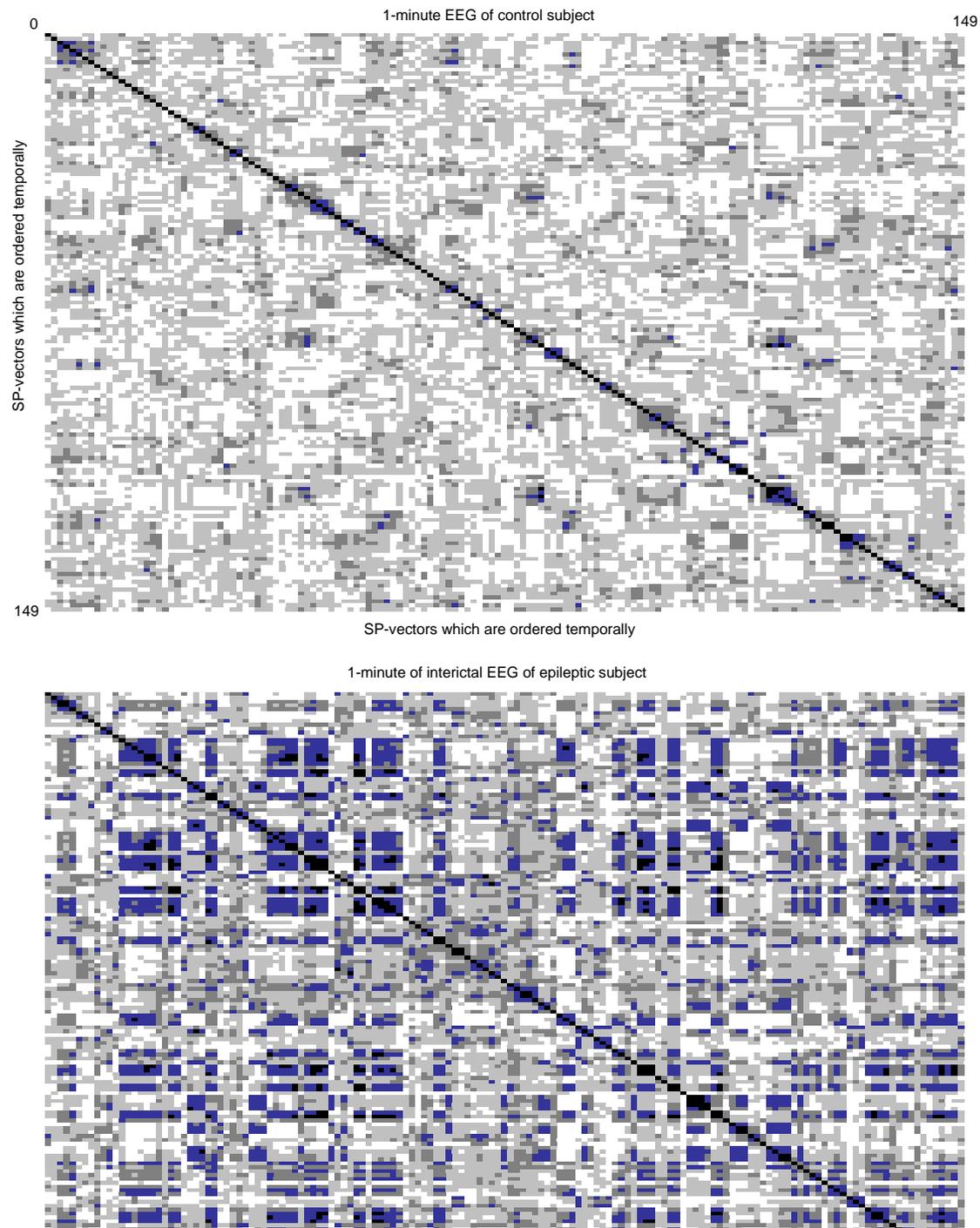


**Figure 5. Spatial SP map.** A spatial SP map is constructed as comparison matrix of all SP-vectors ($n = 149$) for 1-min EEG. In this matrix the axes refer to the SP-vectors which are ordered temporally, horizontally from left to right, and vertically downwards. Each cell represents the mismatch between any two SP-vectors. The degree of mismatch between two SP-vectors was scored by the number of components distinguishing them (from 0 to 16) (see

Methods). Dark cells in this matrix are associated with low values of the mismatch between these SP-vectors, while lighter cells represent high values. Black = 0-3 components distinguishing two SP-vectors; Dark blue = 4-7 components; Dark grey = 8-10 components; Light grey = 11-13 components; White = 14-16 components.

A single EEG spectrum illustrates the particular integral dynamics of tens and hundreds of thousands of neurons in a given cortical area at a particular point in time (Dumermuth and Molinari, 1987). Therefore, the absence of variance of a single spectrum during several analyzed epochs proves that in a given cortical area the same macro-regimen of neuronal pool activity is maintained during that period. This phenomenon of a temporal stabilization may be explained by stabilization of oscillatory patterns in the brain. In such context, the EEG SP stabilization simultaneously in several cortical areas may reflect formation of steady cooperations between cortical areas independently on particular characteristics of these SPs within each EEG channel. Result of such cooperations represents a metastable state (for the resent review on metastability in the brain, see in Fingelkurts and Fingelkurts, 2004; 2005).

*4.1. Topographic stabilization of brain oscillations in interictal EEG*

What are the regularities of such spatio-temporal stabilization of brain oscillations (indexed by SPs) in interictal EEG? It was found that even in strongly overlapping (by 80%) 2-sec analysis epochs in interictal EEG (as well as in control EEG) there are virtually no cases when the unchanged SP type simultaneously persists in all 16 EEG channels at transition from one analysis epoch to another (Table 1). This finding replicates our earlier results (see Kaplan et al., 1999) and suggests that global stabilization of the functional state within *several seconds* is an exception rather than a rule for brain activity even during epileptic condition. It is likely that the pattern of the functional stabilization of the cortical inter-area relations can be expressed as a mosaic of dynamic constellations of different brain regions which exist simultaneously but differ in the moments of their generation and termination. These constellations can be involved in realization of certain macro-operations of brain activity. The lifetime of such spatial "operational modulus" is determined by the duration of the period of joint stabilization of the main dynamic parameters of neuronal activity which are involved in these modules. At the level of EEG, these processes are reflected in stabilization of the SPs in corresponding EEG channels that comprises a metastable state (Kaplan, 1998).

Smaller values of mean estimation of the mismatch between the successive SP-vectors in the interictal EEG than in control EEG (Table 1) signify that changes of SP type during transition from one analysis epoch to another occur in less number of EEG channels in the interictal EEG than in control EEG. Such observation suggests that interictal EEG should have a wider spatial stabilization of SPs than control EEG. In other words, interictal EEG should be characterized by spatial "operational modules" which contain more cortex areas than control EEG. At the same time, a larger shift of the neighboring SP-vectors when the mismatch estimation reaches its maximum in the interictal EEG than in control EEG (Table 2) reflects that interictal EEG has a larger deterministic influence of the SPs of the neighboring analysis epochs on each other than control EEG. It means that brain oscillations of cortex regions involved in operational modules tend to longer periods of temporal stabilization in interictal EEG when compared with control EEG.

These observations were supported by the fact that interictal EEG of epileptics was characterized by a shift of distribution peak of estimation of the mismatch between the neighboring SP-vectors to smaller values when compared with control EEG (Fig. 3). This reflects a decrease of spatio-temporal variability of brain oscillations (indexed by SPs) during epilepsy.

*4.2. Temporal dynamics of SP-vector in interictal EEG*

By specifying the threshold of the maximal mismatch between the neighboring SP-vectors, it is possible to set the spatial scale of operational modules for which the mean duration of stabilization period of inter-area relations is to be determined. Obtained in this study results for interictal EEG demonstrated that stable combinations of SPs in 5-12 EEG channels predominantly persist about 20 sequential SP-vectors, and scatter into smaller spatial modules only at the next step of the analysis of SP-vectors (Fig. 4). This means that interictal EEG was characterized by longer periods of temporal stabilization (up to 9.4 sec) for operational modules, which comprise larger number of cortical areas (from 5 to 12) than control EEG. These observations confirm the suppositions which were based on the results discussed in the previous section that (a) brain oscillations of cortex regions involved in operational modules tend to longer periods of temporal stabilization in interictal EEG when compared with control EEG and (b) interictal EEG should be characterized by spatial operational modules which contain more cortex areas than control EEG.

Presented data suggest that epileptic brain is characterized by larger global coordination of brain oscillations (indexed by SPs) from different cortex areas than intact brain. And this spatial coordination persists for longer time during epileptic than during healthy condition, thus suggesting less dynamic performance of cooperative brain operations (Kaplan et al., 1999) – dynamic rigidity. A substantial increase in the duration of periods of temporal stabilization of different brain oscillations under the influence of benzodiazepine (enhancer of inhibitory brain systems) (Fingelkurts et al., 2004), and during application of neuroleptics (Kinoshita et al., 1995) supports this idea.

Perhaps, results discussed in this section are the reflection of several functional reorganizations at micro- and macro-levels during epilepsy (Steriade, 1993). The mechanism of epileptogenesis in patients with idiopathic generalized epilepsy is thought to involve an increase in diffuse cortical hyperexcitability related to an alteration in thalamocortical interaction due to a profound influence of network activities on the membrane potential, apparent input resistance, and backpropagation of action potentials. The rhythmic recurrence of spike bursts and spike trains fired by thalamic and cortical neurons may lead to plasticity processes in neocortical neurons. If these phenomena are not constrained by inhibitory processes, they induce paroxysmal activity (Steriade, 2001). Thus, it was demonstrated that in epileptic brain neurons have a shift of membrane depolarization (Matsumoto and Ajmone-Marsan, 1964), which causes an increase of generation of action potentials resulting in runaway excitation (Schwartzkroin, 1994). This, in turn, leads to an enlargement of the region of excitement processes in the brain. As a result, new brain areas are involved in coordinated activity. Now, larger than before set of cortex areas may produce larger coordination influences which further recruit and entrain other neuronal assembles from new areas by loss of inhibition and synchronization into a critical mass (Wyler and Ward, 1992).

*4.3. Temporal heterogeneity of the spatial SP map for interictal EEG*

Analysis of spatial SP maps demonstrated that the dynamics of topographic variability of short-term SPs appear to reflect the piecewise stationary process of functional integration of cortical structures in operational modules of different size and lifetime. Thus, the epileptic brain was characterized by a larger size and a lifetime of operational modules than the intact brain (Fig. 5). This means that spatial SP maps during epilepsy were more homogeneous than during normal conditions. One may assume that decrease in spatio-temporal variability of brain oscillations in patients with generalized epilepsy was simply due to background EEG

slowing (the absence of alpha activity). This is unlikely due to the following: in our previous study (Fingelkurts et al., 2005a) where we have analyzed the same patients it was demonstrated that their EEG was characterized by increase in the percentage of alpha-rhythmic segments and by shift to faster frequencies in all observed brain oscillations (Fig. 2 Fingelkurts et al., 2005a).

It seems that chronic epilepsy determined not by a focus of pathological activity, but rather by an epileptic system which contains a set of distributed oscillatory resonances involved in common activity (Saradjeshvili, 1971). This is supported by the fact that spectral topographic differences during epilepsy are reduced (Kambarova et al., 1986; see also Fingelkurts et al., 2005a). Such observations are in line with the facts that (a) increased synchronization was demonstrated during the seizure-free interval (Mormann et al., 2000) and (b) interictal EEG was marked by less complex dynamics than it was observed under healthy conditions (Bhattacharya, 2000; Jing and Takigawa, 2000). When the physiologic system becomes less complex, its information content is degraded (Goldberger et al., 1984). As a result, such system is less able to cope with the demands of a constantly changing environment.

Taken together, these results suggest that functional state of epileptic brain is characterized by a dynamic reorganization of its activity due to altering coordination influences between different neuronal assembles which is probably accompanied by a reduction of afferent input and as a result, - by more dependent neuronal activity on intrinsic mechanisms (Lopes da Silva, 1991). Neuronal assembles operate in these conditions as resonance systems that limits their involvement in new type of activity, thus providing a dynamic rigidity. At the same time, dynamic rigidity is not permanent: epileptic brain is rather characterized by fluctuations between less and more coordinated states (metastability). Indeed, the findings of this study (Fig. 5) and of literature (Martinerie et al., 1998) that interictal EEG had significantly more intermittent recurrence than control EEG suggest that epileptic brain repeatedly make the abrupt transitions into and out of coordinated state thus reflecting the adaptive nature of brain activity during epilepsy.

One may assume that an increased level of regional coordination may increase the likelihood of a possible seizure. Typically, the number and the strength of the coupling of entrained electrode sites increase as the time to seizure onset approaches (Sackellares et al., 1999). Indeed, high regional synchrony between EEG channels was observed near the onset of a seizure (Franaszczuk and Bergey, 1999). Probably, the transition into seizure occurs only

if conditions of a long-term spatio-temporal dynamical entrainment of a critical mass of interconnected regions of brain are met (Iasemidis and Sackellares, 1996).

*4.4. Comparison with surrogate data*

All results of the present study would be difficult to interpret without comparing them with similar data obtained for EEG with complete temporal mismatch of SPs within each EEG channel and between all 16 EEG channels. Present study demonstrated that random combination of components of a 16-dimensional SP-vector "creates" totally different estimates of spatio-temporal stabilization of this SP-vector than is observed under conditions when the EEG channels are functionally correlated (Table 1, 2; Fig. 3, 4). The results of the surrogate tests for statistical validity indicated that our findings are indeed caused by different characteristics of the interictal EEG and cannot be explained by merely random processes.

Before coming to the final conclusions, a technical question should be raised: whether the reported cortical spatio-temporal modules, within which steady relations are formed by the mutual stabilization between the types of SPs in each EEG channel are real or are affected by the volume conduction between electrodes? The latter is unlikely because if results would be determined by volume conduction, then surrogate data (Random-2 EEG) where the natural time relations between EEG channels were completely destroyed would not show any differences from the actual EEG. This was not the case (see Fig. 4). Additionally, in our previous study (Fingelkurts et al., 2005a) where we have analyzed the same patients it was demonstrated that results of the study cannot be attributed to the EEG recording with a linked ear reference electrode or volume conduction for the following reasons: (a) the occipital and frontal regions clearly showed different accentuations in their EEG effects and (b) the analysis revealed that each EEG channel or small group of channels had its own specific SP set.

*4.5. Concluding remarks*

Taken together, results of this study suggest that EEG correlate of chronic epileptization of the brain is not a separate frequency band(s) and is not a correlation between them in different cortex regions, but rather a particular metastable state of biopotential field which can be estimated by SP-vector. It seems that cortical networks can display different states of

coordination independently on their correlation and coherence using brain oscillations at multiple frequencies based on the size and configuration of the neuronal assemblies involved (Lopes da Silva, 1991).

Considering that interictal EEG in the present study had not any signs of epileptiform abnormalities, observed mutual stabilization between the types of SPs in EEG channels independently on their correlation and coherence is an inherent part of the mechanisms of ictogenesis which take place long before the actual onset of a seizure. This conclusion is supported by the fact that there is a gradual spatial entrainment among critical cortical sites that evolves over days preceding the first seizure of a series (Sackellares et al., 1999).

The fact that all results were significantly different from surrogate EEGs reflects a non-occasional and thus, most likely, an adaptive nature of spatio-temporal reorganization of interictal EEG during chronic epilepsy.

Further study with a larger number of patients is required to quantify the specificity and the relationship between the findings of this study and different subtypes of epilepsy.

**Acknowledgements**

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