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INTERICTAL EEG AS A PHYSIOLOGICAL ADAPTATION
Part I: Composition of brain oscillations in interictal EEG

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Abstract: *Objective:* In the present experimental study, we examined the compositions of brain oscillations and their temporal behavior in broad frequency band (0.5-30 Hz) in interictal EEG without epileptiform abnormalities during generalized epilepsy in resting conditions. *Methods:* The exact compositions of brain oscillations and their percent ratio were assessed by a probability-classification analysis of short-term EEG spectral patterns (SPs), which reveals temporal dynamics of these SPs and results in the probability classification profile. *Results:* It has been demonstrated that the interictal EEG was characterized by (a) a shift towards higher frequencies in all observed brain oscillations, (b) an increased amount of polyrhythmic activity, (c) a decrease in SP types diversity, (d) a decreased relative incidence of the SP type change in the transition between neighboring EEG epochs of the same EEG, and (e) an increased temporal stabilization periods of polyrhythmic activity. All these were observed in distributed brain areas. *Conclusions:* It was suggested that these findings reflect a disorganization of neurodynamics in the epileptic brain. At the same time, the fact that all these indices were significantly different from surrogate EEG reflects a non-occasional and thus, most likely, an adaptive nature of the microstructural reorganization of interictal EEG. *Significance:* Parameters of interictal EEG without the signs of epileptiform activity can be considered as additional information in premorbid diagnostics of epistatus.

Keywords: Epilepsy; Interictal electroencephalogram (EEG); Multiple brain oscillations; Short-term spectral patterns; Probability-classification analysis.

1. Introduction

Epilepsy is amongst the most common disorders of the nervous system (Joensen, 1986) and epileptic seizures are a principal brain dysfunction with a significant impact on public health, as they affect 0.8% of humans (Martinerie et al., 1998). For the vast majority of

patients, seizures occur in the absence of any identifiable warning and about 20% of these patients are resistant to drug treatment (Sander and Shorvon, 1987). Such a situation requires further investigation of the characteristics of the epileptogenic brain itself in order to find the rules which determine the epileptic brain functional state and lead to seizure. In addition, the epileptogenic process is a natural model - its main manifestations consist of functional deviations of the healthy brain - permitting researchers to shed the light on many aspects of the healthy brain by studying the pathological changes in different brain functions.

Epilepsy may be considered as the manifestation of re(dis)organization of a highly integrated functional whole (i.e. the brain) governed by certain inherent laws. For example, Iasemidis and co-authors demonstrated that "epileptic seizure occurs when spatiotemporal chaos in the brain dynamics fails:", in other words "the seizure represents a mechanism for returning brain dynamics from so-called order to a more normal (chaotic) state" (Iasemidis and Sackellares, 1996, for the comprehensive review, see Sackellares et al., 1999). This finding strongly suggests that the mechanisms underlying epilepsy cannot be fully understood through investigation of the synaptic transmission and neuronal physiology; rather they should be interpreted in the context of the dynamical properties of a reorganized large-scale system. As is well known, new qualities may emerge at a macroscopic level in a system via self-organization processes (Haken, 1988). Here, electroencephalogram (EEG) and magnetoencephalogram (MEG) provide a satisfactory scale for accessing the large-scale dynamic of the brain's activity (with a temporal resolution in the order of milliseconds) associated with health and disease (Livanov, 1977; Nunez, 2000). Indeed, spontaneous activity at the cortical level does reflect different neurological states and functional properties of neuronal assemblies (Lopes da Silva, 1991).

Recently, the brain has been seen as a massively interactive, dynamic system, without any centralized control which displays a characteristic metastability around certain homeostatic levels (Kaplan 1998; for the resent review on metastability in the brain see Fingelkurts and Fingelkurts, 2004). In the metastable regime of brain functioning, the individual parts of the brain exhibit tendencies of functioning autonomously at the same time as they exhibit tendencies of coordinated activity (Bressler and Kelso, 2001). In this context chronic epilepsy may be conceptualized as a new metastable state around altered homeostatic levels (Velazquez et al., 2003). At this point adaptation may set in, which is a semipermanent self-reorganization of the system which may lead to anatomical, biochemical and functional changes, and to the shift of the receptor sensitivity threshold. Such adaptation makes it possible to live with the disease.

From this point of view the epileptic brain should have characteristic differences from the intact brain even in the interictal period (i.e., EEGs recorded during the seizure-free interval) without signs of any epileptiform abnormalities. There are several converging pieces of evidences to support this idea mentioned above. Thus, it was demonstrated that (a) the degree of EEG complexity in the interictal period is significantly reduced for epileptics for most of the electrodes (Ravelli and Antolini, 1992; Weber, 1998; Bhattacharya, 2000; Jing and Takigawa, 2000); (b) successive changes (decrease in synchronization) in brain dynamics start long before the actual seizure (Mormann et al., 2000); (c) the presence of regional slow-wave activity in interictal EEG (Gastaut et al., 1985; Koutroumanidis et al., 1998; Massa et al., 2001); (d) a number of spectral measures differed between epileptics with normal interictal EEG and healthy control (Drake et al., 1998); (e) a significant slowing of alpha-frequency activity exists (Gelety et al., 1985); and (f) the epileptic process is governed by long-term recurrent trends in spatio-temporal dynamics (Martinerie et al., 1998).

However, in the majority of cases the interictal EEGs without signs of epileptiform patterns are considered normal (Desai et al., 1988). This can be explained by the fact that the interictal EEG is examined often visually or with the help of conventional spectral decomposition. The latter approach uses averaged EEG parameters, based on extended periods of time and/or broad fixed frequency bands for a specific lead. At the same time, as was demonstrated, the averaging of the EEG signal may not only mask the temporal dynamics of the EEG characteristics, but may also lead to ambiguous data interpretation (Kaplan and Shishkin 2000; Fingelkurts et al., 2002, 2004b). Hence, when examining the average brain electromagnetic parameters, it is not clear whether the observed phenomenon is real (not the "virtual" result of averaging procedure) and typical for the whole analyzed signal. For example, it is not clear: whether the total power of particular brain oscillation is typical for the whole analyzed signal or for just a small portion of it. In fact, and as explored in our early work (Fingelkurts et al., 2003a, 2004b) the total power spectrum does not characterize each of the individual power-spectra for each EEG segment. Moreover, according to Dumermuth and Molinari (1987), total EEG power may be affected by polyrhythmic disorganized activity (a mixture of activity of small neuronal subpopulations each with its own mode (Tirsch et al., 2000)). In this case different indices and parameters of EEG may suffer from the influences of such activity, instead of reflecting true rhythmic activity.

Additionally, in all the studies related to spectral analysis of the interictal EEG, the frequency bands were predefined and taken in isolation from each other. This does not permit

researchers to examine the behavior of the actual/natural composition of brain oscillations involved. At the same time, brain functions are indeed represented by multiple oscillations (Basar et al., 2000).

In connection to this, it seems reasonable to examine the actual composition of brain oscillations and their temporal behavior in the broad frequency band (0.5-30 Hz) in interictal EEG without epileptiform abnormalities during resting conditions. To assess the exact composition of brain oscillations, their percent ratio and temporal dynamics one should use a robust, model-independent technique which considers the nonstationarity of EEG, does not require prior knowledge of the underlying dynamics and produces results which are easye to interpret in terms of their neurophysiological correlates. The probability-classification analysis of short-term EEG spectral patterns (SP) (Kaplan et al., 1999; Fingelkurts et al., 2003a) satisfies all these criteria. This analysis results in temporal dynamics of short-term EEG SPs and probability classification profile (PCP): short-term power spectra are computed from a long EEG time series; then the individual power spectra are classified using a set of reference spectra; subsequently, the relative occurrence of each class is determined, resulting in PCP for each electrode and subject.

It was demonstrated that PCP is highly stable over time (Fingelkurts et al., 2005 in press) and provides an adequate and detailed description of electromagnetic brain activity during health (Kaplan et al., 1999; Fingelkurts et al., 2003a,b) and pathological brain conditions (Fingelkurts et al., 2000). Another advantage of using PCP is that polyrhythmic disorganized activity is automatically isolated in a separate class, and thus does not affect classes with true rhythmic activity (Fingelkurts et al., 2003a). At the same time, class with polyrhythmic disorganized activity in its turn could be also subjected to analysis. This is justified since it was reported that the ratio of polyrhythmic disorganized activity in EEG spectrum is strongly influenced by genetic factors (Meshkova, 1988), and as was explored in our early work (Fingelkurts et al., 2003a, 2004b) the amount of polyrhythmic disorganized activity in EEG is dependent on the functional brain state.

Hence, the aim of this study was to investigate the actual composition of brain oscillations and their temporal behavior in the broad frequency band (0.5-30 Hz) in interictal EEG without epileptiform abnormalities during resting conditions. Considering that chronic epilepsy may be conceptualized as a meta-stable state around new homeostatic levels of the brain, we hypothesize that interictal EEG without signs of epileptiform abnormalities have a number of differences from the EEG of healthy subjects. Such differences may constitute a tonic component of EEG microstractural organization (Fingelkurts et al., 2000) which can

serve as the field of action for hidden abnormalities governed by short-term causalities in the time series.

2. Methods

2.1. Subjects

Six medication-free right-handed patients with generalized epilepsy (aged 17-40, 3 females) were selected for the study. Inclusion criteria were the persistent presence of epilepsy for more than one year, and the absence of (a) any epileptiform activity in the interictal EEG, and (b) any neurological condition other than epilepsy, or any acute or chronic medical illness at the time of the EEG registration. 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.

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.

To examine the actual composition of brain oscillations and their temporal behavior in EEG, a total of 18 (for epileptics) and 14 (for control subjects) 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. Thus, 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. The works which have studied the effect of epoch length on the variability of power spectrum (Levy, 1987; Kaplan, 1998) demonstrated that (a) the epoch-to-epoch variability with power spectra computed using 2-sec epochs was significantly less than the variability when power spectra were computed using longer epoch lengths, and (b) analysis using 2-sec epochs identified changes more rapidly than analysis using any longer epoch length, and the differences were clinically significant as well. Moreover, a 2-sec epoch is long enough to get a reliable estimation of the lowest frequency (0.5 Hz), and is short enough to be stationary (McEwen and Anderson, 1975; Inouye et al., 1995). Taken together these findings suggest that 2-sec epoch lengths are preferable when power spectrum

analysis is used. Thus, it is possible to obtain an entire set of individual short-term spectra of various types in accordance with the number of stationary EEG segments. Frequency resolution of 2-sec spectral patterns was a (sampling rate)/(number of samples in 2-sec epoch) = 128/256 = 0.5 Hz. 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. 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.

As a result, the total number of individual spectral patterns (SP) for each channel of 1-min EEG was 149 (Fig. 1). These SPs formed the multitude of the objects for further classification procedure. 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 (SCAN0.1, was suggested by A.Ya. Kaplan, Moscow State University). Details of this procedure can be found in Fingelkurts et al., 2003a. In short, this analysis was undertaken in two stages (Fig. 1). During the first stage, sequential single EEG SPs were adaptively classified in each channel of 1-min EEG using a set of standard SPs.

Standard SPs were generated not before-hand but 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 peak-detection was based on normalizing the SP to within-SP relative percentages of magnitude, where acceptance is achieved when the peak exceeds a given (60%) percent-magnitude (100% corresponds to the magnitude of the highest peak within the SP). 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.

The 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. The current SPs that their CC passed the acceptance criteria of $r \geq 0.71$ were attributed to their respective standard classes. Therefore, the same current SPs may be included simultaneously into different standard classes. The CC acceptance criteria r was determined such as for $r \geq 0.71$ more than 50% of the SP variances were coupled/associated.

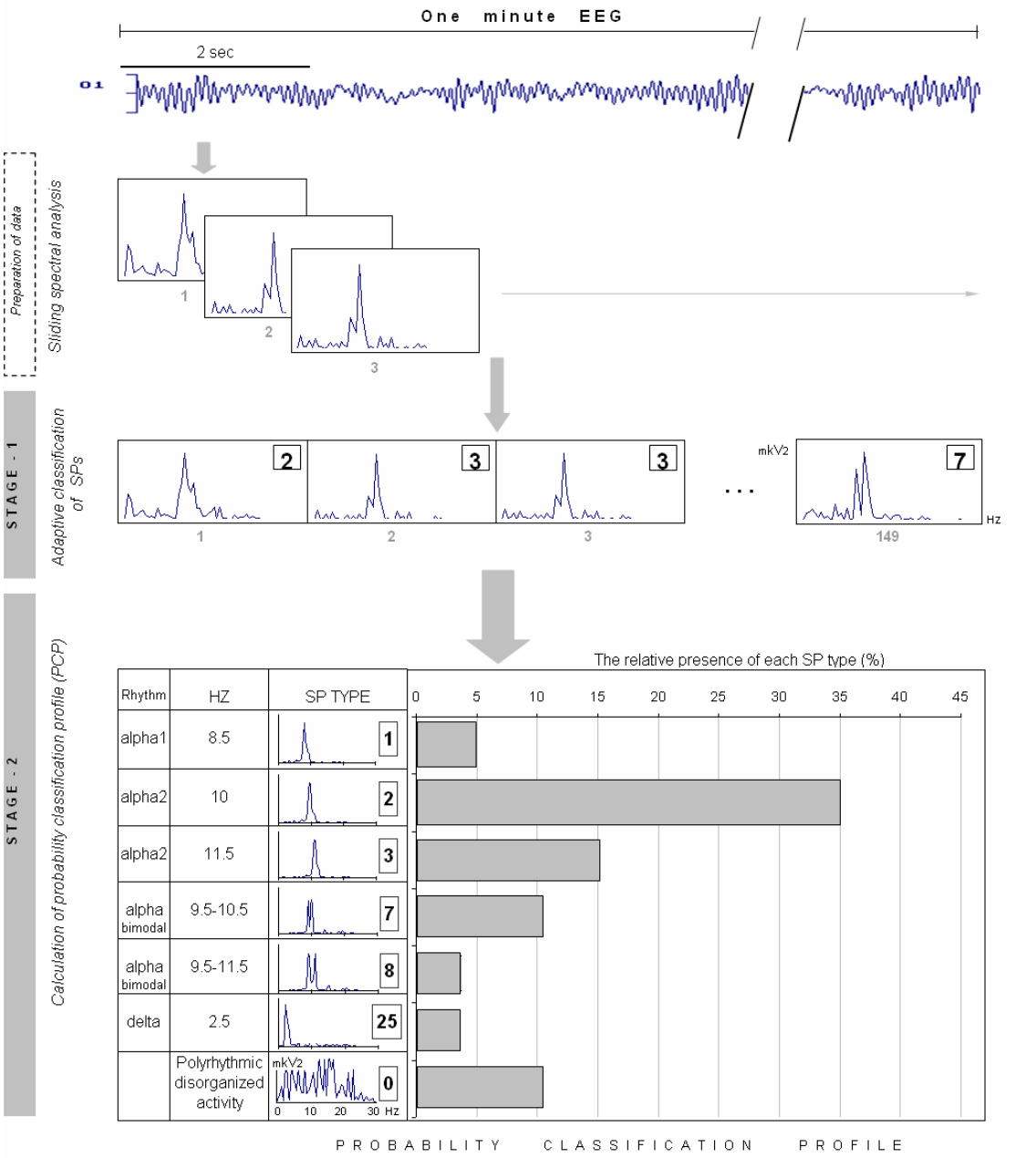


Figure 1. The scheme of the data processing. Sliding spectral analysis, adaptive classification of spectral patterns (SP) and calculation of the probability-classification profiles (PCP) were done separately for each subject and each channel of 1-min EEG. Modified from Fingelkurts et al., Int.J. Psychophysiol, 2005, in press.
Gray small numbers under each SP represent the numbers from 1 to 149. The numbers in the square represent the labels – types of classified SPs. Column "Hz" represents the main dominant peak(s) in particular SP. Presented PCP illustrates the composition and percent ratio of brain oscillations in O1 EEG for control subject during closed eyes condition.

During the *second step*, the current SPs 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, standard SPs 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: each of current SPs was attributed to only one actual SP class for which the CC was the maximum of the set of $r \geq 0.71$.

The adaptive classification technique employs several adequate correction algorithms to achieve a significant reduction in the variance of single spectral estimations and to take into account the relationship between neighbor frequencies in the frequency continuum (Kaplan et al., 1999; Fingelkurts et al., 2003a). This justifies the use of individual short-term SPs and increases the sensitivity of this analytical approach in revealing the dynamics of EEG oscillatory patterns. This SP classification method made it possible to identify up to 100% of the individual single spectra in the EEGs due to the algorithm's ability to adapt to local signals. Considering that 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), it can be said that the SPs within each class are generated by the same or similar dynamics with the same or similar driving force. SPs from different classes, however, have had in effect different driving forces and therefore have been generated by different dynamics (Manuca and Savit, 1996). In this case, one type of SP may be considered as a single event in EEG phenomenology from the viewpoint of its spectral characteristics (see Appendix in Fingelkurts et al., 2005, in press). In this context, this analytical approach implicitly considers the nonstationarity of EEG (for the review on EEG nonstationarity see Kaplan and Shishkin, 2000) and produces results which, in contrast to many other approaches, have a neurophysiologically plausible interpretation and are clinically recognizable.

As a result of the adaptive classification technique, each current SP was labeled according to the index of the class to which it belongs. Thus, a sequence of SP labels that represents the sequence of EEG oscillatory states through which the system passes was obtained. Hence, each EEG signal was reduced to a sequence of individually classified SPs (Fig. 1).

At the second stage, PCPs of SPs for each channel of 1-min EEG in each subject were calculated (Fig. 1). These PCPs were calculated by taking the relative number of cases of an SP type as a percentage of the total amount of all SPs within each EEG channel – presented as the histogram of relative presence of each SP type (Fingelkurts et al., 2003a). PCPs were averaged across 14 (for healthy subjects) and 18 (for epileptics) 1-min EEG signals separately for each EEG channel. It was expected that these PCPs would make it possible to illustrate in detail (in SP description) the composition of brain oscillations and their percent ratio.

In addition, three indices were calculated for each subject separately for each condition and channel of each 1-min EEG:

a) The percentage of *polyrhythmic/disorganized activity* (PA), – represented by polyrhythmic spectral patterns. A polyrhythmic spectral pattern constitutes a pattern where peaks occupy a majority of the frequencies within the studied range. Such a spectral pattern indicates a mixture of activity of small neuronal subpopulations, each with its own mode (Tirsch et al., 2000).

b) Index of *non-homogeneity of classification profile* (NHCP) was estimated as a ratio of the number of SP types detected in a given 1-min EEG to the total number in the standard set (32 standard SPs – 100%). This index indicates how many different SP types participate in PCP.

c) Index of *non-stability of classification profile* (NSCP) is a percent value that reflects how the set of distinct SP types changes across the three EEG sub-segments of 20-sec within a complete 1-min.

$$NSCP = \left(1 - \frac{n1 + n2 + n3}{3 * ns}\right) * 100 ,$$

Where n_i, is the number of distinct SP types found in a 20-sec EEG segment i; n_s is the number of SP types found in all three 20-sec EEG segments. The range of this index is 0–67.

2.4. Statistics

We studied the behavior of each type of spectral patterns separately and did not make any conclusions *per se* about any differences between PCPs. In order to reveal any statistically significant differences in the relative presence of each SP type in PCPs between

epileptics and control subjects, the Wilcoxon test was used separately for each type of SPs presented in the PCPs. Statistical significance was assumed where $P < 0.05$ (only statistically significant values are displayed). Since we intended to assess each variable in its own right, no Bonferroni correction was applied (for the problems associated with Bonferroni adjustments, see Perneger, 1998). The decision not to make adjustments for multiple comparisons will lead to fewer errors of interpretation when the data under evaluation are not random numbers but actual observations of nature (Rothman, 1990).

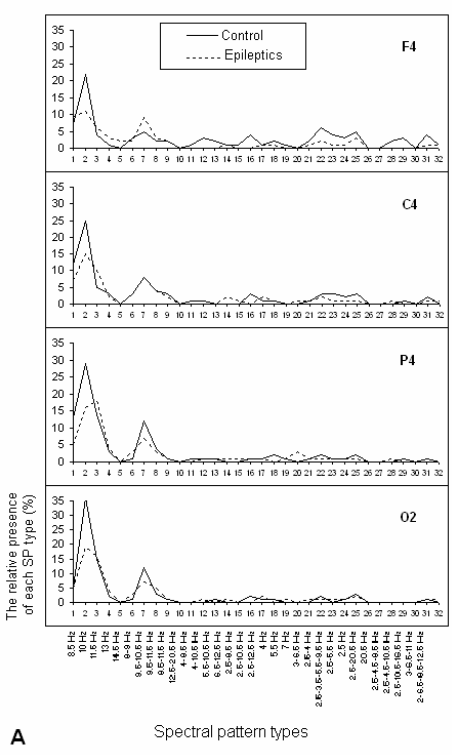
Surrogate data were used to control for the neural origin of the temporal dynamics of SPs, which is commonly applied as direct probing a signal for a non-random temporal structure (Ivanov et al., 1996). Surrogate signals have identical parameters with the original signals but do not have temporal correlations. Thus, each channel of the actual EEG was subjected to a randomized mixing of SPs. In such a way, the natural dynamics of the 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".

3. Results

3.1. General description of the interictal EEG of epileptics

By using the adaptive classification method, 100% of individual EEG SPs were successfully classified. Both the interictal EEG of epileptics and the EEG of the control subjects were characterized by alpha-rhythmic SPs which were the most probable in PCPs (Fig. 2.A). At the same time, epileptics and control subjects differed from each other according to the probability estimation of the occurrence of SP types in PCPs (Fig. 2.B). Thus, the interictal EEG of epileptics was characterized by a larger percentage of fast-theta-, delta–fast-theta–alpha-, delta–slow-alpha-, fast-theta–fast-alpha-, and fast-alpha- rhythmic segments when compared with the control subjects ($P < 0.05$–$P < 0.0001$ for different channels). By contrast, the EEG of control subjects was described by a larger percentage of delta-, delta–slow-theta-, slow-theta-, delta–theta–slow-alpha-, delta–fast-alpha-, theta–slow-alpha-, and slow-alpha- rhythmic segments when compared with the interictal EEG of epileptics ($P < 0.05$–$P < 0.0001$ for different channels) (Fig. 2.B). In general, it can be seen that the interictal EEG of epileptics has more segments with faster frequencies of each brain oscillation than the EEG of control subjects.

The spatial distribution of SPs was generally consistent with that revealed in earlier studies. Thus, a significant ($P < 0.05$–$P < 0.001$) increase for alpha- and decrease for delta- and theta-rhythmic EEG segments in frontal-to-occipital direction was observed (Fig. 2.A). At the same time, temporal, central, and anterior cortical areas demonstrated the highest number of statistically significant differences in SPs relative presence in PCPs (mentioned above) between epileptics and control subjects.



	C > E	C < E	
Delta	2.5 Hz	-	O1, C3, C4
Delta-theta	2.5-4 Hz 2.5-55 Hz	- -	P4, T6, F7 Cz, T4, T5, T6, F3, F4, Fz, F7, F8
Theta	4 Hz 3-6.5 Hz	5.5 Hz 7 Hz	O2, P4, C3, T5, T6, F7, F8 O1, P4, C3, Cz, T4, T5, F3
Delta-Theta-Alpha	2.5-4.5-8.5 Hz 2.5-4.5-10.5 Hz 2.5-3.5-5.5-9.5 Hz	2-6.5-8.5-12.5 Hz	C3, C4, Cz, T3, T4, F3, F4 Cz, T3, T4, F3, Fz, F7, F8 F3, F4
Delta-Alpha	2.5-10.5 Hz	2.5-8.5 Hz	O1, O2, P4, C4, T4, T5, F3, F4, Fz, F7,F8
Theta-Alpha	4-8.5 Hz 4-10.5 Hz 5.5-10.5 Hz 3-6.5-11 Hz	6.5-12.5 Hz	C3, Cz, T4, F7, F8 O1, C3, C4, Cz, T4, F3, F4, Fz, F7, F8 O2, C3, Cz, T3, T4, F3, F4, Fz, F8 T3, F3, F4, Fz
Alpha	10 Hz 9.5-10.5 Hz	11.5 Hz 13 Hz 14.5 Hz 9.5-11.5 Hz	Cz, T3, T4, F3 O1, P4, T3, T5 P4, T3, F4, Fz C4
Rhythm	Frequency		EEG channels

B

Figure 2. Probability-classification profiles (A), and composition of brain oscillations (indexed by spectral patterns) (B) typical for interictal EEG of epileptics and EEG of control subjects (averaged across subjects and all 1-min EEGs).
For (A): O2 = occipital, P4 = parietal, C4 = central, and F4 = frontal EEG channels placed at the right hemisphere of the brain. The *x*-axis displays the labels (numbers) of the standard spectral patterns (SP) from 1 to 32 and their main frequency peaks. The *y*-axis displays the share of the corresponding SPs out of the total number of classified SPs in percentage. A line graphic was chosen instead of a bar for ease of comparison. (Note that the *x*-axis consists of 32 discrete values, all the in-between values are meaningless). For (B): C = control EEG; E = epileptic EEG; "Rhythm" column represents brain oscillations; "Frequency" column marks frequency of the main peaks for each SP type; "EEG channels" column represents EEG channels for which C > E and/or C < E condition was fulfilled; "–" = given SP did not exist.

Additionally, the interictal EEG of epileptics was characterized by more polyrhythmic spectra (see Methods) than the EEG of control subjects (27% *vs* 14% of EEG segments, averaged across channels, $P < 0.0001$) (Fig. 3A). Both groups showed more polyrhythmic SPs in anterior sites than in posterior areas.

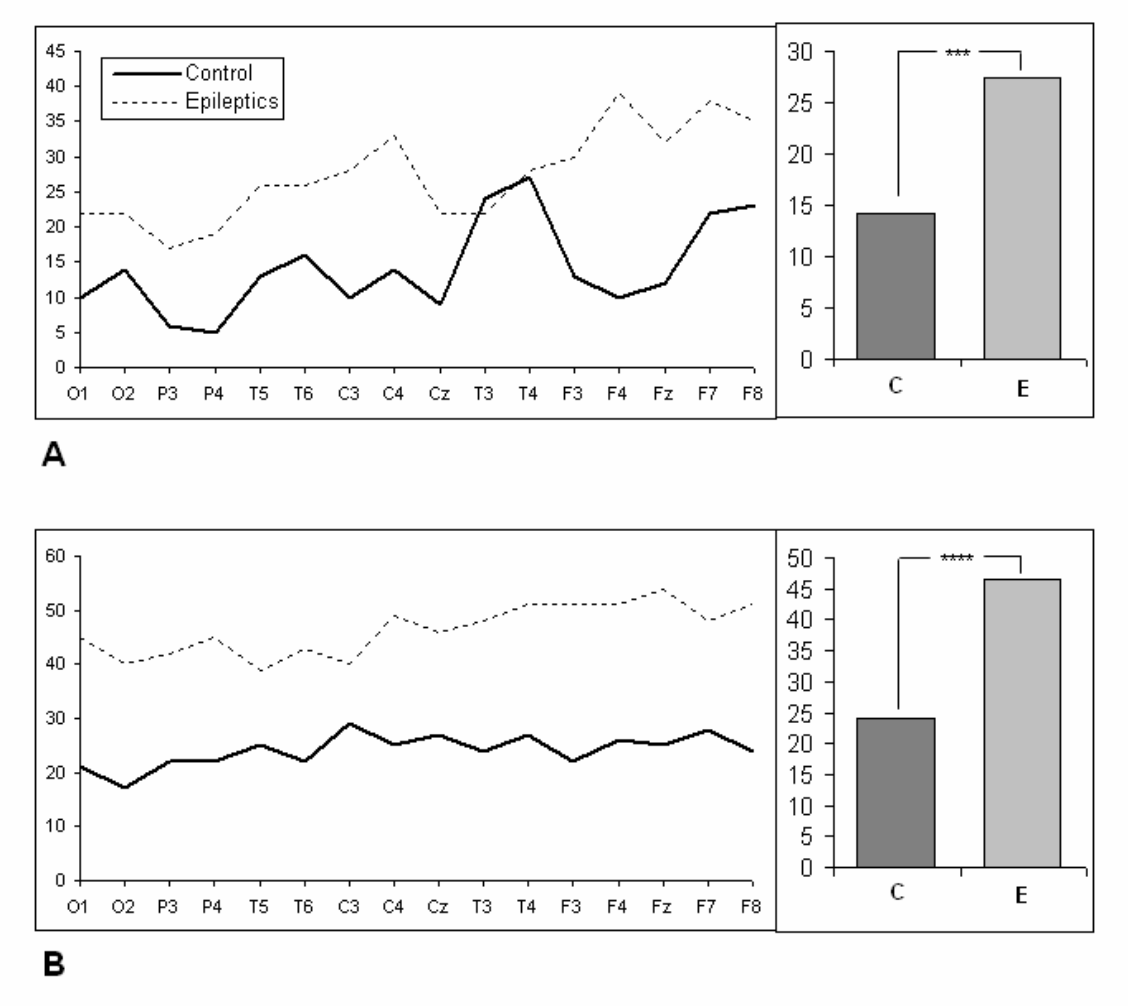


Figure 3. Number of polyrhythmic spectral patterns (in % from the total number of spectral patterns in EEG) (A), and index of non-stability of probability-classification profiles (B) for interictal EEG of epileptics and EEG of control subjects (averaged across subjects and all 1-min EEGs separately for each EEG channel). Insertion illustrates the same, but averaged across subjects, all 1-min EEGs, and all EEG channels.
C = control EEG; E = epileptic EEG; *** = $P < 0.0001$; **** = $P < 0.00003$

Both the interictal EEG of epileptics and the EEG of control subjects showed a similar diversity of SP types in PCPs (indexed by NHCP, see Methods) (Table 1). Diversity for different channels varied in the range of 26 - 41% (for control subjects) and 27 - 34% (for epileptics). The least diversity was observed in the posterior part of the brain. There was a

specific SP set in each channel or small group of channels, because the diversity of SP types in all channels taken together was substantially larger (69±1.9% for control, and 61±4.9% for epileptics) than in each individual channel for both epileptics and control subjects ($P < 0.001$ – $P < 0.0001$) (Table 1). However, this index was higher for control subjects than for epileptics ($P < 0.001$), reflecting a lower SP-type variability among EEG channels in the interictal EEG of epileptics. If the SP types which occurred in less than 2% of cases are not taken into account, then this value decreases to 28±2.0% (for control), and 21±2.0% (for epileptics) (these were significantly larger for the controls than the epileptics, $P < 0.001$, Table 1). This indicates that more than half of SP types occur very rarely; i.e., not more than 2-3 times per 149 analysis epochs in a 1-minute EEG.

Table 1.
The EEG spectral pattern types diversity (in %) for various EEG channels (averaged across all subjects and all EEGs).

EEG channels	Control (n = 14)	Epileptics (n = 18)
O1	26±3.1	28±3.6
O2	20±1.5	28±3.6
P3	27±3.4	27±3.0
P4	30±4.1	28±3.2
T5	32±3.4	29±2.8
T6	26±2.2	28±2.9
C3	36±3.4	31±3.4
C4	31±3.0	31±3.0
Cz	35±4.0	27±2.9
T3	34±2.4	31±2.4
T4	29±2.7	30±2.4
F3	38±2.7	31±3.2
F4	41±2.9	28±2.5
Fz	39±3.0	34±3.5
F7	36±2.4	31±3.4
F8	34±3.0	32±3.3
Mean	32±2.9	29.6±3.1
Ns	69±1.9	61±4.9
Ns (>2)	28±2.0	21±2.0

± Mean error
Ns - spectral pattern type diversity for all EEG channels taken together;
Ns(>2) - the same like Ns, but without spectral pattern types, which were presented in classification profiles less then in 2% cases.

The non-stability of PCPs (indexed by NSCP, see Methods) was significantly higher for the interictal EEG of epileptics than the EEG of the control subjects ($P < 0.00003$) (Fig. 3.B).

3.2. Dynamics of temporal stabilization of the spectral patterns in the interictal EEG of epileptics

Since the averaged power spectrum (often used in clinical practice) constitutes a 'static' picture which eliminates dynamic aspects of EEG organization, its temporal characteristics remain a mystery. Hence, the purpose of this section is to study the dynamics of the temporal characteristics of the SPs in the interictal EEG.

3.2.1. General description of spectral pattern type variability

The interictal EEG of epileptics demonstrated a less relative incidence of the SP type change in the transition between neighboring EEG epochs of the same EEG than in the EEG of the control subjects ($P < 0.0001$) (Table 2). This means that the interictal EEG has less frequent changes in the type of SPs (see periods of temporal stabilization of SPs below). The posterior and anterior regions of the brain demonstrated the largest difference of this index between the interictal EEG and EEG of control subjects.

Table 2.
The relative incidence of the spectral pattern type change for various EEG channels (averaged across all subjects and all EEGs).

EEG channels	Control (n = 14)	Epileptics (n = 18)	Random (n = 16)
O1	0.46±0.02	0.39±0.05	0.80±0.01
O2	0.42±0.03	0.37±0.05	0.81±0.02
P3	0.44±0.05	0.42±0.04	0.78±0.02
P4	0.46±0.03	0.41±0.05	0.81±0.01
T5	0.46±0.03	0.44±0.04	0.81±0.03
T6	0.44±0.03	0.41±0.04	0.80±0.03
C3	0.46±0.04	0.46±0.05	0.79±0.03
C4	0.42±0.04	0.39±0.05	0.85±0.02
Cz	0.43±0.04	0.39±0.05	0.78±0.03
T3	0.47±0.04	0.45±0.04	0.82±0.04
T4	0.41±0.04	0.42±0.05	0.87±0.04
F3	0.51±0.04	0.40±0.05	0.87±0.05
F4	0.52±0.04	0.38±0.05	0.83±0.04
Fz	0.50±0.05	0.41±0.05	0.86±0.05
F7	0.48±0.03	0.39±0.06	0.87±0.05
F8	0.49±0.06	0.38±0.05	0.85±0.03
Mean	0.46±0.04	0.41±0.05	0.83±0.03

± Mean error

These data refer to the level of variability of SPs in the neighboring epochs which overlapped by 80% (see Methods). It would be expected that where the epochs overlap to a lesser extent (until they converge completely in time), the variability in type of SPs should increase to a certain value which is characterized by a stochastic level of the incidence of the SP type change. In order to find the value of the relative rate of SP stochastic alternation in the actual EEG, we used a "random" 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). Thus, the relative rate of the SP type alternation from the first and to the last interepoch shifts in "random" EEG was 0.825±0.007 (Table 3). This value presents an estimation of the maximum possible rate of relative alteration in the type of SPs for a given EEG. They testify the attenuation of mutual SPs determination between the neighboring EEG analysis epochs.

Table 3. Averaged across all EEG channels mean values of the estimation of the relative incidence of SP type change in sequential EEG analysis epochs at different time shifts between them.

Shift	50	100	150	200	250	300	350	400	450	500	550
Control	0.46±0.01	0.6±0.02	0.68±0.01	0.72±0.02	0.75±0.02	**0.76±0.01**	0.76±0.02	0.77±0.01	0.76±0.01	0.77±0.02	0.77±0.02
Epileptics	0.41±0.01	0.55±0.01	0.62±0.01	0.66±0.02	0.68±0.01	**0.68±0.02**	0.69±0.02	0.69±0.02	0.69±0.01	0.69±0.02	0.69±0.02
Random	**0.83±0.02**	0.82±0.01	0.82±0.01	0.82±0.01	0.83±0.02	0.83±0.01	0.83±0.02	0.83±0.01	0.83±0.01	0.83±0.01	0.83±0.01

Shift designates the number of counts of a digitized EEG signal between the initial moments of the neighboring analysis epochs;
"Random" = 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.

Table 3 presents the average values of the relative SP alternation rate in the EEG (interictal, control, and "random") for different shifts between the initial moments of the analyzed epochs (256 points). The maximum rate of change in the SP type was reached at the shift in 300 points for both interictal and control EEGs. This rate remains constant when the time interval between the epochs is increased. At the same time, both the interictal EEG of epileptics and the EEG of control subjects significantly differed from a "random" EEG ($P <$ 0.00003), and the values of this index were significantly smaller for the interictal EEG than the control EEG for all shifts ($P < 0.05$). Thus, the deterministic influence of the SPs of the neighboring analysis epochs on each other was absent for "random" EEG, was medium for the EEG of the control subjects, and was maximal for the interictal EEG of epileptics.

3.2.2. The dynamics of temporal stabilization of spectral patterns in local EEGs

The temporal stabilization of SP types was evaluated by computing the average number (for all EEG channels) of successive *m* EEG epochs of the same SP type (including polyrhythmic spectra – the type "0") where *m* is the range from 1 to 149, and was then described as a "block". In this case the particular block length reflects the particular period of temporal stabilization of brain oscillations. The results of this analysis for EEG are summarized in Figure 4.

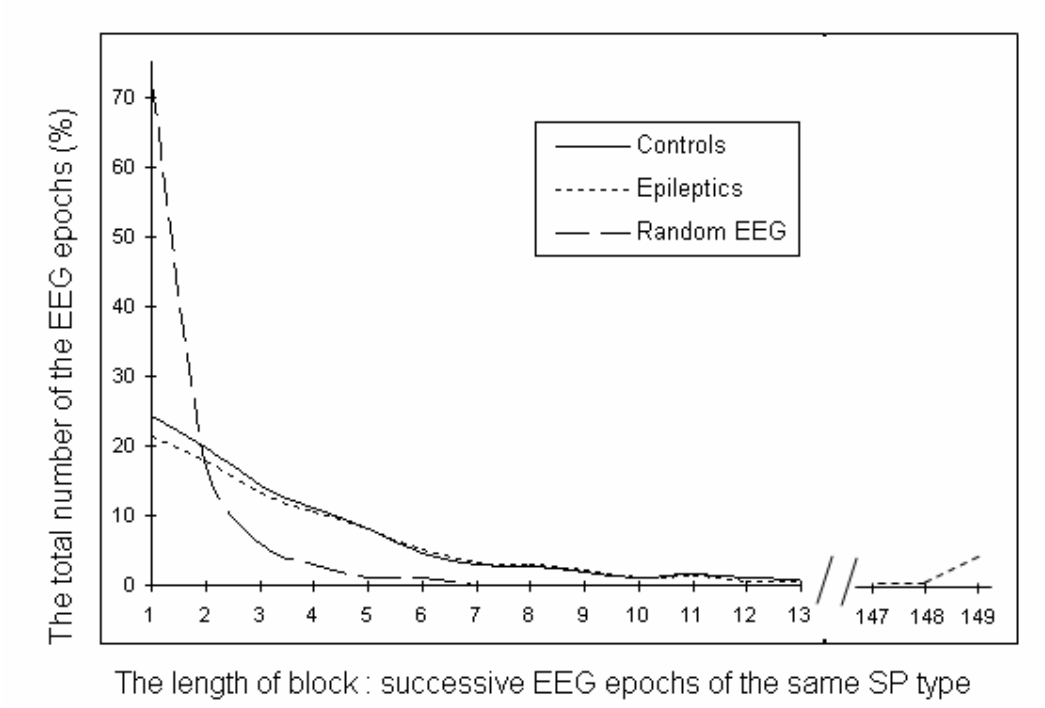


Figure 4. The average number (for all EEG channels, *n* = 16) of successive *m* EEG epochs of the same SP type (including polyrhythmic spectra) (the *y*-axis), where *m* is the range from 1 to 149 (the *x*-axis). The values are presented as a percentage of the total number of the epochs in all EEGs, for 6 epileptics ($n = 2682$) and for 7 control subjects ($n = 2086$). "Random EEG" = EEG which natural sequence of spectral pattern types has been completely removed in each individual channel**.**

The effect of the temporal stabilization of SPs in both the interictal EEG of epileptics and the EEG of control subjects was similar, demonstrating a common characteristic: this index decreased as the length of block increased. At the same time, the control EEG was characterized by greater index values for small periods of temporal stabilization ($P < 0.001$–$P < 0.000001$ for different block lengths) and smaller index values for large periods of

temporal stabilization ($P < 0.003$–$P < 0.000001$ for different block lengths) when compared with the interictal EEG (Fig. 4).

However, it is obvious that even in the absence of any correlation between the EEG SPs, there should be a temporary stochastic stabilization of the SPs, which may reflect merely occasional combinations of SP types. As control for the neural origin of temporal dynamics of SPs, "random" EEG (an EEG with a random mix of different SP types separately for each channel) was used. From Figure 4, it can be seen that the actual EEG data substantially differed from the "random EEG". An excessive increase in the number of blocks of length 1 for "random EEG" may indicate a stochastic process.

It should be noted that the analysis presented above could not reveal the dependence between the periods of temporal stabilization and the type of SPs. In other words, does specific type of brain oscillations (in terms of SPs) maintain a particular period of temporal stabilization? Therefore, we analyzed the maximum periods of temporal stabilization for all SP types which were found in PCPs for the interictal EEG of epileptics and the EEG of control subjects (Fig. 5.A). The maximum periods of temporal stabilization for SP types presented in Figure 5.A as block length were recalculated in time-scale. This analysis showed that the brain "maintains" the stabilization period of neural activity for the interictal EEG between 3.56 and 5.51 sec (for different SPs), whereas for the control EEG, periods of temporal stabilization was shorter: 2.78–4.73 sec (for different SPs). In separate cases, the maximum periods of temporal stabilization for the interictal EEG reached 34-60 sec. Note that for the interictal EEG of epileptics, the largest maximum period of temporal stabilization was found for polyrhythmic activity, whereas for the EEG of control subjects, the maximum period of temporal stabilization was longest for 10 Hz alpha activity.

Moreover, for the interictal EEG, all SPs with delta–fast-alpha, fast-theta, fast-theta–fast-alpha, fast- and bimodal-alpha, and polyrhythmic activity were characterized by longer maximum periods of temporal stabilization than for the control EEG ($P < 0.05$). At the same time, for the control EEG, all SPs with delta, delta–theta, theta, delta–alpha, delta–theta–alpha, theta–alpha, and alpha activity were characterized by longer maximum periods of temporal stabilization than for the interictal EEG ($P < 0.05$) (Fig. 5.A). The duration of such periods for "random EEG" (an EEG with a random mix of different SP types) was different from the actual EEG and reached up to 2.3–2.6 sec (for different SP types) (Fig. 5.A).

Finally the maximum periods of temporal stabilization (averaged across all SP types and EEG channels) were longer for the interictal EEG than for the control EEG ($P < 0.01$) (Fig. 5.B).

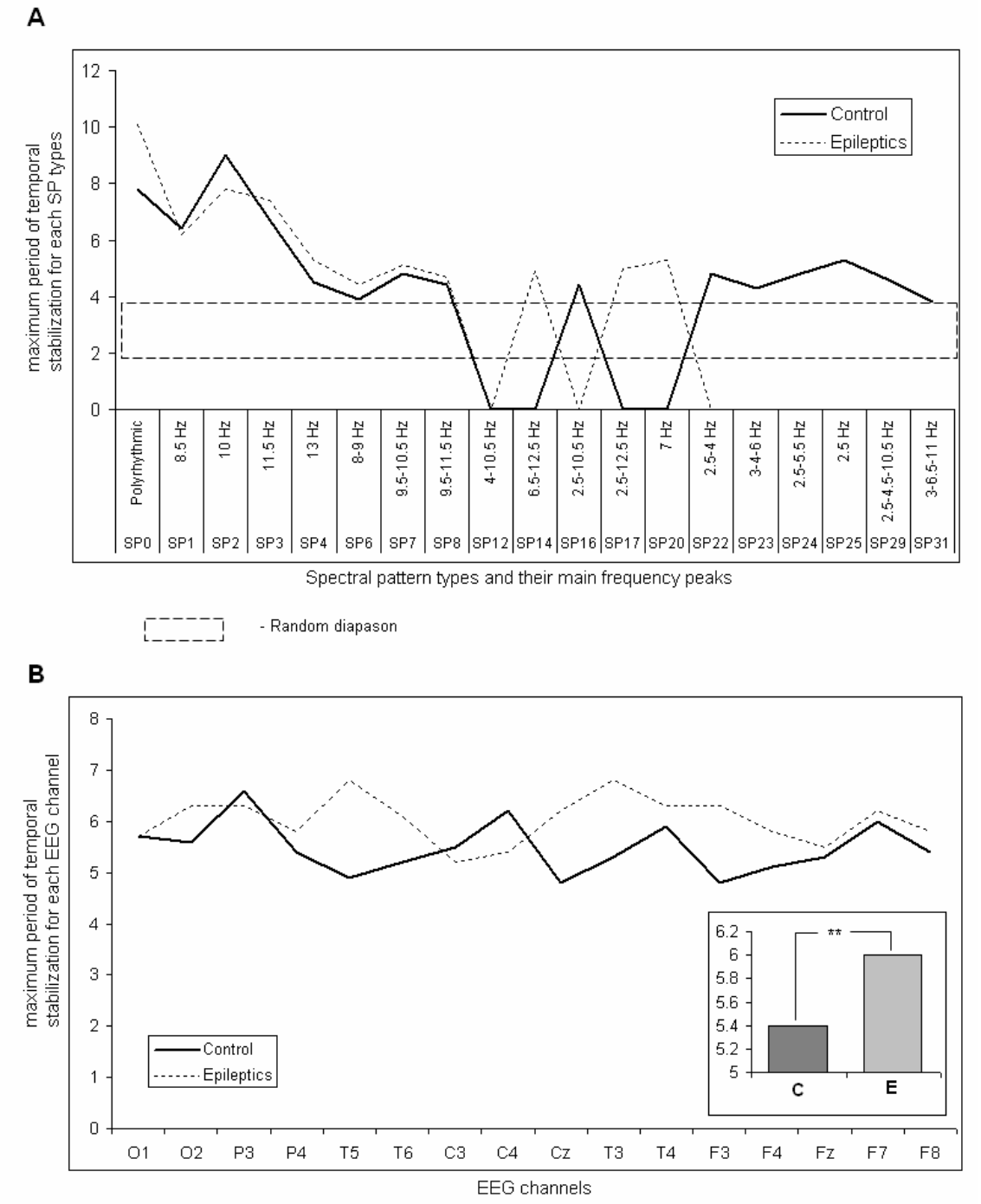


Figure 5. The maximum periods of temporal stabilization: (A) for all spectral pattern types, which were found in the EEG probability-classification profiles. The *x*-axis displays the labels (numbers) of the EEG spectral patterns (SP) corresponding to the standard SP set (including polyrhythmic spectra – type "0"). The *y*-axis displays the maximum periods of temporal stabilization for each SP types (in terms of block length – *m* EEG epochs follow in succession without SP type change, where *m* is the range from 1 to 149). Data averaged across all subjects and all EEG channels. Horizontal dotted line bar represents random range

of the maximum periods of temporal stabilization for "Random EEG" (EEG whose natural sequence of spectral pattern types has been completely removed in each individual channel); (B) for all EEG channels. Data averaged across all subjects and all SP types observed in the EEG probability-classification profiles. In the insertion the maximum periods of temporal stabilization averaged across all subjects, all SP types, and all EEG channels are presented. C = control EEG; E = epileptic EEG; ** = $P < 0.01$;

4. Discussion

In spite of the fact that the interictal EEGs in this study had no visible signs of epileptiform activity, the use of probability-classification analysis of the individual SPs enabled us to identify the number of differences in microstructural organization of the interictal EEG from the EEG of the control subjects. These differences support our hypothesis that epileptic brain should have characteristic differences from the intact brain even in the interictal period.

4.1. Composition of multiple brain oscillations in interictal EEG

In general, although the compositions of brain oscillations were similar for both the interictal EEG of epileptics and the EEG of control subjects, the brain oscillations in the interictal EEG were characterized by faster frequencies than in the control EEG (Fig. 2). This finding may reflect chronic epileptization of the brain (Hooshmand et al., 1980; Brumback and Staton, 1981; Yaari and Beck, 2002). In terms of its relevance to epileptogenesis, increased neuronal activity changes the ionic environment of neurons (Heinemann et al., 1986) that can lead to increased burst firing of neurons (Jensen et al., 1994). The observed shift towards higher frequencies of alpha activity in the interictal EEG (this present study) reflects increased activation and an excitation of neuronal ensembles (Knyazeva and Vildavskii, 1986). At the same time, the interictal EEG demonstrated a marked decrease in the percent of delta- and delta–theta-rhythmic segments (Fig. 2), thus confirming the fact that a decrease in slow brain oscillations is the most frequent and specific sign of EEG during brain dysfunction (Coutin-Churchmana et al, 2003). According to Coutin-Churchmana et al., (2003) both a decrease in slow and an increase in fast activity closely correspond with data from anatomic and functional neuroimaging studies, which report both atrophy and increased metabolism in different areas of brain with dysfunctions. Indeed, the characteristic circuit abnormalities during epilepsy include a drop out of neurons, a simplification of the dendritic

tree (reduced synaptic input), an increase in the number of excitatory-excitatory feedback connections, and increase in glial cell elements (Sackellares et al., 1999).

A significant decrease in slow brain oscillations observed in the present study contradicts earlier research which demonstrated the presence of regional slow-wave activity in interictal EEG (Gastaut et al., 1985; Koutroumanidis et al., 1998; Massa et al., 2001). This finding of these authors may be due to several reasons: (a) the subjects used anticonvulsant medication; (b) the regional slow-wave activity may be a consequence of structural brain pathology (for example lesions), and (c) researchers used averaged spectral analysis where the frequency bands were predefined and taken in isolation from each other.

This present study demonstrated that the number of EEG segments with polyrhythmic activity was larger in the interictal EEG than the control EEG. This finding is consistent with the results of our previous study, where we reported that different pathologies of the brain were characterized by increased percent of EEG segments with polyrhythmic activity (Fingelkurts et al., 2000). It seems that some (small) percent of polyrhythmic activity always exists in healthy EEG (Fingelkurts et al., 2002; 2003a; 2004), and pathological processes cause its elevation (Grindel, 1973; Fingelkurts et al., 2000). In this study, a relatively high percentage of polyrhythmic activity in the interictal EEG (up to 27%) may reflect neurodynamic transitions of the same type independently from the nature of ongoing activity. It seems that polyrhythmic activity is necessary to maintain a high level of activity in neuronal networks for sustained periods of time (Gutkin et al., 2001). The fact that the frequency spectrum becomes increasingly peaked as the system approaches a change of state (Lopes da Silva, 1991; Sampson, 2002) suggests that the amount of polyrhythmic activity would increase while approaching the seizure. If this idea is correct, and considering that stochastic resonance is an important mechanism here by which very small signals can be amplified and emerge from the random noise of physiological oscillations (Torres and Ruiz, 1996), we can speculate further that the increased percent of polyrhythmic activity would increase the probability of seizure.

Similarly to polyrhythmic SPs, there is some optimal level of diversity of SP types in PCPs (Fingelkurts et al., 2002; 2003a; 2004) which may increase or decrease depending on the type of pathology (Fingelkurts et al., 2000). In the present study, the diversity of SP types was smaller (non-significantly) in the interictal EEG of epileptics than in the EEG of the control subjects (Table 1). At the same time, the stability of PCPs for interictal EEG was significantly reduced when compared with the control EEG (Fig. 3.B).

When taken together, all these findings suggest a chaotization (but not randomization) process in interictal EEG of epileptics: an increased amount of polyrhythmic disorganized activity, a decreased diversity of SPs in PCPs, and a reduced stability of PCPs. This idea is supported by the fact that interictal period represents a relatively less orderly state with multiple frequencies, and the chaotic behavior of the signal (Bergey and Franaszczuk, 2001).

4.2. Distributed property of brain oscillations in interictal EEG

The temporal, central, and anterior cortical areas demonstrated the highest number of statistically significant differences in SPs relative presence in PCPs between the epileptics and control subjects (Fig.2). Because the main differences described in this paper have been observed in several cortical regions, it appears that the distributed neuronal networks were involved in epileptization process. This result is in agreement with other studies presenting evidence for the involvement of different distant brain areas in the epileptogenic process (Le Van Quyen et al., 1997, 2000; Mormann et al., 2003; Fogarasi et al., 2003; Vadlamudi et al., 2004). Perhaps the distributed delta, theta, and alpha oscillatory systems observed in the present study act as resonant communication networks through large populations of neurons (for the review, see Basar et al., 2001). Another finding of the present study which supports the distributed effect of epileptization process in interictal EEG, was a reduced SP type variability among EEG channels in the interictal EEG of epileptics when compared with the EEG of control subjects (Table. 1). This means that the interictal EEG was characterized by a more homogeneous topological pattern than the control EEG. This finding is consistent with the loss of spatio-temporal complexity in the interictal EEG (Weber et al., 1998; Bhattacharya, 2000) that suggests that there are spatially more dependent functional processes active in the epileptic brain than in the healthy brain.

The converging results of this section suggest that epilepsy can be conceptualized as a dysfunction in distributed neural circuits, rather than local focal changes.

4.3. Temporal dynamics of brain oscillations in interictal EEG

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 the stabilization of oscillatory patterns in the brain. In the present study, the interictal EEG was characterized by longer periods of SP temporal stabilization than in the control EEG (Fig. 4, Fig. 5). This was determined by concrete parameters in the lifetime of each of the SP type: Thus, the interictal EEG of epileptics demonstrated (a) a less relative incidence of the SP type change in the transition between neighboring epochs of the same EEG when compared with EEG of the control subjects (Table 2); and (b) a lower maximum rate of change in the SP type (for all shifts) when compared with the control EEG (Table 3). It seems that the interictal EEG has high deterministic influence of the SPs of the neighboring analysis epochs on each other. Perhaps, increased stabilization periods of SPs in the interictal EEG indicate that the brain's operations completed less dynamically and that there exists a transition to a less differential organization of spectral relations, where neural elements become less independent and are able to function as united informational channels (Lindsley, 1961). All these may suggest a reduction of brain information processing.

Furthermore, the maximum period of SP temporary stabilization depended on the type of dominant frequency. Thus, for the interictal EEG of epileptics, the maximum period of temporal stabilization was found for polyrhythmic activity, whereas for the EEG of the control subjects, the maximum period of temporal stabilization was observed for 10 Hz alpha activity (Fig. 5.A). This finding is consistent with our previous study (Fingelkurts, 1998) where we demonstrated that the normally functioning brain is characterized by temporal stabilization of dominant alpha-activity (~10 Hz), whereas the temporal stabilization of polyrhythmic activity is typical for pathological processes. Stabilization of alpha activity as "building blocks" was demonstrated also earlier in the work of Lehman and Koenig (1997).

When taken together, the analysis of the different indices presented in this section show various (but converging) aspects of the temporal dynamics of variability in SP types. Note that all these estimations differed significantly in the "random EEG" (EEG whose natural sequence of SP type has been completely removed in each individual channel). This means that the temporal stabilization of the main dynamic parameters of neuronal activity observed in the present study had a non-occasional character.

Before coming to the final conclusions, an alternative explanation for the distributed phenomena of brain oscillations discussed in Section 4.2 should be considered. It could be suggested that these results may be attributed to the EEG recording with a linked ear reference electrode or volume conduction. This explanation seems unlikely for the following reasons: (a) the occipital and frontal regions clearly showed different accentuations in their

EEG effects; (b) the analysis revealed that each EEG channel or small group of channels had its own specific SP set (see Results), and (c) it was shown that there is little effect of volume conduction on the shape of the spectrum below about 25 Hz and spatial filtering is significant only for frequencies above the major rhythms (Robinson et al., 2001).

The findings of the present study that the interictal EEG was characterized by (a) a shift towards higher frequencies in all observed brain oscillations in distributed neuronal networks, (b) an increased amount of polyrhythmic disorganized activity, (c) a decrease in SP types diversity, (d) a decreased relative incidence of the SP type change in the transition between neighboring EEG epochs of the same EEG, (e) an increased temporal stabilization of periods of polyrhythmic activity, may suggest a chaotization of neurodynamics in epileptics. At the same time, the fact that all these indices were significantly different from "random" EEG reflects a non-occasional and thus, most likely, an adaptive nature of the microstructural reorganization of interictal EEG.

4.4. Theoretical considerations

Based on the functional significance of individual SPs (Dumermuth and Molinari, 1987; Kaplan 1998; Fingelkurts et al., 2003b; 2005, in press), the type of SP may represent a particular oscillatory state of neurodynamics in a given cortical area. If this is the case, then the diversity of SP types represents the range of the probable states in this area. Each such state (indexed by SP type) is determined by a fixed level of relatively stable functioning for a particular period of time (periods of SP temporal stabilization). It was demonstrated that the brain has mechanisms which determine variations in the level of relatively stable functioning of cortex areas within the range of their probable states (Fingelkurts et al., 2003a,b). Parameters of the lifetime of each of the SP type and of their diversity determine these mechanisms. Considering that physiological activity of local cortex regions depends on their states, one can speculate that depending on the "position" in the state-continuum which can be "occupied" by a particular cortex region, the peculiarities of compensation of local changes in the current state within this continuum is determined. Thus, during epilepsy, cortical areas were characterized by decreased repertoire of the probable states (reduction of the number of SP types in interictal EEGs). This represents the increased rigidity in the brain activity. Among all oscillatory states observed for epilepsy in the present study, a polyrhythmic state had the largest period of relatively stable functioning.

4.5. Concluding remarks

When taken together, the findings of the present study lead to the conclusion that the peculiarities of the microstructural organization of the interictal EEG without the signs of epileptiform activity reflect the natural adaptive reorganization of this microstructure. This reorganization is expressed in the physiological limits of the brain and manifests itself in metastable settling around new homeostatic levels. This metastable state of epileptic brain is a background (or field of action) for ictogenesis. In such a way, the actual decrease of epileptiform activity threshold is the natural result of preceding successive changes in brain dynamics.

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.

In this study we examined the neurodynamics in local interictal EEGs. Further research is needed in order to assess the integrative neurodynamics in the interictal EEG where the metastability of the epileptic brain can be estimated directly (Fingelkurts et al., in preparation).

The practical implications of the present study for epileptic patients are that (a) parameters of interictal EEG without the signs of epileptiform activity can be considered as additional information in premorbid diagnostics of epistatus; (b) new approaches to the diagnosis and treatment of epilepsy could be suggested, and (c) a therapeutic intervention could aim to restore the actual composition of brain oscillations and their temporal behavior, similar to those of the normal EEG.

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