Coexistence of intermittencies in the neuronal network of the epileptic brain

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Intermittent behavior occurs widely in nature. At present, several types of intermittencies are known and well-studied. However, consideration of intermittency has usually been limited to the analysis of cases when only one certain type of intermittency takes place. In this paper, we report on the temporal behavior of the complex neuronal network in the epileptic brain, when two types of intermittent behavior coexist and alternate with each other. We prove the presence of this phenomenon in physiological experiments with WAG/Rij rats being the model living system of absence epilepsy. In our paper, the deduced theoretical law for distributions of the lengths of laminar phases prescribing the power law with a degree of −2 agrees well with the experimental neurophysiological data.

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Intermittent behavior is known to occur widely in nature and must be considered to be a generic phenomenon. It has been observed in many model and natural systems [1–5]. One of the important features of intermittency is its inherent relation with the cooperative dynamics of coupled nonlinear systems, since different types of intermittent behavior accompany the transition from the asynchronous regime to the synchronous mode. The intermittent behavior is revealed in coupled chaotic oscillator dynamics for phase synchronization [6–8], generalized synchronization [9,10], lag synchronization [11,12], complete synchronization [13,14], and time-scale synchronization [15] regimes. The very important manifestation of intermittency is the intermittent dynamics observed in living systems [16–23], since this aspect has both fundamental and practical significance connected with the understanding of deep mechanisms of complex living systems (such as, e.g., the brain) and with possible applications in medical practice.

Different intermittencies, in turn, may coexist and alternate with each other, resulting in a new level of organization of the temporal behavior of complex nonlinear systems. For this type of intermittent behavior that has been revealed recently [24], universal analytical expressions for statistical characteristics [namely for the distribution of laminar phase lengths, $p(\tau)$, and for the dependence of the mean length of laminar phases, $\langle\tau\rangle$, on system control parameters] have been deduced. The derivation of the analytical expression of the probability distribution of laminar phase lengths $p(\tau)$ has been based on assumptions that the laws of laminar phase length distributions $p_{1,2}(\tau)$ for each coexisting type of intermittent behavior are known. The obtained analytical expressions have been compared with the results of numerical simulation of dynamical systems demonstrating the coexistence of eyelet and ring intermittencies, and excellent agreement between the analytical formulas and the direct numerical calculation data has been found [24,25].

The developed theory for the coexistence of intermittencies has been proven to be relevant from the point of view of the study of epileptic brain dynamics. Indeed, several works reported on the existence of on-off intermittency in spontaneous oscillatory patterns on the rat and human electroencephalogram (EEG) [16–18]. More precisely, on-off intermittency has been revealed both for spike-wave discharges (SWDs) and sleep spindles (SSs) [19].

Sleep spindles are one of the most attractive types of oscillatory activity in the EEG signal, which manifests itself during sleep. They represent short (0.5–1.5 s) episodes of oscillations with frequencies of 10–16 Hz and a characteristic spindle shape [26]. Sleep spindles are known to be formed due to the synchronous activity of a neural network that consists of cortex and thalamus neurons.

Spike-wave discharges, in turn, serve as diagnostic markers of absence epilepsy, and their presence in EEG is accompanied by the characteristic clinical manifestations. SWDs are characterized by the frequency range of 7–15 Hz, and they consist of a relatively high-frequency component (the spike) with peak amplitude significantly exceeding the background activity and the low-frequency "wave" [27,28].

Spike-wave discharges and sleep spindles are known to share a common thalamo-cortical mechanism, suggesting that absence seizures might affect some intrinsic properties of sleep spindles [29,30]. Although spike-wave discharges and sleep spindles are considered to be thalamo-cortical oscillations and are known to be closely related, the functional relation between them is very complicated and has not yet been revealed. For example, the thalamo-cortical neural network that normally generates sleep spindles is known to be able to produce seizure activity (i.e., spike-wave discharges) under certain conditions [31,32]. In many cases, the shape and amplitude of sleep spindles is very similar to that in spike-wave discharges [30,33]. Both types of patterns can be observed in one EEG track simultaneously (see Fig. 1), with their dynamics adhering to on-off intermittency regularities. Therefore, it seems reasonable to consider the neuronal network dynamics of an epileptic brain containing both spike-wave discharges and sleep spindles from the point of view of the phenomenon of the coexistence of intermittencies.

As an object under study, we have used electroencephalographic records obtained from WAG/Rij rats [the experiments

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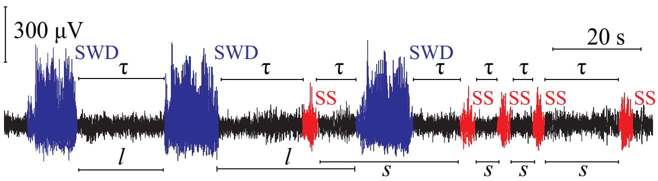

FIG. 1. EEG record containing both spike-wave discharges (SWDs) and sleep spindles (SSs). The time intervals between consequent events in EEG (marked as τ) correspond to the laminar phases of the dynamics of electrical brain activity. The time intervals marked as s and l correspond to the laminar phases in the dynamics of SSs and SWDs, respectively, considered separately.

were performed at the Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences (Moscow)]. WAG/Rij (Wistar Albino Glaxo/Rij) rats are genetically prone to develop absence seizures due to a genetic predisposition, and they are considered to be a reliable animal model of this disease [32]. These rats are perfect candidates for epilepsy research because of the almost guaranteed presence of absence epilepsy and easier (in comparison with human) EEG data acquisition design [27]. At the same time, the results obtained in WAG/Rij rats can be applied in clinical research and practice.

EEGs were recorded in ten male WAG/Rij rats (7–9 months old, body weight 320–360 g). The experiments were conducted in accordance with the legislations and regulations for animal care and approved by the Institution Ethical committee; distress and suffering of the animals was kept to a minimum. A recording electrode was implanted epidurally over the frontal cortex because the SWD and spindles showed maximal amplitude in this zone (coordinates: AP +2 mm and L 2.5 mm relative to the bregma). Ground and reference electrodes were placed over two symmetrical sides of the cerebellum. EEG recordings were made in freely moving rats continuously during a period of 24 h.

Oscillatory patterns in the recorded EEGs were detected, localized, and marked with the help of wavelet-based methods described in [19,34], with the markings being verified by an expert neurophysiologist. The time intervals between SWDs examined separately are considered to be the laminar phases of spike-wave discharge dynamics. The dependence of the number of laminar phases ("off"-phases) on their duration, l, is known to be governed by the power law [18]

$$N_1(l) \sim l^{-3/2}. \tag{1}$$

The power law with the exponent $-3/2$ is known to be observed in the case of both on-off intermittency [3,4] and type-III intermittency [1]. The presence of type-III intermittency can be easily revealed with the help of the analysis of the second return map in the same way as was done in [2,16]. In Ref. [18], the second return map obtained from electroencephalograms was analyzed, and the presence of on-off (but not type-III) intermittency was proven. Similarly, the time intervals s between SSs considered also separately and interpreted as the laminar phases of sleep spindle dynamics also obey the same power law,

$$N_2(s) \sim s^{-3/2}, \tag{2}$$

and the intermittent behavior belongs also to on-off intermittency [19]. In our case, let index "1" correspond to SWD dynamics, where index "2" is used to refer to the processes of SS appearance.

Both spike-wave discharges and sleep spindles obey the law of on-off intermittency (see [18,19] for details). Since both oscillatory patterns are presented simultaneously in one EEG record, and taking into account the close relationship between these types of oscillatory patterns, one can consider the recorded EEG as the intermittent time series, where the intervals of the background activity (marked as τ in Fig. 1) correspond to laminar phases, whereas the episodes of oscillatory activity (namely SWDs and SSs) should be considered as turbulent phases. In this case, such dynamics is, in fact, the coexistence of two intermittent processes with on-off intermittent behavior yet with different quantitative characteristics. Therefore, we can use the approach developed earlier [24] to describe the above-mentioned dynamics.

One of the most important characteristics providing researchers with sufficient information on the system behavior in the intermittent regimes is the probability distribution of the laminar phase lengths, $p(\tau)$ (see, e.g., [1,6,8,12,15–17]), which, in turn, is connected with the distribution of the laminar phase lengths, $N(\tau)$, that may be obtained easily from the experimental measurements. Therefore, in our study we focus on these characteristics, allowing us to describe statistically the episodes of the background activity of the brain. The probability distribution of the laminar phase lengths for the coexistence of intermittencies is known to be

$$\begin{aligned} p(\tau) = \frac{1}{T_1+T_2}\Bigg[\int_\tau^\infty \frac{ds}{s} \int_\tau^\infty [p_1(l)p_2(s)T_2 \\ + p_1(s)p_2(l)T_1]\,dl + \int_\tau^\infty \left(1-\frac{\tau}{s}\right) \\ \times [p_1(\tau)p_2(s)T_2 + p_1(s)p_2(\tau)T_1]\,ds\Bigg], \end{aligned} \tag{3}$$

where $p_{1,2}(\xi)$ are probability distributions of laminar phase lengths of the alternating intermittencies considered separately, and

$$T_{1,2} = \int_0^\infty s p_{1,2}(s)\,ds \tag{4}$$

are the mean lengths of laminar phases in these intermittencies. The laws for the probability distributions of laminar phase lengths $p_{1,2}(\xi)$ are expected to be known, whereas the coexisting intermittent processes are supposed to be independent (see [24] for more details).

The probability distribution of laminar phase lengths in on-off intermittency is known to be governed by the power law

$$p(x) = Ax^{-3/2}. \tag{5}$$

At the same time, the direct use of this law for the probability densities $p_1(l)$ and $p_2(s)$ in the form of Eq. (5) in Eq. (3) is not possible due to the particularities of the power law. Indeed, the integral $\int_0^\infty p(x)\,dx$ diverges for $x \to 0$, whereas the integral $\int_0^\infty xp(x)\,dx$ determining the mean length of laminar phases tends to be infinity for $x \to \infty$. Therefore, Eq. (3) should be

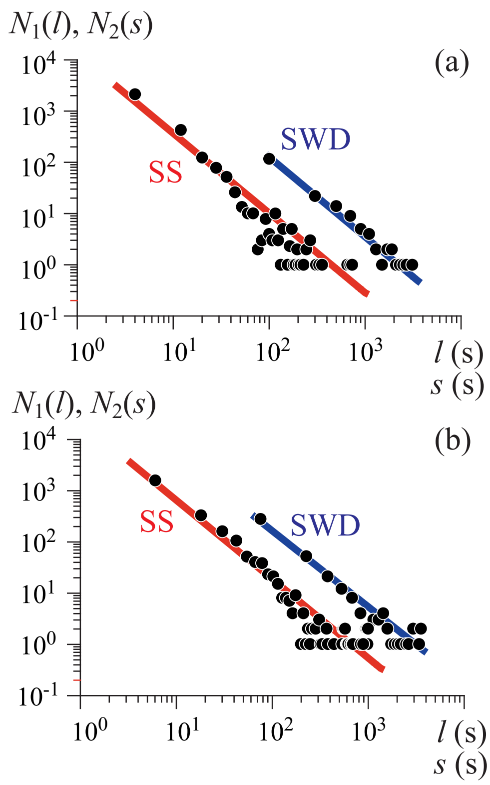

FIG. 2. Distributions of the laminar phase lengths for spike-wave discharges and sleep spindles obtained experimentally for two rats [rat no. 2 (a) and rat no. 6 (b)] on a log-log scale. Solid lines correspond to the theoretical laws (1) and (2), and the experimental data are shown by circles.

adapted to the case of on-off intermittency in comparison with the eyelet or ring intermittent behavior, for which Eq. (3) is appropriate [24,25].

To adapt Eq. (3) to on-off intermittency observed in the experimental EEG records, we take into account the finiteness of time series with length L^* in which N_1 spike-wave discharges and N_2 sleep spindles are observed. Due to the finiteness of the experimental time series, distributions of laminar phase lengths of SWDs and SSs, $N_1(l)$ and $N_2(l)$, are located within the intervals of $[L_{1\,\min},L_{1\,\max}]$ and $[L_{2\,\min},L_{2\,\max}]$, respectively (Fig. 2). For these distributions, the following normalization conditions are satisfied:

$$\sum_j N_i(l_j) = N_i, \quad \sum_j l_j N_i(l_j) = L, \tag{6}$$

where L is the sum of the lengths of laminar phases [as the first approximation, one can use $L \approx L^*$ due to the small length of the turbulent phases (both SSs and SWDs) in comparison with the full length of time series under study], and $i = 1,2$ correspond to the spike-wave discharges and sleep spindles, respectively. Having undergone the continuous distributions of laminar phase lengths, $n_i(l)$, one has to rewrite Eq. (6) as

$$\int_{L_{i\,\min}}^{L_{i\,\max}} n_i(l)\,dl = N_i, \quad \int_{L_{i\,\min}}^{L_{i\,\max}} n_i(l) l\,dl = L. \tag{7}$$

Having supposed that within the ranges $[L_{i\,\min},L_{i\,\max}]$ the distributions of the laminar phase lengths, $n_i(l)$, obey the power law (5), i.e., $n_i(l) = A_i l^{-3/2}$, and taking into account the normalization condition (7), one can obtain the expressions for the normalization coefficients A_i and the mean laminar phase lengths T_i as

$$A_i = \frac{L}{2(\sqrt{L_{i\,\max}} - \sqrt{L_{i\,\min}})}, \quad T_i = \sqrt{L_{i\,\min} L_{i\,\max}}. \tag{8}$$

Finally, for the probability densities of the laminar phase distributions $p_{1,2}(l)$ to be used in Eq. (3), the following expression can be derived:

$$p_i(l) = \frac{L}{2(\sqrt{L_{i\,\max}} - \sqrt{L_{i\,\min}})} l^{-3/2}. \tag{9}$$

Due to the particularities of the power-law distributions mentioned above, the probability densities $p_{1,2}(l)$ determined by Eq. (9) do not obey the classical normalization condition

$$\int_0^\infty p_i(l)\,dl = 1, \tag{10}$$

since for Eq. (9) the integral $\int_0^\infty p_i(l)\,dl$ in (10) diverges for $x \to 0$. At the same time, Eq. (9) describe absolutely correctly the relationship between the frequencies of detections of laminar phases with different lengths. Therefore, these probability distributions $p_{1,2}(l)$ together with the obtained expressions for the mean lengths of the laminar phases, $T_{1,2}$, may be used in Eq. (9), with the only limitation being that the final expression of the laminar phase length distribution in the regime of the coexistence of intermittencies, $p(\tau)$, given by Eq. (3) will not also obey the classical normalization condition (10), since the integral in Eq. (10) also does not converge for $p(\tau)$. Nevertheless, it is correct for the description of the laminar phase length distributions prescribing the relationship between the detection frequencies for the different laminar phase lengths.

Having substituted the probability densities of the laminar phase lengths (9) for $p_{1,2}(l)$ and the mean lengths given by Eq. (8) for $T_{1,2}$ in Eq. (3), we obtain the formula for the distribution of the laminar phase lengths of two coexisting intermittencies, each of which belongs to on-off type intermittent dynamics,

$$p(\tau) = \frac{\sqrt{L_{1\,\max}L_{2\,\max}L_{1\,\min}L_{2\,\min}}}{(\sqrt{L_{1\,\max}} - \sqrt{L_{1\,\min}})(\sqrt{L_{2\,\max}} - \sqrt{L_{2\,\min}})} \times \left[4 - 3\sqrt{\frac{\tau}{L}} + \left(\frac{\tau}{L}\right)^{3/2}\right]\tau^{-2}. \tag{11}$$

Since in the considered EEG records the durations of laminar phases are bounded above by the value $L_u = \min(L_{1\,\max},L_{2\,\max})$, where $L_u \ll L$, the terms $3(\tau/L)^{1/2}$ and $(\tau/L)^{3/2}$ in Eq. (11) may be neglected, and, as a consequence, one can obtain that

$$p(\tau) \sim \tau^{-2}. \tag{12}$$

In other words, in the considered case of epileptic brain activity, the number of laminar phases with length from interval $[\tau,\tau + d\tau)$ should be inversely proportional to the square of length τ. Since in the experimental measurements the distribution of the laminar phase lengths, $N(\tau)$, is obtained [instead of the probability density $p(\tau)$], that distribution is

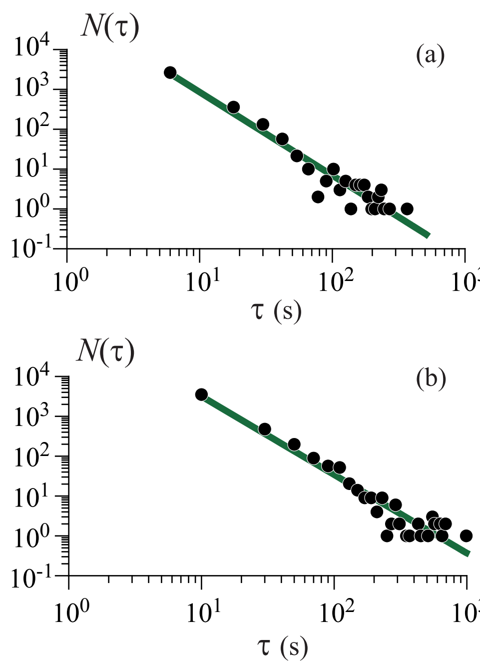

FIG. 3. Distributions of the time intervals between oscillatory patterns in EEG obtained experimentally for two rats [rat no. 2 (a) and rat no. 6 (b)] on a log-log scale. Solid lines correspond to the deduced theoretical law (13), and the experimental distributions are shown by circles.

more suitable to compare the theoretical predictions with the experimental data. Obviously, the distribution of the laminar phase lengths, $N(\tau)$, should also obey the power law

$$N(\tau) \sim \tau^{-2}. \tag{13}$$

To verify the deduced theoretical prediction (13), we have processed carefully the EEG records of WAG/Rij rats described above to get the distributions of time intervals between oscillatory patterns (SWDs and SSs) in EEG corresponding to the laminar phases of epileptic brain activity. The obtained distributions of the laminar phase lengths in EEG records of two rats are shown in Fig. 3. One can see in Fig. 3 that the obtained distributions of the laminar phase lengths, $N(\tau)$, characterizing the dynamics of the neuronal network in the epileptic brain are in very good agreement with the deduced theoretical law (13). Very similar results have also been obtained for the other examined EEG records (for long-term 24 h EEG recordings of all ten rats). In other words, the presence of the coexistence of intermittencies in epileptic brain activity is proven, whereas the theoretical law for this type of intermittent dynamics deduced in our paper has been confirmed by the results of neurophysiological experiments.

In conclusion, in our paper we report on the type of intermittent behavior in the thalamo-cortical neuronal network activity in the epileptic brain when two different on-off intermittency processes are alternated with each other. We have deduced the theoretical law for the distribution of the lengths of the laminar phases, which is characterized by the power law with a degree of -2 for the systems in which two on-off intermittencies coexist. This value of the power-law degree is the result of the "cooperation" of two intermittent processes belonging to the on-off intermittency class. Since on-off intermittency may be caused, e.g., by the random fluctuations of the control parameter [4], the degree -2 reported in our work may also reflect the random dynamics. We have also proven the existence of this phenomenon by means of physiological experimental data in WAG/Rij rats. We have shown that the obtained experimental results are in very good agreement with the deduced theoretical law.

There is no doubt that there is a neurophysiological substrate for the observed type of behavior. The revealed particularities of the dynamics of the epileptic brain (in the dynamics of a normal brain, spike-wave discharges do not take place, and, as a consequence, the coexistence of the intermittent behaviors of SSs and SWDs cannot be realized) provide additional information concerning the functional relation between spike-wave discharges and sleep spindles. It is well known that both SWDs and SSs are generated by the same (thalamocortical) network, but they originate from different parts of the network and are maintained by different neuronal network mechanisms [30–32]. We have demonstrated the presence of on-off intermittency in both SS and SWD, which confirms their close physiological relationship. Considering the fact that SS can be seen in a healthy neuronal system and SWD can be seen in the epileptic brain, it is important that a thalamo-cortical neuronal network can operate in the same mode (demonstrate the same behavior) in both healthy and unhealthy conditions, resulting in epileptic discharges and normal sleep spindles. Therefore, we believe that the revealed phenomena have a functional significance in the epileptic brain dynamics, and they deserve further comprehensive studies from the point of view of neurophysiology. In general, our results indicate a deep relationship between neuronal network mechanisms underlying SSs and SWDs.

Moreover, we believe firmly that the significance of our results is not limited to epileptic brain activity studies. We are sure that both the revealed natural law and the developed technique will be useful for studying the wide spectrum of different systems of interest for the broad scientific community as well as for the understanding of laws of different manifestations of the complicated intermittent behavior, which as yet have not been explained (e.g., as in the case of multistate intermittency and extreme pulses in a fiber laser [35,36]).

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