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ABSTRACT

In this paper we study specific oscillatory patterns on EEG signals of WAG/Rij rats. These patterns are known as proepileptic because they occur in time period during the development of absence-epilepsy before fully-formed epileptic seizures. In the paper we analyze EEG signals of WAG/Rij rats with continuous wavelet transform and empirical mode decomposition in order to find particular features of epileptic spike-wave discharges and non-epileptic sleep spindles. Then we introduce proepileptic activity as patterns that combine features of epileptic and non-epileptic activity. We analyze proepileptic activity in order to specify its features and time-frequency structure.

Keywords: Electroencephalogram, continuous wavelet analysis, empirical mode decomposition, oscillatory patterns, absence epilepsy, proepileptic activity

1. INTRODUCTION

In present days the study of brain neural network activity attracts many researchers from various fields of science. An intensive progress in developing of methods for experimental investigation and mathematical data processing leads to increasing number of interdisciplinary publications during last years.[1,2] Modern studies in neuroscience combine approaches of mathematics, physics and nonlinear dynamics with neurophysiological and biological view on the processes in brain neural structures.[3–5]

Brain neural ensemble is commonly considered as very complex oscillatory network with great number of elements – neurons. Activity of individual neurons and their clusters along with inter-neural interactions lead to complex dynamics in activity of brain neural networks. Studying of such activity is an important task since some features of brain activity can provide information about functional state of living organism.[6] Research on particular rhythms and oscillatory patterns in brain neural activity is especially important in case of central nervous system disorders, because some types of brain neural activity can be considered as biomarkers of the disorder.

One of the most common methods for obtaining information about brain activity in normal and pathological conditions is electroencephalogram (EEG).[7] EEG method involves non-invasive placing of special electrodes on scalp and recording of EEG signals which represent sum of electric currents generated by a group of neurons near each electrode.[8] Since brain is a complex neural network EEG signal also has a complex timefrequency structure and consists of various rhythmic components, specific oscillatory patterns, background activity, artifacts, etc.[9]

Several frequency ranges are traditionally considered for EEG signal such as alpha, beta, gamma rhythms, etc.[10] There is a strong correlation between the nature of rhythmic activity in EEG in a specific frequency range (i.e. the presence of a rhythm or an oscillatory pattern[1]) and the functional state of the organism.[11] Thus, research on specific rhythmic EEG components becomes important especially in aspect of studying disorders of the central nervous system since certain features of EEG signals as formation of some patterns and their special

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time-frequency dynamics may be treated as biological markers of the disorder and used for monitoring or even early treatment.

Epilepsy is a common and dangerous disorder that attracts considerable attention of researchers. Among the more than 30 types of epilepsy, absence epilepsy is the most difficult to recognize.[12] It is a nonconvulsive form of the disease characterized by spontaneous brief episodes of unconsciousness, of which the patient may be unaware. On the one hand, the properties of absence epilepsy make diagnostics with conventional clinical methods quite difficult, on the other hand, absence seizures are accompanied by characteristic oscillatory EEG patterns – spike-wave discharges (SWD).[13,14] SWDs serve as diagnostic markers of absence epilepsy, and their occurrence in EEG is accompanied by characteristic clinical manifestations.

SWDs are specific oscillatory patterns characterized by high amplitude and frequencies of 7–10 Hz with from one to several harmonics. These oscillations are of generalized character, i.e., SWD involves nearly whole thalamocortical brain network in synchronous activity (hypersynchronous state). However, thalamocortical neural networks can also generate such nonepileptic activity as sleep spindles, which are brief (0.5-1.5 s) episodes of oscillation characterized by frequencies of 10-16 Hz and spindle-like shapes.[15] Sleep spindles are formed due to the synchronous activity of neural network that consists of cortex and thalamus neurons. The interest in studying of sleep spindles is caused by their possible connection with SWDs and absence epilepsy. There is a hypothesis that neural network which normally generates sleep spindles can produce seizure activity under certain epileptic conditions (i.e., SWDs).[13] There is a relationship between neurophysiological mechanisms of SWDs and sleep spindles, however, this relationship is complex and not obvious.[16,17]

Absence epilepsy has an efficient animal model – special line of WAG/Rij rats.[18] These rats have genetic predisposition to absence epilepsy and demonstrate pronounced SWDs. Important feature of absence epilepsy is its tendency to take some time for full development. Younger WAG/Rij demonstrate no absence seizures and thus there are no SWDs on their EEG recordings, in the age of 5–7 month rats can demonstrate first, mostly undeveloped SWDs, and after 9 month almost all WAG/Rij rats have pronounced SWDs.[19] Since there is a time period of absence epilepsy development and hypothesis states that sleep spindles can transform to SWDs in epileptic brain, one may expect to observe some kind of transition activity between spindles and SWDs or so-called proepileptic patterns. Moreover, one can assume that this transition activity combines features of both sleep spindles and SWDs.

In this work we studied EEG recording of WAG/Rij rats obtained in different ages: 5-7 month (state of absence epilepsy development) and 9-11 month (state of fully developed epilepsy). We analyzed 9-11 month EEG signals in order to define time-frequency features of sleep spindles and SWDs. Then we analyzed 5-7 month EEG signals in search of patterns that combine some features of sleep spindles with those of SWDs.

2. METHODS

The current study was performed in WAG/Rij rats with a genetic predisposition to the absence epilepsy[18] at Institute of Higher Nervous Activity and Neurophysiology RAS, Moscow, Russia in accordance with the Guide for the Care and Use of Laboratory Animals. Experimental protocols were approved by the animal ethics committee of this institution. In current experiments, EEG was recorded in twelve WAG/Rij rats (body weight 320-350 g) during 24 h. EEG recording was made twice for each rat: first in the age of 5-7 month, then in the age of 9-11 month, which provides opportunity to study the process of development of the absence epilepsy.

EEG signals were recorded with epidural screw electrodes placed over the frontal cortex (AP +2 mm and L 2.5 mm relatively to the bregma), band-pass filtered between 0.5-200 Hz, digitized with 400 samples/second/per channel and stored in a hard disk. SWD in this EEG data represented a sequence of high-voltage repetitive 7–10 Hz spikes and waves with minimal duration of 1 s.[20] Sleep spindles were recognized in EEG as oscillations with waxing and waning amplitude, frequency in spindle range (10-16 Hz) and duration $>$ 300 ms.[21] Onsets and offsets of SWDs and sleep spindles were marked on EEG recordings by special recognition software[22] and verified by expert-neurophysiologist.

For preliminary analysis and filtration of EEG signals from artifacts empirical mode decomposition (EMD) method was used. Empirical mode decomposition is a part of Hilbert-Huang transform.[23,24] It is one of the modern methods for time-frequency analysis of complex nonlinear and nonstationary signals including EEG. The method allows to decompose the initial signal into a sum of amplitude-modulated components with zero mean – so-called empirical modes (EMs).

In terms of time-frequency analysis EMD is different from most methods such as Fourier and wavelet transform. Basic functions in EMD are not predetermined but are constructed from analyzed signal itself during decomposition. Time-frequency properties of each empirical mode and total number of empirical modes are highly dependent on the initial signal. This feature makesEMD a highly adaptive instrument for signal analysis. The first empirical mode has the highest frequency, and the higher the ordinal number of subsequent mode the lower its frequency. Research shows that in many cases frequency ranges of different empirical modes correspond to ranges of different oscillatory patterns on EEG.[25] Thus time-frequency analysis of some specific oscillatory patterns (including artifacts) can be reduced to analysis of one or few individual empirical modes.[26]

For further time-frequency analysis of EEG signals continuous wavelet transform (CWT) was used.[1,27,28] The CWT is widely accepted method for timefrequency analysis of multimodal nonstationary processes.[29] During the last decades, this method has been effectively used for analyses of experimental biological data providing essential information about complex dynamics of physiological systems.[30] The energy of CWT, $W(s,\tau)$, was obtained by convolution of EEG signal, $x(t)$ with wavelet basis function $\varphi_{s,\tau}$:

$$W(s,\tau) = \frac{1}{\sqrt{s}} \int_{-\infty}^{\infty} x(t)\varphi^*_{s,\tau}(t)dt \tag{1}$$

Each basis function $\varphi_{s,\tau}$ can be obtained from one function φ_0 called mother wavelet: $\varphi_{s,\tau}$:

$$\varphi_{s,\tau}(t) = \frac{1}{\sqrt{s}}\varphi_0\left(\frac{t-\tau}{s}\right) \tag{2}$$

Complex Morlet-wavelet with parameter $\omega_0 = 2\pi$ was used as mother wavelet:

$$\varphi_0(\eta) = \pi^{-\frac{1}{4}} e^{j\omega_0\eta} e^{-\frac{\eta^2}{2}} \tag{3}$$

Surface of CWT gives common information about time-frequency structure of the signal, such as length of some pronounced oscillatory patterns and their dominate frequencies. In order to study changes of EEG time-frequency structure within each pattern we analyzed momentary distribution of wavelet energy. Such distribution provides detailed information about frequencies in the signal at given time moment, and we can compare distributions for several consequent time moments to find some changes.

3. RESULTS

In the first part of our work we analyzed EEG recordings of 9-11 month old WAG/Rij rats in order to specify time-frequency features of SWDs and sleep spindles. We filtered EEG recordings with EMD-based method to remove some physiological artifacts that can interfere during time-frequency analysis of SWDs and sleep spindles. Then we calculated wavelet energy distributions for short episodes of EEG with SWDs and sleep spindles. Also we calculated momentary wavelet energy distribution for onset and offset of each SWD and sleep spindle. Examples of time-frequency analysis on EEG are illustrated on Fig. 1 for SWDs and Fig. 2 for sleep spindles.

Fig. 1 demonstrates short episode of EEG recording with singular well-pronounced SWD (Fig. 1a) and wavelet energy surface (wavelet spectrum) (Fig. 1b). Onset of SWD is marked with blue dotted line on Fig. 1b, offset – with red dotted line, corresponding momentary wavelet energy distributions are marked with the same colors and placed on Fig. 1c.

It is clear from Fig. 1b, that SWD has main frequency of 7-10 Hz with pronounced first harmonic and less pronounced second harmonic. Statistical analysis shows that duration of SWDs in this set of WAG/Rij rat EEG data varies from 4 to 20 seconds. These features are characteristic for SWDs in WAG/Rij rats but more important result is complex dynamics of SWD frequency structure. As seen from picture Fig. 1c, main frequency along with harmonics changes from onset of SWD to its offset: main frequency in the beginning is 8-9 Hz, while in the end it decreases to 7 Hz. Thus, main frequency of SWD decreases from its start to its end, which is very typical for SWDs in WAG/Rij rats.

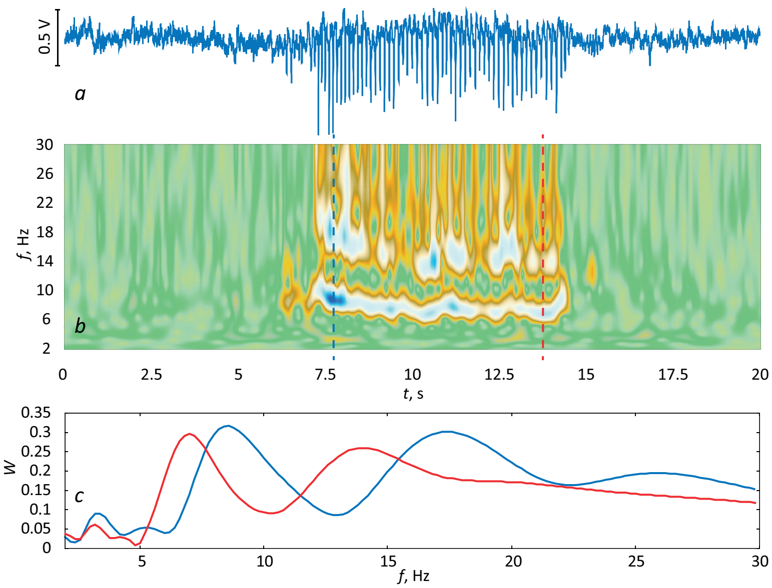

Figure 1. Example of time-frequency EEG analysis for SWD: episode of EEG recording with SWD (a), wavelet spectrum with onset and offset of SWD (marked with blue and red dotted lines) (b), momentary wavelet energy distribution for onset and offset of SWD (c).

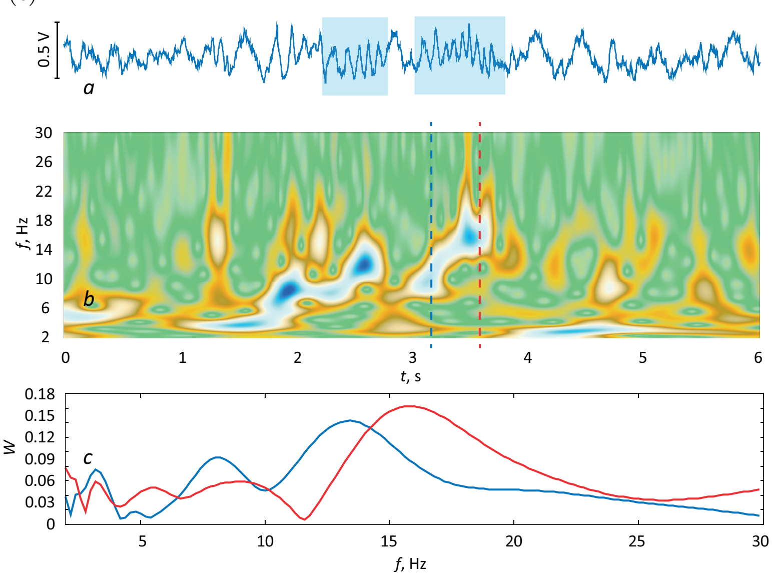

Figure 2. Example of time-frequency EEG analysis for sleep spindles: episode of EEG recording with two spindles (marked with blue frames) (a), wavelet spectrum with onset and offset of one spindle (marked with blue and red dotted lines) (b), momentary wavelet energy distribution for onset and offset of spindle (c).

Fig. 2 demonstrates short episode of EEG recording with two well-pronounced sleep spindles (marked with blue frames) (Fig. 2a) and wavelet energy surface (wavelet spectrum) (Fig. 2b). Onset of one spindle is marked with blue dotted line on Fig. 2b, offset – with red dotted line, corresponding momentary wavelet energy distributions are marked with the same colors and placed on Fig. 2c.

Fig. 2b shows that sleep spindles have one dominant frequency, which can vary greatly – the first spindle on Fig. 2b has frequency of 10-11 Hz, while the second one has frequency of 16 Hz. Therefore, frequency range of sleep spindles is 10-16 Hz, which is very different from frequency range of SWDs. Analysis shows, that duration of sleep spindle is 0.5-1.5 seconds, so spindles can never be as along as even shortest SWDs. And the most important distinction of sleep spindles lies in dynamics of thier frequency. As seen from Fig. 2c main frequency of sleep spindle has tendency to increase from onset to offset of spindle, which is complete opposite to frequency dynamics of SWD.

In the second part of our work we studied EEG signals from 5-7 month old WAG/Rij rats in search of proepileptic activity, that combines features of SWDs and sleep spindles. We also filtered these EEG recordings from artifacts with EMD-based method. Then we applied methods for automated detection of SWDs and sleep spindles, developed in our previous works,[26] and consider cases of false positive. We expected that in case of false positive our methods can detect activity, which possess some properties of SWDs/sleep spindles, but is not exactly SWD or spindle. So we looked for patterns that would be such false positives. Results of research on proepileptic activity are showed in Fig. 3.

Fig. 3 demonstrates two short episodes of EEG recording with two examples of proepileptic patterns (marked with blue frames) (Fig. 3a,d) and wavelet energy surface (wavelet spectrum) (Fig. 3b,e). Onset of proepileptic pattern is marked with blue dotted line on Fig. 3b, offset – with red dotted line, corresponding momentary wavelet energy distributions are marked with the same colors and placed in Fig. 3c,f.

A seen in Fig. 3a,d proepileptic patterns are rather short (0.3-1.5 s) and closer in duration to sleep spindles. Also proepileptic patterns possess mostly spindle-like waveform, but with sharp spikes similar lo ones in SWD. However, Fig. 3b,e shows that main frequency of proepileptic patterns is closer to one of SWDs (7-10 Hz) and it also has at least one harmonics. Main frequency and its harmonic decreases from onset to offset of pattern as illustrated on Fig. 3c,f. So we can assume, that proepileptic patterns combine properties of sleep spindles and SWDs. Analysis shows that there are no proepileptic patterns in rats of 9–11 month with fully developed epilepsy, so proepileptic patterns must be some kind of transition activity during process of epilepsy development.

4. CONCLUSION

In this paper we studied EEG recordings of WAG/Rij rats with genetic predisposition to absence epilepsy. With help of continuous wavelet transform we analyzed two blocks of EEG data: for rats with fully developed epilepsy and for rats with epilepsy in process of development. We studied time frequency structure and features of two types of patterns in rats with developed epilepsy: epileptic spike-wave discharges and non-epileptic sleep spindles. In rats with developing epilepsy we found new type of activity – proepileptic activity, which combines properties of spike-wave discharges and sleep spindles. We assumed that proepileptic patterns should be transition type of activity in brain with developing epilepsy.

Obtained results can be helpful for further fundamental studies on absence epilepsy. Knowledge on proepileptic activity can prove (or disprove) hypothesis about transformation of some sleep spindles into spike-wave discharges in epileptic brain. Also studies on proepileptic activity can be useful in clinical medicine for monitoring of progress of absence epilepsy or even for early treatment.

5. ACKNOWLEDGMENTS

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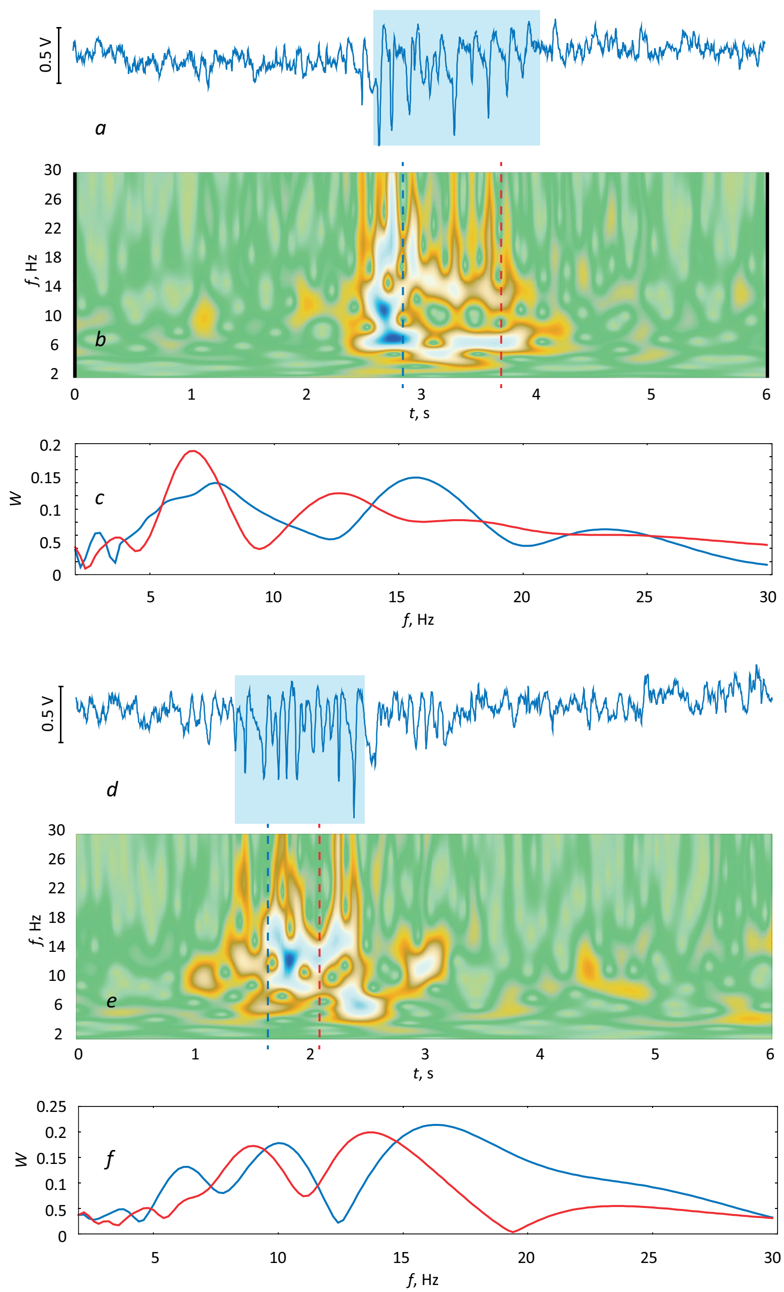

Figure 3. Example of time-frequency EEG analysis for peopileptic patterns: episodes of EEG recording with proepileptic patterns (marked with blue frames) (a, d), wavelet spectrum with onset and offset of proepileptic pattern (marked with blue and red dotted lines) (b, e), momentary wavelet energy distribution for onset and offset of proepileptic pattern (c, f).

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