Age-dependent seizures of absence epilepsy and sleep spindles dynamics in WAG/Rij rats

Vadim V. Grubov[a,b], Evgenia Yu. Sitnikova[c], Alexey N. Pavlov[b,d], Marina V. Khramova[b,e], Alexey A. Koronovskii[a,b], Alexander E. Hramov[a,b]

[a]Faculty of Nonlinear Processes, Saratov State University, Astrakhanskaya Str. 83, Saratov, 410012, Russia;
[b]Research and Educational Center "Nonlinear Dynamics of Complex Systems", Saratov State Technical University, Polytechnicheskaya Str. 77, Saratov, 410054, Russia;
[c]Institute of the Higher Nervous Activity and Neurophysiology of Russian Academy of Sciences, Butlerova Str. 5a, Moscow, 117485, Russia;
[d]Physics Dept., Saratov State University, Astrakhanskaya Str. 83, Saratov, 410012, Russia;
[e]Faculty of Computer Sciences and Information Technologies, Saratov State University, Astrakhanskaya Str. 83, Saratov, 410012, Russia

ABSTRACT

In the given paper, a relation between time-frequency characteristics of sleep spindles and the age-dependent epileptic activity in WAG/Rij rats is discussed. Analysis of sleep spindles based on the continuous wavelet transform is performed for rats of different ages. It is shown that the epileptic activity affects the time-frequency intrinsic dynamics of sleep spindles.

Keywords: Electroencephalogram, wavelet analysis, oscillatory pattern, absence epilepsy, age-dependent dynamics

1. INTRODUCTION

Analysis of complex neural network of the brain is typically based on the electroencephalogram (EEG)[1,2] reflecting a summary electrical activity of large groups of neurons in the region of the recording electrode. EEG contains rhythmic activity in different frequency ranges (such as, e.g., alpha, beta, gamma rhythms, etc.) and specific oscillatory patterns that are important for characterization of the functional state of an organism[2–4]). Thus, studying specific rhythmic components becomes important especially in the case of disorders of the central nervous system because certain EEG patterns may be treated as biological markers of these disorders.

Absence epilepsy is an example of such disorders that occurs in humans and animals.[5] An important feature of the absence epilepsy is the appearance of specific oscillatory patterns in EEG, namely, the spike-wave discharges (SWD) being the manifestation of the epilepsy seizures. Recent neurophysiological studies established a strong relation between SWD-patterns and another type of specific oscillatory patterns on EEG, the sleep spindles.[6] Both types of patterns appear due to the synchronous activity of neural network that includes neurons from the cortex and the thalamus.[7] While sleep spindles are generated as the result of normal activity of the thalamo-cortical network, SWDs are produced only under certain epileptic conditions.[8]

Due to complexity of the brain activity, advanced data processing tools are widely used to characterize its dynamics. In the case of sleep spindles, for instance, the intra-spindle frequency is an important quantity characterizing intrinsic properties of the thalamo-cortical neural network. Time-frequency characteristics of sleep spindles in epileptic and non-epileptic subjects have notable distinctions.[9] When studying the structure of oscillatory patterns it should be noted that they are age-dependent. Thus, it was shown[10] that the number

Further author information: (Send correspondence to A.E.Hramov, V.V. Grubov)
A.E. Hramov: E-mail: hramovae@gmail.com, Telephone: +7 8452 51 42 94,
V.V. Grubov: E-mail: vvgrubov@gmail.com, Telephone: +7 8452 51 42 94

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and the duration of SWD-patterns in WAG/Rij rats increase with age, although age-dependent changes in sleep spindles are still uncertain.

Here, we consider a relationship between the epileptic spike-wave discharges and the physiological sleep spindles assuming that the age-dependent increase of the epileptic activity may affect the time-frequency characteristics of sleep spindles. In order to examine this hypothesis, we use the continuous wavelet transform (CWT)[4,11] to analyze the dynamics of the intra-spindle frequency and to compare this dynamics in young WAG/Rij rats (preclinical state) and older animals (symptomatic state) with fully developed SWDs.

2. METHODS

2.1 EEG Data

In this work we used a convenient animal model to study the absence epilepsy, namely, the WAG/Rij rats.[10] Studying of the EEG in rats provides a possibility to get a better resolution when the recording electrodes are implanted directly into the brain structures. Results obtained in rats can further be extended for humans.[10]

WAG/Rij is a special line of rats with a genetic predisposition to the absence epilepsy,[10] and epileptic seizures are almost guaranteed in EEG signals of WAG/Rij rats. Besides, the absence epilepsy in WAG/Rij rats is age-dependent that is important for the aim of this study.

In the given work we consider EEG signals of WAG/Rij rats at three different ages: 5 months (preclinical state without epileptic seizures), 7 months (symptomatic age characterized by the growth of epileptic activity) and 9 months (symptomatic age with the fully developed absence epilepsy). We analyzed 24 h multichannel recordings that include episodes with different oscillatory patterns: sleep spindles, spike-wave discharges, artifacts of different nature and the background activity. Because sleep spindles and SWDs show maximum amplitude in the frontal region, we are mainly concentrated on studying electrical activity of the brain recorded from the frontal cortex channels. All experiments were performed by neurophysiologists from the Moscow Institute of Higher Nervous Activity and Neurophysiology.

2.2 Wavelet-based methods

Our analysis was based on the continuous wavelet transform[4,11] for time-frequency characterization of sleep spindles. CWT represents a convolution of a studied signal $x(t)$ and a set of soliton-like functions $\varphi(s,\tau)$:

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

Each function from this set is constructed from a single function φ_0, called as the mother wavelet, as follows

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

where s is the time scale determining the dilations of the function φ_0, and τ characterizes the translation of the function along the time axis.

Time-frequency analysis is typically based on the Morlet wavelet

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

that possesses an additional parameter ω_0 called as the central frequency. This parameter provides a compromise between resolutions of the function φ_0 in time and in frequency domains. Here, we use the value $\omega_0=2\pi$. Due to its good time-frequency resolution, the Morlet wavelet is widely used in studying EEG-data.[9,12]

Sleep spindles were automatically detected in the frontal EEG using the earlier developed wavelet-based method.[9,13] This method assumes estimations of the CWT energy $W(f_s,t)$ and its averaging in the frequency band $F\in(8,16)$ Hz that is associated with sleep spindles

$$w(t)=\int_F|W(f_s,t)|^2df_s. \tag{4}$$

The value of $w(t)$ was also averaged within the time window T. We used $T = 0,5$ s that is nearly close to the averaged duration of sleep spindle

$$\langle w(t) \rangle = \int_{t-T}^{t+T} w\left(t'\right) dt'. \tag{5}$$

Finally, the averaged wavelet energy $\langle w(t) \rangle$ was compared with the threshold value w_c. Sleep spindles were detected under the condition $\langle w(t) \rangle > w_c$. The threshold value w_c was empirically defined (individually for each rat). This method provides a detection of about 90-95% of sleep spindles (visually selected by an expect).

Intra-spindle frequency dynamics was investigated using "skeletons" of the wavelet surfaces.[9] They were identified according to the following procedure. First, the instantaneous energy distribution $E_i(f_s, t_0)$ was estimated at some time moment t_0

$$E_i(f_s, t_0) = |W(f_s, t_0)|^2. \tag{6}$$

Second, the function $E_i(f_s, t_0)$ was examined for the presence of local maxima E_{max}. If several local maxima $E_{max,k}$ were detected, the highest maximum was selected and its frequency was considered as the dominant frequency of sleep spindle at the given time moment t_0. In order to construct full "skeleton" of the wavelet surface, this procedure was repeated consequently for each time moment.

The non-parametric Friedman's ANOVA was used for statistical analysis of the age-dependent changes of analyzed parameters and the Wilcoxon matched pairs test was used for the subsequent post hoc analysis.

3. RESULTS

Because the epileptic activity in WAG/Rij rats increases with age, at the first stage we analyzed the development of the absence epilepsy based on experimentally recorded EEG signals. For this purpose we performed a statistical analysis of 6-hour EEG-recordings in six WAG/Rij rats of three different ages (5, 7 and 9 months) using the Friedman and the Wilcoxon tests. It was found, that the number of SWDs increased between 5 and 9 months of age from 3 to 38 discharges (the Friedman test, $\chi^2_{N=6,df=2} = 6.5, P < 0.05$), as well as the total duration of seizure activity (from 34 ± 20 s to 439 ± 281 s, $\chi^2_{N=6,df=2} = 8.0, P < 0.05$). It should be noted that SWDs were absent in EGG signals of 4 out of 6 rats at the age of 5 months, while 2 rats showed few discharges with unstable characteristics being different from normal SWDs. Thus, this age was considered as the preclinical state of the absence epilepsy in WAG/Rij rats, while 9 months is a symptomatic state with notable differences in the parameter of EEG patterns.

In order to investigate age-related changes in sleep spindles, we automatically selected the corresponding patterns in all available data sets using the wavelet-based approach.[9,13] In total, 115 sleep spindles were selected for 5 months old WAG/Rij rats, 117 – in 7 months old and 115 – in 9-months old animals. Further analysis of intra-spindle frequency dynamics was performed using "skeletons" of wavelet surfaces. "Skeletons" were constructed for 2-second segments of EEG signals with sleep spindles for all experimental recordings. Frequency band was selected as 9-14 Hz that corresponds to typical main frequencies of sleep spindles. The performed analysis showed that intra-spindle frequency can slightly change from the beginning to the end in some sleep spindle events.

Figure 1 illustrates three typical examples of frequency dynamics of sleep spindles in WAG/Rij rats of different ages: 5 (A), 7 (B) and 9 (C) months. As we can see from figure 1(A), the corresponding frequency in EEG of a 5 months old rat demonstrates a notable growth (about +1 Hz) from the beginning to the end. However, this feature of the frequency dynamics does not observed (or is significantly less expressed) in spindles shown in Figires 1(B, C).

To provide a statistical analysis, instantaneous frequencies at the beginning (f_{start}) and at the end (f_{end}) of each spindle were estimated from "skeletons" and then analyzed with the pairwise Wilcoxon test. Table 1 illustrates results of such analysis. It was found that the value of f_{start} increases with age ($\chi^2_{N=115,df=2} = 12.6, P < 0.005$). Besides, the value of f_{start} in EEG of 5 months old rats was lower compared with EEGS of 7 and 9 months old animals (the pairwise Wilcoxon test, all $P's < 0.05$, see table 1). It should be also noted that the difference between f_{start} and f_{end} significantly changes with the age ($\chi^2_{N=115,df=2} = 11.3, P < 0.005$). According to the pairwise Wilcoxon test, the growth of the intra-spindle frequency ($f_{start} < f_{end}$) was significant

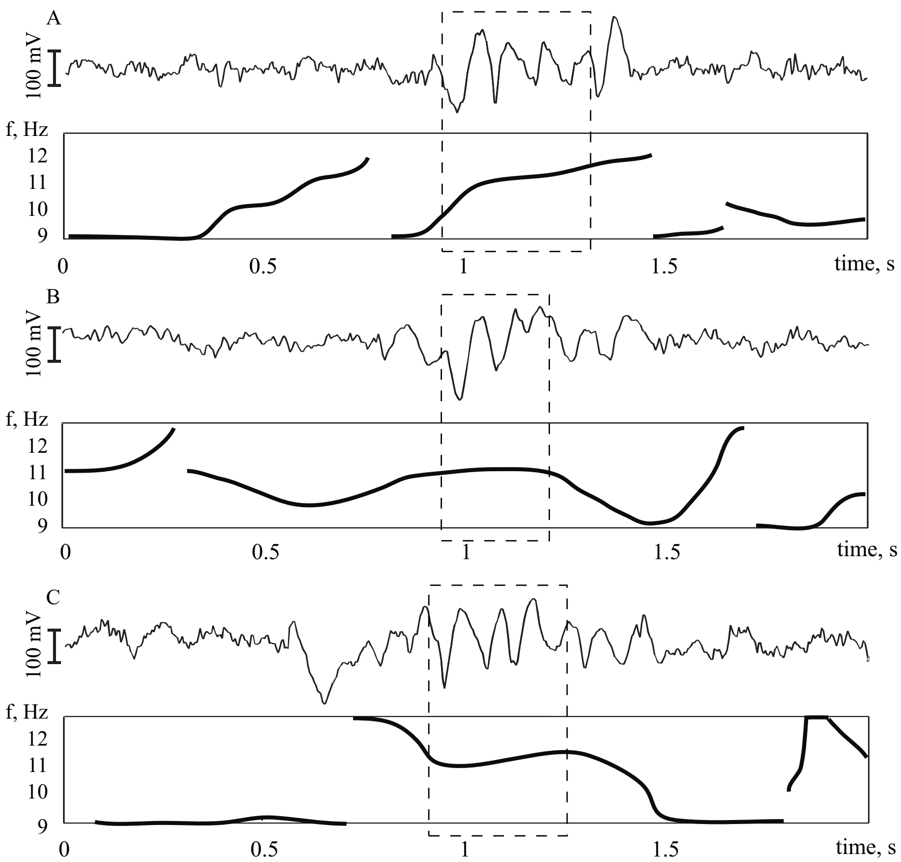

Figure 1. EEG signals with sleep spindles (marked with dotted frames) from WAG/Rij rats and the corresponding "skeletons" for three different ages: 5 (A), 7 (B) and 9 (C) months.

only for 5 months old WAG/Rij rats ($P < 0.005$). For other rat groups, the differences between f_{start} and f_{end} are nearly close to zero value, see table 1).

Summarizing the obtained results, we can speak about a connection between the age-related changes in SWDs and sleep spindles. Indeed, the beginning value of the spindle frequency (f_{start}) in preclinical (5 months old) WAG/Rij rats was significantly lower as compared with the corresponding frequency in older animals (7 and 9 months old), when the epileptic discharges became more numerous, and the epileptic activity became longer. Moreover, the age-dependent increase of absence seizures could be associated with the changes of the intra-spindle frequency. This can be caused by stronger synchronization (hyper-synchronization) of thalamo-cortical network while a low beginning value of the intra-spindle frequency f_{start} in preclinical (5 months old) WAG/Rij rats can reflect a "normal" rhythmic activity of this network.

Table 1. Dynamics of the intra-spindle frequency in WAG/Rij rats of different ages.

Age, months	Frequency at start (M.V. ± S.D.), Hz	Frequency at end (M.V. ± S.D.), Hz	Frequency change, Hz
5	10.45 ± 0.4	11.5 ± 0.4	1.05
7	11.2 ± 0.4	11.4 ± 0.4	0.2
9	11.3 ± 0.4	11.35 ± 0.4	0.05

4. CONCLUSIONS

In the present paper, wavelet-based methods were used for analysis of the time-frequency structure of sleep spindles in EEG signals of WAG/Rij rats characterized by the genetic predisposition to the absence epilepsy. Statistical analysis showed differences in the frequency dynamics of sleep spindles in rats of different ages: 5 months old animals (preclinical state) demonstrated a higher beginning frequency of sleep spindles and the overall growth of the main frequency in sleep spindle while animals with the developed epilepsy (7 and 9 months old, symptomatic state) had lower beginning frequencies and smaller changes of the intra-spindle frequency. This assumes that the age-dependent development of the epileptic activity in WAG/Rij rats affects intrinsic dynamics of sleep spindle frequency.

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REFERENCES

[1] Buzsaki, G., and Draguhn, A., "Neuronal oscillations in cortical networks," *Science* **304**, 1926–1929 (2004).

[2] Niedermeyer, E. and da Silva, F. L., [*Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*], Lippincot Williams & Wilkins (2004).

[3] Hramov, A. E., Sitnikova, E. Y., Pavlov, A. N., Makarov, V. A., and Koronovskii, A. A., [*Wavelets in neurodynamics and neurophysiology (In Russian)*], Moscow, Fizmatlit (2013).

[4] Hramov, A. E., Koronovskii, A. A., Makarov, V. A., Pavlov, A. N., and Sitnikova, E. Y., [*Wavelets in Neuroscience*], Springer, Berlin, Heidelberg (2015).

[5] Steriade, M., [*Neuronal substrates of sleep and epilepsy*], Cambridge University Press, Cambridge (2003).

[6] De Gennaro, L. and Ferrara, M., "Sleep spindles: an overview," *Sleep Med. Rev.* **7**, 423–440 (2003).

[7] Kostopoulos, G. K., "Spike-and-wave discharges of absence seizures as a transformation of sleep spindles: the continuing development of a hypothesis," *Clinical Neurophysiology* **111**(Suppl. 2), S27–S38 (2000).

[8] Van Luijtelaar, E. L., "Spike-wave discharges and sleep spindles in rats.," *Acta neurobiologiae experimentalis* **57**(2), 113–121 (1997).

[9] Sitnikova, E., Hramov, A. E., Grubov, V. V., and Koronovsky, A. A., "Time-frequency characteristics and dynamics of sleepspindles in wag/rij rats with absence epilepsy," *Brain Research* **1543**, 290–299 (2014).

[10] Coenen, A. M. and Van Luijtelaar, E. L., "The wag/rij rat model for absence epilepsy: age and sex factors," *Epilepsy Res.* **1**(5), 297–301 (1987).

[11] Pavlov, A. N., Hramov, A. E., Koronovskii, A. A., Sitnikova, E. Y., Makarov, V. A., and Ovchinnikov, A. A., "Wavelet analysis in neurodynamics," *Physics-Uspekhi* **55**(9), 845–875 (2012).

[12] Luijtelaar van, E. L. M., Hramov, A. E., Sitnikova, E., and Koronovskii, A. A., "Spike-wave discharges in WAG/Rij rats are preceded by delta and theta precursor activity in cortex and thalamus," *Clinical Neurophysiology* **122**, 687–695 (2011).

[13] Ovchinnikov, A. A., Luttjohann, A., Hramov, A. E., and Luijtelaar van, G., "An algorithm for real-time detection of spike-wave discharges in rodents," *Journal of Neuroscience Methods* **194**, 172–178 (2010).