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Control of epileptic seizures in WAG/Rij Rats by means of brain-computer interface

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ABSTRACT

The main issue of epileptology is the elimination of epileptic events. This can be achieved by a system that predicts the emergence of seizures in conjunction with a system that interferes with the process that leads to the onset of seizure. The prediction of seizures remains, for the present, unresolved in the absence epilepsy, due to the sudden onset of seizures. We developed an algorithm for predicting seizures in real time, evaluated it and implemented it into an online closed-loop brain stimulation system designed to prevent typical for the absence of epilepsy of spike waves (SWD) in the genetic rat model. The algorithm correctly predicts more than 85% of the seizures and the rest were successfully detected. Unlike the old beliefs that SWDs are unpredictable, current results show that they can be predicted and that the development of systems for predicting and preventing closed-loop capture is a feasible step on the way to intervention to achieve control and freedom from epileptic seizures.

Keywords: epilepsy, spike-wave discharge

1. INTRODUCTION

Nowadays there are about 50 million people all over the world suffering from epileptic diseases. Among them about 30% of patients do not respond to available medical treatments.[1,2] The main problems encountered in the diagnosis and treatment of epileptic disorders, specifically, absence epilepsy, connected with the unpredictable nature of neuron dynamics.[3,4] The epileptic patterns of neuron activity emerge spontaneously and the analysis of background activity between them in the most cases cannot provide the evidence and reasons for these abnormalities.[5]

An exciting application of absence seizure prediction technology is its potential for use in therapeutic epilepsy devices to trigger intervention to prevent seizures before they begin.[6,7] A very promising recent work of Antal Berényi and colleagues[8] shown the strong theoretical and experimental possibility to reduce pathological brain patterns via the electrical stimulation.

One of the common problems connected with the development of seizure prediction algorithm is the lack of experimental data, on which the proposed technique can be tested. The epileptic seizures appear spontaneously and its still not possible to explain how and over what time it happens. So, the very long EEG recordings are needed to collect several episodes of pathological dynamics. To avoid it some recent studies deal with so known

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Dynamics and Fluctuations in Biomedical Photonics XV, edited by Valery V. Tuchin, Kirill V. Larin, Martin J. Leahy, Ruikang K. Wang, Proc. of SPIE Vol. 10493, 1049311 · © 2018 SPIE
CCC code: 1605-7422/18/$18 · doi: 10.1117/12.2291696

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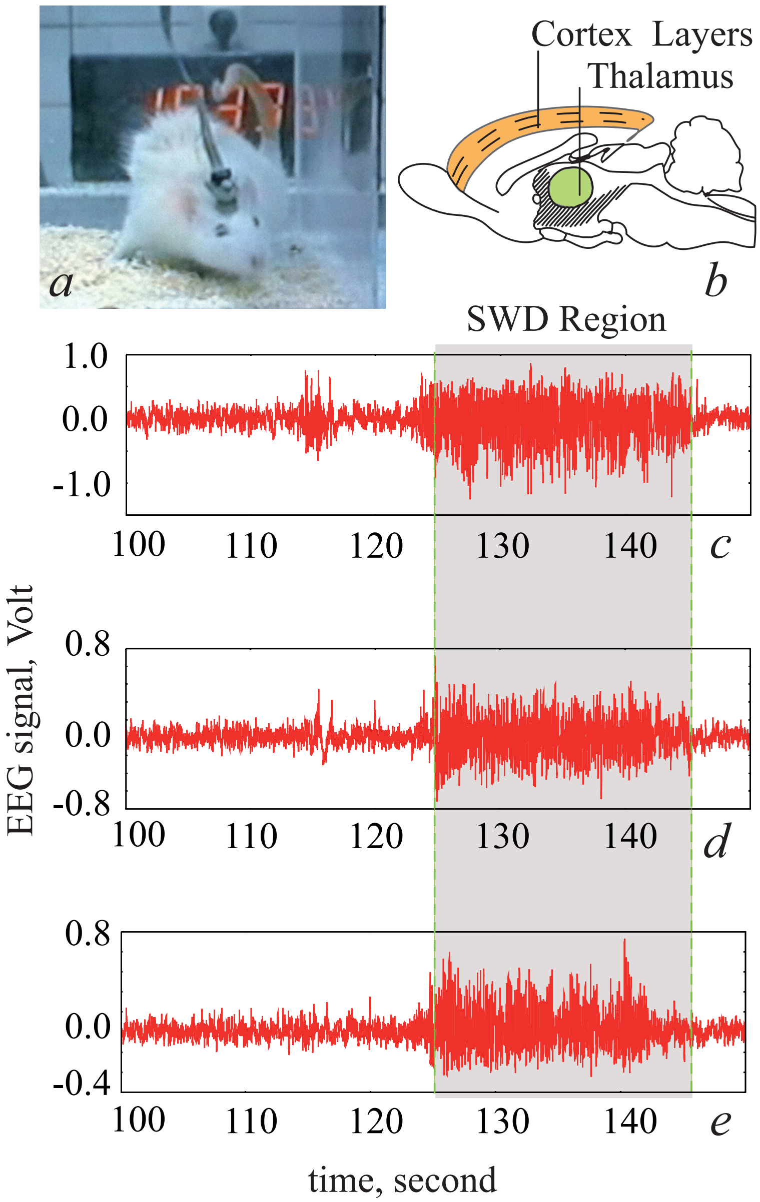

Figure 1. the foto of WAGRij rat (a) with the set of electrodes in Donders Centre, Neimegen, the schematic illustration of the regions of brain (cortex and thalamus) (b) from which the EEG recordings are taken and the EEG recordings, corresponding to the cortical electrode (c), anterior (d) and posterior (e) nuclei of thalamus. The time interval, corresponding to the SWD activity is marked by shadow area

animal seizure models.[9] Such models involve the artificial induction of seizures in normal animals by means of chemical or electrical stimulation.[10,11] The major critique to the seizure models is that seizures are only induced in an otherwise 'healthy' brain, so that studying the mechanisms of their occurrence might not resemble the exact pathological state.

In our study we used the epilepsy model, based on the rats WAG/R_{ij} with genetic predisposition to the absence epilepsy.[12] About 90% of these animals has the epileptic disorders which progress with the rats age and the adult animals (aged about 6 months) demonstrate the seizures regularly without any kind of stimulation. The collecting of EEG signals was performed during 5 hour period when rats have normal activity and permanent access to food and water.

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2. METHOD

The recent studies evident that the so known multivariate methods based on the multichannel EEG recordings are the most appropriate tool for seizure prediction problem.[13] It give the information about interaction of different regions of brain which is useful since there is often some interaction (e.g., synchronization) leading up to a seizure. So, the proposed multivariate methods[14] are focused on the detection of synchronization regimes (lag-synchronization, phase-synchronization, etc.) and analysis of correlation structure (phase correlation) of multichannel EEG recordings.[?, 15, 17] All these algorithms are unable to provide the good prediction accuracy due to the complexity and noisiness of analyzed EEG signals.[18] In the present research we used the wavelet transform for the detection of multichannel synchronization. The wavelet transform is traditionally the most powerful tool for analysis of non-stationary signals has earlier been applied for development of seizure prediction methods.[19] But its application was reduced by the single EEG recordings and did not led to successful prediction.[20] Moreover, the use of wavelets for the realtime analysis was problematic due to the necessity of integrating over the window. We was able to solve this problem by the modification of the basis Morlet function, provided the reduction of the window length. As the result, the wavelet transform for the every moment of time was following

$$W_i(s,t) = \int\limits_{t-s}^{t+s} \frac{1}{\sqrt{s}} X_i(t') \psi^* \left(\frac{t-t'}{s} \right) dt', \tag{1}$$

where the mother wavelet function is

$$\psi\left(\eta\right) = \pi^{-1/4} \mathrm{Exp}(i\omega_0 \eta) \mathrm{Exp}\left(\frac{-10\eta^4}{2} \right). \tag{2}$$

Here $\omega_0 = 2.0$ is the parameter of wavelet function, s — timescale, t — the current moment of time, $X_i(t)$ — EEG signal corresponding to the selected channel.

In our study we used three different channels, obtained from both invasive and noninvasive electrodes. The resulting wavelet energy surface was obtained as the product of amplitudes of the wavelet transform of observed channels

$$|W(s,t)| = |W_1(s,t)| \times |W_2(s,t)| \times |W_3(s,t)|. \tag{3}$$

W_1, W_2, W_3 — wavelet energy surfaces corresponding to the EEG recordings taken from cortex layer (noninvasive electrode), anterior nucleus of thalamus (invasive electrode) and posterior nucleus of thalamus (invasive electrode). Analysis of the obtained wavelet surface allows to detect the synchronous activity in the timescale region, corresponding to the epileptic behavior as the isolated high-amplitude pattern appeared for a few seconds before the SWD start. These precursors occur before the every SWD event which we observe on the long EEG recording of several WAG/R_{ij} rats in laboratory of Nijmegen.

3. RESULTS

It is known that the onset of epileptic seizures is associated with the emergence of a global synchronous mode, involving either all neurons of brain or the most of them. The EEG recordings, corresponding to this event, has a form of periodically repeated spike-wave patterns, occurred in the all recordings of multichannel set (Fig. 1, *c, d, e*). The EEG signals, illustrated in Fig. 1, demonstrates that the seizure is also characterized by the sharp increase of the amplitude, that can be the evidence of the appearance of large neuron cluster, generating the spike-wave oscillations.[21]

It can be assumed that the processes of neuron synchronization in a local areas and its interaction, leading to the global synchrony, are gradual and can be observed some seconds before the seizure onset. So, the precursor of the seizure can be detected when the transition from the spontaneous behaviour of single neurons to its synchronic dynamics takes place.

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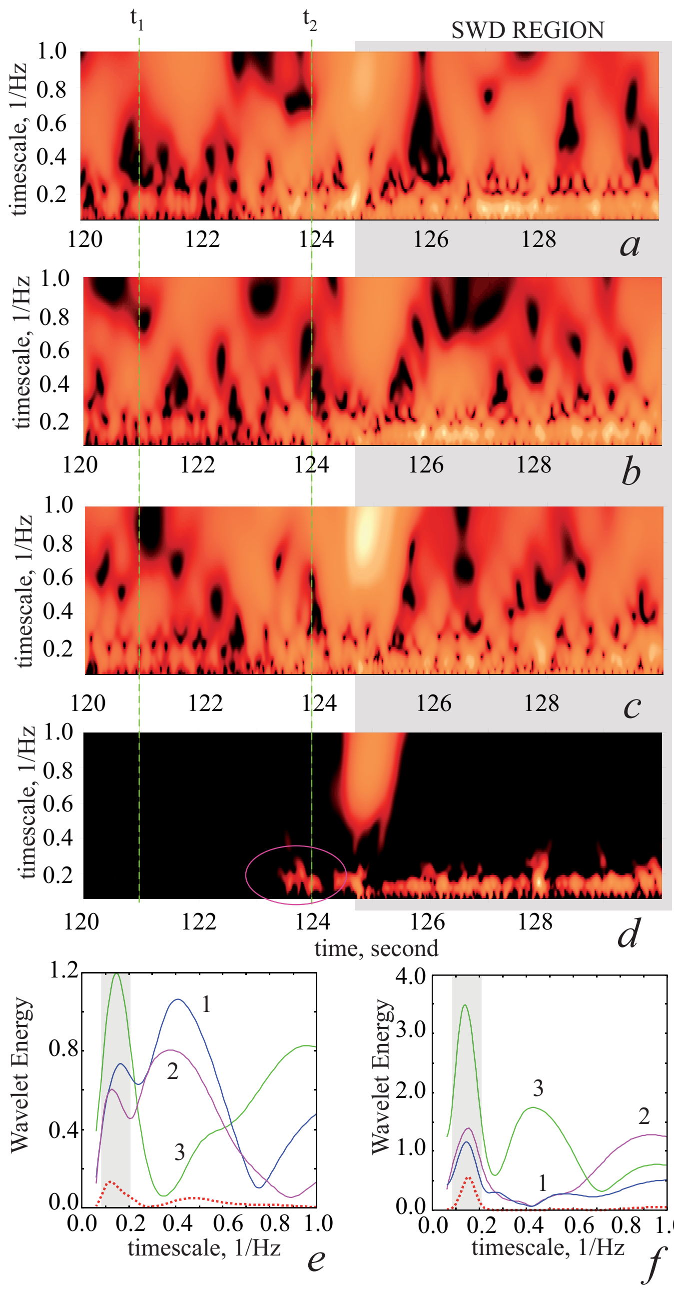

Figure 2. The wavelet energy surfaces, cooresponding to the differen channels: cortex (a), anterior nucleus of thalamus (b) and posterior nucleus of thalamus (c and the product of these energies (d). The SWD region is marked by the shadow area. t_1 and t_2 correspond to the moments of time for which the wavelet energy distributions of different channels (anterior nucleus of thalamus — 1, posterior nucleus of thalamus — 2, cortex — 3) and the producted energy (dotted line) are presented (e, f). The shaded region corresponds to the timescales area of SWD activity.

In the following research we have shown how the processes of local and global synchronous regimes in neural network and therefore, the precursor dynamics can be effectively detected via the multichannel EEG analysis.

Let the every EEG channel be the macroscopic characteristic[22] of the single neuron ensemble of brain, which takes part in a seizure. To find the synchronic mode within the every ensemble, the corresponding EEG signal was analyzed with the help of wavelet transform. As a result, the distribution of the power of neuron oscillations over the timescales was obtained for the every moment of time.

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In Fig. 2, *a, b, c* such dependencies are illustrated for the EEG recordings (Fig. 1, *c, d, e*), containing the area of seizure. It can be seen, that energy is distributed mostly homogeneously when the seizure is absent (t_1), but at the same time, the initial manifestations of synchronization take place. It can be observed as isolated patterns appeared in the timescale area $s \in (0.08, 0.2)$, corresponding to the seizure dynamics. Such situation is observed for $t = t_1$. In Fig. 2, *e* the energy distributions, corresponding to the observed channels for this case are shown. Here one can identify the isolated peaks in the area $s \in (0.08, 0.2)$ (the shaded area in Fig.2, *e, f*). Then, as we approach the beginning of seizure, two mechanisms become prevailing: (i) The increase of the synchronization within each neuron ensemble, which is accompanied by the energy transition to the timescales $s \in (0.08, 0.2)$. It results in increase of amplitude of the observed peaks on dependencies 1, 2, 3 (see Fig. 2, *f*); (ii) The emergence of the global synchronic mode between these ensembles, which causes peaks to line up under each other in the timescales region $s \in (0.08, 0.2)$ (see Fig. 2, *f*).

As a result, the high amplitude isolated patterns appear on the wavelet energy surfaces, corresponded to the different EEG recordings (see Fig. 2, *a, b, c*). To show the appearance of channel synchronization we used the product of obtained wavelet surfaces. It is shown in Fig. 2, *d* for the EEG recordings, described above. Is should be noted, that the obtained synchronic regime, including both local and global neuron synchronization, occures before the seizure starts (in Fig. 2, *a - d* the seizure area is shaded) that allows us to interpret this as a seizure precursor and detect it effectively.

To confirm the possibility of precursor detection via the proposed approach, we analyzed the long-term multichannel EEG recordings, taken from the six epileptic rats. The each recording contained about 8-10 seizures which emerged spontaneously without any kind of stimulation (see Methods). The performed analysis shown that the precursors appeared for 3-1 seconds before the seizure started.

4. CONCLUSION

In this report we have shown the feasibility to predict and control the absence epileptic seizures via the brain-computer interface. We used the epilepsy model, based on the rats WAG/R_{ij} with genetic predisposition to the absence epilepsy. About 90% of these animals has the epileptic disorders which progress with the rats age and the adult animals (aged about 6 months) demonstrate the seizures regularly without any kind of stimulation. The present research shows, that in contrast to the long- standing opinion that SWDs are unpredictable in nature, SWDs can be predicted to a substantial degree and that a prediction algorithm can successfully be implemented in a brain computer interface that will greatly reduce SWD activity based on a combination of SWD prediction, prevention, detection and disruption.[23]

5. ACKNOWLEDGMENTS

This work has been supported by the project of Ministry of Education and Science of Russia (Grant 3.861.2017/4.6) in the part of the development of seizure prediction system. A.E.H. acknowledges individual support from the Ministry of Education and Science of Russia (project 3.4593.2017/6.7).

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