DETECTION OF SPIKE-WAVE DISCHARGE RESTARTS IN GENETIC RAT MODEL BASED ON FREQUENCY DYNAMICS

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Abstract

The spike-wave discharges in epileptic brain can be maintained by one or more sequential restarts, which should have mechanisms similar to those of discharge initiation. To examine this hypothesis an original algorithm for automatically determining restarts was developed. To implement the algorithm the windowed fast Fourier transform with a Hann window was used. The method was to track the frequency consecutive drops on a skeleton constructed from a spectrogram in a selected frequency range (7–12 Hz). The method does not rely on changes in the amplitude of the oscillations, while most of the known methods clearly rely on an increase in power in certain spectral ranges. Discharge restarts were successfully detected and were found to be not different from initial starts in terms of main frequency dynamics. Restarts were diagnosed in about four less often than starts. The existence of restarts confirms that different factors are responsible for maintenance of long spike-wave discharges: some discharges are supported by the special maintenance mechanism, others are continuous chains of short discharges.

1 Introduction

Currently, epilepsy is one of the most common disorders of the nervous system, having a significant impact on a person quality of life. Epilepsy, regardless of its type, is generally characterized by occurrences of high-amplitude electric discharges in the brain, which are the result of the simultaneous excitation of many neurons [Berg et al. (2010)] both in humans [Spencer (2002)] and animals [Coenen and van Luijtelaar (2003)]. Electroencephalography (EEG) is a fairly common method for recording this phenomenon.

Absence epilepsy is a mild form with short-time non-convulsive seizures, often repeated (from tens to hundreds per day) with the suspension of current activity and the presence of characteristic bilateral-synchronous discharges of the spike-wave type (SWDs) in EEG and local field potentials (LFPs) with a main frequency $\approx$3 Hz in humans. The frequency composition of EEG/LFP

characterizing the electrical activity of local fields in the brain depends significantly on what types of cells and in which order take part in the activity and the propagation characteristics (scalp filtering in the case of surface EEGs). The very specific and nonlinear nature of SWDs was mentioned earlier [Feucht et al. (1998); Sitnikova et al. (2009); Gabova et al. (2009)]. Similar spike-wave discharges with a frequency of 6–8 Hz manifested themselves in rats with a genetic predisposition to absence epilepsy [Russo et al. (2016); Depaulis and Charpier (2017)], including WAG/Rij rats (Wistar albino Glaxo of Rijswijk) [Coenen and van Luijtelaar (2003)] and GAERS (genetic absence epileptic rats from Strasbourg) [Marescaux et al. (1992)]. Despite the difference in frequency parameters, the frequency-time structure of spontaneous spike-wave discharges is the same for humans and rats [Destexhe (1998, 1999)], at least for typical SWDs [Bosnyakova et al. (2007)]. We do not consider recently found by [Taylor et al. (2017)] so called nonepileptic SWDs, and we cannot make any decision about whether the proposed approach occur to be efficient and whether restarts exist in this new type of SWDs.

In the case of absences of short or average duration, the frequency-time structure of the discharge is quite integral. Contrary, in the case of absences of large duration (the median length is about 6 s and SWDs twice longer are usually considered to be long, see [van Rijn et al. (2010)]), there are several types of frequency-time organization. Either epileptic activity is quite stable, or repeated increases and decreases in frequency are observed as it was detected using skeletons in time-frequency plots [Obukhov et al. (2014)]. Such dynamics was observed as an effect of pharmacological treating [van Rijn et al. (2010)]. However, long discharges can be observed without exposure to drugs. Their time-frequency organization may also experience repeated frequency increases and decreases. In this case, it can be assumed that there are restarts in a discharge, which can contribute to the maintenance of long seizures. Thus, a restart is accompanied by a repeated sharp increase in the seizure frequency, typical for the initial start, which is followed by a relatively fast decline, with all this activity being within a single discharge. Such long discharge is different from two subsequent SWDs, since when the discharge stops completely, the main frequency of pathological activity disappears completely, with switching to baseline activity. But when a restart takes place, there could be (or could not) a reduction of signal amplitude for some seconds before it, but the main frequency and its harmonics still stay in the signal; so, when a neurophysiologist makes markers of epileptic activity, a discharge with restarts is considered as a single one.

Understanding the mechanisms of long absences is crucial for their study and modeling. Existing results on connectivity analysis show that connectivity in the brain changes not only before, but also during a discharge. The analysis was performed using different measures, including nonlinear correlation [Lüttjohann and van Luijtelaar (2012)], mutual information function [Grishchenko et al. (2017)], nonlinear Granger causality specially adapted to the data [Sysoeva et al. (2016c,b)], transfer entropy [Grishchenko et al. (2020a)]. In all cases this averaging over numerous seizures was done. Based on these results, when modeling spike-wave discharges with non-stationary transients (metastable states, [Medvedeva et al. (2020)]), a special process was introduced into the mathematical model, reflecting changes in connectivity in the thalamocortical network 2–4 s after the discharge initiation. So, the maintenance of the discharge was modeled separately. At the same time, the coupling changes involved in discharge maintenance are not identical to those involved in its initiation. Simulation of discharge maintaining as a separate process makes it possible to obtain the distribution of discharge duration in the mathematical model close to the experimentally observed one [Medvedeva et al. (2020)]. This paper uses the approach based on splitting the entire model network into part (normal and epileptic) as some other studies do [Andreev and Maksimenko (2019)] in which only smaller part is responsible for the main frequency generation since otherwise it is too complex to get synchronization in a large ensemble.

If the mechanisms responsible for long discharges may be different discharge modeling must be adjusted. For example, some of them are indeed supported by special mechanisms in which the caudal part of the reticular nucleus of thalamus take primary role, as shown in [Sysoeva et al. (2016a)], and others are just a series of "sticky" discharges. Also, various mechanisms for generating long discharges can explain that the electrophysiological effects now tested to stop discharges are successful in some cases and ineffective in others [Lüttjohann and van Luijtelaar (2016)].

Here we aim to study whether the SWD restarts indeed take place, assuming that restart connectivity mechanisms do not differ from those of initiation. To investigate this question we develop an algorithm for automatic detection of possible SWD restarts and test this method on the time series of activity of brain local field potentials in rats of the WAG/Rij strain. We base this algorithm on a suggestion that if the mechanisms of restarts and initial starts are the same, the corresponding time-frequency dynamics is also similar.

2 Data

This study was performed in accordance with the guidelines of the European Community for the use of experimental animals. All animals of the WAG/Rij strain of 5–7 months age exhibited spontaneous spike-wave discharges. Seven electrodes were implanted under anesthesia. Four electrodes were placed on the surface of the cortex, one in the frontal cortex (FC) region [AP +3.5; L3], the second in the parietal cortex (PC) region [AP −1.6; L4]; signals from these electrodes were

used in this work. Reference electrode was placed above the cerebellum. Valid signals from the occipital cortex and hippocampus also present in the data were not used in this work since these areas are not considered as primary generators of epileptic activity for absence epilepsy [Meeren et al. (2002)]. Therefore, use of them could produce mistakes when detecting time moments of SWD initiation. Another electrode was placed on the brain stem, but because of the poor signal quality, this data could not be used. The presence of epileptic activity in each animal was determined by occurrence of spike-wave discharges in LFPs and due to their behavior. Signals were recorded with a 16-channel ADC with hardware 50-Hz band-stop filter. Because of the low signal level, a preamplifier was used. Then, the obtained LFPs were software filtered in the band $[0.1; 100]$ Hz, digitized with a sampling frequency of 512 Hz and stored for an off-line analysis using Windaq system (DATAQ Instruments, Akron, OH, U.S.A.).

To test the method here, we used data from 11 experiments, for which the signal level was sufficient high, noises were insignificant, and histology showed correct electrode placement. Rats No. 1, No. 6, No. 10, No. 13 had two recordings made in different days. Rats No. 14, No. 27, No. 29 had only one recording. The studied discharges for each rat were selected considering their duration to be more than ten seconds (the median duration of discharges was about 6 s [van Rijn et al. (2010)]), since we were interested only in long seizures, for which reinitiation was expected. The average length of such absences was 12–15 s, being different for different animals. There were also some cases lasting more than 30 s. The number of discharges for each animal is given in the Tab. 1. In total, 203 discharges were studied in seven animals in 11 experiments. In each experiment, we aimed to consider 20 discharges, but in two cases a sufficient number of discharges of the desired length could not be found.

3 Method

The main idea of this paper is that discharge initiation and reinitiation are the same process. Therefore, to detect restarts in a discharge, it is necessary to be able to detect a discharge initiation. There is a sufficient number of methods for automated detection of absences [van Luijtelaar et al. (2016)], including method special developed for real time analysis [Ovchinnikov et al. (2010)]. The main idea of many of them is to track the evolution of the main frequency of oscillations by means of either Fourier analysis in a moving time window or wavelet analysis using Morlet wavelets [Ovchinnikov et al. (2010)]. We adapted this idea and developed our own algorithm for detecting discharge starts and restarts. The algorithm is relatively simple to implement and it does not pretend to be highly sensitive, since its main goal is to show that discharge restarts exist and they are not different from the initial starts in terms of

main frequency dynamics, rather than provide the best tool for discharge detection. It is important that the algorithm suitable for reinitiation detection must not rely on changes in the amplitude of oscillations as most known methods do. They explicitly rely on increase of power in certain spectral ranges or indirectly use this fact to improve sensitivity and specificity [van Luijtelaar et al. (2016)]. The exception is some approaches based on predictive models [Startceva et al. (2015)]. For reinitiation detection using amplitude dynamics is unacceptable since we assume that a restart often supports discharge, that is, a significant drop in amplitude does not occur or is very short-term. A restart is "surrounded" by the discharge. Of course, refusing to consider amplitude dynamics we reduce the sensitivity and specificity of the method when detecting seizure starts, but this task is not a primary goal in this work.

To implement the algorithm the most common method for obtaining the frequency spectrum of signal is fast Fourier transform. The time window was shifted along the entire studied epoch with the minimal possible time step equal to one sampling interval $\Delta t = 1/512$ s. In this work, a Hann window was used, the length of this window was 1 s. This choice was a compromise between better time resolution and better spectral sensitivity. A spectrogram – the dependence of the spectral power density on time — was built for each considered seizure for both considered channels for the discharges themselves and the time intervals of 5 s before and after them. Calculations were implemented in Python using the `scipy` package [Virtanen et al. (2020)].

The obtained spectrograms were not analyzed in the entire frequency band, but were limited to the range of interest. Since the spike-wave discharge frequency in WAG/Rij rats is 7–12 Hz, this frequency range was chosen. It should be noticed that spike-wave discharges are a strongly nonlinear process, for which the second harmonic in the spectrum can be of the same amplitude or even larger than the first one. Narrowing the considered range was intended to cut off the second harmonic, which at its power could lead to irregular "jumps" in a skeleton between the main frequency and its harmonic. Thus, it was possible to construct not only spectrograms, but also their skeletons, which are a dependence of the main frequency on time. A skeleton is much simpler to interpret and use for automatization than a spectrogram, since it is a scalar dependence.

Due to finite frequency resolution of 1 Hz, all obtained skeletons were actually sequences of discrete levels. The raw skeletons had a significant number of rapid short-term jumps between frequencies, which made it difficult to detect the patterns characterizing a seizure start. Therefore, in addition to the signal processing described above, skeletons were filtered (smoothened) in a time domain. For this, the entire time series of skeletons were divided into successive pairs of values (duration, frequency), i.e. for each subsequent value of the main frequency its duration was calculated. Then, the following
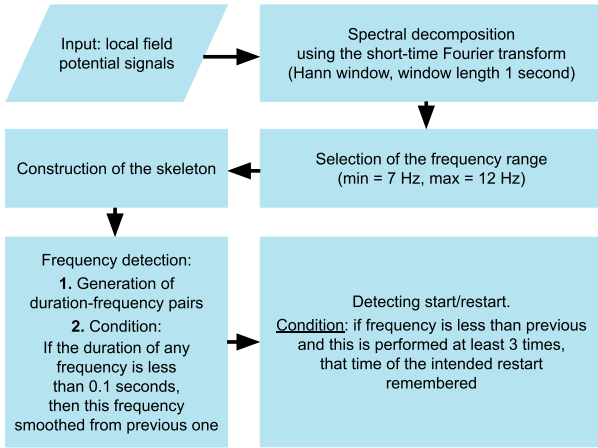
Figure 2.   Block diagram of the original algorithm for determining restart in discharge.
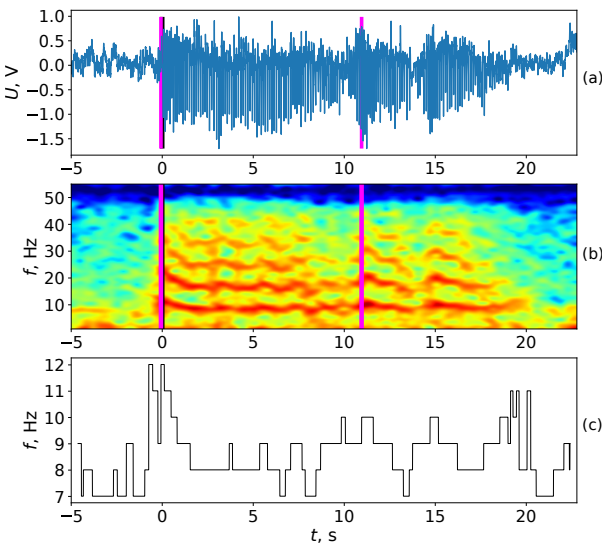

Figure 1.   The structure of the discharge from rat No. 27, recording No. 1. The first graph at the top (a) is the EEG time series, the second graph (b) is the spectrogram of spike-wave discharge, and the third graph (c) is its skeleton. The horizontal axis shows time in seconds from the seizure onset, the vertical axis shows voltage in V for the upper graph, and frequency in Hz for the second and third graphs. Vertical black lines on the time series and spectrogram indicate time moments corresponding to the seizure onset marked by an experienced neurophysiologist, and vertical magenta lines indicate time moments determined by the algorithm.

algorithm was applied: if the duration in some (duration, frequency) pair was less than the threshold (we chose the value 0.1 s), this time interval was appended to the previous. In this case, the duration of one spike-wave complex for WAG/Rij rats is about 0.09–0.13 s. So, the temporal resolution obtained for smoothened skeletons corresponded to the minimum reasonable value – about 1 oscillation. This made it possible to get rid of high-frequency short-term jumps and to interpret the results. The Fig. 1 shows time series of a discharge together with

± 5 s time intervals before and after it, see Fig. 1(a), its spectrogram, see Fig. 1(b) and smoothened skeleton, see Fig. 1(c).

In WAG/Rij rats the beginning of a typical spike-wave discharge is characterized by an appearance on the spectrogram of a well pronounced frequency component at 10–11 Hz, which rapid decreases to 8–8.5 Hz in first 1–2 s. Later frequency changes are slow or the frequency remains at the reached level up to the end of the discharge [Coenen and van Luijtelaar (2003); Bosnyakova et al. (2006, 2007); Sitnikova et al. (2014)]. However, this frequency dynamics is possible not only at the start of a spike-wave discharge, but can be observed a number of times throughout the seizure, as it can be visually detected. For instance, for the discharge plotted in Fig. 1(a), it can be clear seen that after the seizure onset, the amplitude becomes much smaller for a few seconds in the time interval $5.5 < t < 7$ s, and then, at the time moment $t \approx 7$ s it increases several times again. On the spectrogram (see, Fig. 1(b)), it can be observed how spike-wave activity is divided into two parts. Moreover, it is clearly seen that the second part has a similar structure to the first one with the same pattern of decreasing frequencies. In more details, the frequency-time structure allows evaluating the skeleton in Fig. 1(c). Both at the seizure onset and at the time moment of amplitude increase ($t \approx 7$ s) the going down "staircases" of frequencies are visually well detectable. Recurrence of these patterns of frequency dynamics inside the SWD can be explained by the hypothesis that there can be repeated triggers (restarts) within one discharge, and maintenance of long spike-wave discharges can be carried out due to such restarts. But visual analysis of spectrograms is not reliable approach to prove this hypothesis.

For automatic detection of SWD restarts, we propose the following algorithm. We consider the sequence of triplets (frequency, duration, starting time moment), let denote them (f_n, d_n, t_n), where n is the number of triplet. If the frequency at the next interval is less than the frequency in the previous one by 1 Hz and this is repeated at least 3 times in a row (i.ė., a conditional staircase of frequencies is formed), then the is memorized. In other words, we look for such t_n, for which $f_{n-1} < f_n = f_{n+1} + 1 = f_{n+2} + 2 = f_{n+3} + 3$. This condition is based on the idea, the start of SWD is characterized by an appearance of the main frequency of 10–12 Hz, and it should then drop. We also assume that the frequency decrease is not very fast and not larger than 1 Hz per 0.1 s, otherwise our frequency smoothing procedure would prevent detection of such fast drops. The developed algorithm is briefly presented as a block diagram on the Fig. 2.

It is known that SWD frequency in WAG/Rij rats with a genetic predisposition to absence epilepsy is 7–12 Hz, in contrast to people in which the SWD frequency is recorded at 3–4 Hz. This is due to differences in brain structure of rodents from other mammals and was de-

scribed in [Destexhe (1998, 1999)]. But despite the difference, the time-frequency pattern of spontaneous spike-wave discharges is the same for humans and rats and can be obtained by scaling in the frequency domain [Bai et al. (2010); Sitnikova et al. (2011); Tenney et al. (2014)]. Therefore, it should be expected that the proposed technique can be transferred to human research by simply scaling the frequency ranges in which the main discharge frequency is allocated.

4 Results

Time-frequency analysis of the SWD organization was performed for all 203 considered seizures. The plots of SWD structure during SWD with 5 s indent before and after it were constructed according to seizure onset and termination markers made by an experienced neurophysiologist (black lines), see Fig. 3 for example.

The start and restarts of a discharge marked automatically by the proposed method were shown with vertical magenta lines. The SWD shown on Fig. 3 is a typical representative of discharges with a single restart. It is characterized by several widespread features, including decrease of signal amplitude at some seconds before the restart (see Fig. 3a,d), a lower initial frequency for the second part than for the first one (after the restart the SWD main frequency is about 11 Hz in PC channel and the initial start frequency is about 12 Hz, see Fig. 3c,f), and a shorter duration of the restarted part in comparison to the first one. It should be mentioned that the SWD is a single discharge: the main frequency and its second and third harmonics are still well detectable during the whole episode, see Fig. 3. Not all the restarted seizures behave similarly, but most of them keep some of these features, including seizures with two restarts detected and seizures with no eye-detectable amplitude fall before a restart.

In order to rely on the proposed method in the sense of estimating the discharge restart existence, it is necessary to evaluate its sensitivity in estimating the starts marked by an neurophysiologist. Start detection was considered to be correct if the absolute difference between the start marked by an neurophysiologist and automatically marked start (absolute distance between black and magenta lines) was less than 0.6 s. The restarts were considered to be diagnosed if they were automatically marked starts located inside the SWD marked by a neurophysiologist, which were at least 0.6 s after the manually marked start and not less than 0.6 s before the manually marked termination.

Statistics of starts and restarts detected by the proposed method for all rats analyzed is presented in the Table 1. From a total amount of 203 analyzed discharges, the method was able to find **starts** of 140 discharges using FC channel ($\sim 69\%$ sensitivity) and 132 discharges using PC channel ($\sim 65\%$ sensitivity). The start of 107 discharges ($\sim 53\%$ sensitivity) was detected in both channels together (see Tab. 1, column "SB"). These results

are beyond most methods reported previously [Ovchinnikov et al. (2010); Startceva et al. (2015); van Luijtelaar et al. (2016)], though it is not absolutely disastrous for our purpose, because the method is able to detect most event of interest.

In the example shown on the Fig. 3a,d one can see that the SWD is better pronounced in the PC channel than in FC one. In particular, SWD amplitude is two times larger in PC. This is a particular property of the studied recording. Different animals had different channels (either PC, or FC) with larger amplitude. Usually, both SWD starts and restarts were detected better in the channel with a larger amplitude, i. e. with a better signal to noise ratio. Indeed, according to the table, we can see that the number of automatically determined starts varies considerably for some animals. E. g. for the recordings No. 10.2, No. 14.1, No. 27.1 and No. 29.1 the number of detected starts in FC was greater than in PC, and for the recordings No. 1 and No. 10.1 on the contrary, more starts were detected in PC than in FC.

Discharge *restarts* were diagnosed in 116 cases in all 11 recordings for all seven rats: in the FC channel — in 54 cases and in the PC channel — in 62 cases. There were up to four restarts detected for a single SWD at least in one of two considered channels. 46 cases from total 116 ones corresponded to the simultaneous restart detection in both channels, providing simultaneous detections for 23 seizures, see Tab. 1, "RB" column. Such simultaneous detection was achieved for all recordings except No. 29.1, i. e. for 10 of 11 recordings and for six of seven rats. In seven cases (for four different animals) both start and restart were detected for the same seizure in both channels simultaneously, see column "BB" in the Tab. 1, one of which is plotted in Fig. 3. Since the method sensitivity was estimate to be ~ 0.53 if both channels are used for the better reliability, the number of detected restarts seems to be about a half of all number. So, if we estimate that 13 bi-channel restarts actually exist in the seizure, the probability to lack them all would be < 0.0003, assuming that the method sensitivity is enough to detect the existence of restarts as a phenomenon for the considered data, though we cannot pretend for precise quantification of restart appearance rate.

To test the results of the method for specificity, we considered 203 seizure free (based on markers by a neurophysiologist) time episodes of 10 s length. The epoch length was chosen to match the minimal duration of the considered SWDs. The number of episodes for each recording was the same as a number of seizures reported in Tab. 1. During this background activity simultaneous "start" was detected in 12 cases, which is ~ 9 times less than the number of actual detection for real SWD analysis. However, the detailed analysis of these 12 cases indicated that in two cases the SWD missed by a neurophysiologist was detected. Nine cases were of doubtful nature corresponding either to signal quality artifacts or to SWD precursors, or to short SWDs of the second type [Coenen et al. (1995); Midzianovskaia et al. (2001)]. In
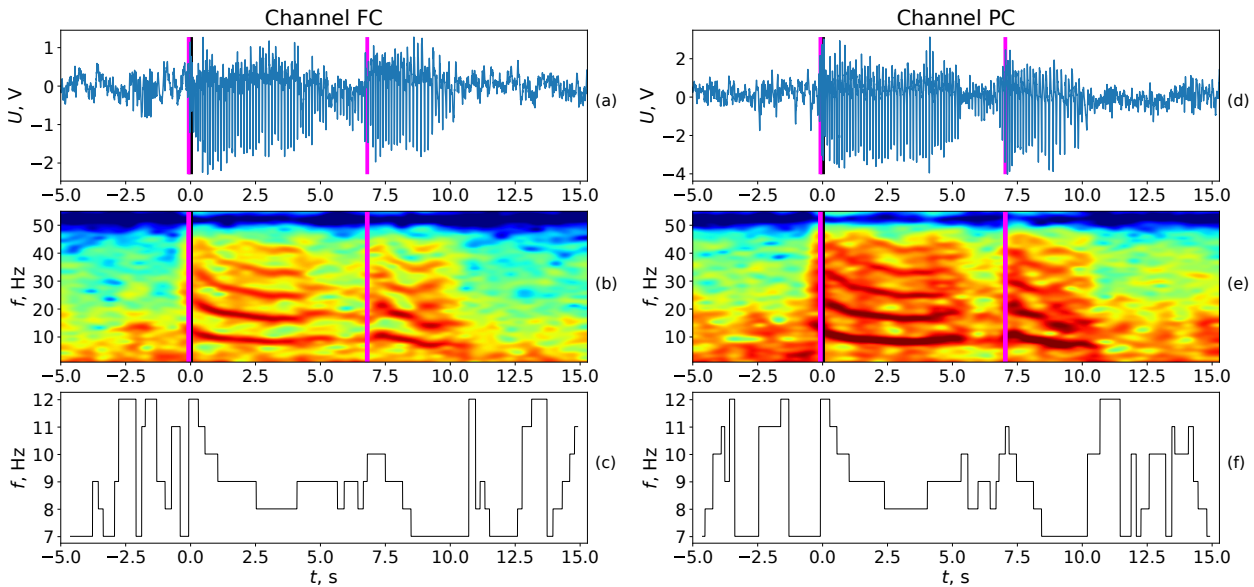
Figure 3. The structure of the discharge from the rat No. 6, recording No. 1. Frontal (left) and parietal (right) cortical channels were analyzed. The first graphs at the top (a, d) are the EEG time series, the second graphs (b, e) are the spectrograms of the spike-wave discharge, and the third graphs (c, f) are its skeletons. The horizontal axis shows time in seconds from the seizure onset, the vertical axis shows voltage in Volts for the upper graph, and frequency in Hertz for the second and third graphs. Vertical black lines on the time series and spectrogram indicate time moments corresponding to the seizure onset marked by an experienced neurophysiologist, and vertical magenta lines indicate the time moments determined by the algorithm.

particular, in five cases we detected the main rhythm at 10–12 Hz, but the spectrogram showed no higher harmonics, so the oscillations were mostly linear. The presence of the main rhythm before SWD was statistically shown by [Grishchenko et al. (2020b)]. In one case we could reasonable say that the method was able to detect the frequency pattern we use for SWD detection during the normal behavior, so this was a clear fail.

So, if we even consider all ten mistakes as false positives and if we scale results for difference between total SWD and control epochs length (the mean SWD length was about 12 s being largely different for different animals), we get the method specificity about 94%, i. e. the probability of the second type error was ~ 0.06 for the considered data. Therefore, the probability that all 23 bi-channel detections of restarts were false positives is $\sim 0.06^{23} < 10^{-28}$, that is absolutely impossible. Following this statistics even two of 23 detected restarts can be false positives with probability ~ 0.044, so 22 of 23 restarts were real at the commonly acceptable confidence level 0.05; and 20 of them were real at the confidence level 0.001.

5   Discussion and Conclusion

Time-frequency analysis of spike-wave discharges was multiple used to determine differences in duration and structure of discharges, to detect mechanisms of their initiation, maintenance and termination of absence seizures [Gabova et al. (2009); Bosnyakova et al. (2006, 2007); Obukhov et al. (2014)]. Here, we focused on the

peculiarities of long SWDs, taking into account only discharges of duration of 10 s and more, while an average duration is about 6 s [van Rijn et al. (2010)]. Based on connectivity analysis [Sysoeva et al. (2016a)] one can assume that long seizures last because they have mechanisms for maintaining and these mechanisms are differ from the mechanism of seizure initiation. Such a mechanism (increase in thalamocortical connectivity) was embedded in the mathematical model of spike-wave discharges and made it possible to achieve the distribution of model discharges by duration close to the experimentally observed [Medvedeva et al. (2020)]. However, the analysis of the frequency structure of long discharges showed that some of them have a certain specificity of their course: the patterns very similar to those accompanying the SWD start appear again during the seizure, sometimes two or three times. Thus, it was suggested that some of the long discharges may be maintained not by a separate maintenance process, but due to one or a number of sequential restarts which are not different from the initial start, but occur before the previous discharge segment has finished. This mechanism can be considered as complementary to the maintenance mechanisms. It is also known that SWDs of a non-epileptic nature were detected in normal laboratory rats [Rodgers et al. (2015); Pearce et al. (2014)], among which long-duration discharges were observed. At the moment, we cannot say for sure whether restarts would be observed for non-epileptic SWDs and would be are unique to absence seizures.

To confirm the restart hypotheses, an original algo-

Table 1.   Number of discharges for each rat with automatically defined starts and restarts for FC and PC channels. The first column (No.) is the number of the rat and the number of the recording for each animal. The second column ($\sum$) is the total number of analyzed discharges for each rat. The third column (Start) is the number of automatically determined starts of absence seizures for each channel. The fourth column (Restart) is the number of discharges with automatically defined restarts. The fifth column (SB) is the number of starts diagnosed on both channels at the same time. The sixth column (BB) is the number of discharges for which both channels at the same time determined both start and restart (at least one). The seventh column (RB) is the number of restarts diagnosed on both channels at the same time.

No.	$\sum$	Start		Restart		SB	BB	RB
		PC	FC	PC	FC			
1.1	20	17	8	11	8	7	0	1
1.2	20	3	2	6	1	0	0	1
6.1	20	18	18	2	3	17	2	2
6.2	8	8	8	1	1	8	0	1
10.1	20	11	9	9	10	7	1	3
10.2	20	13	15	5	7	11	0	3
13.1	15	15	15	1	1	15	0	1
13.2	20	17	17	4	2	15	1	2
14.1	20	10	17	8	9	9	2	6
27.1	20	12	15	7	9	10	1	3
29.1	20	8	16	8	3	8	0	0
Total	203	132	140	62	54	107	7	23

rithm for automatic restart detection was developed. The idea was to track the frequency drop on a skeleton constructed from a spectrogram in a selected frequency range. The algorithm was used without any changes to define both SWD starts and restarts. The method was developed to have as less hand set parameters as possible: actually, it does not require adjustment to experimental data, with the exception of taking into account the main discharge frequency, which can be different in humans and animals [Destexhe (1998, 1999)]. To reach the high sensitivity was not a primary goal of the developed approach: there has been already developed a sufficient number of methods for automated detection of spike-wave discharges [van Luijtelaar et al. (2016)]. The main task of the developed method was to show that discharge restarts exist and are not different from initial starts in terms of main frequency dynamics. Bi-channel analysis was applied to increase the method specificity: the SWD starts and restarts were considered to be detected reliably only if they were detected in two channels simultaneously with possible shift between detections in different channels not larger than 0.6 s. The sensitivity of bi-channel detection was about 53%. The relatively low detection rate is explained by three main assumptions. First, we specially ignored one of the fundamental signs of SWD start – a sharp increase in the oscillation amplitude since such an increase specific for the initial seizure start is not necessary for restarts "immersed" into the SWD. If we include patterns of amplitude dynamics

into the technique, this would contradict to the primary thesis of this study that initial starts and restarts do not differ. Second, we refused to base the technique upon the fact of appearance of the main frequency around 8 Hz, since this frequency often takes place in the signal both before the restart for already lasting seizures and during preictal activity as the careful analysis showed in many cases [Grishchenko et al. (2020b)]. Third, we considered only detections in both channels simultaneously, if we switch to detections in either PC or FC channel, the sensitivity would increase up to 76%.

As a result of analysis of 203 discharges in 11 two-channel (parietal and frontal cortical channels) recordings in seven animals, 107 starts and 23 restarts were found on both channels at the same time, including seven cases, when both starts and restarts were detected in the both considered channels. I. e. restarts were diagnosed in about four less often than starts. Statistical analysis of the seizure clear epochs showed that the method specificity is enough to state that the most detected seizure restarts are real detection, in particular, 20 of 23 were detected at the confidence level < 0.001. So, we can declare that the SWD restarts do exist.

Understanding the mechanisms for maintaining long lasting absences is very important for modeling. Existence of restarts confirms that different factors are responsible for maintenance of long spike-wave discharges: some discharges are supported by the special maintenance mechanism as it was proposed in [Sysoeva

et al. (2016a)], others are continuous chains of short discharges. This means that reproducing only one mechanism in the models is not sufficient to reproduce the SWD duration distribution completely. Different mechanisms of long SWD generation can also help to explain why the protocols used to stop the SWD may be successful in some cases and not effective in others (only part of the seizures can be effectively interrupted), which was found in WAG/Rij [Lüttjohann and van Luijtelaar (2016); van Heukelum et al. (2016)] and GAERS [Nelson et al. (2011); Saillet et al. (2013); Akman et al. (2010)] rat models.

6 Acknowledgments

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