



Dynamical characteristics of pre-epileptic seizures in rats with recurrence quantification analysis

Xiaoli Li^{a,*}, Gaoxiang Ouyang^b, Xin Yao^a, Xinping Guan^b

^a CERCIA, School of Computer Science, The University of Birmingham, Birmingham B15 2TT, UK

^b Institute of Electrical Engineering, Yanshan University, Qin-Huangdao, Hebei 066004, China

Received 9 June 2004; received in revised form 30 September 2004; accepted 1 October 2004

Available online 21 October 2004

Communicated by C.R. Doering

Abstract

Understanding the transition of brain activity towards an epileptic seizure, called pre-epileptic seizure, is a challenge in epilepsy. In this Letter, a recurrence quantification analysis (RQA) is proposed to describe dynamical characteristics of EEG (electroencephalograph) recordings on rat experiments, which is helpful to predict seizures. One of the advantages of this method does not require any assumptions to EEG data, such as linear, stationary, noiseless and so on. A series of experimental tests in this study show that the dynamical characteristics of EEG data with RQA can identify the differences among inter-ictal, pre-ictal and ictal phases; and support the hypothesis that complexity of brain electrical activity has a significant decrease prior to an epileptic seizure. This change could be useful in predicting epileptic seizures.

© 2004 Elsevier B.V. All rights reserved.

Keywords: Recurrence quantification analysis; EEG; Epileptic seizure; Prediction

1. Introduction

EEG monitoring systems have become important clinical tools for evaluation and treatment of epilepsy [1]. Recently, it has also been applied to predict epileptic seizures. The prediction of epileptic seizures plays an important role in epileptology [2],

because we can propose a new diagnostic tool and a novel approach to seizure control based on this prediction [3]. So far, many methods have been proposed to analyze EEG data for the prediction of epileptic seizures. In particular, new measures of brain's activity based on discipline of non-linear dynamical systems (chaos) have been developed in the last decade [4–11], which mainly include the Lyapunov exponents [5–7] and correlation dimension [4,8,11]. Lyapunov exponents and correlation dimension can describe the complexity of an EEG data. However,

* Corresponding author.

E-mail address: x.li@cs.bham.ac.uk (X. Li).

chaos-based approaches need to assume that EEG data possesses a non-evolving low-dimensional attractor, and require a long, stationary and noiseless EEG data to compute the reconstructed attractor's properties [12]. Actually, a real epileptic EEG data includes a transient signal embedded in noise and non-stationary [13,14]. Therefore, the approach based on chaotic dynamics to detect of the evolutionary characteristics of an EEG data is still challenging.

To overcome the drawbacks of above method, a new method, called *recurrence quantification analysis* (RQA), was proposed by Webber and Zbilut [15]. The novelty of this method is that it can measure the complexity of a short and non-stationary signal with noise [16,17]. Recently, RQA is broadly applied in the analysis of physiological data [14,18–22]. In contrast with chaos method, an important advantage of RQA is that it can deal with a noisy and short time series. In addition, RQA can deal with a linear and non-linear time series to quantify the activity of a system irrespective of the number or dynamical nature of the individual sources [23].

In this Letter, RQA is applied to discover hidden dynamics of an epileptic EEG data, including the detection of the evolving fluctuations of an EEG signal and the measure of the complexity changes of the brain electrical activity from inter-ictal to ictal phase. The test results of 12 long-term EEG recordings on rats show that recurrence rate, determinism and entropy based on RQA is capable of representing the dynamical characteristics of brain activity. An important principle, i.e., complexity decrease prior to an epileptic seizure can be confirmed with this method. So we suggest that three measures based on RQA, i.e., recurrence rate, determinism and entropy could be applied to predict the epileptic seizures.

2. Experiments

In this Letter, adult Sprague–Dawley rats are used to study the epileptic seizures in EEG recordings. (1) Installation of electrodes. The rats is anaesthetized with an intraperitoneal (i.p.) injection of nembutal (sodium pentobarbital, 65 mg/kg of body weight), and mounted in a stereotaxic apparatus. An electrode is

Table 1

The time recordings of each experiment

Subject No.	Injection time	Seizure time	End time
1	08:02	11:38	31:42
2	10:44	15:50	25:36
3	15:05	20:18	25:00
4	07:00	11:15	36:00
5	07:41	10:32	32:30
6	07:29	10:12	49:06
7	06:09	10:39	41:49
8	05:01	09:48	40:00
9	11:48	14:38	20:35
10	05:24	10:41	25:36
11	10:20	12:49	25:36
12	11:08	13:48	25:00

The time format is minute:second. Starting time is always from 00:00.

placed in epidural space to record the EEG signals from temporal lobe. The animals are housed separately postoperatively with free access to food and water, allowed 2–3 days to recover, handled gently to familiarize them with the recording procedure; (2) EEG recordings. During the experiments, each rat is initially anaesthetized with a dose of pentobarbital (65 mg/kg, i.p.), while constant body temperature is maintained (36.5–37.5 °C) with a blanket covering. The degree of anesthesia is assessed by continuously monitoring the EEG, and additional doses of anesthetic is administered at the slightest change towards an awake pattern (i.e., an increase in the frequency and reduction in the amplitude of the EEG waves). Then, bicuculline i.p. injection is used to induce epileptic seizures. EEG signals are recorded using an amplifier with band-pass filter setting of 0.5–50 Hz. The sampling rate is 200 Hz, and the analog-to-digital conversion is performed at 12-bit resolution. The start time, injection time, seizure time and seizure end time are written down, as shown in Table 1. The seizure onset time is determined by visual identification of a clear electrographic seizure discharge, and then looking backwards in the recordings for the earliest EEG changes from baseline associated with the seizure. The earliest EEG change is selected as the seizure onset time. The interval between the seizure onset time and injection time are considered as the maximum prediction duration or extended pre-ictal phase.

3. Methods

The recurrence of states is a fundamental property of a deterministic dynamical system [18]. Recurrence plots (RP) proposed by Eckmann et al., [24] can describe the recurrence property of a deterministic dynamical system, i.e., visualizing the time dependent behavior of orbits x_i in a phase space. The key step of RP is to calculate the following $N \times N$ matrix

$$R_{i,j} = \Theta(\varepsilon - \|x_i - x_j\|), \quad i, j = 1, \dots, N, \quad (1)$$

where N is the numbers, ε is a predefined cutoff distance, $\|\cdot\|$ is the norm (e.g., the Euclidean norm) and $\Theta(x)$ is a Heaviside function. The phase space vector x_i can be reconstructed by using the Taken's time delay method, $x_i = (u_i, u_{i+\tau}, \dots, u_{i+(m-1)\tau})$ [25], based on the observations u_i . The cutoff distance ε defines a sphere centered at x_i , if x_j falls within this sphere, i.e., the state is close to x_j , then $R_{i,j} = 1$; otherwise $R_{i,j} = 0$. The binary values of $R_{i,j}$ can be simply visualized with the black (1) and white (0). Thereby, RP can be considered as a visual inspection of a high-dimensional phase space trajectory, in other words, RP can show a hint about the time evolution of a trajectory. The additional advantage of RP is suitable to analyze short and non-stationary data. In short, RP can describe the characteristics of large-scale and small-scale patterns of a dynamical system [19,24].

The quantitative analysis of RP, called RQA, was proposed in [15,19,26]. The more details of RQA can be found in [27]. We only introduced three measure variables: recurrence rate (%REC), determinism (%DET) and entropy (ENTR). The recurrence rate (%REC) is calculated by

$$\%REC = \frac{1}{N^2} \sum_{i,j=1}^N R_{i,j}, \quad (2)$$

which simply counts the black dots in the RP. %REC is a measure of the density of recurrence points. Stochastic behavior causes non or short diagonals, whereas deterministic behavior causes longer diagonals and less single, isolated recurrence points.

The ratio of recurrence points on the diagonal structures to all recurrence points is called %DET, its formulate is below:

$$\%DET = \frac{\sum_{l=l_{\min}}^N IP(l)}{\sum_{i,j}^N R_{i,j}}, \quad (3)$$

where $P(l)$ the frequency distribution of the lengths of the diagonal structures in the RP. l_{\min} is the threshold, which excludes the diagonal lines formed by the tangential motion of a phase space trajectory, in this Letter we fix $l_{\min} = 2$. %DET is a determinism (or predictability) measure of a system.

ENTR refers to the Shannon entropy of the frequency distribution of the diagonal line lengths,

$$\text{ENTR} = - \sum_{l=l_{\min}}^N p(l) \ln p(l),$$

$$\text{where } p(l) = P(l) / \sum_{l=l_{\min}}^N P(l), \quad (4)$$

where ENTR is considered as a complexity measure of a deterministic structure in a dynamical system. The more complex the deterministic structure, the larger ENTR value.

The embedding dimension determination plays an important role for RQA, like chaos methods. In general, a low embedding dimension leads to false recurrences; on the other hand, a high embedding dimension does not theoretically distort the reconstructed phase trajectory [19]. The calculation details of RQA can be found in [14,19]; and software for RQA is available at <http://www.recurrence-plot.tk>.

4. Results

In this Letter, RQA is firstly used to analyze the EEG data of three distinct periods; the aim is to discover the difference of dynamical characteristics at the three different phases. The first corresponds to the period of preceding the injection time (length of 5 seconds of EEG data), namely the inter-ictal phase. The second corresponds to the interval between the injection time and seizure onset time (length of 5 seconds of EEG data), the pre-ictal phase must exist within this interval, so it is called the extended pre-ictal phase. The third is the interval from the seizure onset time to the end of the seizure (length of 5 seconds of EEG data), namely the ictal phase. The averages of %REC, %DET and ENTR of each period are calculated with a dimension of 15, a delay of 11, and a radius of 1.5 and represented as a histogram, as shown in Fig. 1(A)–(C), respectively. Fig. 1 shows the significant differences of

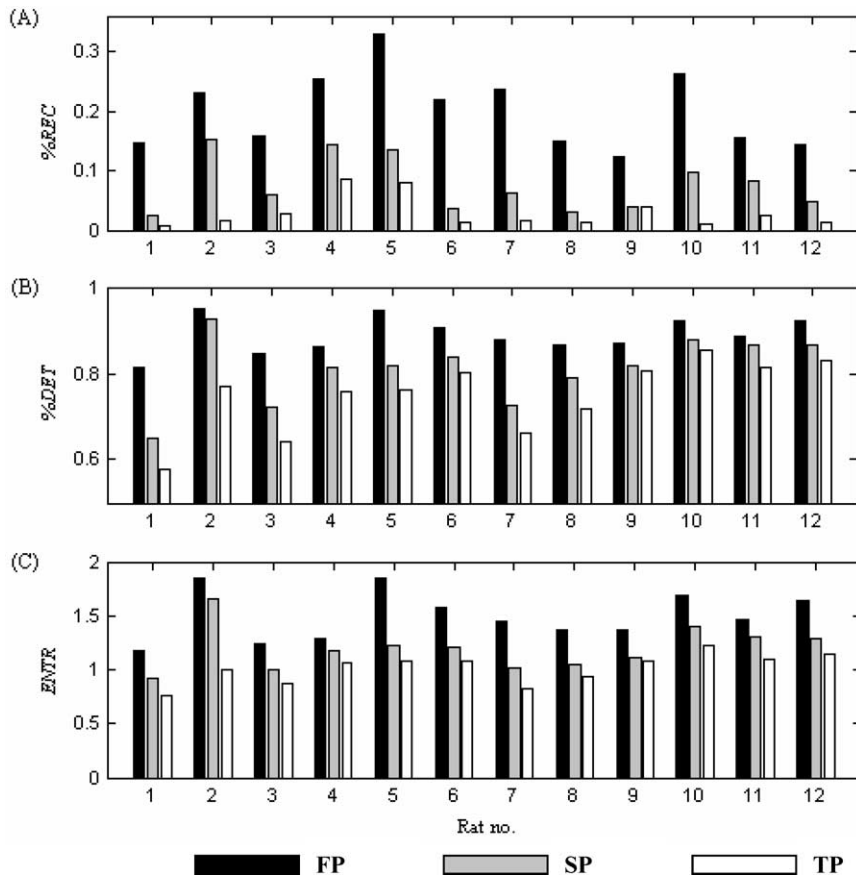


Fig. 1. Three RQA measures of three periods. In all rats, the average values of %REC (A), %DET (B) and ENTR (C) over the pre-ictal phase are lower than ones over inter-ictal phase, but higher than ones over the ictal phase. *Abbreviations.* FP, the first period, namely the inter-ictal phase; SP, the second period, namely the extended pre-epileptic seizure phase; TP, the third period, namely the ictal phase.

the evolution of complexity of the brain electric activity over these different periods. The one-way repeated measure ANOVA (analysis of variance) with Scheffe's *post-hoc* test is carried out to verify this conclusion.

Fig. 1(A) shows a large decrease of average %REC from the inter-ictal to ictal phases for all of rats. The same observation can also be made for the %DET in Fig. 1(B) and ENTR in Fig. 1(C). These observations indicated that the alterations of brain electrical activity dynamics could be characterized by the three measures of RQA. The statistical analysis is carried out to determine whether their distributions over the three periods are significant difference or not. First, the one-way repeated measures ANOVA with Scheffe's *post-hoc* test are performed for average %REC values of three different periods, as shown in Table 2. The

F-test is significant at the $P < 0.001$ level of probability, so we suggest the null hypothesis, i.e., there are no differences among three periods should be rejected. Application of Scheffe's test to all pairwise comparisons between the means suggests that the extended pre-ictal phase and ictal phase each has significantly lower values than the inter-ictal phase. In addition, the average %REC values during pre-ictal phase are significantly higher than ones during the ictal phase. Similar statistical results can be also obtained from the %DET values (as shown in Table 3) and ENTR values (as shown in Table 4). In short, these analysis results indicate that the complexity during pre-ictal phase is statistically lower than ones during the inter-ictal phase, whereas higher than ones during the ictal phase.

Table 2

One-way ANOVA with comparisons between the means using Scheffe's test. Data are the %REC values of the inter-ictal phase, the extended pre-ictal phase and the ictal phase

Subjects No.	Inter-ictal	Pre-ictal	Ictal
1	0.1461	0.0240	0.0064
2	0.2296	0.1535	0.0163
3	0.1586	0.0581	0.0266
4	0.2549	0.1436	0.0860
5	0.3290	0.1349	0.0794
6	0.2200	0.0359	0.0142
7	0.2360	0.0631	0.0158
8	0.1497	0.0293	0.0136
9	0.1237	0.0396	0.0387
10	0.2638	0.0962	0.0096
11	0.1548	0.0818	0.0250
12	0.1449	0.0493	0.0127
Mean	0.2009	0.0758	0.0287
Standard error	0.0635	0.0462	0.0267

ANOVA source of variation	Sums of squares (SS)	Degrees of freedom (DF)	Mean square (MS)	F-test
Treatment	0.1903	2	0.09510	91.44 $P < 0.001$
Error	0.0229	22	0.00104	
Subject	0.0528	11		
Total	0.2660	35		

Scheffe's test: the inter-ictal phase vs the pre-ictal phase $S = 45.14$ ($P < 0.05$), the inter-ictal phase vs the ictal phase $S = 85.53$ ($P < 0.05$), the pre-ictal phase vs the ictal phase $S = 6.39$ ($P < 0.05$).

Table 3

One-way ANOVA with comparisons between the means using Scheffe's test. Data are the %DET values of the inter-ictal phase, the extended pre-ictal phase and the ictal phase

ANOVA source of variation	Sums of squares (SS)	Degrees of freedom (DF)	Mean square (MS)	F-test
Treatment	0.1180	2	0.0590	45.38 $P < 0.001$
Error	0.0287	22	0.0013	
Subject	0.1341	11		
Total	0.2808	35		

Scheffe's test: the inter-ictal phase vs the pre-ictal phase $S = 14.95$ ($P < 0.05$), the inter-ictal phase vs the ictal phase $S = 44.97$ ($P < 0.05$), the pre-ictal phase vs the ictal phase $S = 8.06$ ($P < 0.05$).

Table 4

One-way ANOVA with comparisons between the means using Scheffe's test. Data are the ENTR values of the inter-ictal phase, the extended pre-ictal phase and the ictal phase

ANOVA source of variation	Sums of squares (SS)	Degrees of freedom (DF)	Mean square (MS)	F-test
Treatment	1.4211	2	0.7106	55.95 $P < 0.001$
Error	0.2794	22	0.0127	
Subject	0.9159	11		
Total	2.6164	35		

Scheffe's test: the inter-ictal phase vs the pre-ictal phase $S = 21.11$ ($P < 0.05$), the inter-ictal phase vs the ictal phase $S = 54.90$ ($P < 0.05$), the pre-ictal phase vs the ictal phase $S = 7.91$ ($P < 0.05$).

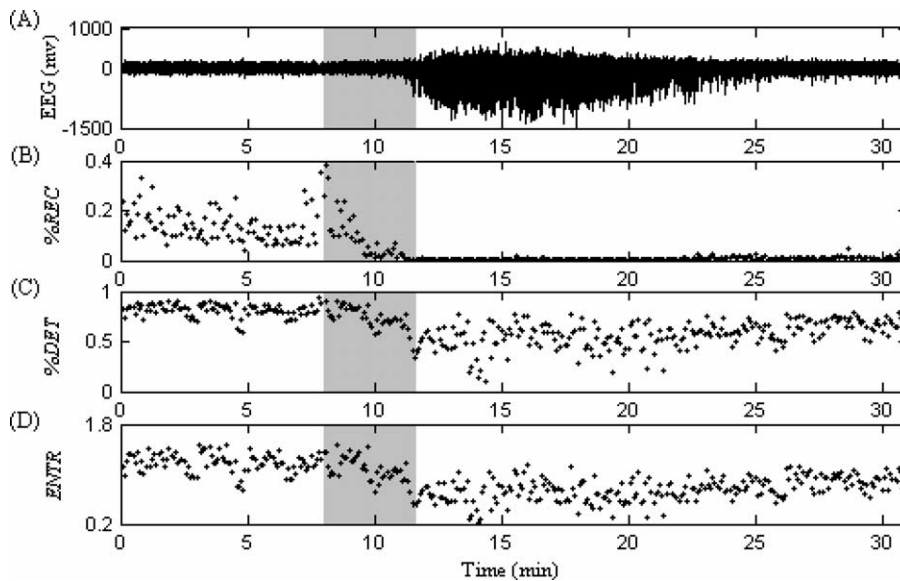


Fig. 2. The long-term EEG recordings of rat 1 and their three RQA measures. The gray vertical bar marked represents the interval from injection time to seizure time. Visual inspections of the signals (A) show no visible changes during the pre-ictal phase. Three RQA measures clearly show the dynamic changes of EEG signal preceding the seizures (B, C, D), e.g., %REC (B), %DET (C), and ENTR (D) progressively decrease from the inter-ictal to ictal phases.

To follow the changes of these RQA measures over time, a moving-window technique is applied to a long-term rat EEG data. EEG signal firstly is divided into segments of 5 seconds (1000 points), then the RP is computed after embedding the EEG segment with a dimension of $m = 15$, a delay of $\tau = 11$ [28], and a radius of $\varepsilon = 1.5$ (in units of the standard deviation σ). Finally, three RQA measures are calculated to discover the EEG dynamics over time. Herein, two case studies were shown, since the results of others ten cases were similar with ones of two cases.

Figs. 2(A) and 3(A) showed the long-term EEG recordings of two rats, respectively. A gray vertical bar marked the extended pre-ictal phase. From the observation of %REC, %DET, and ENTR over the entire EEG recordings (seeing Figs. 2(B)–(D) and 3(B)–(D)), it is found that these three measures can track the complexity changes of brain electrical activity over time. As can be seen in Figs. 2 and 3, three RQA measures reveal a progressive decrease during the pre-ictal phase, then reach a minimum value before the onset of a seizure.

High %REC represents high probabilities of the occurrence of the same state at the different time. %REC in Figs. 2(B) and 3(B) appears in the higher level dur-

ing the inter-ictal phase, which indicated that the brain electrical activity share a similar underlying dynamic in this period. During the extended pre-ictal phase, %REC decreases to a minimum value prior to the onset of the seizures. However, an altered state of the brain dynamics is hard to be observable from EEG time series itself. In Figs. 2(C) and 3(C), %DET are sensitive to quickly and highly the fluctuating EEG, the values of the %DET fluctuate but still remain in relatively small bounds during the inter-ictal phase, from 0.8 to 0.9. It is found that %DET decreases from the inter-ictal to ictal phase, the dynamics of brain electrical activity experienced changes prior to the epileptic seizure. Also, ENTR in Figs. 2(D) and 3(D) are high during the inter-ictal phase (large diversity in the diagonal line lengths), but lowered during the ictal phase (small diversity in the diagonal line lengths), which indicate the loss of recurrence complexity.

5. Discussions and conclusions

Up to now the seizure-generating mechanisms is not very clear [29]. Some methods are being explored to discover the mechanism of the phase transition from

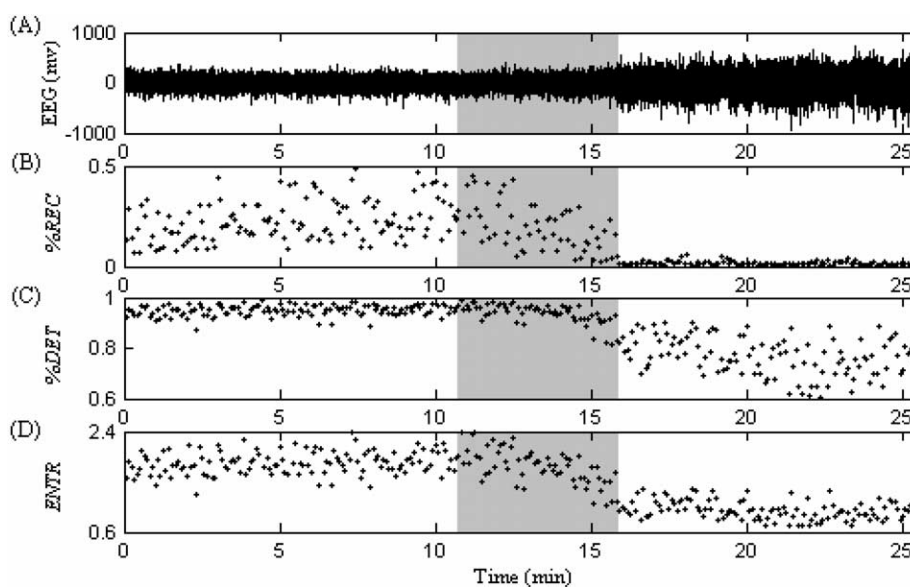


Fig. 3. The long-term EEG recordings of rat 2 and their three RQA measures. The gray vertical bar marked represents the interval from injection time to seizure time. Visual inspections of the signals (A) show no visible changes during the pre-ictal phase. Three RQA variables clearly show the dynamic changes of EEG signal preceding the seizures (B, C, D), e.g., %REC (B), %DET (C), and ENTR (D) progressively decreased from the inter-ictal to ictal phases.

an inter-ictal to ictal phase in EEG. The ‘traditional’ methods (such as spectral analysis and AR modeling) are based on an assumption that the observed variations of electrical field of brain activity are random processes [30,31]. However, these traditional methods fail to detect the critical feature of an EEG data during the pre-ictal phase and indicate the inter-ictal–ictal transition, because this assumption is far from the real EEG dynamics. Other investigators assume that the behavior of the neural networks in the brain is non-linear, so various non-linear methods such as chaotic measures are proposed to analyze an EEG data. Application of non-linear dynamics can describe the complexity of an EEG data [8]. Unfortunately, chaotic measures need a long, stationary and noiseless EEG time series to compute the reconstructed attractor’s properties. These requirements are, however, very hard to obtain during analyzing real EEG recordings. Especially, these non-linear methods are not ideally suited to analyze rapidly changing signals, such as epileptic seizures.

To overcome the drawbacks of traditional and non-linear methods, this Letter used RQA proposed in Webber et al. [15] to describe the hidden dynamic

characteristics of EEG data. RQA can discover the different complexity of EEG data at the different phase (see Fig. 1). We found that a continuous significant decrease of the recurrent dynamics of the EEG data from an inter-ictal phase to ictal phase (see Figs. 2 and 3). The one-way repeated measures ANOVA with Scheffe’s *post-hoc* analysis of %REC, %DET and ENTR indicate that the recurrent dynamics during pre-ictal phase are statistically lower than ones during the inter-ictal phase, but higher than one during the ictal phase. During seizure initiation, the complexity of EEG signal is relatively low. As the seizure evolves further, the complexity of EEG signal decrease. Higher degrees of synchronization can be reflected in the lower signal complexity, and conversely, desynchronization is accompanied by a higher signal complexity. One of the greatest advantages of RQA is its ability to analyze linear and non-linear time signals to quantify the activity of a system [23] while making no initial assumptions regarding linearity or non-linearity of the signal. From this point of view, the application of RQA to reveal the changing dynamics of EEG data at various times is the most satisfactory choice.

In vitro models of epilepsy, reduction of EEG complexity can precede the onset of epileptiform activity, but not other activities [32]; also, examinations of intracranial inter-ictal recordings from patients with temporal lobe epilepsy showed neuronal complexity loss on the side of seizure onset [33,34]. As mentioned above, the characterizations of recurrent changes of brain electrical activity could be considered as a candidate precursor of the impending seizures. It is the intent of future studies to analyze EEG recordings with three RQA measures for predicting the seizures through the complexity change of neural network. In addition, the current study is limited to a single channel; we believe that the potential exists for multi-channel analyses based on RQA as well.

Acknowledgements

The partial support of Wellcome Trust and Advantage West Midland (AWM) are gratefully acknowledged.

References

- [1] C.D. Binnie, E.M. Mizrahi, The epilepsy monitoring unit, in: J. Engel Jr., T.A. Pedley (Eds.), *Epilepsy: A Comprehensive Textbook*, Lippincot-Raven, Philadelphia, PA, 1997.
- [2] B. Litt, E. Javier, *Lancet Neurol.* 1 (2002) 22.
- [3] L.D. Iasemidis, *IEEE Trans. Biomed. Eng.* 50 (5) (2003) 548.
- [4] C.E. Elger, K. Lehnertz, *Eur. J. Neurosci.* 10 (1998) 786.
- [5] L.D. Iasemidis, J. Sackellares, H. Zaveri, W. Williams, *Brain Topogr.* 2 (1990) 187.
- [6] L.D. Iasemidis, J. Sackellares, *Neuroscientist* 2 (1996) 118.
- [7] L.D. Iasemidis, P. Pardalos, J. Sackellares, D. Shiau, *J. Combin. Optimizat.* 5 (2001) 9.
- [8] K. Lehnertz, C. Elger, *Phys. Rev. Lett.* 80 (1998) 5019.
- [9] F. Mormann, R.G. Andrzejak, T. Kreuz, C. Rieke, P. David, C.E. Elger, K. Lehnertz, *Phys. Rev. E* 67 (2003) 021912.
- [10] V. Navarro, J. Martinerie, M. Le Van Quyen, S. Clemenceau, M. Baulac, C. Adam, F. Varela, *Brain* 125 (2002) 640.
- [11] G. Widman, K. Lehnertz, H. Urback, C.E. Elger, *Epilepsia* 41 (2000) 811.
- [12] J.P. Eckmann, D. Ruelle, *Physica D* 56 (1992) 185.
- [13] D. Gribkov, V. Gribkova, *Phys. Rev. E* 61 (2000) 6538.
- [14] N. Thomasson, T.J. Hoepfner, C.L. Webber Jr., J.P. Zbilut, *Phys. Lett. A* 279 (2001) 94.
- [15] C.L. Webber Jr., J.P. Zbilut, *J. Appl. Physiol.* 76 (1994) 965.
- [16] J.P. Zbilut, A. Giuliani, C.L. Webber Jr., *Phys. Lett. A* 237 (3) (1998) 131.
- [17] J.P. Zbilut, A. Giuliani, C.L. Webber Jr., *Phys. Lett. A* 267 (2000) 174, 707.
- [18] M.C. Casdagli, *Physica D* 108 (1997) 12.
- [19] N. Marwan, N. Wessel, J. Kurths, *Phys. Rev. E* 66 (2) (2002) 026702.
- [20] P. Faure, H. Korn, *Physica D* 122 (1998) 265.
- [21] P. Gallois, G. Forzy, J.J. Leduc, F. Andres, L. Peyrodie, E. Lefebvre, P. Hauteceur, *Clinical Neurophys.* 32 (5) (2002) 297.
- [22] N. Marwan, A. Meinke, *Int. J. Bifur. Chaos* 14 (2) (2004) 761.
- [23] A.A. Marino, E. Nilsen, C. Frilot, *Brain Res.* 964 (2) (2003) 317.
- [24] J.P. Eckmann, S.O. Kamphorst, D. Ruelle, *Europhys. Lett.* 5 (1987) 973.
- [25] F. Takens, in: D.A. Rand, L.S. Young (Eds.), *Dynamical Systems and Turbulence*, in: *Lecture Notes in Mathematics*, vol. 898, Springer-Verlag, Berlin, 1981, p. 336.
- [26] L.L. Trulla, A. Giuliani, J.P. Zbilut, C.L. Webber Jr., *Phys. Lett. A* 223 (4) (1996) 255.
- [27] N. Marwan, *Encounters with neighbours-current developments of concepts based on recurrence plots and their applications*, Ph.D. Thesis, University of Potsdam, 2003.
- [28] Y.C. Lai, I. Osorio, M.A.F. Harrison, M.G. Frei, *Phys. Rev. E* 65 (3) (2002) 031921.
- [29] F.H.L. da Silva, W. Blanes, S.N. Kalitzin, J. Parra, P. Suffczynski, D.N. Velis, *IEEE Trans. Biomed. Eng.* 50 (2003) 540.
- [30] I.A. Rezek, S.J. Robertsthe, *IEEE Trans. Biomed. Eng.* 45 (1998) 1186.
- [31] R. Vandenhousten, M. Lambertz, P. Langhorst, R. Grebe, *IEEE Trans. Biomed. Eng.* 47 (2000) 729.
- [32] B. Weber, K. Lehnertz, C.E. Elger, H.G. Wieser, *Epilepsia* 39 (1998) 922.
- [33] K. Lehnertz, C.E. Elger, *Electroenceph. Clin. Neurophysiol.* 95 (1995) 108.
- [34] G. Widman, D. Bingmann, K. Lehnertz, C.E. Elger, *Brain Res.* 836 (1999) 156.