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Dynamical analysis of epileptic characteristics based on recurrence quantification of SEEG recordings

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HIGHLIGHTS

- We investigate the dynamical differences between epileptic states as well as regions.
- Epileptogenic channels are identified with longer diagonal structures.
- Synchronizations between epileptogenic channels are strengthened when seizures occur.

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ABSTRACT

The evolution of epilepsy is always accompanied with the transitions of dynamics. Characterizing these dynamical processes can be beneficial for understanding the mechanism of seizures. Meanwhile, there also exist dynamical differences between regions, especially in the epileptogenic and non-epileptogenic areas. Hence, in this study stereo-electroencephalograph (SEEG) recordings from 10 patients with refractory focal epilepsy were collected, and recurrence plot was used to investigate the dynamical differences between different epilepsy stages as well as regions. All dynamical characteristics were quantified by means of recurrence quantification analysis. Furthermore, synchronization between channels were also revealed through cross recurrence plot. Results suggested that almost all channels in the pre-ictal and ictal stages had higher recurrence rate than those in the inter-ictal. And epileptogenic channels were identified with longer diagonal structures, which indicated that recordings from epileptogenic regions were more deterministic and recurrent. When seizures occurred, the synchronizations between these epileptogenic channels were strengthened and dominated the dynamics of epileptic brain. This might provide additional insights into the dynamical nature of epileptic phenomena.

1. Introduction

Epilepsy can be regarded as a dynamical disease of brain system [1]. Different processes are involved, including the inter-ictal, pre-ictal and ictal phases, and the dynamics from normal to epileptic seizures still attract particular attentions. Computation models were widely used to investigate the transition mechanism during the epileptic seizures [2–4]. Meanwhile, the data-driven statistical methods (e.g., correlation, phase synchronization, granger causality) also provided novel insights into the process of epilepsy [5,6]. Ictal stage is characterized by paroxysmal hypersynchronous oscillations,

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often interpreted as deterministic recurrent trajectories (e.g., limit cycle attractor) [7–9]. Inter-ictal state can be described as a stable point and the occurrence of sporadic epileptiform discharges is considered as the result of random walks between two different states [7]. Pre-ictal stage, characterized by the presence of rapid discharges, is an important transient process [10]. In addition, epileptogenic and non-epileptogenic areas exhibit unlike dynamical behaviors during the evolution of seizures [11]. Recordings from epileptogenic areas were less random and more nonlinear dependent than those from non-epileptogenic areas [12]. Therefore, we are committed to investigating the dynamical differences between stages as well as regions, and identifying the epileptogenic areas accordingly.

Recurrence plot (RP), a non-linear analysis technique, was first introduced by Eckmann et al. to visualize the basic dynamical characteristics of a dynamical system in phase space in 1987 [13]. High dimensional phase space trajectory was projected into a binary matrix, where the value was set to 1 whenever two points in the trajectory were close enough. This technique has been widely used to analyze the changes and transitions between states [14,15]. And the potential patterns within RPs can be revealed through recurrence quantification analysis (RQA), a statistical quantification approach [16]. Furthermore, in order to explore the interrelations between observations, cross recurrence plot (CRP) was then proposed [17]. The basic idea of this approach was to compare the trajectories of two processes in the same phase space. Based on this, synchronization phenomena can be detected.

Since recurrence analysis is performed without any assumptions, it can usually objectively reveal the dynamics behind physiological data [18–21]. Electroencephalograph (EEG) has become an important clinical tool for diagnosis and treatment of epilepsy [22]. Over the past years, different measures based on RPs have been proposed and applied to the EEG analysis [23]. Determinism (DET), a variable in RQA, was adopted to indicate the deterministic dynamics of EEG epochs obtained from genetic absence epilepsy rats [24]. DET in the pre-ictal was higher than that in the inter-ictal state, but lower than that in the ictal state. Similar measures also indicated that different epilepsy phases could be distinguished on the basis of dynamical characteristics, which were applied in automatic classification of EEG epochs or even the prediction of seizures [25–28]. And different dynamical scenarios also implied different prospects for finding reliable control strategies [29–32]. However, not all regions share the same dynamical characteristics at a specific stage. A number of studies provided evidence that brain electrical activity within the non-epileptogenic regions resembled a stochastic process, while nonlinear determinism was found in the epileptogenic areas [12,33,34]. Meanwhile, epileptic seizures are thought as the result of network disorder [35–37]. Substantial studies showed that the synchronization of neuronal firing in the epileptic regions was enhanced, facilitating the generation of epileptiform discharge [38]. The role of epileptogenic zones in the network synchronization mechanism is of particular concern. In this study, stereo-electroencephalograph (SEEG) recordings from 10 patients were used, which directly recorded intracranial electrophysiological activity and were considered as the gold standard for the epileptogenic region identification. The dynamical changes in different states and regions were revealed through quantification analysis of RPs. Epileptogenic areas were identified by nontrivial dynamical characteristics. Meanwhile, CRPs were used to demonstrate the synchronization phenomena between regions at different stages. It is helpful for further understanding the role of epileptogenic areas from the epileptic network prospective.

This paper is organized as follows. First, the details of SEEG data and preprocessing procedure are given. Second, the construction of RP and CRP as well as quantitative analysis method is introduced. Third, recurrence rate (RR) and DET are calculated to quantify the recurrence structures at different stages. Average diagonal line length (AL) is used to reveal the dynamical difference between regions and identify epileptogenic areas. Then we investigate the relationships between regions, which are described by the AL of CRP. Lastly, we summarize these dynamical differences and explain their implications.

2. Materials and methods

2.1. Dataset

SEEG dataset was obtained from 10 patients (5 males) with refractory epilepsy at Sanbo Brain Hospital of Capital Medical University in Beijing, which was described previously in Yang et al. [39]. This study protocol was approved by the Ethics Committee of Sanbo Brain Hospital of Capital Medical University and all subjects were written informed consent. These recordings were resampled to 256 Hz and band-pass filtered from 0.1 to 70 Hz. Then amplitude values were normalized to zero mean and unit variance for each signal channel. In addition, the data covered different stages of epilepsy, including inter-ictal, pre-ictal and ictal stage. Each stage was divided into 10-s windows without overlaps.

2.2. Recurrence plot and cross recurrence plot

SEEG signals can be regarded as the observation of brain system. According to Takens' theorem [40], when appropriate time delay τ and sufficient embedding dimension d are given, reconstructed phase space from the observation results is equivalent to the original state space topologically. Given a univariate time series $\{u_i\}_{i=1}^{N}$ with the length N, a construction of the phase space trajectory can be represented by:

$$X_i = \left(u_i, u_{i+\tau}, \ldots, u_{i+(d-1)\tau}\right), i = 1, 2, \ldots, N-(d-1)\tau \quad (1)$$

The time delay τ is estimated through the mutual information function and the embedding dimension d is determined by Cao's method [41,42]. In this paper, the phase space is constructed with the time delay τ =12 and the embedding dimension $d = 8$.

Recurrence plot (RP) is a practical tool to transform the high-dimensional phase space trajectory into a two-dimensional map. It enables us to visualize the dynamical properties of a system, especially recurrent behaviors. A RP is defined as:

$$R_{ij} = \Theta\left(\varepsilon - \left\|X_i - X_j\right\|\right), i, j = 1, 2, \ldots, N - (d-1)\tau \tag{2}$$

where $\Theta(\cdot)$ is the Heaviside function, ε is the threshold distance and $\|\cdot\|$ is a norm (e.g., the Euclidean norm). Among them, the threshold ε is selected when the percentage of recurring points rises sharply off the noise floor [43].

As a matter of fact, RP is an effective method to investigate the dynamics of single signal channel. However, there exist scenarios where the relationship between channels is required. Depending on this purpose and application, cross recurrence plot (CRP), a bivariate extension of the RP, was developed. Similar to RP, CRP can be defined as:

$$CR_{ij} = \Theta\left(\varepsilon - \left\|X_i - Y_j\right\|\right), i, j = 1, 2, \ldots, N - (d-1)\tau \tag{3}$$

where X_i and Y_j represent the trajectories in the same d-dimensional phase space from two different signal channels. $CR_{ij} = 1$ represents that they own similar space state at a certain time. If these points form a regular pattern or structure, dynamical characteristics may emerge.

2.3. Recurrence quantification analysis

RPs or CRPs can provide useful insights into the dynamics of a system. However, visual inspections are inevitably restrained by subjectivity, and quantification analysis is required to investigate the complex structure and potential recurrent patterns. As a result, the definition and procedures to quantify RPs were introduced, which were also applicable for CRPs.

Recurrence rate (RR) is the first metrics of recurrence quantification analysis (RQA), which simply measures the relative density of recurrence points. It is calculated by:

$$RR = \frac{\sum_{i,j=1}^{L} map_{ij}}{L^2}, L = N - (d-1)\tau \tag{4}$$

where map_{ij} represents the element of RP or CRP.

The second variable in RQA is the percent determinism (DET), defined as the proportion of diagonal structures (angle $\pi/4$):

$$DET = \frac{\sum_{l=l_{\min}}^{L} lp(l)}{\sum_{i,j=1}^{L} map_{ij}} \tag{5}$$

where $p(l)$ is the frequency distribution of diagonally oriented line with length l. $l_{\min}$ is the predefined minimum length of the diagonal structures. Similar to DET, average diagonal line length (AL) is another measure to quantify the diagonal structures.

$$AL = \frac{\sum_{l=l_{\min}}^{L} lp(l)}{\sum_{l=l_{\min}}^{L} p(l)} \tag{6}$$

As a matter of fact, diagonal structures are so valued because they indicate parallel movement of phase space trajectories, which can demonstrate the recurrent behavior or synchronization phenomenon of a complex system. Based on these measures, dynamical characteristics of each channel in different states of epilepsy can be investigated. Meanwhile, the relationships between channels are also revealed.

2.4. Statistical significance

Variations in these quantitative measures are mostly of relative nature, hence statistical tests are indispensable. Paired t-test was performed to compare RR and DET between different epilepsy stages and determine whether there exist significant differences in the recurrence structures. Meanwhile, epileptogenic channels, related with seizure onset, were identified, the ALs of which were disobedient from the overall distribution.

3. Results

3.1. Time-variant RPs

A RP is often made up of isolated dots and points forming diagonally oriented lines as well as vertical or horizontal lines. Thereinto, isolated dots represent random behaviors that two phase space trajectories get close to each other by chance, while diagonal lines indicate synchronization phenomenon and vertical or horizontal lines represent typical intermittency

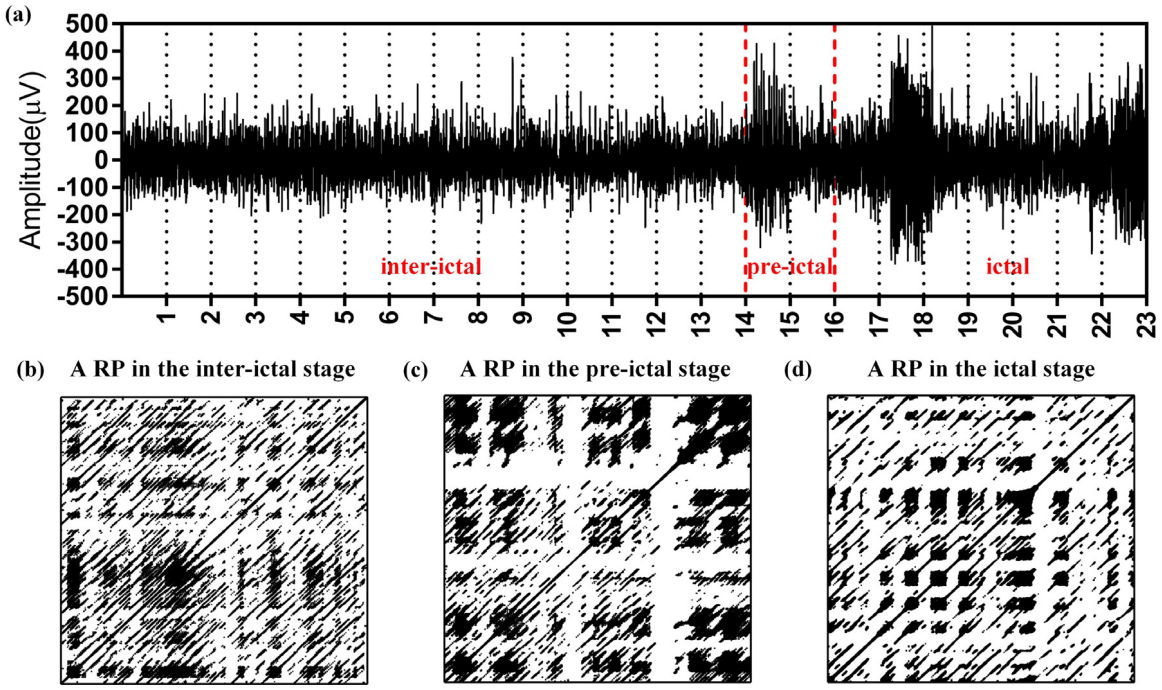

Fig. 1. The upper is the raw SEEG recordings from a channel, where the first 14 windows belong to the inter-ictal stage, the next 2 windows are in the pre-ictal stage, and the rest are seizures. The lower is the RPs corresponding to time window 1/16/21 in turn.

of a system. In order to investigate the dynamical evolution of epileptic brain, SEEG recordings from each channel was divided into inter-ictal, pre-ictal and ictal stages with the help of two electrophysiologists and each stage consists as a combination of 10-s windows (Fig. 1a). As a result, the dynamical behaviors of epileptic brain can be visually demonstrated through time-variant RPs. There seems to be a number of isolated dots in the inter-ictal RP, though diagonal lines also emerge (Fig. 1b). The ictal RP exhibits relatively regular diagonal structure (Fig. 1d), and pre-ictal state is more like a transient process between randomness and determinism (Fig. 1c). In order to quantify these differences of recurrence structures, RQA is performed.

3.2. Recurrence structures of different epilepsy stages

Structural patterns in RPs reveal hints about recurrent behaviors of reconstructed trajectories. RR was calculated to measure the prevalence of recurrence phenomenon macroscopically and DET was adopted to reduce the interference of accidental recurrence points and find significant diagonal structures. Meanwhile, in order to reduce the influence of fluctuations and noise, we averaged the quantification analysis results within the same stages.

For patient No.2 (Pat. 2), the average RRs of channels at different stages were calculated (Fig. 2a). Compared with inter-ictal state, almost all channels in the pre-ictal and ictal stages had higher RRs. And there existed several channels whose RRs rise sharply when it came to the pre-ictal stage. It might imply that the onset of seizures was associated with abnormal enhancement of RRs in local region. Meanwhile, the average RRs of different stages for 10 patients were demonstrated in Fig. 2b. RRs in the ictal stage was generally higher than those in the inter-ictal except for pat. 3, pat. 7 and pat. 8. To ensure the difference was significant, a paired t-test with 1176 pairs of samples (10 patients, 1176 channels) was performed. Results suggested that the difference was statistically significant (p value < 0.0001) and the average difference value (ictal minus inter-ictal) was 0.03928. In a similar way, a paired t-test with 709 pairs of samples (6 patients, 709 channels) was implemented and the difference value (pre-ictal minus inter-ictal) was 0.03097 (p value < 0.0001). However, there was no significant difference between the pre-ictal and ictal stages (p value $= 0.3662$). As a matter of fact, patients with epilepsy also usually had higher RRs than healthy subjects, which can help to diagnose epilepsy and the accuracy of classification can reach 86.8% [44]. The enhancement of RR implied that time course of ictal activity was more recurrent.

DET, defined as the proportion of diagonal structures, is a vivid description of recurrent behaviors. However, its value can be affected by the choice of $l_{\min}$ in Eq. (5). Diagonally oriented lines shorter than $l_{\min}$ will be treated as invalid diagonal structures, equivalent to isolated dots. Therefore, DET decreased with the increase of $l_{\min}$ (Fig. 2c). Selecting a smaller $l_{\min}$ would introduce more random factors, while a larger $l_{\min}$ would exclude too many deterministic results. In this study, $l_{\min}=3$ was adopted to balance the effects.

The average DETs of different stages for 10 patients were demonstrated in Fig. 2d. Paired t-tests suggested that DETs in the pre-ictal were significantly higher than those in the inter-ictal (p-value $= 0.0013$) and ictal (p value < 0.0001) stages, while

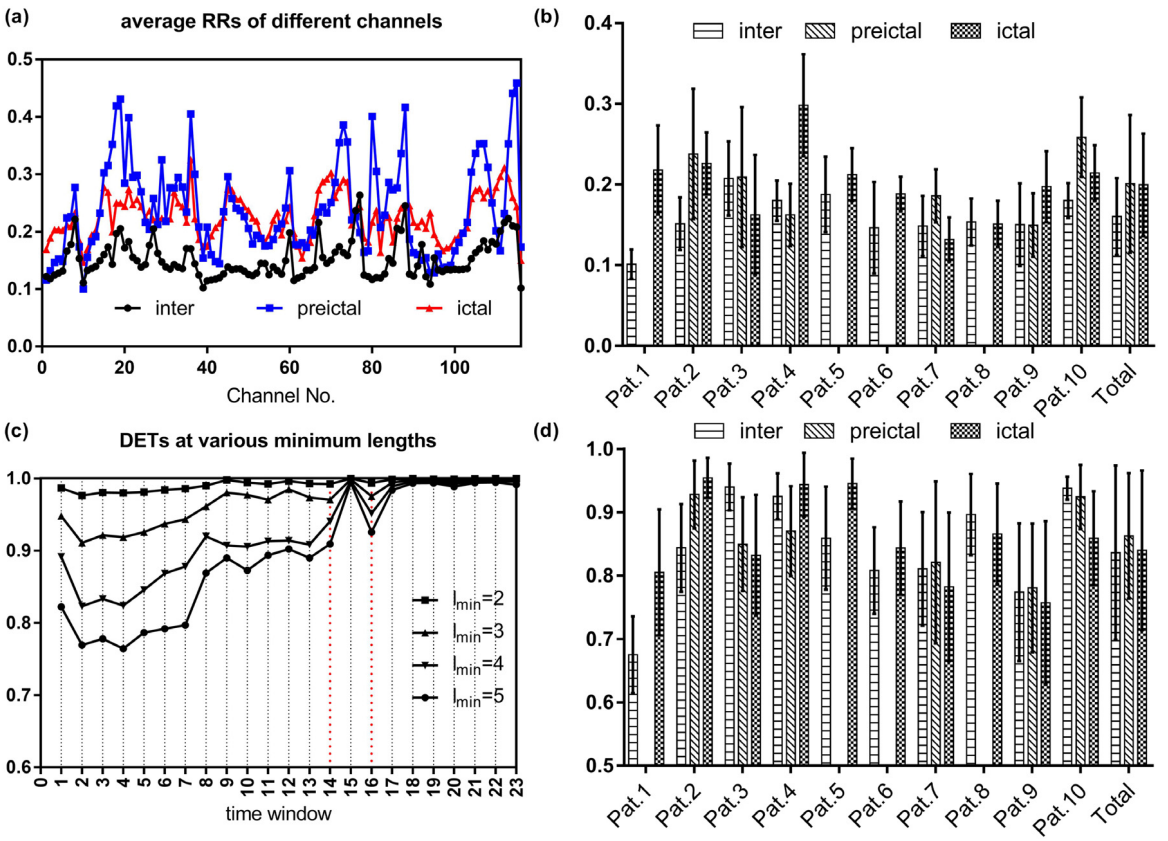

Fig. 2. (a) Take Pat. 2 as an example, the average recurrence rates of each channel in different epilepsy stages are depicted. (b) The mean and standard deviation of RRs in different stages (Pat. 1, pat. 5, pat. 6 and pat. 8 have no definite pre-ictal stage). (c) DETs vary with the choice of minimum lengths of the diagonal structure. (d) The mean and standard deviation of DETs in different stages.

there was no significant difference between the inter-ictal and ictal stages (p value = 0.3810). In addition, it was noteworthy that individual results were not consistent. The study on scalp EEG indicated that DET seemed to increase with an increasing distance to the epileptogenic focus [11]. However, this conclusion is obviously not suitable for SEEG data. Because SEEG recordings are more localized and the distribution of electrodes is individual. The reason why DET failed to characterize the epileptic phases was that the epileptogenic and non-epileptogenic regions had different recurrent characteristics. To further understand the diagonal structures, it is necessary to identify those epileptogenic channels.

3.3. The identification of epileptogenic channels

Compared with DET, AL can magnify the differences of determinism between channels. It is essentially a weighted result according to the length of diagonal structure. Longer diagonal oriented lines provide stronger indications that the system has a deterministic dynamics. Results suggested that epileptogenic channels tended to have longer average diagonal structures (Fig. 3). Meanwhile, such dynamical behavior spread from the onset zone to other regions [45]. As a result, the channels in the primary propagation areas also emerged with similar dynamical characteristics. Based on clinical conclusions, channel 36, 88, 112 and channel 19, 73 were recognized as seizure onset zones and primary propagation areas, respectively. The ALs of these channels were significantly higher than the mean at one or more stages. Furthermore, their neighboring channels exhibited similar recurrent behaviors (Fig. 3d). And all the calculation results and clinical conclusions were listed in Table 1, where the channels were represented by the combinations of letters and numbers (e.g., R2-3 represented the second to third contacts of electrode R). The seizure onset zones of 7 patients (except for pat.1, pat. 3 and pat. 8) were identified and 73.91% (17/23) of the primary propagation areas were well included.

Generally speaking, the inter-ictal process involves more randomness, while the dynamics of pre-ictal and ictal epochs differ from that, which seem to be governed by subtle deterministic mechanisms [7]. As a matter of fact, the epileptogenic regions played a dominant role in the evolution of seizures. Long diagonal structures indicated that their activities were more deterministic and recurrent. Their existence was likely to alter the dynamical characteristics of epileptic brain and provide a basis for seizures. In addition, as early as the inter-ictal stage, they started to exhibit such nontrivial dynamics.

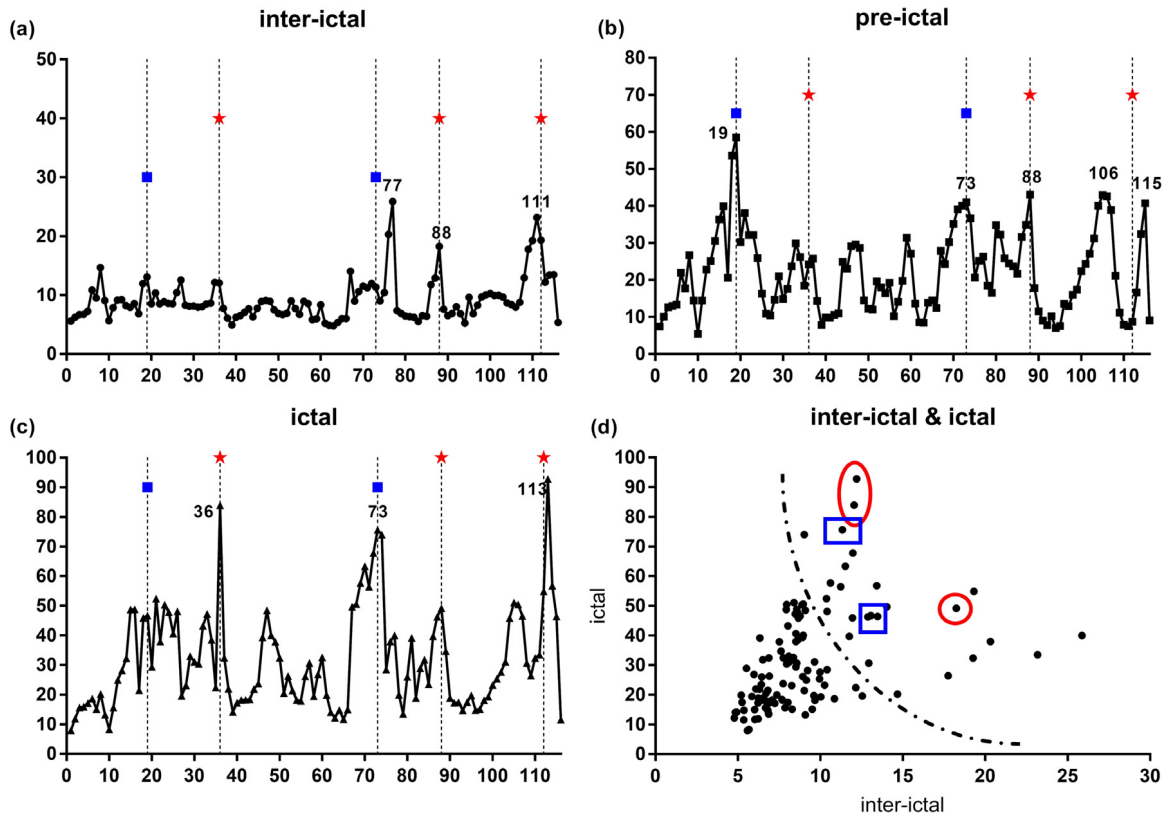

Fig. 3. Take Pat. 2 as an example, the average ALs of different channels in the inter-ictal (a), pre-ictal (b) and ictal (c) stages. The channels located in seizure onset zones and primary propagation areas, identified by electrophysiologists, are marked by red stars and blue squares, respectively. (d) The average ALs during the inter-ictal and ictal stages are plotted in a plane. Trivial and nontrivial points are separated by the black dotted line, and previously marked channels are circled by the corresponding color.

Table 1
Recurrence quantification analysis results and clinical conclusions of all patients. Those channels with significantly longer diagonal structure were identified, which were associated with clinically defined epileptogenic zones as well as primary propagation areas.

No.	Recurrence quantification analysis	Clinical conclusions	
		Seizure onset zones	Primary propagation areas
1	R2-3, X2, K3	D11-12	R2-3, X3
2	E4, M4-6, J13, H7, C10, L14	E4, J13, M5	H7-8, C10
3	A14, E13, D4, N12-13, M6	P8, E7, G6	D2-4, F10
4	H13, L11-13, J1-3, D10, G8-10	L9-11, H13	J2-3, G9, E4, D10
5	F8, J7-10, C6, M5	F8, D3	J7-8, M4-5, C6
6	H4, L2-5, K2-4, A10	L4, H4	K2, J2
7	E8-11, C4, D1-3, A3, F1	E10, C2, D1	B4, A1-3
8	F3, M12-14, L5	G10, H10	F2-3, M12
9	A1, B1-3, E6, G8–9	A1, B1	G7-9, E3, H2
10	G10-12, D4-6, C2, A5-7	G11, K9	D6-7

3.4. Synchronization between channels

Dynamical characteristics of single channel were revealed through the quantification analysis of RPs, however the dynamics of brain network also deserved particular attentions. After all, epilepsy is increasingly understood to be network disorder, and seizures arises from abnormal synchronization. Cross recurrence was introduced for the investigation of synchronous evolution of two different phase space trajectories, allowing the study of relationships between channels. The ALs of cross recurrence plots of arbitrary two channels were calculated and then averaged within the same stages (Fig. 4). If the AL was not significantly greater than the overall mean (z-score < 3), it would be considered unrelated to each other. Compared with inter-ictal state, the ALs during the pre-ictal and ictal were clearly higher, indicating the enhancement of synchronization. Meanwhile, such synchronization phenomena mainly involved those epileptogenic channels as well

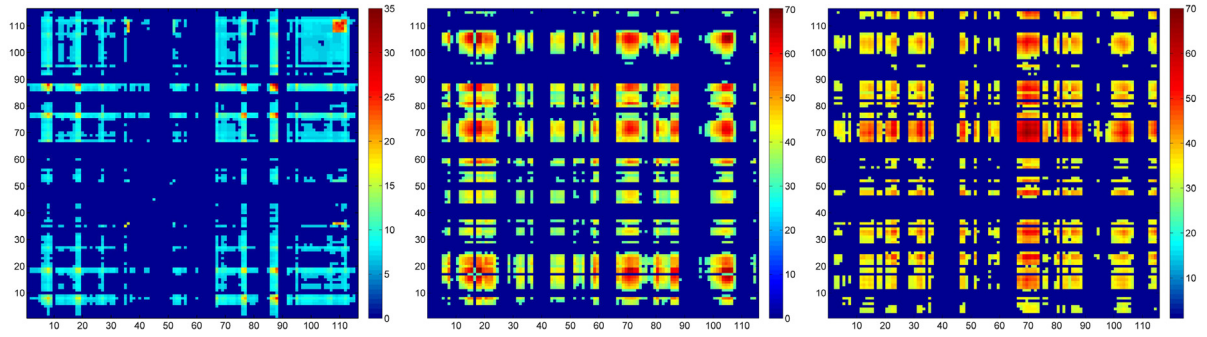

Fig. 4. The average ALs of cross recurrence plots between channels during the inter-ictal, pre-ictal and ictal stages, respectively. Compared with inter-ictal state, the ALs during the pre-ictal and ictal were clearly higher. And such high ALs mainly occurs between epileptogenic channels as well as primary propagation areas.

as primary propagation areas and their neighbors. This suggested that epileptogenic channels not only had deterministic recurrent characteristics themselves, but also kept considerable synchronization with each other. Meanwhile, they might affect the dynamical behaviors of other regions and promote a higher intensity, greater range of synchronization, eventually leading to network disorder. It was similar to previous findings of connectivity patterns that epileptogenic focus was characterized by the topological hub of network [6,39,46]. Here it was also dynamical hub. The removal of it might improve network disorder and reduce or even suppress ictal activities.

4. Conclusions

In this study, recurrence plots were used to investigate the dynamical characteristics of different epilepsy stages and regions, based on SEEG recordings from 10 patients with refractory focal epilepsy. Recurrence quantification analysis was performed to reveal the significant differences of recurrence structures and identify the epileptogenic channels which were related to seizure onset. Results suggested that RRs significantly increased with the inter-ictal state moved into the pre-ictal or ictal states. Meanwhile, the channels with longer diagonal structures were recognized as the epileptogenic regions and primary propagation areas, mostly consistent with the clinical conclusions. Furthermore, with the help of cross recurrence plots, the relationships between channels were clearly revealed. These channels with nontrivial diagonal structures remained synchronized, and such synchronizations were strengthened with the evolution of epileptic states. To some extent, they made up the main body of epileptogenic networks and dominated the dynamics of epileptic brain. When the epileptogenic areas were resected, pathological networks might be corrected and epilepsy got controlled accordingly.

In summary, RQA was an effective tool to understand the dynamical differences underlying the spatiotemporal evolution of epileptic seizures. Compared with inter-ictal stage, pre-ictal and ictal phases had more deterministic recurrent trajectories. And epileptogenic areas played a dominant role in the process, which could be identified by nontrivial diagonal structures. Furthermore, the synchronizations between them were strengthened with seizure onset and governed the dynamics of epileptic network. This may provide additional insights into the dynamical nature of the occurrence and control of epileptic seizures.

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Ethics statement

This study protocol was approved by the Ethics Committee of Sanbo Brain Hospital of Capital Medical University and all subjects were written informed consent.

Author contributions

All authors designed the research, performed the research and analyzed the data. CZY and QYW wrote the paper.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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