Multifractal Analysis of Intracranial EEG in Epilepticus Rats

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Abstract. Networks of living neurons exhibit diverse patterns of activity, which are always operating far from equilibrium in the mammalian central nervous system. In this study, a blocker of glutamate transporter was employed to detect if nonlinear interactions changed when extra glutamate acted as a potent neurotoxin to neural activity in hippocampus of epileptic Wistar rats. A hypothesis was made that a decrease of complexity of information could be occurred by accumulation of glutamate in hippocampus. An investigation was performed to measure intracranial EEG, which were obtained from two parts of brain in three rat's groups, by using multifractal detrended fluctuation analysis. The results demonstrate that the change of nonlinear interactions in neural network can be clearly detected by multifractal analysis. Moreover, small fluctuation in activity of network exhibited a decrease in multifractal behavior, suggested that the complexity of information transmitting and storing in brain network was weakened by glutamate accumulation.

Keywords: multifractal detrended fluctuation analysis, epileptic rats, glutamate transporter.

1 Introduction

Nonlinear dynamics has been shown to be important in describing complex neural networks and time series, such as electroencephalogram (EEG) [1]. Previous investigations indicated that there were non-trivial long-range correlations within the human EEG signals [2], which was one of fractal features related to self-similar fluctuations [3]. However, neural dynamical systems, driven by multiple-component feedback interactions, actually showed non-equilibrium, variable fractal behaviors, multifractal [4], and their fractal features were hard to be characterized by traditional fractal measurements, such as detrended fluctuation analysis and multiscale entropy [5]. In this case, the method of multifractal analysis becomes a more reasonable approach for measurement of the fractal characteristics of EEG signals. The earliest studies of the nonequilibrium of cardiac interbeat interval time series revealed that the healthy subjects showed more multifractal structure than diseased subjects. Moreover, studying multifractal EEG using wavelet transform modulus maxima (WTMM) method was employed as a new direction for brain dynamics [6]. Recently, Kantelhardt *et al*. developed a new mathematical algorithm named Multifractal detrended

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fluctuation analysis (MF-DFA), which made analyzing multifractals in nonstationary time series feasible [7]. MF-DFA is based on a generalization of detrended fluctuation analysis (DFA) , and allows more reliable multifractal characterizations for multifractal nonstationary time series than the method of WTMM [8].

Glutamate is the primary excitatory neurotransmitter in the mammalian central nervous system and acts as a potent neurotoxin, implicated as a neurotoxic agent in several neurologic disorders including epilepsy, ischemia, and certain neurodegenerative diseases. The termination of neurotransmission is mediated by sodium-dependent high affinity glutamate transporters, which play an important role in maintaining the extracellular glutamate concentration below neurotoxic levels. A disturbance in glutamate-mediated excitatory neurotransmission has been implicated as a critical factor in the etiology of adult forms of epilepsy. Manipulation of glutamate transporter expression can lead to various neurologic dysfunctions. For example, in epileptic mice deficient in GLT-1, it has shown lethal spontaneous seizures and increased susceptibility to acute injury. Disruption of transporter activity could lead to changes in network activity as a result of enhanced interneuron excitability. Changing glutamate transporter may affect the patterns of complicated EEG and the structure of brain network, particularly when associated with neuronal diseases, such as epilepsy.

In the present study, disruption of glutamate transporter activity could lead to changes in neural network activity as a result of enhanced interneuron excitability, particularly seizures when associated with neuronal diseases such as epilepsy. Therefore, MF-DFA was employed to analyze continuous EEG time series obtained from intracranial depth electrodes placed in the dentate gyrus (DG), which was studied as the focus of temporal lobe epilepsy in hippocampus, and the perforant pathway (PP) investigated as the path for transmitting information from the entorhinal cortex. The changes in nonlinear dynamic were found by multifractal analysis among three groups of animals. And decreasing multifractals caused by hyperexcitability in neural network oscillations were discussed as well.

2 Methods

2.1 Multifractal Detrended Fluctuation Analysis

The approach of multifractal detrended fluctuation analysis (MF-DFA) was employed to calculate the singular spectrum of the intracranial EEG signals, the details of algorithm can be found in the reference [7].

2.2 Surrogate Data Analysis

Whether the MF-DFA analysis truly reflects a multifractal behavior in the EEG or just a broad probability density function for the values is tested by simply shuffling the original intracranial EEG sequences to construct surrogate data. The results are subsequently compared with that of the original sequences for all three groups, respectively. The averaged result was obtained from surrogate data, which were shuffled 20 times for each segment of original intracranial EEG.

2.3 Animal Modeling and Local Field Potential (Intracranial EEG)

The experiments were performed on 18 male Wister rats weighing 304±13 g. The rats were randomly divided into 3 groups, which were control group, epilepsy group and TBOA group. TBOA was administrated intracerebrally in hippocampus for TBOA group. The signals of local field potential (intracranial EEG) were sampled and filtered by high- and low-pass filters set at 0.3Hz and 300 Hz. All the signals were digitized with sampling frequency of 250 Hz (PowerLab/8S, AD Instruments, Australia). All the data are expressed as the Mean ± SEM. Significant differences would be taken when $P < 0.05$.

3 Decreases of Multifractality from Normal State to Epileptic Model

Fig1a illustrates MF-DFA measurement and multifractal singularity spectrum of intracranial EEG in hippocampal DG, obtained from the control and epilepsy groups. Both *h(q)* curves show dependence on *q*, *i.e.* the values of *h(q)* decrease along with increase of *q*. It was found that the multifractal scaling exponent sloped faster in the control group compared to that of the epilepsy group (P<0.05 – 0.01, *P<0.05, **P<0.01). Furthermore, to investigate the variation of scaling behavior quantitively, the values of slope at each scale of *h(q)* curves was employed to describe the complexity from small fluctuation to large fluctuation. It was found that there were larger slopes at scales from 1 to 9. In addition, the multifractal singularity spectrum (Fig1b), which shows two separated *f(α)* curves, can be generated via a Legendre transform. There is a wider scaling exponent distribution in the control data. Fig2c shows the group data of $\Delta\alpha$, and it can be seen that the strength of multifractality is greater in the control group than that in the epilepsy group (0.82±0.03 *vs.* 0.68±0.02, *P<0.05).

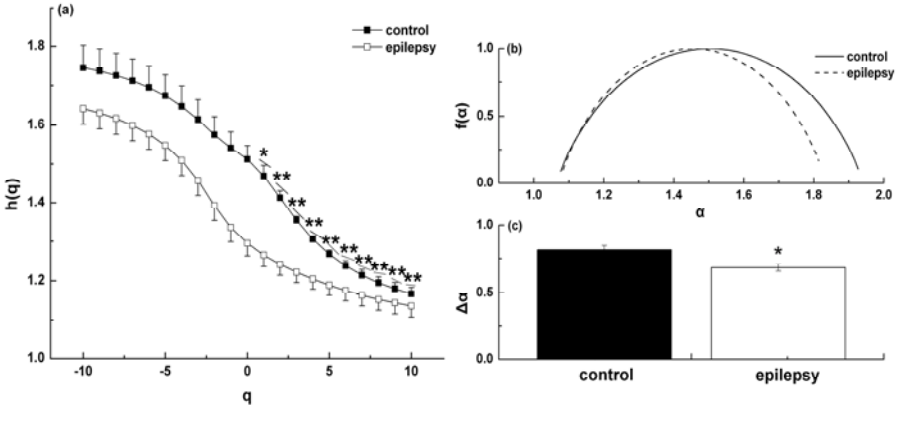

Fig. 1. Comparison of the singularity spectra, obtained from MF-DFA analysis, between the control and epilepsy groups

According to the result from Fig.1c, the $\Delta\alpha$ values indicate significant weakness in the complex structure of dynamic system in epilepsy group over that of the control group. In this case, the complexity of information transmission and storage in DG neural network is weakened. Moreover, the study of segment slope in MF-DFA curves revealed that it was the large fluctuation of oscillation contributing to the weakened complexity in epilepsy group.

4 Changes of Multifractality between Epileptic Rats and TBOA Injection Rats in Hippocampal DG

In the present study, a hypothesis was tested that effects on glutamate transporters were correlated with complexity of neural network oscillations and a loss of multifractality could be associated with brain pathology. Fig2a illustrates the results of MF-DFA measurement of intracranial EEG in hippocampal DG obtained from the epilepsy and TBOA animals, respectively. After TBOA was injected, *h(q)* curve on most *q* scales kept relatively constant value, especially for *h(2)*, which was the Hurst exponent (1.24±0.03 *vs*.1.20±0.03, P>0.05). However, there are significant differences of the slops at scales -2 and -3 between these two groups (-0.06 ± 0.004 *vs*. -0.05 ± 0.005, *P < 0.05). Thus, the generalized Hurst exponent in epilepsy group was decreased much greater compared to that in TBOA group. It can be seen that value of *h(q)* in epilepsy group decreased from 1.64±0.04 to 1.14±0.03 at scales varying from -10 to 10, while it reduced from 1.53±0.02 to 1.11±0.03 in TBOA group. Fig2b shows multifractal singularity spectrums obtained from an epileptic rat and TBOA one, respectively. The group data of Δα are represented in Fig2c, however, it was found that there was no significant difference between these two groups (0.68 ± 0.02 *vs*. 0.64 ± 0.02, P>0.05).

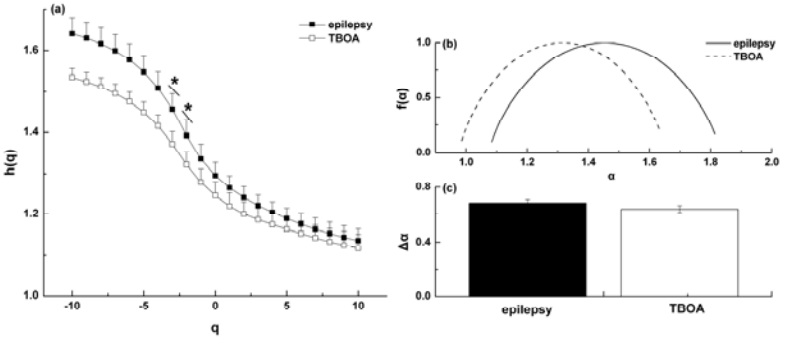

Fig. 2. Comparison of the singularity spectra, obtained from MF-DFA analysis, between the epilepsy and TBOA groups in hippocampal DG

Comparing MF-DFA results from epilepsy group and TBOA group, the constant value of Hurst exponent suggests that the fractal character of dynamic network may not have a change after TBOA injection. However, significant decrease in the slope of

TBOA on relatively small fluctuation MF-DFA curve was observed, indicating that the activities with small amplitude were less complex in TBOA group than that in epilepsy group. Based on the MF-DFA curves through slope of segment in Fig2a, it showed significant difference (P<0.05) between epilepsy group and TBOA group. Thus, according to the decrease of complexity, it was found that accumulation of glutamate brought seizures, and caused the decreasing complexity of information storing and transmitting in the neural network at that time. The glutamate transporters were inhibited by using DL-TBOA, which induced accumulation of glutamate in synaptic space and glial cells dysfunction. The dysfunction, evoked by nerotoxity of glutamate, enhanced neuronal hyperexcitability which led to more regular behavior. This suggests that the reduced complexity of neural network oscillations in hippocampus may be associated with brain dysfunction induced by nerotoxity of glutamate.

5 Decreases of Multifractality from Epileptic Model to TBOA Injection

Fig3a shows MF-DFA measurement and multifractal singularity spectrum of intracranial EEG in hippocampal PP, obtained from the epilepsy and TBOA groups, respectively. It can be seen that the value $h(q)$ in epilepsy group decreased from1.49±0.02 to 0.80±0.02, while the value $h(q)$ in TBOA group reduced from 1.49±0.04 to 0.99±0.05. The generalized Hurst exponent in the epilepsy group declines faster than that in the TBOA group. The slopes of $h(q)$ in the epilepsy group are significantly steeper than that in the TBOA group at scales from -4 to 1 ((P<0.05 – 0.01, *P<0.05, **P<0.01). Fig3b presents multifractal singularity spectrums obtained from an epileptic rat and TBOA one, respectively. It can be seen that the strength of multifractality is greater in the epilepsy group than that in the TBOA group (0.86±0.04 *vs*.0.69±0.04,* P<0.05, Fig 3c).

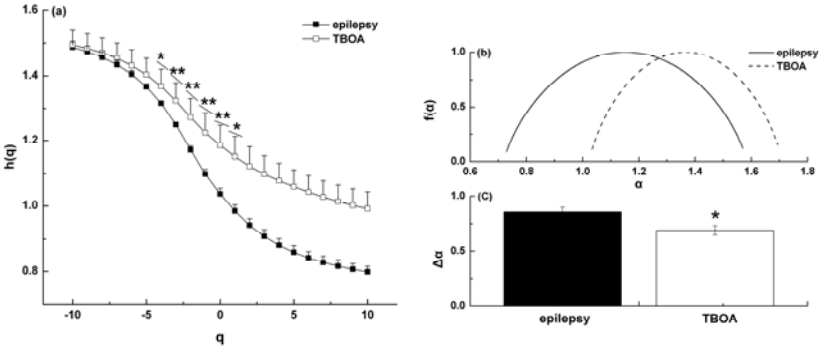

Fig. 3. Comparison of the singularity spectra, obtained from MF-DFA analysis, between the epilepsy and TBOA groups in hippocampal PP

While the use of TBOA inhibited the glutamate transporters, the inhibition caused accumulation of glutamate in neural network of DG, and has the neurotoxicity for dysfunction of neurons and glial cells. The dysfunction evoked by neurotoxicity of glutamate is what we conclude that enhanced excitability leads to more regular behavior, which shows smaller degree of complexity in DG. The seizures were triggered in entorhinal cortex by glutamate accumulation from DG in TBOA group. A previous study indicated that in models of temporal lobe epilepsy, an entorhinal cortex delivers excessive, synchronous, excitatory synaptic input from PP to DG. In the dynamic system of entorhinal cortex, hyperexcitability leads to more synchronized activity, indicating that the input to DG has smaller degree of complexity.

6 Conclusions

In the present study, we discussed the multifractal behavior in the neural network to clarify how the multifractality is related to physiological states in hippocampus of rats. The issue was addresses as to whether multifractal characterizations of intracranial EEG signals, could be detected by the method of MF-DFA. Furthermore, the hypothesis was tested that effects on glutamate transporters were correlated with complexity of neural network oscillations and a loss of multifractality could be associated with brain pathology. Since DL-TBOA can induce glutamate accumulation, which evokes sustained seizures and excitatory neurotoxic effect, the results show that the weakened activity of neuronal network can be detected by MF-DFA. In summary, this study presents that the analysis of MF-DFA can be applied to determine fractal characteristics in EEG signals. Our results demonstrate that (1) Multifractal properties of brain neuron signals obtained from DG and PP in hippocampus were related to the complexity of information transmission and storage in the dynamic neural network in the brain; (2) the complexity of information of neural network in hippocampus could be significantly weakened by epilepsy; (3) the changes of multifractal behavior induced by glutamate accumulation suggests that the neural information could be undermined by disruption of glutamate transporter activity in epileptic animals.

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