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Assessing severity of obstructive sleep apnea by fractal dimension sequence analysis of sleep EEG

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ABSTRACT

Different sleep stages are associated with distinct dynamical patterns in EEG signals. In this article, we explored the relationship between the sleep architecture and fractal dimension (FD) of sleep EEG. In particular, we applied the FD analysis to the sleep EEG of patients with obstructive sleep apnea–hypopnea syndrome (OSAHS), which is characterized by recurrent oxyhemoglobin desaturation and arousals from sleep, a disease which received increasing public attention due to its significant potential impact on health. We showed that the variation of FD reflects the macrostructure of sleep. Furthermore, the fast fluctuation of FD, as measured by the zero-crossing rate of detrended FD (zDFD), is a useful indicator of sleep disturbance, and therefore, correlates with apnea–hypopnea index (AHI), and hourly number of blood oxygen saturation (SpO_2) decreases greater than 4%, as obstructive apnea/hypopnea disturbs sleep architecture. For practical purpose, a modified index combining zDFD of EEG and body mass index (BMI) may be useful for evaluating the severity of OSAHS symptoms.

1. Introduction

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is the most common type of sleep-disordered breathing characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, i.e., the airflow decreases (hypopnea) or is completely interrupted (apnea) despite respiratory effort. There was evidence that untreated OSAHS could increase not only the risk of hypertension, heart attack, stroke, and diabetes, but also the chance of having work-related or driving accidents [1]. According to recent epidemiological studies, nearly 20% of people suffer from OSAHS [2–4]. Moreover the incidences of OSAHS are increasing [5].

Clinically, the polysomnography (PSG), which records a variety of physiologic signals during sleep, such as the electrical activities of the brain, eye movements, muscle activities, heart rates, respiratory efforts, air flow, and blood oxygen levels, is commonly used to diagnose sleep apnea and to determine its severity. The polysomnography derived apnea/hypopnea index (AHI), which counts the number of apneas/hypopneas event per hour, provides a reasonable way to evaluate the severity of OSAHS. According to the clinical guideline, OSAHS is divided into mild, moderate and severe, based on the AHI [6].

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Table 1
The severity distributions of subjects in groups.

Severity	Number of subjects	Mean AHI (/h)	AHI range (/h)
Simple snoring	7	2.27	$0 \leq \text{AHI} < 5$
MILD	20	9.49	$5 \leq \text{AHI} < 15$
MODERATE	13	23.03	$15 \leq \text{AHI} < 30$
SEVER	40	59.73	$\text{AHI} \geq 30$

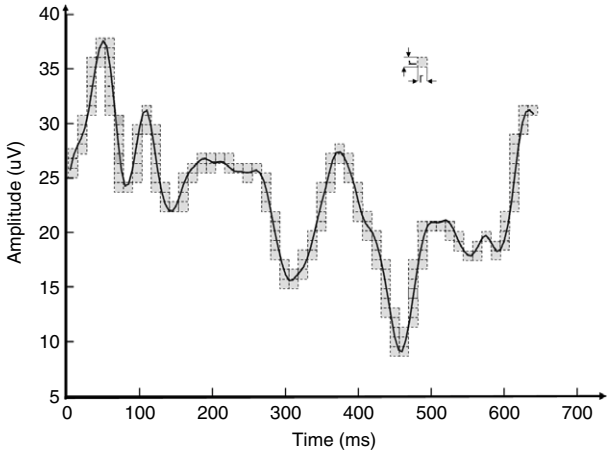

Fig. 1. Illustration of the box-counting algorithm. The number of covering boxes varied with different box side lengths of r, and fractal dimension is calculated by $FD = -\lim_{r\to 0} \frac{\log_2[N(r)]}{\log_2(r)}$.

Recent studies showed that patients with OSAHS could exhibit different disruptions in sleep macro-architecture [7]. Methods based on the quantifications of dynamic properties of physiological signals, such as the Hurst exponent, correlation dimension and Lyapunov exponent analyses [8], have been applied to analyze sleep Electroencephalogram (EEG). These methods have been shown to be useful in describing sleep architecture. In this study, we decide to investigate the utility of applying fractal dimension (FD) analysis to sleep EEG to extract the sleep macro-architecture of each subject and find a new descriptor to quantify the disruption in the macro-architecture of sleep. Furthermore, the temporal fluctuation of the local FD (as measured within a 30-s moving window) time series should provide an indication of how disruptive the sleep is, and, therefore, may provide useful information about the severity of OSAHS.

2. Subjects and data

The sleep EEG of 80 patients (mean age 48.5 ± 14.2 years, range 19–82 years, 16 females and 64 males) with different levels of severity of OSAHS was analyzed retrospectively. The whole night polysomnographic data were attained from the Sleep Laboratory of Department of Pumimonary Medicine of Peking University First Hospital (Siesta Wireless Sleep Monitoring System, manufactured by Compumedics. Ltd., Australia). For each subject, sleep stages and apnea episodes were determined based on the annotation of multi-channel signals including EEG, ECG, electro-oculogram (EOG), SpO_2, airflow, thorax efforts, abdominal efforts, snoring sound, leg movement, and body position, with respect to sleep stages and apnea. EEG signals Analyzed were from the C3 derivation with a sampling rate of 128 Hz. The sleep stages were visually scored for each 30-s epoch by experienced clinical staffs, according to the 2007 AASM (American Academy of Sleep Medicine) sleep scoring manual. Groups of subjects with different levels of severity of OSAHS are summarized in Table 1.

3. Fractal dimension measurement of EEG

Fractal dimension (FD) was originally introduced as a description of self-similar objects [9] and subsequently utilized in a variety of scientific disciplines [10–12,27].

The local FD of sleep EEG signals in each 30s' epoch was estimated by a standard "box-counting" algorithm as illustrated in Fig. 1. By covering a structure such as EEG signal with boxes of side length r, the fractal dimension FD is given by

$$FD = -\lim_{r\to 0} \frac{\log_2[N(r)]}{\log_2(r)} \tag{1}$$

where $N(r)$ is number of non-empty boxes needed to completely cover the structure, and FD corresponds to the slope of the plot $\log_2[N(r)]$ versus $\log_2 r$. An FD time series was generated by sequentially moving 30-s window forward in time.

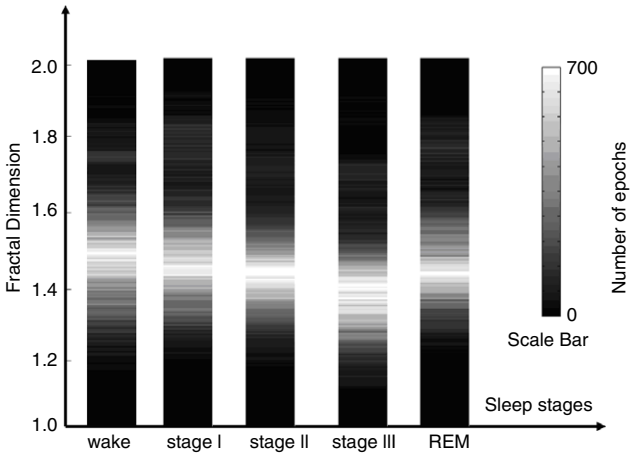

Fig. 2. Histogram of FD with different sleep stages for subjects. From this figure, it is demonstrated that the mode (the value that occurs most frequently in a data set,) of the FD value for typical individual subject decreased from awake to sleep stages 1, 2 and 3, but increased during REM sleep.

Table 2
FD in different sleep stages.

p value	Wake	Stage I	Stage II	Stage III	REM
	FD (mean $\pm$ std)				
	1.47 ± 0.13	1.48 ± 0.14	1.44 ± 0.13	1.37 ± 0.13	1.47 ± 0.13
Wake					
Stage I	0.986*				
Stage II	0.000	0.000			
Stage III	0.000	0.000	0.000		
REM	0.022	0.11*	0.000	0.000	

* $P > 0.05$, the difference between Stage I and Wake, and the difference between Stage I and REM are of no statistical significance.

The histogram indicating the distribution of the sleep EEG FD exponent values of all eighty subjects for each sleep stage is displayed in Fig. 2. The results showed that the mode, the value that occurs most frequently in a data set, of the FD value for typical individual subject decreased from awake to sleep stages 1, 2 and 3, but increased during REM sleep. Our result is consistent with previous findings [13,14] that suggested that there are significant differences in dynamical indices, such as the Hurst exponent and the Lyapunov exponent, between different sleep stages. Fig. 2 demonstrates the distribution of FD in different sleep stages.

The distributional normality of FD values calculated from epochs of different sleep stages was rejected by the Kolmogorov–Smirnov test and thus nonparametric test was utilized [15]. The statistical results demonstrated that differences among groups are of statistical significance except the difference between REM and stage 1 ($p = 0.101$) and the difference between wake and stage 1 (0.986), as demonstrated in Table 2.

To further test whether the FD time series can describe the sleep architecture, correlation between FD time series and sleep stage time series was analyzed. Fig. 3 illustrated the procedure performed by us to study the correlation. Data from one subject was shown as an example. Fig. 3A and B show the annotated sleep stage sequence and FD time series, respectively. Since only the macrostructure of sleep is concerned in the study, both time series were smoothed by using a finite impulse response (FIR) low-pass filter (64 order). In this case, the maximum cross correlation coefficient (MCCC) between these two smoothed time series is 0.944 (absolute value, as FD decreases while sleep goes into deeper stages). As a group, the MCCC of 54 out of 80 subjects are greater than 0.5 (absolute value).

Overnight recordings of 6 OSAHS patients were chosen from the entire sample group. The recordings we selected exhibited relatively less fluctuation and seemed less affected by noise disturbances, from which the sleep stages could be distinctively scored and sleep respiratory events could be clearly found. These consisted of 1 snoring (AHI $=$ 1.6), 2 mild (AHI $=$ 5.2 and 7.5), 1 moderate (AHI $=$ 20.9), and 2 severe (AHI $=$ 63.9 and 65.9) recordings.

Since OSAHS could disturb the normal sleep architecture, there may be significant difference in dynamical properties of EEG during sleep epochs with and without respiratory events. The fractal dimensions for every consecutive epoch were calculated and all sleep epochs of the 6 OSAHS patients were divided into two groups, based on whether sleep respiratory events had appeared. The mean and standard deviation of the fractal dimension of the normal groups (FD_normal) and the respiratory event groups (FD_event) for each sleep stage were obtained (Table 3). Through the Kolmogorov–Smirnov test, it is demonstrated that FD_normal and FD_event in stage II, III and REM have a statistically significant difference, with all $p < 0.001$.

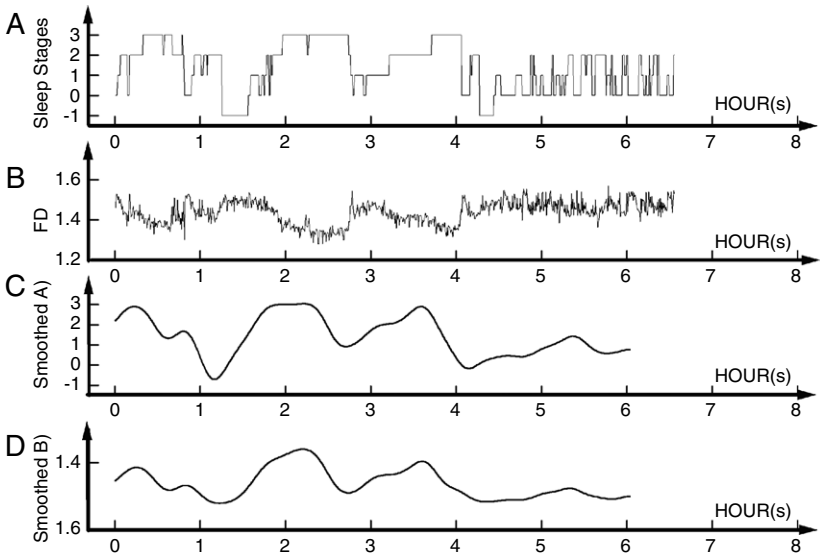

Fig. 3. Typical FD sequence versus Sleep macro-architecture of a patient with AHI = 41.7. The correlation coefficient between filtered fractal dimension and filtered stage is 0.944. Note that the absolute value of correlation coefficient is utilized here as the fractal dimension decreases while sleep goes into deeper stages.

Table 3
FD in two groups with different sleep stages.

Stage	FD_normal	FD_event	*P* value
Awake	1.56 ± 0.12 (560)	1.62 ± 0.18 (71)*	0.0044 (<0.01)
1	1.54 ± 0.12 (283)	1.54 ± 0.16 (189)	0.159 (N)
2	1.53 ± 0.13 (1810)	1.57 ± 0.16 (722)*	1.63E−65 (<0.001)
3	1.47 ± 0.10 (719)	1.66 ± 0.14 (179)*	1.85E−70 (<0.001)
REM	1.57 ± 0.14 (525)	1.50 ± 0.14 (286)*	7.72E−04 (<0.001)

* $P < 0.05$, compared with FD_normal, difference was significant.

4. Temporal fluctuation of FD measurement

We demonstrated in the previous section that the sleep architecture and its corresponding FD exponent sequence have a strong correlation. Thus, it is reasonable to assume that the disturbance of sleep architecture by OSAHS will be reflected in abnormal fluctuation of FD sequence. Since each respiratory event happens in a rather short time, the sleep pattern could be affected quickly and the FD sequence fluctuates in a transient time. Our result demonstrated that respiratory event is characterized by higher value of FD. For people with different AHI, FD fluctuations may be used to describe the severity of OSAHS. In order to quantify the property of the FD fluctuation in an accurate way, the removal of the slower "trend" – the relatively normal sleep architecture – is necessary. To this end, we apply an adaptive data analysis technique, called empirical mode decomposition (EMD) algorithm [16,28], to detrend the FD sequence.

Different from the traditional filter that is based on the Fourier spectrum approach, the EMD algorithm, introduced by Huang et al. [17], has been developed to be applicable to non-stationary signals, such as EEG signals. In this study, EMD algorithm was employed to smooth the fractal dimension sequences of whole night EEG in an adaptive way.

Briefly, detrending time domain signals with the EMD algorithm contains the following steps (see Fig. 4): Firstly, identify all the local extreme from known signals $S(t)$, and then fit all those local maxima as knots by the natural cubic spline interpolation as the upper envelope $U(t)$; Secondly, repeat the procedure for the local minima to produce the lower envelope $L(t)$. Then the mean curve $M(t)$ is obtained according to the upper and lower envelopes. The detrended signal is the difference between $S(t)$ and $M(t)$.

It is common to employ the zero-crossing rate (ZCR) to indicate the rate of sign-changes along a signal, i.e., the rate at which the signal changes from positive to negative or vice versa: ZCR is defined as [18]

$$ZCR = \frac{1}{T}\sum_{t=0}^{T-1} II\{s_t s_{t-1} < 0\} \tag{2}$$

where s is a signal of length T and the indicator function $II\{A\}$ is 1 if its argument A is true and 0 otherwise.

It is shown above that FD sequence of sleep EEG resembles the architecture of sleep. It can be derived from the hypothesis that the OSAHS-induced disturbance on sleep architecture can be reflected by disturbed FD sequence. The index reflecting

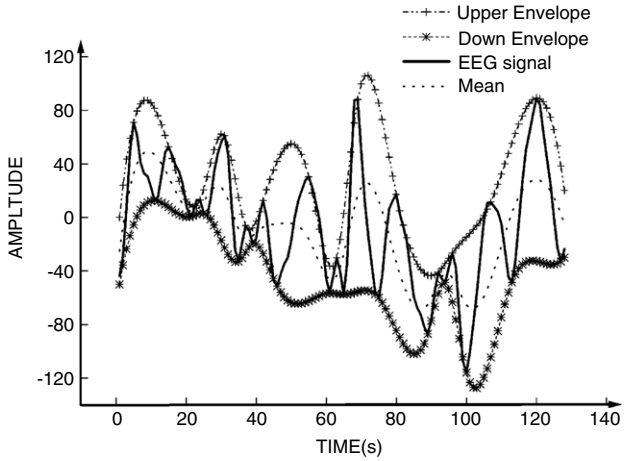

Fig. 4. Diagram of the envelope filtering for sleep EEG signals.

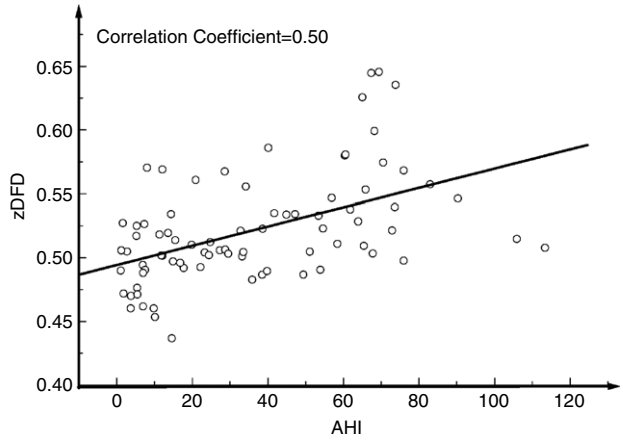

Fig. 5. Correlation between zDFD and AHI.

Table 4
Distribution of OSAHS patients in different severity groups and corresponding zDFDr (mean ± standard error).

Group	Number of subjects	zDFDr
Simple snoring	7	0.490 ± 0.024
Mild OSAHS	20	0.501 ± 0.036
Moderate OSAHS	13	0.513 ± 0.024
Severe OSAHS	40	0.541 ± 0.044

disturbance of FD sequence, namely the zero-crossing rate, is utilized here. And the correlation between zero-crossing rate of detrended fractal dimension (zDFD) and Apnea and Hypopnea Index is shown in Fig. 5. The correlation coefficient between zDFD and AHI is 0.50.

5. Optimization of FD based index for OSAHS assessment

As demonstrated above, zDFD is correlated with AHI, but the correlation needs to be improved for practical purpose. Therefore, we test the correlation between a combined index of zDFD and BMI, called zDFDr, and AHI. Basically, the zDFD index is weighted with the BMI index by the following formula:

$$zDFD_r = zDFD \times e^{\left[0.6\times \frac{(BMI-BMI^*)}{BMI^*}\right]} \tag{3}$$

where BMI stands for the body mass index of each subject, and BMI*, a BMI value of 20 kg/m^2 was used as a reference point. Significantly stronger correlation between zDFDr and AHI is observed (see Fig. 7).

One-way Analysis of Variance (ANOVA) is employed after the variance homogeneity test confirms that variances in different groups are homogenic. The result shown in Fig. 6 and Table 4, demonstrated that the difference of zDFDr in different severity groups is of statistical significance ($p < 0.001$).The subsequent post hoc procedure with S-N-K statistic reveals that

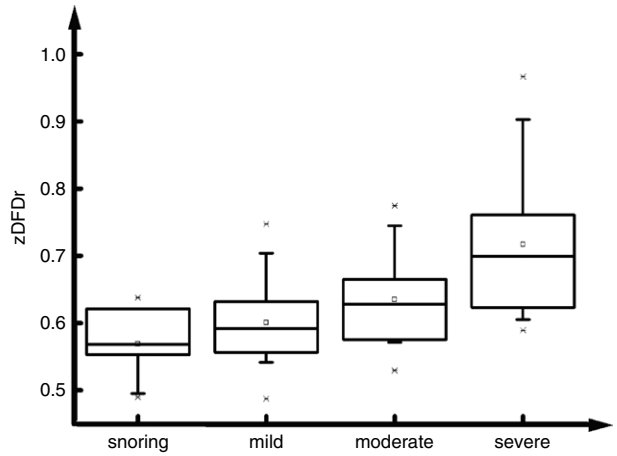

Fig. 6. Box-plotting of zDFDr in OSAHS population with different severities.

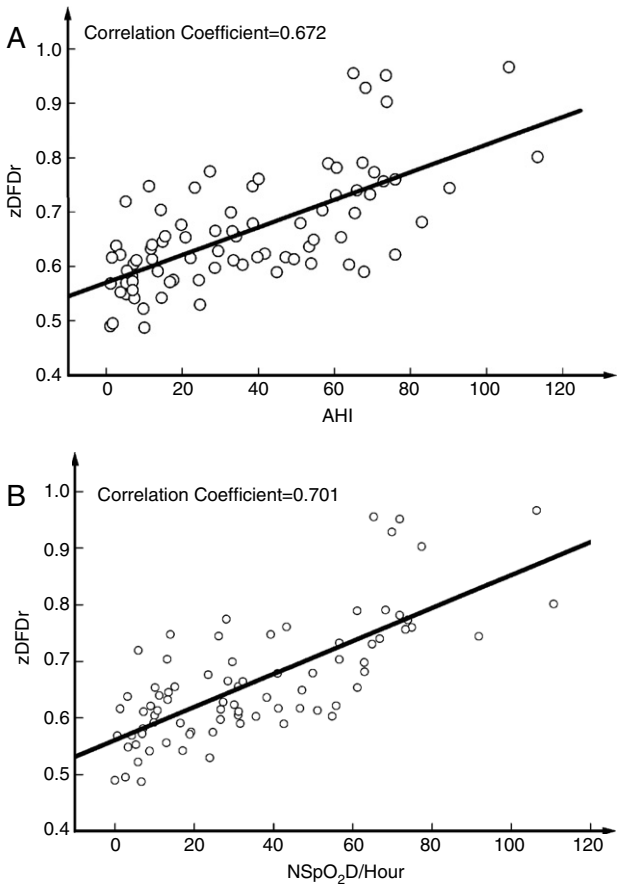

Fig. 7. Correlation between zDFDr and AHI. Note that the relatively strong correlation between zDFDr and AHI/ $NSpO_2D$/hour, is not solely caused by BMI, as in this study the correlation coefficient between BMI and AHI is 0.53, which is in accordance with previous reports [19–21]. (A) Correlation between zDFDr and AHI (B) Correlation between zDFDr and $NSpO_2D$/hour.

differences of statistical significance lie between snoring group and severe group ($p = 0.010$), and between mild group and severe group ($p = 0.002$) (significance level of 0.05).

Analysis of variance analysis (ANOVA) was employed to compare the mean zDFDr among groups with different OSAHS severities (simple snoring, mild, moderate and severe groups) after the homogeneity of variance and the distributional normality were verified by the Bartlett test and the Kolmogorov–Smirnov test, respectively. The Student–Newman–Keuls test, a typical post hoc procedure, was utilized to determine whether or not there is statistical significance in zDFDr between

two different groups with different levels of severities. Furthermore, the Pearson correlation analysis was used to evaluate the correlation coefficient between AHI and zDFDr. All the statistical analysis was carried out by SPSS 13.0 for Windows.

After the distribution normality is confirmed by the Kolmogorov–Smirnov test for normality, the correlation between BMI-revised zDFDr and AHI is analyzed by the Pearson correlation analysis, the correlation coefficient of which is 0.672. The correlation between zDFDr and another important index to describe the severity of OSAHS, hourly number of blood oxygen saturation (SpO_2) decreases greater than 4% ($NSpO_2D$/hour), is also analyzed after the procedure of the Kolmogorov–Smirnov test for normality. The correlation coefficient of which is 0.701. (The correlation coefficient between AHI and BMI in subjects studied here is 0.53, which is in accordance with previous reports [19–21], based on the correlation coefficient between AHI and BMI, and the correlation coefficient between AHI and zDFDr, it is obvious that the correlation between BMI and AHI is listed here to demonstrate that the relatively strong correlation between zDFDr and AHI is not solely dependent on BMI, i.e. part of the contribution of zDFDr to OSAHS severity is not included in BMI.)

6. Discussions and conclusions

In this study, the FD sequences of overnight EEG were evaluated. Our results are consistent with previous dynamical analysis of EEG [22,13], the FD of overnight EEG was highly correlated to different sleep stages (as illustrated in Figs. 2 and 3).

Our results showed that for the normal sleep epochs, fractal dimensions decreased significantly as the sleep goes into deeper stages. This result is consistent with previous findings using correlation dimensions and the principal Lyapunov exponent. Our results indicated that, as sleep becomes deeper, the brain function becomes less activated and the complexity of brain activity characterized by fractal dimension of EEG signal was reduced. Moreover, the smoothed FD sequences could reveal the sleep macro-architecture. (as illustrated in Fig. 3). With fractal analysis, sleep EEG as a typical non-stationary physiological signal could provide more thorough understanding of the shift in sleep stages.

Compared with normal sleep, the value of FD_event was significantly higher than its corresponding FD_normal during deep sleep stages (as demonstrated in Table 3). It is known that as the sleep stage becomes deeper, the dynamics of brain are likely to be less complex and normal EEG pattern is likely to become more of Brownian noise; when external stimuli such as respiratory events happen, the brain tends to react and in a transient moment falls into disordered state, then the reflected EEG pattern is characterized by higher FD exponent values. From this point of view we could explain the significance between the FD_event and FD_value and the relatively large variance of FD_event.

As for the REM stage, we obtained the result that FD_event was significantly lower than its corresponding FD_normal, a different phenomena from other stages. It might be that the respiratory center had been suppressed by neurohumoral regulation, because neuron responses to chemical stimuli are different during REM compared to those during other sleep stages [23].

It has been reported that OSAHS presents significantly disturbed sleep architecture [24] due to hypoxia, hypercapnia or possible acidosis and etc. Thus, zero-crossing rate in EEG-derived FD sequences may serve as a biomarker of OSAHS-derived sleep disturbance, namely, the extent of disturbance to the normal sleep macro-architecture. The proposed novel zDFDr measure showed statistic significant increase in severe group. Possible explanation is that the respiratory episodes and body movements increase with the severity of OSAHS, which may contribute to the sleep fragmentation and the degree of EEG disturbance [25] and increasing zDFDr.

This retrospective study was performed on an existing database collected under typical clinical settings, therefore, there are some limitations for our analysis. For example, it is desirable to study the correlation between FD-derived zDFDr and other descriptors of sleep quality, such as the Epworth Sleepiness Scale (ESS), an index for daytime sleepiness. Unfortunately, in our database, only a few patients whose Epworth Sleepiness Scale (ESS) are available. Furthermore, there are no non-snorers in this database. The correlation between ESS and FD-derived zDFDr, as well as evaluating zDFDr for non-snorers will all be useful information for future prospective study. In addition, comparing zDFDr of patients before and after CPAP (continuous positive airway pressure) therapy will also be very informative and should be included in the design of study protocol.

Currently, AHI is the standard parameter for evaluating the severity of OSAHS. But increasing number of studies have shown poor correlation between AHI and some of the patient's symptoms such as sleepiness [26]. Identifying a better index of the severity of OSAHS is of great clinical importance. The proposed novel zDFDr is strongly associated with traditional measures of OSAHS severity (AHI and rate of SpO_2 decreases). Furthermore, it has been a consensus that the body weight has positive correlation with the severity of OSAHS. However, the correlation between the severity of OSAHS and BMI alone is not very strong (correlation coefficient $= 0.50$). The proposed index of zDFDr incorporates the component of BMI into its calculation, and significantly improves its correlation to OSAHS severity (as demonstrated in Figs. 6 and 7). Therefore, zDFDr may be a potential integrative index that utilizes the complementary aspect of two completely different physiologic measures, namely disturbance of sleep and body weight. In addition, the novel zDFDr mainly described the disturbance of EEG, which may have closer relationship with the perturbation of cerebral function than AHI. Further evaluation is needed to study the association between the zDFDr index and other clinical information, such as the severity of symptoms, physiological function, neuropsychological test, the involvement of target organs and prognosis.

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