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Scaling Exponents of EEG Are Related to the Temporal Process of the Therapeutic Hypothermia following Ischemic Brain Injury

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Abstract— **Several markers based on quantitative electroencephalogram (qEEG) analysis have been associated with the neuroprotective effects of therapeutic hypothermia on hypoxic-ischemic encephalopathy (HIE) after cardiac arrest (CA). Nevertheless, the makers by far have not been linked to the temporal process of the ischemic neuronal death. In this study, we investigated the long-range correlations in EEG power in θ and α bands before and after CA by detrended fluctuation analysis (DFA). The scaling components by DFA showed that the short-term scaling exponent in α band (i.e. γ_1^{α}) was well correlated with recovery of brain injury during the latent phase. While the short-term scaling exponent in θ band (i.e. γ_1^{θ}) and the long-term scaling exponent in α band (i.e. γ_2^{α}) were correlated with the delayed neuronal death after CA. Our preliminary results showed that the long-range correlations in θ and α bands could be related the detail temporal process of therapeutic hypothermia.**

I. INTRODUCTION

Annually, there are 294,851 emergency medical services (EMS)-treated out-of-hospital cardiac arrests (CAs) in the United States [1]. Among these patients, few are able to rehabilitate without residual neurologic deficits. Most of them would live with disabilities or die due to the subsequent hypoxic-ischemic encephalopathy (HIE). Neuroscientists and neurologists have been working on neurprotection following global ischemic brain injury, and clinical trials [2][3] have demonstrated that therapeutic hypothermia has beneficial effects on neurologic outcome after CA. Jia *et al.* [4] also found that the rats treated with therapeutic hypothermia would have better neurological deficit score (NDS) compared with the normothermic controls.

It is now well established that HIE after CA is an evolving process, which mainly consists of three sequential phases: a) primary neuron death stage when many neurons may die within 1 hr after the hypoxic-ischemic (HI) onset; b) latent phase when some neurons recover at least partially from primary insults in 6 hrs ; and c) delayed neuronal death stage when neurons die 6∼15 hours or even days later after primary insults [4]. Both experimental and clinical observations indicated that cooling could suppress a number of pathways leading to secondary deterioration [4][5], and timing and duration of cooling are crucial for the therapeutic effects of post-CA hypothermia [4]. Although several experiments [4][6][7] have studied the therapeutic time window of delayed hypothermia and suggested that hypothermia should be initiated as soon as possible before the delayed neuronal death for a sufficient duration, the optimal duration of cooling is still not well justified due to the high variations in subjects. These experiments [3][6][7] usually evaluated the neurologic outcome either by histological or by functional assessments a few days or up to years after HI insults.

Recently, some quantitative electroencephalogram (qEEG) based markers [8][9] were proposed for studying brain activities during the early hours following CA. These markers measured at 4∼6 hrs after return of spontaneous circulation (ROSC) showed strong correlations with the 72 hrs NDS. However, the results, either by information quantity (IQ) [8] or by complexity measure of EEG signals [9], were not directly related to the temporal process of the ischemic neuronal injury. On the other hand, a marker related to the temporal process of neuron death definitely would be a useful reference for the temperature administration in therapeutic hypothermia.

In this paper, we propose a new nonlinear qEEG measure based on the long-range correlations in sub-band EEG signals by detrended fluctuation analysis (DFA), to study the temporal processing of brain injury and therapeutic hypothermia following CA.

II. EXPERIMENT

The EEG recordings were obtained from rodent experiments for studying the neuroprotection of therapeutic hypothermia from hypoxic-ischemic brain injury following CA [8]. The experimental protocols of brain injury were approved by the animal care and usage committee of the Johns Hopkins Medicine Institutions. Twenty adult male Wistar rats (normothermia/hypothermia=10/10, weighting 350±25g) were used in this study. Details of the animal handling procedures of the experiments were reported in Ref. [8]. Briefly:

(a). Anesthesia was induced with 4% halothane with 50:50% nitrous oxide:oxygen, and body temperature of 37.0 ± 0.5°C was maintained;
(b). 5 min EEG was recorded as baseline;
(c). 5 min washout was induced to remove the effect of halothane;

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(d). Asphyxia of 7 min was induced by stopping oxygen supply;

(e). Cardiopulmonary resuscitation (CPR) was performed until ROSC;

(f). Hypothermia was undertaken by external cooling in hypothermia group. The rectal temperatures were reduced to 33°C within 15 minutes and were maintained between 32°C and 34°C for the following 12 hrs. The animals were rewarmed 13 hrs after ROSC to the target temperature (37°C) within 2 hrs. In normothermia group, the temperatures were maintained between 36.5°C and 37.5°C throughout the experiments.

Two-channel EEGs were recorded continuously throughout the experiment from right and left parietal areas using DI700 Windaq system (DATAQ Instruments Inc., OH., USA). The sampling frequency (F_s) was 977Hz for 4 channels. NDS was also evaluated by an independent examiner as the neurological outcome. Whereafter, θ and α waves were analyzed since these two rhythms were known to be closely related to neurological outcome after CA [10][11].

III. Methods

A. Calculating the sub-band power series by wavelet packet decomposition

Let $\{S(i), i = 1,2,\cdots,N\}$ ($N = 73,275$, i.e. 5 min data in this study) denote a segment of raw EEG. To analyze the temporal evolution of sub-band power of EEG, we applied wavelet packet decomposition (WPDEC) to the raw EEG in each sliding window. WPDEC is not only able to remove high frequency noises but also decompose the signal into sub-bands corresponding to the standard clinical rhythms (e.g. δ, θ, α and β waves). The raw EEG segment will then be analyzed with sliding windows $\{S_n(i)\}$:

$$S_n(i) = \{S(i), i = 1+n\triangle, 2+n\triangle, \cdots, w+n\triangle\} \quad (1)$$

where w is the size of sliding window, $\triangle$ is the sliding step and $n = 0,1,2,\cdots,[(N-w)/\triangle]+1$ ($[x]$ denotes the integer part of x). Then, $S_n(i)$ is decomposed with WPDEC at depth r:

$$[C^1, C^2, \cdots, C^{N_r}] = WPDEC_r(S_n(i)) \quad (2)$$

where $N_r = 2^r$ and $[C^1, C^2, \cdots, C^{N_r}]$ denote the coefficients of the terminal nodes of the wavelet packet tree in ascending index order. Thus, the bandwidth of each node was $F_s/(2N_r)$. Finally, the power in the standard clinical bands in $S_n(i)$ can be calculated from WPDEC coefficients as:

$$P_B(n) = \frac{1}{w}\sum_{j=l}^{m}\sum_{k=1}^{n_j}(C_k^j)^2 \quad (3)$$

where n_j is the number of the coefficients contained in the j-th node, and $j = l,\cdots,m$ denotes the indexes of nodes for θ or α waves in this study.

B. Detrended fluctuation analysis (DFA)

DFA was first proposed by Peng *et al.* to detect the long-range correlations in a nonstationary time series [12]. The details of DFA have been reported in Ref. [12]. A power-law relation will be found between the fluctuation $F(s)$ and the time scale s, if a long-range correlation exists in the series:

$$F(s) \propto s^{\gamma} \quad (4)$$

In particular, scaling exponent $\gamma = 0.5$ corresponds to a white noise. $0.5 < \gamma \leq 1.0$ indicates the existence of long-range correlation that a large power value is more likely followed by a large power value and vice versa. $0 < \gamma < 0.5$ indicates persistent long-range anti-correlations that the power is more likely to alternate between large and small values. In particular, $\gamma = 1$ corresponds to a $1/f$ noise, and $\gamma = 1.5$ indicates a Brownian noise [12]. The smoother the series are, the larger the scaling exponent (γ) will be.

IV. Results

Ten 5-min segments of raw EEG were chosen from each rat, including a baseline segment (denoted as 0h hereafter) and the segments that were selected after 1, 2, 3, 4, 5, 6, 24, 48 or 72 hrs of ROSC (denoted as 1h, 2h, 3h, 4h, 5h, 6h, 24h, 48h and 72h hereafter, respectively). In hypothermia group, the segment for 1h was corresponding to the start of hypothermia. The following parameters were used in this study: 1) $w = 1024$ samples ($\approx 4.19sec$), to meet both the stationarity assumption of EEG and the amount of data for appropriately calculating subband energy; 2) $r = 8$; 3) $l = 9, m = 18$ for θ band ($4 \sim 8.5Hz$); 4) $l = 19, m = 29$ for α band ($9 \sim 14Hz$); and 5) $\triangle = 48$ samples ($\approx 0.2sec$), approximately equal to the cycle of the lowest frequency component of two analyzed subbands. The subbands were classified according to the Ref. [13]. A representative epoch of raw EEG and its corresponding power series in θ and α bands were shown in Fig.1. The corresponding DFA results were also presented in the bottom panels. Most plots of

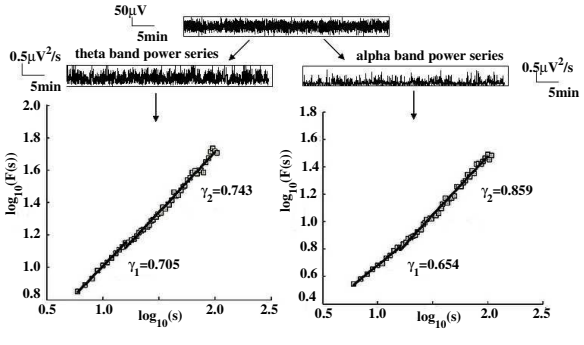

Fig. 1. Representative raw EEG data, its corresponding θ and α band power series, and the DFA results of θ and α band power series. The EEG was recorded at 1 hour after ROSC for 5 min.

$log_{10}(F(s)) \sim log_{10}(s)$ showed clear crossovers. Therefore, both short-term scaling (i.e. γ_1) and the long-term scaling exponents (i.e. γ_2) were calculated for the smaller scale and the larger scale, respectively. For the convenience of description, we denote γ_1 (γ_2) in θ band as γ_1^θ (γ_2^θ) and γ_1 (γ_2) in α band as γ_1^α (γ_2^α). By t-test, we found that γ_2^α was significantly greater than γ_1^α in each epoch ($P < 0.00001$), and γ_2^θ was also significantly greater than γ_1^θ in all epochs

TABLE I

STATISTICS OF SCALING EXPONENTS (MEAN ± SEM) OF THE θ BAND POWER SERIES. t-TESTS BETWEEN THE GROUPS ARE ALSO LISTED. THE SIGNIFICANT CHANGE OF SCALING EXPONENTS AFTER ROSC ARE DESIGNATED AS WELL

time(h)	γ_1^θ			γ_2^θ		
	Normothermia	Hypothermia	t-test (p)	Normothermia	Hypothermia	t-test (p)
0	$0.569 \pm 0.006^{\dagger}$	$0.591 \pm 0.025^{\dagger}$	0.787	$0.660 \pm 0.016^{\dagger}$	$0.639 \pm 0.014^{\dagger}$	0.367
1	$0.747 \pm 0.041^{*}$	$0.690 \pm 0.037^{*}$	0.156	$0.723 \pm 0.029^{*}$	$0.699 \pm 0.019^{*}$	0.242
2	$0.669 \pm 0.033^{*}$	0.653 ± 0.031	0.363	0.693 ± 0.023	0.678 ± 0.022	0.320
3	$0.625 \pm 0.034^{\dagger}$	$0.611 \pm 0.022^{\dagger}$	0.368	0.697 ± 0.021	0.685 ± 0.019	0.334
4	$0.585 \pm 0.027^{\dagger}$	$0.613 \pm 0.022^{\dagger}$	0.789	0.712 ± 0.020	0.689 ± 0.021	0.450
5	$0.612 \pm 0.017^{*\dagger}$	$0.623 \pm 0.017^{\dagger}$	0.672	0.695 ± 0.019	0.705 ± 0.017	0.479
6	$0.605 \pm 0.018^{*\dagger}$	$0.605 \pm 0.016^{\dagger}$	0.512	$0.716 \pm 0.023^{*}$	$0.705 \pm 0.019^{*}$	0.367
24	$0.655 \pm 0.021^{*\dagger}$	$0.615 \pm 0.011^{\dagger}$	***0.045***	$0.732 \pm 0.016^{*}$	$0.732 \pm 0.018^{*}$	0.489
48	$0.631 \pm 0.011^{*\dagger}$	$0.611 \pm 0.016^{\dagger}$	0.161	$0.702 \pm 0.011^{*}$	$0.715 \pm 0.013^{*}$	0.755
72	$0.637 \pm 0.012^{*\dagger}$	$0.618 \pm 0.020^{\dagger}$	0.218	$0.745 \pm 0.010^{*}$	$0.728 \pm 0.020^{*}$	0.244

* Significance of differences compared with 0h, $P < 0.05$; † Significance of differences compared with 1h, $P < 0.05$;

($P < 0.001$) except at 1h and 2h. The statistics of scaling exponents in both groups are listed in Table I and Table II. Here are the main findings:

1) *Primary cell death Stage (∼1h):* All the scaling exponents increased in this stage. Each scaling exponent at 1h in both groups was significantly greater than that at 0h.
2) *Latent phase (2h∼4h):* Some scaling exponents transiently recovered during this stage. In hypothermia group, γ_1^α and γ_1^θ returned quickly after hypothermia was initiated. After 2h to 4h, γ_1^α and γ_1^θ already recovered to the comparable level of 0h ($P > 0.1$). In contrast, γ_1^θ at 2h in normothermia group was still significantly greater than that at 0h ($P = 0.016$), while γ_1^α didn't return to baseline level until 4h in normothermia group. Besides, both γ_1^α at 2h and 3h and γ_2^α at 2h in normothermia group were significantly greater than those in hypothermia group (γ_1^α: $P < 0.025$; γ_2^α: $P = 0.035$).
3) *Delayed neuronal death stage (5h∼6h later):* A few scaling exponents showed a 2nd peak in this stage. In normothermia group, however, γ_1^θ at 5h increased and was significantly larger than that at 0h again ($P = 0.036$), which didn't return to its baseline level later. While γ_1^θ in hypothermia group didn't show any significant differences compared with that at 0h in this stage. Also, γ_2^α at 5h in normothermia group increased to a level similar to that at 1h and 2h after a significant decrease at 3h and 4h. In contrast, we noticed that such an increase of γ_2^α in hypothermia group delayed and appeared at 6h, and γ_2^α at 5h in hypothermia group tended to be smaller than that in normothermia group ($P = 0.079$). It was shown that both γ_1^θ and γ_2^α at 24h in normothermia were significantly greater than those in hypothermia.

V. DISCUSSIONS AND CONCLUSIONS

It has been demonstrated that the long-range correlations existed in both broad band EEG [14] and in sub-band oscillations [15]. This study specifically focused on the long-range correlations in the θ and α bands since these two rhythms were known to be closely related to neurological outcome after CA [10][11]. Our results confirmed the long-range correlations in the θ and α band power series with scaling exponents between 0.5 and 1.0. Meanwhile, we found these scaling exponents could provided more temporal details related to the neuroprotective effects of therapeutic hypothermia during the delayed neuronal death stage than the previous markers [8][9].

A. Changes of long-range correlations following the primary neuronal death

By analyzing the scale components, we found that ischemia significantly influenced the brain activities, which was consistent with the previous results [8][9]. In both normothermia and hypothermia groups, the scaling exponent at 1h was significantly greater than that at 0h, indicating the weakening fluctuations in these two sub-band power series after CA. These scaling exponents were significantly correlated with the temporal process of ischemic neuronal injury after CA.

B. Changes of long-range correlations in the latent phase

Previous work [8][9] had demonstrated that those qEEG measures during the latent phase returned faster in hypothermia group than those in normothermia group. Similarly, γ_1^α and γ_1^θ by DFA in this study decreased more rapidly in hypothermia group during the latent phase stage, e.g. γ_1^α at 2h and 3h in hypothermia group were significantly smaller than those in normothermia group. Besides, γ_2^α at 2h was significantly smaller in hypothermia group. Our results confirmed that therapeutic hypothermia significantly improved the transient recovery of neurophysiological activities of the brain during the latent phase. Therefore, as some clinical and experimental researches [4][6][7] suggested, therapeutic hypothermia should be initiated as soon as possible to get better outcome after CA.

C. Changes of long-range correlations in the delayed neuronal death stage

The cooling duration is another critical parameter in hypothermic treatments. Previous studies [4][16] on newborn infants with HI showed that the delayed neuronal death usually occurred 6 to 15 hours later after primary insults

TABLE II

STATISTICS OF SCALING EXPONENTS (MEAN ± SEM) OF THE α BAND POWER SERIES. t-TESTS BETWEEN THE GROUPS ARE ALSO LISTED. THE SIGNIFICANT CHANGE OF SCALING EXPONENTS AFTER ROSC ARE DESIGNATED AS WELL

time(h)	γ_1^α			γ_2^α		
	Normothermia	Hypothermia	t-test (p)	Normothermia	Hypothermia	t-test (p)
0	$0.588 \pm 0.007^{\dagger}$	$0.575 \pm 0.014^{\dagger}$	0.536	$0.641 \pm 0.007^{\dagger}$	$0.633 \pm 0.014^{\dagger}$	0.617
1	$0.712 \pm 0.024^{*}$	$0.676 \pm 0.021^{*}$	0.133	$0.856 \pm 0.033^{*}$	$0.789 \pm 0.023^{*}$	0.064
2	$0.692 \pm 0.029^{*}$	$0.621 \pm 0.017^{\dagger}$	***0.019***	$0.799 \pm 0.027^{*}$	$0.725 \pm 0.028^{*}$	***0.035***
3	$0.630 \pm 0.015^{*\dagger}$	$0.592 \pm 0.011^{\dagger}$	***0.025***	$0.742 \pm 0.022^{*\dagger}$	$0.702 \pm 0.023^{*\dagger}$	0.117
4	$0.582 \pm 0.011^{\dagger}$	$0.592 \pm 0.010^{\dagger}$	0.761	$0.719 \pm 0.017^{*\dagger}$	$0.693 \pm 0.021^{*\dagger}$	0.175
5	$0.617 \pm 0.015^{\dagger}$	$0.609 \pm 0.012^{\dagger}$	0.338	$0.759 \pm 0.025^{*}$	$0.706 \pm 0.025^{*\dagger}$	0.079
6	$0.603 \pm 0.013^{\dagger}$	$0.590 \pm 0.011^{\dagger}$	0.219	$0.761 \pm 0.030^{*}$	$0.727 \pm 0.030^{*}$	0.219
24	$0.606 \pm 0.008^{\dagger}$	$0.595 \pm 0.005^{\dagger}$	0.119	$0.727 \pm 0.016^{*\dagger}$	$0.672 \pm 0.010^{*\dagger}$	***0.003***
48	$0.603 \pm 0.004^{\dagger}$	$0.587 \pm 0.004^{\dagger}$	0.109	$0.706 \pm 0.010^{*\dagger}$	$0.708 \pm 0.015^{*\dagger}$	0.695
72	$0.591 \pm 0.004^{\dagger}$	$0.598 \pm 0.008^{\dagger}$	0.768	$0.698 \pm 0.011^{*\dagger}$	$0.703 \pm 0.013^{*\dagger}$	0.803

* Significance of differences compared with 0h, $P < 0.05$; † Significance of differences compared with 1h, $P < 0.05$;

and even lasted for about 3 days. Though prolonged cooling could reduce the delayed neuronal death, it would also increase the risks owing to its side effects [4]. Researches on brain activities during the delayed neuronal death stage would be helpful to determine how long the cooling should be maintained in treatments.

However, markers obtained in previous work [8][9] provided little information on the brain activities during the delayed neuronal death stage. In contrast, we found that γ_1^θ at 5h in normothermia group became significantly larger than that at 0h again and didn't return to the baseline level later; while in hypothermia group, γ_1^θ after 4h didn't show any significant differences compared with that at 0h. Moreover, we found that the increase of γ_2^α started later in hypothermia group (at 6h) than that in normothermia group (at 5h). The second peaks for γ_2^α in the two groups deferred, and meanwhile, γ_1^θ and γ_2^α at 24h in hypothermia group were significantly smaller than those in normothermia group, which might implied that the the second peaks for γ_1^θ and γ_2^α be likely corresponding to the delayed neuronal death in rats following the HI after CA.

On conclusion, though could not be directly transferred to humans, our results demonstrated that long-range correlation analysis by DFA revealed more details of temporal process corresponding to ischemic neuronal death following CA. The scaling exponents in therapeutic hypothermia group recovered more faster than the normothermia group during the latent phase. γ_1^α was well correlated with early recovery of brain dynamics during the latent phase; while recovery of γ_1^θ and γ_2^α were well correlated with time courses for delayed neuronal death. Thus, long-range correlations in θ and α band power series would be helpful for understanding the temporal process of ischemic neuronal injury.

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