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ORIGINAL ARTICLE

Frontal Alpha EEG Asymmetry Variation of Depression Patients Assessed by Entropy Measures and Lemple–Ziv Complexity

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Abstract

Purpose As depression has been a major contributor to the global disease burden, objective and effective computer-aided diagnosis has become an urgent problem. This study aims to assess the frontal asymmetry variation of alpha electroencephalography (EEG) in different severity depression patients and to find promising biomarkers for future depression recognition.

Methods Three-channel EEG signals from 69 depression patients (divided into three groups according to illness severity) and 14 healthy subjects were collected. Except for cross-sample entropy (CSEn), two new asymmetry indexes (Asy_SEn and Asy_LZC) based on complexity measures were proposed to quantify the difference among the four groups. One-way ANOVA was used to test the difference among all four groups, followed by the group *t*-test to test the difference between each two groups.

Results All indexes show significantly increased frontal alpha asymmetry in depressive groups compared with the healthy group, and the asymmetry keeps increasing as the depression deepens. The Asy_LZC value of the confirmed depression group (0.0015 ± 0.0008) is substantially higher than the other three groups (-0.0010 ± 0.0008, -0.0006 ± 0.0008, and -0.0007 ± 0.0006). And the Asy_SEn value of the healthy group (-0.0023 ± 0.0007) is significantly lower than the two depressive groups (0.0001 ± 0.0005 and 0.0007 ± 0.0007). All healthy CSEn between each two channels is considerably lower than depressive groups with $p < 0.01$.

Conclusion This study confirms the increased frontal alpha asymmetry in depression patients and suggests that two new indexes could be promising biomarkers in future clinical depression detection.

Keywords Sample entropy · Cross-sample entropy · Lemple–Ziv complexity · Frontal asymmetry · Depression

1 Introduction

As a common mental disorder, there are more than 322 million people suffering from depression [1]. Unfortunately, fewer than half of the depression patients (even fewer than 10% in some counties) can receive effective treatments, due to lack of source and trained health-care providers as well as inaccurate assessment [2]. A computer-aided diagnosis system could help to solve those obstacles and replenish the objective diagnostic method to nowadays' questionnaire-based diagnosis. Therefore, the discovery of objective and effective biomarkers in depression turns out to be an urgent and meaningful exploration. Besides, accurate assessment of depression by physiological signals can also suggest a further understanding of the pathogenesis.

It is suggested by a growing number of studies that the resting frontal asymmetry (usually defined as the difference of alpha-band power between the right frontal site and left frontal site when the subject is in a resting state) is reliable in the assessment of clinical depression patients [3–6], i.e. Beeney presented that individuals with major depressive disorder (MDD) evidenced greater resting asymmetry at the pre-task baseline. And works by Stewart indicated that

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current source density—referenced frontal electroencephalography (EEG) asymmetry was an endophenotype related to risk for depression in both women and men, with lifetime MDD participants displaying less relative left frontal activity than never-depressed participants [5]. However, some other studies had different conclusions [7, 8], i.e. Gold found that depressive frontal alpha asymmetry was close to the general population, and correlations with psychiatric tests were mostly small and non-significant [9], while Kaiser suggested that the frontal alpha symmetry was more related with age rather than depression or anxiety [10]. It is worth noting that most previous studies took alpha band power of frontal EEG as an assessing parameter for the frontal asymmetry, i.e. the difference of the alpha power natural logarithm between site F4 and F3 (lnF4 – lnF3) [11]. However, the simple linear methods may not be generally suitable to exhibit the complex dynamical variations in EEG signals which record the nonlinear, non-stationary, and chaotic brain activities [12, 13]. Therefore, it is necessary to re-examine the validity of frontal alpha asymmetry in depression discrimination by employing nonlinear methods.

In previous studies, entropy measures such as sample entropy (SEn) and approximate entropy have been proved widely validity in the depression EEG evaluation, which are used to assess the comlexity of time series [12, 14]. Acharya suggested more EEG variability in the healthy group by finding significantly higher sample entropy in healthy controls compared to the depression patients [12]. Significantly higher sample entropy and approximate entropy were also found by Faust in healthy controls, which indicated less complexity and more predictability in depression patients [14]. Considering the algorithm advantage compared with approximate entropy [15], SEn was selected as an index in frontal asymmetry assessment in this study. Except for entropy measures, more nonlinear measures such as Lemple–Ziv Complexity (LZC), Kolmogorov complexity, and Higuchi's fractal dimension have also been employed in depression EEG analysis [7, 16]. Among the above multiple measurements, LZC as another method in complexity calculation of the finite length series is especially popular and recommended as it is nonparametric, model-independent, and easily calculated [17]. Finally, LZC and SEn were both employed in this study, as a first exploration of depressive frontal asymmetry analysis with the perspective of nonlinear complexity. Refer to the definition of common frontal asymmetry, two new indexes, asymmetry measure based on LZC (Asy_LZC) and SEn (Asy_SEn) were proposed to assess the frontal asymmetry variation of depressive alpha EEG. Besides, as a generalized algorithm of SEn, cross sample entropy (CSEn) evaluates the asynchronous degree of two series, which was also employed in this study to assess the frontal asymmetry in another way. This is also the first try in depressive brain analysis.

This study aims to evaluate the frontal alpha asymmetry variation of depression patients by nonlinear complexity methods, therefore to suggest meaningful biomarkers in depression recognition. Two new indexes Asy_LZC and Asy_SEn were proposed to evaluate the variation of frontal alpha asymmetry in different severity depression patients, and CSEn was also employed to assess the asymmetry from the view of synchronization.

2 Materials and Methods

2.1 Subjects and Data Acquisition

EEG signals were collected from 69 depression patients and 14 healthy subjects. All patients were recruited from the Second Affiliated Hospital of Jining Medical College, China between October 2017 and June 2018. All patients were recruited from inpatients with a current ICD-10 criteria diagnosis of depression (International Classification of Diseases, 10th Edition) by at least two staff psychiatrists of the hospital. All patients were assessed by the 17-item Hamilton Depression Rating Scale (HDRS) and then were divided into three groups according to the depression rating scale [18]: Non-De Group, including 15 patients with 0–7 scores, for whom non-depressive state were concluded; Mil-De Group, including 34 patients with 8–17 scores, for whom mild depression were suggested; and Con-De Group, including 20 patients with scores over 17, for whom depression were confirmed. Fourteen healthy subjects were recruited from Shandong University, who had no psychiatric disorders in the past. Sociodemographic features and HDRS scores of all four groups are shown in Table 1.

According to the international 10–20 systems, 3 channels EEG signals including Fp1, Fz, and Fp2 were recorded with a 1000 Hz sample rate by using RM6280C, a multichannel physiological acquisition system (Chengdu Instrument Factory, Sichuan, China). Figure 1 shows the poles' distribution in the international 10–20 systems and the 3 poles used in this study. The sensitive parameter was set as 100 μV, time constant was 0.2 s. The signal recording was turned on and lasted for at least 5.5 min after all signals were stable. More details of the data acquisition environment and matters needing attention could refer to our previous study [19].

2.2 Data Preprocessing and Feature Extraction

2.2.1 Data Preprocessing

In data preprocessing, the wavelet threshold filter was used firstly to remove artifacts caused by electrooculograms. Since the Wavelet basis function of sym3 is most similar to the electrooculogram waveform, this study adopted

Table 1 Sociodemographic features and HDRS scores of four groups

	Group			
	Health	Depression patients		
		Non-De	Mil-De	Con-De
No.	14	15	34	20
Gender, male/female	9/5	5/10	10/24	6/14
Age (year)	45 ± 15	47 ± 16	42 ± 16	44 ± 15
Height (cm)	169.4 ± 9.2	162.9 ± 6.5	163.9 ± 8.1	165.7 ± 7.6
Weight (kg)	71.7 ± 11.7	66.7 ± 10.2	65.2 ± 12.2	67.8 ± 14.1
Education, ≤12 years/≥13 years	3/11	13/2	30/4	14/6
Occupation, yes/no	12/2	12/3	22/12	12/8
Right handedness, yes/no	13/1	14/1	34/0	17/3
Smoking, yes/no	3/11	3/12	3/31	3/17
Drinking, yes/no	0/14	1/14	0/34	0/20
Depression type, MDD/bipolar disorder	–	13/2	31/3	16/4
HDRS score	–	3.9 ± 2.5	13.2 ± 3.0	20.9 ± 2.2

Data are expressed as number or mean ± standard deviation (std)

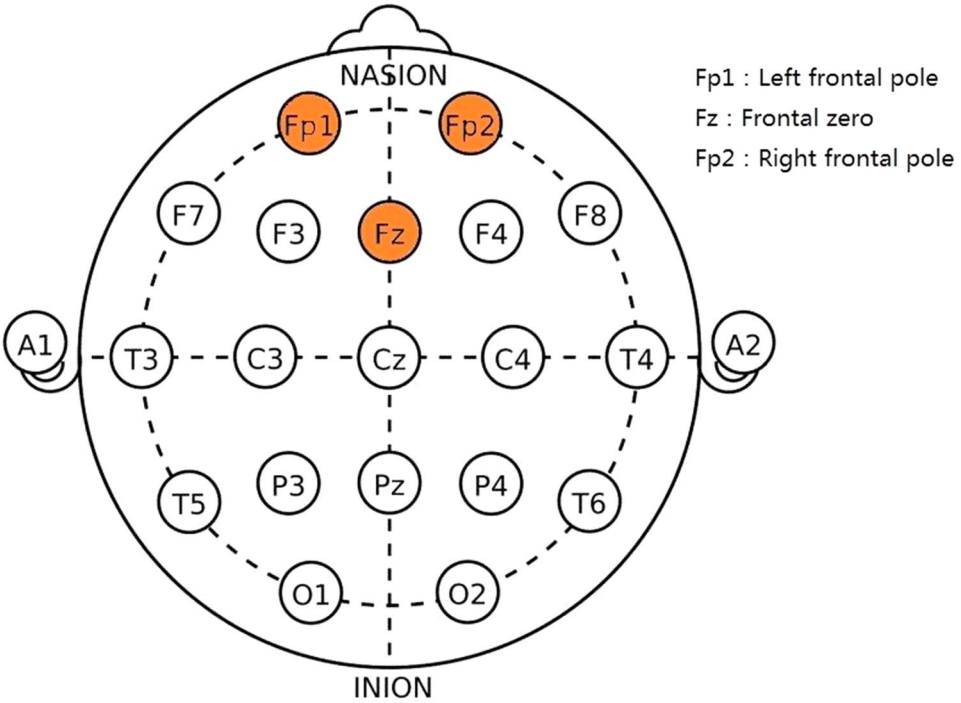

Fig. 1 Pole locations of the international 10–20 system. Three poles used in this study, Fp1, Fz, and Fp2 were marked in orange

the sym3 basis function of 6 layers to decompose and reconstruct the signal. Only third to sixth components were retained in reconstruction to collect signals between 3.65 and 50.875 Hz, by which electrooculogram and other low-frequency noises were removed and the sufficiently valid signal was acquired. To reduce the data volume and improve computing efficiency, the signal was resampling from 1000 to 200 Hz. After that, the Butterworth filter was used to extract the alpha band signal, which was in the 8–13 Hz frequency band. Finally, a 5-min clean alpha band signal was acquired. Figure 2 shows the 30 s example waveforms of alpha-band EEG signals from four different groups after preprocessing.

2.2.2 Feature Extraction

SEn is the negative natural logarithm of the conditional probability, therefore it measures the irregularity of the

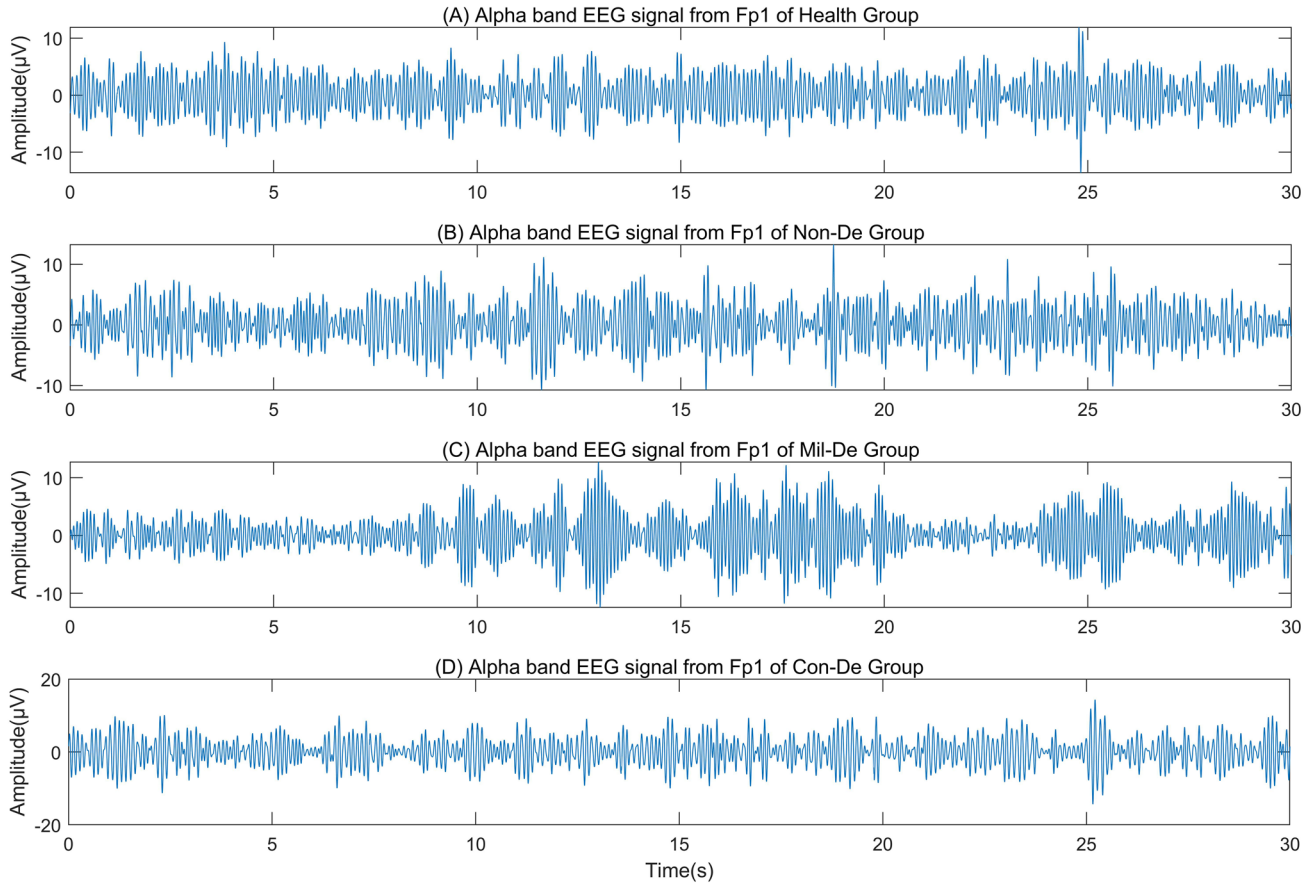

Fig. 2 Example waveforms of alpha-band EEG signals after preprocessing from four different groups. (**a**) Health Group; (**b**) Non-De Group; (**c**) Mil-De Group; (**d**) Con-De Group

data that is related to signal complexity [20]. And it is usually influenced by changes in temporal dynamics of time-series data rather than changes in the underlying amplitude of signals [11]. Larger SEn values indicate a higher complexity since it is negatively correlated with the overall regularity of a time series [19]. To be consistent with the usual EEG frontal asymmetry valuation, which is commonly calculated as the natural logarithm of alpha power at the right site minus the left site [11], the new index based on SEn is defined as

$$\text{Asy\_}SEn = SEn(Fp2) - SEn(Fp1), \tag{1}$$

where $SEn(Fp1)$ and $SEn(Fp2)$ are the sample entropy of frontal alpha EEG signals collected from frontal pole Fp1 and Fp2 respectively. And according to the previous studies, the SEn of N points time sequence could be calculated as

$$SEn(m, r, N) = -\ln \frac{A^{m+1}(r)}{A^m(r)}, \tag{2}$$

where $A^m(r)$ is the total number of template matches of length m, and the detailed calculation algorithm could be found in the literature [15]. m and r are embedding dimension and tolerance threshold respectively. According to a previous study [21] and comparisons of different parameters' combinations, $m=2$ and $r=0.1$ were employed.

As a parameter in the complexity calculation of a finite length series, LZC was proposed by Lemple and Ziv in 1976 [22]. LZC estimates the sequence complexity by counting the rate of new patterns appearing in a time series. In the calculation of LZC, the time series should be converted into a binary sequence $s(n)$ firstly as follows:

$$s(n) = \begin{cases} 0, & if\ x(n) \le m, \\ 1, & if\ x(n) > m, \end{cases} \tag{3}$$

where $x(n)$ is the original time series, and m is the threshold which is usually taken as the median value of $x(n)$ [23]. After that, the $s(n)$ is scanned from left to right to count the number of different patterns, and the complexity value $c(n)$ is increased every time a new pattern is encountered. The calculation algorithm of $c(n)$ is as follows. Assume S and Q denote subsequences of the sequence $s(n) = s_1, s_2, s_3, \ldots, s_n$, and $SQ\pi = SQ$ *deletes the last character of* SQ, while $v(SQ\pi)$

denotes the vocabulary of all subsequences of $SQ\pi$. Now suppose $S = s_1, s_2, \ldots, s_r$, $Q = s_{r+1}$, then $SQ\pi = s_1, s_2, \ldots, s_r$. If $Q \in v(SQ\pi)$, then Q is not a new pattern. In this case, $c(n)$ and S do not change and Q is renewed into s_{r+1}, s_{r+2}, and then judge if the new Q belongs to $v(SQ\pi)$ or not. Continue until $Q \notin v(SQ\pi)$, now $Q = s_{r+1}, s_{r+2}, \ldots, s_{r+i}$ is a new pattern and $c(n)$ is increased by one. After that, S is renewed to be $SQ = s_1, s_2, s_3, \ldots, s_{r+i}$, and the new $Q = s_{r+i+1}$. Repeat the above procedures until Q is the last character [24]. It has been proved that the upper bound of $c(n)$ is

$$\lim_{n\to\infty} c(n) = b(N) = \frac{N}{\log_a N}, \tag{4}$$

where a is the number of different patterns, and N is the length of the sequence. Finally, to avoid the variations caused by the sequence length, normalized LZC is defined as

$$LZC = \frac{c(N)}{b(N)}. \tag{5}$$

Therefore, the new asymmetry calculation based on LZC could be defined as

$$\text{Asy\_}LZC = LZC(Fp2) - LZC(Fp1), \tag{6}$$

where $LZC(Fp1)$ and $LZC(Fp2)$ are the Lemple–Ziv Complexity of frontal alpha EEG signals collected from frontal pole Fp1 and Fp2 respectively.

As SEn evaluates the irregularity of a data series, the generalized CSEn could reflect the asynchrony degree of two time series [25]. CSEn measures of each two channels, which are CSEn12 (CSEn of signals from channels Fp1 and Fz), CSEn13 (CSEn of signals from channels Fp1 and Fp2), and CSEn23 (CSEn of signals from channels Fz and Fp2) were extracted in this study. It could be speculated that a larger CSEn value suggests a weaker association and lower synchrony between two time series [19]. Therefore, the asymmetric state could be reflected by the variation of CSEn values. The definition and calculation of CSEn could be consulted in Liu's study [26].

2.3 Statistical Analysis

The whole process of data was performed in MATLAB (Ver. R2019a, MathWorks, United States). In difference analysis, the Kolmogorov–Smirnov test was employed to test the normal distribution of all parameter series firstly. For the parameters which passed the normal distribution test, one-way ANOVA was used to test the difference among all four groups, followed by group t-test to test the difference between each two groups. Otherwise, for parameter series that was not a normal distribution, the Kruskal–Wallis rank test and Wilcoxon rank sum test were used instead. Statistically significance with p-value lower than 0.05 was admitted for all statistical results.

3 Results

Five indexes were acquired finally for each group, and among which only Asy_SEn passed the normal distribution and variance homogeneity test simultaneously, therefore the one-way ANOVA was used for it while the Kruskal Wallis rank test was used for the rest. The results are shown in Table 2, which confirm the asymmetry difference among the four groups. Significant differences are confirmed for indexes except for Asy_LZC. All three cross entropy measures show significant differences with $p < 0.01$, while Asy_SEn shows significance with $p < 0.05$.

To further explore the difference between each two groups, the group t-test or Wilcoxon rank sum test was performed. The feature values of each group are shown in the form of mean ± standard error in Table 3, and the difference significances between each pair of groups are also listed in detail. All the five indexes show overall upward trends as the depression deepens, except for a slight decrease in the Con-De group for cross entropy measures. More intuitive difference significances are shown in Fig. 3. For Asy_LZC, the Con-De group value is significantly higher than the other three groups with $p < 0.05$. While for Asy_SEn, the Health group shows significant difference to both Mil-De and Con-De groups, with $p < 0.05$ and $p < 0.01$ separately. The three cross entropy measures of the Health group are all significantly different from depression groups with $p < 0.01$.

4 Discussion

This study confirms that the frontal asymmetry, either evaluated by two new indexes extracted in this study or by cross entropy measures, has increased significantly in depression patients compared with the healthy group. Furthermore, the asymmetry escalates as the depression severity deepens.

Table 2 One-way ANOVA test results for all four groups

	F (one-way ANOVA)	Chi-sq (Kruskal–Wallis rank test)	P
Asy_LZC		7.5600	0.056
Asy_SEn	3.06*		0.028
CSEn12		58.44**	0.000
CSEn13		76.55**	0.000
CSEn23		79.05**	0.000

*Statistical difference significance among four groups with $p < 0.05$

**Statistical difference significance among four groups with $p < 0.01$

Table 3 Index values of each group and difference significance results

	Health	Non-De	Mil-De	Con-De
Asy_LZC	-0.0010 ± 0.0008	-0.0006 ± 0.0008	-0.0007 ± 0.0006	0.0015 ± 0.0008^{abc}
Asy_SEn	-0.0023 ± 0.0007	-0.0003 ± 0.0007	0.0001 ± 0.0005^{a}	0.0007 ± 0.0007^{aa}
CSEn12	0.6551 ± 0.0007	0.6623 ± 0.0011^{aa}	0.6643 ± 0.0008^{aa}	0.6610 ± 0.0008^{aacc}
CSEn13	0.6544 ± 0.0006	0.6633 ± 0.0010^{aa}	0.6643 ± 0.0007^{aa}	0.6612 ± 0.0008^{aacc}
CSEn23	0.6544 ± 0.0007	0.6636 ± 0.0010^{aa}	0.6646 ± 0.0007^{aa}	0.6619 ± 0.0008^{aac}

Index values are expressed as mean ± standard error (SE). [a]: significant difference compared with the Health group with $p < 0.05$. [aa]: significant difference compared with the Health group with $p < 0.01$. [b]: significant difference compared with the Non-De group with $p < 0.05$. [c]: significant difference compared with the Mil-De group with $p < 0.05$. [cc]: significant difference compared with Mil-De group with $p < 0.01$

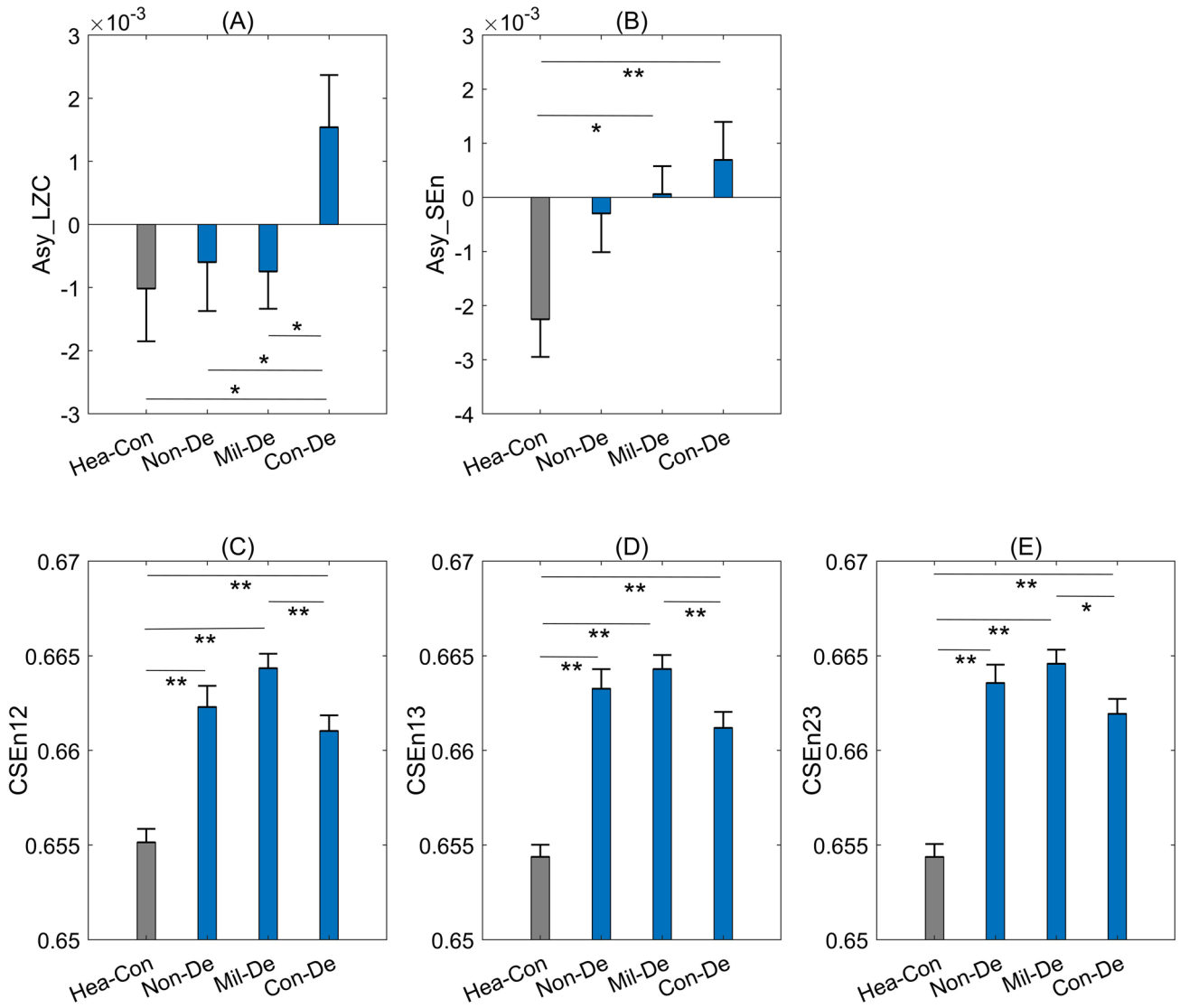

Fig. 3 Index distribution among different depression severities and healthy controls. Each panel shows one of the five features' distribution: (**a**) Asy_LZC, (**b**) Asy_SEn, (**c**) CSEn12, (**d**) CSEn13, (**e**) CSEn23. The mean feature value of each group is shown by the height of the bar, while the standard error is shown by the length of the horizontal bar exceeding the main bar. *: significant difference between two groups with $p < 0.05$. **: significant difference between two groups with $p < 0.01$

The results from this study help better understanding the frontal brain variation and vagal modulation dysregulation in depression patients, as well as present evidence that the frontal asymmetry analysis of EEG signals could offer a good way to evaluate clinical depression.

As mentioned above, previous studies assessed the depressive frontal asymmetry by the alpha band power of frontal EEG directly, normally computed as the natural logarithm of alpha power at the right site minus the left site. Under this kind of calculation algorithm, Debener calculated this asymmetry on four site combinations (anterior: F8–F7, F4–F3, T4–T3; posterior: P4–P3) which all showed decreased asymmetry values of depression patients compared with healthy controls [4]. Chang acquired a negative value for depressive asymmetry while the asymmetry value of the healthy controls was positive, which suggested a greater right frontal activity because alpha power values are inversely related to brain activity [11]. Although it is the first time to assess the frontal asymmetry by nonlinear complexity methods in this study, the characteristic of brain activity in depression patients reflected by our results is consistent with the previous findings. As shown in Fig. 3, there are developmental increasings of both Asy_LZC and Asy_SEn among four different groups. Higher Asy_LZC and Asy_SEn values indicate a higher complexity difference value of frontal alpha, which suggests that depression leads to higher alpha complexity in the right hemisphere than left hemisphere. Therefore, a greater right brain activity could be speculated, which is in line with the above findings.

Besides, there is evidence to suggest that frontal activity could inhibit the cardio acceleratory circuits [27], and the right hemisphere activity is associated with the sympathetic system with inherently inhibitory function [28]. Furthermore, many studies have confirmed the altered heart rate variability and vagal modulation dysfunction in depression patients [29, 30]. Our previous study also found increased cardiorespiratory coupling among different depression stages [19]. Therefore, the increased right frontal complexity of depression patients found in this study not only suggests promising biomarkers for depression diagnosis but also provides an explanation for the changes in heart rate variability of depression patients.

Although both new indexes exhibit a consistently increasing trend among the four groups, the difference significances of them are not the same. Panel (a) of Fig. 3 shows that the Con-De group has significant difference compared with all the other three groups, while panel (b) shows a significant difference only when the Health group is compared with Mil-De and Con-De, which may suggest that Asy_LZC perform better in severe depression recognition while Asy_SEn perform better in discriminating healthy group from depressive groups.

Panel (d) shows the distribution of CSEn13 among four groups, which assesses the asynchroniazation of alpha EEG signals obtained from frontal pole Fp1 and Fp2. The CSEn13 value of all depressive groups are significantly higher than the healthy group with $p < 0.01$, which indicates that the above two EEG signals of depression patients have a significantly weaker association and lower synchronization. A similar explanation is also applicable to CSEn12 and CSEn23. However, in the exploration of two series' relative relationships the cross entropy measure has a limitation which is decided by its non-directional mathematical property. The small unexpected decrease of Con-De compared with the other two depressive groups may be on account of this shortage. Therefore, Asy_LZC and Asy_SEn show their advantage in this respect.

This study has certain limitations. Firstly, the medication and gender factors have not been analyzed as the initial experiment was aimed at analyzing the general influence of depression. More thorough consideration is needed in future experimental design. Secondly, aiming at the computer-aided evaluation and detection of depression, recognition accuracy should be explored further by employing powerful parameters confirmed in this study as well as other previous studies.

5 Conclusions

In conclusion, this study suggests significantly increased frontal alpha asymmetry in depression patients compared with the healthy group, and specific higher right frontal complexity than the left frontal cortex is proven by two new proposed indexes Asy_SEn and Asy_LZC. Furthermore, this asymmetry increases as the level of depression deepens. The increased frontal asymmetry confirms that the depression alters the frontal brain activation, therefore leads to sympathovagal imbalance and autonomic nervous system dysfunction. Two indexes proposed in this study confirm the validity of frontal alpha EEG asymmetry based on entropy measures and LZC in depression evaluation, and extend the index library of future computer-aided depression recognition systems.

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Author Contributions Conceptualization, LY and CL; Data curation, LZ, BL and ZS; Formal analysis, LZ; Funding acquisition, LY and CL; Investigation, LZ and CL; Methodology, LZ; Project administration, CL; Resources, LY and CL; Software, LZ; Supervision, LY and CL; Validation, LZ, LY, and BL; Writing—original draft, LZ; Writing—review & editing, LY and CL.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

Ethical Approval The protocol of this study was approved by the Ethics Committee of the Second Affiliated Hospital of Jining Medical College.

Informed Consent Written informed consent was given by all participants in accordance with the Declaration of Helsinki.

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