Alterations in Patients With First-Episode Depression in the Eyes-Open and Eyes-Closed Conditions: A Resting-State EEG Study

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Abstract—Altered resting-state EEG activity has been repeatedly reported in major depressive disorder (MDD), but no robust biomarkers have been identified until now. The poor consistency of EEG alterations may be due to inconsistent resting conditions; that is, the eyes-open (EO) and eyes-closed (EC) conditions. Here, we explored the effect of the EO and EC conditions on EEG biomarkers for discriminating MDD subjects and healthy control (HC) subjects. EEG data were recorded from 30 first-episode MDD and 26 HC subjects during an 8-min resting-state session. The features were extracted using spectral power, Lempel–Ziv complexity, and detrended fluctuation analysis. Significant features were further selected via the sequential backward feature selection algorithm. Support vector machine (SVM), logistic regression, and linear discriminate analysis were used to determine a better resting condition to provide more reliable estimates for identifying MDD. Compared with the HC group, we found that the MDD group exhibited widespread increased β and γ powers ($p < 0.01$) in both conditions. In the EO condition, the MDD group showed increased complexity and scaling exponents in the α band relative to HC subjects ($p < 0.05$). The best classification performance of the combined feature sets was found in the EO condition, with the leave-one-out classification accuracy of 89.29%, sensitivity of 90.00%, and specificity of 88.46% using SVM with the linear kernel classifier when the threshold was set to 0.7, followed by the β and γ spectral features with an average accuracy of 83.93%. Overall, EO and EC conditions indeed affected the between-group variance, and the EO condition is suggested as the more separable resting condition to identify depression. Specially, the β and γ powers are suggested as potential biomarkers for first-episode MDD.

Index Terms—Resting EEG, eyes-open, eyes-closed, high-frequency oscillation, depression.

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I. Introduction

MAJOR depressive disorder (MDD) is a highly prevalent mental disorder characterized by significant and persistent low mood [1]. More than 340 million people suffer from different degrees of depression worldwide [2]. However, most MDD patients are not diagnosed correctly, which could deprive them from appropriate treatment. Clinically, MDD diagnosis is made using a combination of behavioral and psychological assessments, such as clinical symptoms and various assessment scales. The limitations of these assessments, as they are subjective and inconsistent, have given rise to a keen interest in developing objective and reliable biomarkers for MDD.

Electroencephalography (EEG), as a non-invasive technique for obtaining objective information about brain activities and mental state [3], has the potential to reveal specific frequency oscillations with high temporal resolution [4]. The oscillations of δ, θ, α, β, and γ have been reported to provide information on MDD [5]–[10]. Due to the characteristics of EEG—for example, it is nonlinear and non-stationary—clinical researchers have noted many nonlinear dynamics of MDD [11]–[15]. The Lempel–Ziv complexity (LZC) has been extensively utilized to measure the complexity of EEGs [16], and it is especially recommended because it is nonparametric, model-independent, and easily calculable [17]. Bachmann *et al.* found that MDD patients exhibited increased complexity in EEG oscillations of 0.5–40 Hz under the eyes-closed condition compared to healthy control (HC)

subjects [18]. Numerous studies have noted that MDD is related to the changes in the imbalance E/I of networks [19], [20], which are associated with long-range temporal correlations (LRTCs). LRTCs provide a quantitative index of statistical dependencies in oscillations on different time scales. The essential feature of LRTCs is their power-law behavior, which indicates that the mechanisms contributing to their build-up are similar at different time scales [21]. Abnormal LRTCs of EEG oscillations in the range of 0.5–30 Hz have been observed in MDD [22]. Detrended fluctuation analysis (DFA) is a well-established method for the detection of LRTC in time series with non-stationarities. Based on the advantage of DFA—namely that it can systematically eliminate trends of different orders—we can gain insight into the scaling behavior of natural variability, as well as into the trends in the considered time series [21].

Resting-state EEG (Rs-EEG) has been widely used in studies of MDD since no cognitive effort is required [23]. In addition, oscillatory activities observed at rest are more likely to reflect intrinsic defects in underlying cortical neurons in MDD [24]. However, there is no one agreed upon method to acquire an Rs-EEG. Some researchers instruct their subjects to keep their eyes open (EO), whereas others instruct them to keep their eyes closed (EC). Importantly, numerous studies have pointed out when alternating between the EO and EC conditions, the neural spontaneous activities change accordingly [25]–[27]. Specifically, the α activity is dominant in EC condition compared with EO condition [28]. Besides, an LRTC study has provided evidence that EO and EC conditions could be distinguished by scaling exponents, not only in the α band but also in the lower and higher frequency bands [29]. Apparently, it is important to consider EC and EO conditions as variational factors in the analysis of Rs-EEG, which would help reduce the variability of Rs-EEG findings across studies.

Despite many studies on Rs-EEG oscillations, which have improved the diagnostics of MDD, the findings differ markedly and are partly contradictory. For example, compared to HC subjects, an EEG study reported increased γ in the frontal and temporal regions in MDD patients under the EC condition [30], whereas MDD patients showed no significant difference in the γ band under the EC condition in another work [31]. Previous studies have identified a frontal α asymmetry in MDD. Initial reports provided evidence for higher left-frontal α activity in MDD patients under the EC condition compared with HC subjects [8], [33]. However, subsequent reports demonstrated competing findings in MDD under both the EO and EC conditions [34], [35]. Akar *et al.* found that MDD patients showed significantly higher LZC values in the range of 0.5–50Hz in frontal and central-parietal regions under the EC condition compared to HC subjects [36]. Kalev *et al.* found that MDD patients showed lower LZC/MLZC values from the δ to β bands under the EO condition relative to HC subjects [37].

However, few studies have conducted comparative analysis of the differences between the two conditions in MDD, let alone the patients with first-episode depression. It is unclear which of the two conditions provide more reliable estimates of alteration in brain activities in first-episode MDD. To address this issue, we aimed to systematically investigate the effects of the EO and EC conditions on EEG alterations to find out the better resting condition that can provide more reliable estimates for first-episode MDD. Our work could also help point to promising biomarkers that efficiently recognize depression. Power spectrum (i.e., PSD) and nonlinear dynamics (i.e., LZC and DFA) features were extracted to provide a comprehensive view of the effects of the EO and EC conditions. Sequential backward feature selection (SBFS) was employed to select the best subset of features and enhance classification performance. Various classifiers, such as support vector machine (SVM), logistic regression (LR), and linear discriminate analysis (LDA), were tested to explore the separability of features in the spectral and nonlinear dimensions and then to identify candidate EEG biomarkers with high specificity and sensitivity, which would be critical for making a more objective diagnosis, ultimately enabling better prognosis with more effective treatment.

II. MATERIALS

A. Participants

Thirty MDD patients (age range: 18–38 years) were recruited from the outpatient clinics of the Second Xiangya Hospital of Central South University and the Tianjin Anding Hospital. Twenty-six HC subjects (age range: 20–30 years) were recruited from Tianjin University. Inclusion criteria for all participants were: a) no history of major physical or neurological impairment (e.g., epilepsy); b) no history of electroconvulsive therapy; c) no history of alcohol or substance abuse; d) no current substance use disorder (i.e., within the last 6 months). A thorough history was taken to obtain the demographics of the participants, who are right-handed with normal-hearing and normal or corrected-to-normal visual acuity. The study protocol was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (Approval Number: 2018(076)) and the Ethics Committee of the Tianjin Anding Hospital (Approval Number: 2020(2020-05)). All participants gave written informed consent after being informed about the study.

B. Diagnostic Criteria

All patients were first-episode drug-naive with MDD. The diagnoses of patients were assessed by two professional psychiatrists based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V, American Psychiatric Association, 2013) [38]. In addition, all patients were assessed via the 17-item Hamilton Depression Rating Scale (HAMD-17) and the Young Mania Rating Scale (YMRS). For MDD patients, the Hamilton Depression Scale scores were ≥ 14 and the Young Mania Rating Scale scores were ≤ 6, indicating that they were in depression [39], [40] and not at risk of turning manic. Meanwhile, HC subjects received the annual psychological test from the Psychological Center of Tianjin University, and the test results showed that the HC subjects did not have mental diseases.
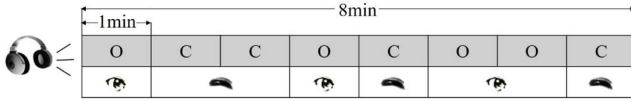
Fig. 1. The OCCOCOOC paradigm.

C. Experimental Conditions

All participants underwent an 8-min resting-state session. The resting-state session was recorded for eight 1-min trials. Each 1-min trial was either in the open eyes (O) or closed eyes (C) condition, and the order of open or closed eyes alternated across trials [41]. Specially, the OCCOCOOC paradigm was selected in this study (see Figure 1); that is, there were 4-min EO and 4-min EC signals in the 8-min resting-state session.

The experiment was performed in a sound-attenuated chamber with standard ceiling lighting. Participants were seated in front of the screen at a distance of 70–80 cm, separated from the experimenter. When the session started, participants were required to look at a white solid circle on a black background on the stimulus interface and instructed to try to not think of anything and relax for the duration of the scan. When the participants pressed the space key to confirm the start, a computerized audio stating "Please open your eyes" was played, according to which participants adjusted to open their eyes. After the audio cue, the EO trial was labeled. One minute later, the audio cue "Please close your eyes" was played, then the participants were required to close their eyes, and the EC trial was labeled. The sequence of the audio cues is shown in Figure 1.

D. Data Acquisition and Preprocessing

EEGs were recorded from 64-channel surface electrodes positioned according to the international 10/20 system using the SynAmps2 system (Neuroscan, USA). The system acquisition bandpass was 0.1–200 Hz. Data recording was referenced to a linked left mastoid electrode ("M1") with the ground electrode located at "AFz". The EEG was continuously recorded at a 1,000 Hz sampling rate, and the interelectrode impedance was kept below 10 kΩ.

EEGs were preprocessed using the EEGLAB toolbox (version 2020.0) along with custom MATLAB scripts (version R2020a; The MathWorks, Inc, USA) [42]. Offline signals were re-referenced to the average bilateral mastoid electrodes (["M1" + "M2"]/2) and down-sampled to 500 Hz. The function *pop_eegfiltnew.m* was applied for the 0.5–120 Hz bandpass filter (finite impulse response filter, cutoff frequency (−6 dB): [0.25 Hz 120.25 Hz], zero-phase). Artifacts generated by eyeblinks, eye movements, and muscle activity were manually removed through independent component analysis [43] using the EEGLAB plugin *ADJUST* toolbox. In this study, the definition of EEG oscillation ranged from 0.5 to 120 Hz, including δ (0.5–4 Hz), θ (4–8 Hz), α (8–13 Hz), β (13–30 Hz), and γ (30–120 Hz). Specifically, the γ band was subdivided by defining low γ as 30–50 Hz (referred to as $\gamma 1$) and high γ as 50–120 Hz (referred to as $\gamma 2$).

III. METHODS

A. Statistical Analyses

Demographic statistical analysis was carried out using SPSS (version 20.0; IBM Corporation, USA). Normality was tested using the Shapiro–Wilk test. Since the education level of both groups did not meet parametric assumptions for the normal distribution, the non-parametric (Kolmogorov–Smirnov) test was conducted for education level between the MDD and HC groups. The two-sample t-test (two-tailed) was employed to compare the age between the two groups, and the chi-squared test was employed for the sex comparison. To assess differences in Rs-EEG measures between MDD patients and HC subjects, the two-sample t-test (two-tailed) was conducted with $\alpha = 0.05$ while controlling for 60 multiple comparisons across channels using false-discovery rate (FDR) correction [24].

B. Feature Extraction

1) Welch FFT: Welch's FFT method [44] was performed to calculate the absolute power spectral density (PSD) of the δ, θ, α, β, $\gamma 1$, and $\gamma 2$ bands [45]. MATLAB provides a built-in command called the *pwelch.m* function to obtain the PSD. In this study, 4-min EO/EC EEG signals were split into 5 s segments with 50% overlap [46], resulting in 48 equal segments in each condition. The Hamming window was applied to each segment, and the PSD estimate was found by averaging the resulting periodograms.

2) Lempel-Ziv Complexity: LZC counts the number of new occurring patterns for the sequences of finite length [16]. Previous studies have presented that LZC has been successfully used for detecting mental disorders due to it being more sensitive to temporal amplitude distribution [18], [47]. In this study, the EEG signals were band-pass filtered using a second-order Butterworth filter to obtain the oscillations from δ to $\gamma 2$ [48]; then, they were divided into 5 s segments. The LZC was calculated for each segment x(n). Each segment x(n) was converted into binary sequences s(n) by comparing with the median value (M) of the segment x(n) as follows:

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

This resulted in 48 binarized sequences for the EO condition and 48 binarized sequences for the EC condition. After the binarization, the resulting binary sequence s(n) is scanned from left to right counting the number of different patterns occurring. The complexity c(n) is increased every time a new pattern is encountered [49], [50], and it has been previously proven that the upper bound of c(n) is

$$\lim_{n \to \infty} c(n) = b(n) = n / \log_2 n \tag{2}$$

In order to obtain a metric independent of the length of the time series, the complexity measure is often normalized with respect to the rate of new patterns. Mostly, c(n) is normalized using its upper limit b(n):
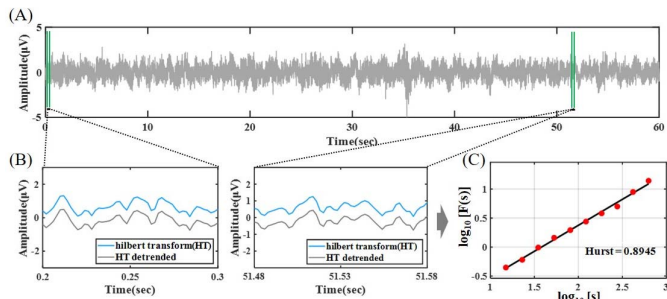
$$LZC = c(n) / b(n) \tag{3}$$

Fig. 2. Some basic steps of the DFA analysis. (A) The 1-min band-pass filtered (β band) EEG signals (channel 28 = Cz) in healthy subject no. 16 under the EC condition. (B) The amplitude envelope before (blue line) and after (gray line) detrending (i.e., removal of the linear trend). (C) DFA results of the 12th 5s epochs. The hurst value is the slope of the log–log plot between fluctuation F and window size s. In this example case, the hurst value for the β oscillations in Cz was 0.8945.

3) Detrended Fluctuation Analysis: DFA as an important nonlinear analysis technique. It has been used for the detection of LRTCs, and it is known for its robustness against non-stationarity [51], [52]. In this study, the EEG signals were band-pass filtered using a third-order Butterworth filter to obtain the oscillations from δ to γ 2 [53]. To ensure the length of the time series, we intercepted EEG signals in continuous 2-min EO and 2-min EC conditions. Then, the intercepted data were segmented into 5 s epochs, resulting in 24 sequences in each condition, which served as the database for DFA analysis. The DFA involved four steps: (a) Constructing an envelope. The Hilbert transformation was applied to extract the amplitude envelope. The mean was subtracted from this time series: (x(i), i = 1, . . . , N}, N is length of the epochs), and the time series was integrated:

$$y(k) = \sum_{i=1}^{k} [x(i) - \bar{x}] \tag{4}$$

where $\bar{x}$ indicates the mean of x(i). (b) Dividing the de-meaned value, integrated time series y (k) into segments of length s. Based on previous studies [54], the following segment lengths were set: 15, 25, 35, 55, 80, 120, 185, 280, 420, and 625 samples (from 0.03 to 1.25 s) in this study. The number of points should be a positive number for the nature of the analysis. Therefore, the numbers were rounded-off. (c) For each segment, the local least-squares linear fit was determined. The ensuing piecewise linear fit was designated $y_s(k)$. (d) Finally, the DFA fluctuation function F(s) was calculated:

$$F(s) = \sqrt{\frac{1}{N} \sum_{k=1}^{N} [y(k)\text{-}y_s(k)]^2} \tag{5}$$

Figure 2 depicts some basic steps of the DFA analysis. The slope of the least-squares line is called the scaling exponent (Hurst value), which quantifies how steeply the fluctuations increase with the time scale of reference [55]. $0 < \text{Hurst} < 0.5$ indicates negative correlations; $0.5 < \text{Hurst} < 1$ indicates positive correlations such that large fluctuations are likely to be followed by large fluctuations; Hurst = 0.5 indicates a completely uncorrelated (random process); Hurst = 1 indicates a special one that corresponds to 1/f noise [56].

C. Feature Selection

Feature selection is one of the main ways to improve the classification performance. It entails selecting a better subset of features. In this study, the sequential backward feature selection algorithm was utilized to reduce the dimensionality of the feature matrix for improving the classification performance. The algorithm first considers the whole feature set, then sequentially removes features from the feature set until the elimination of further features leads to an increase in the misclassification rates [14]. The classifier in the SBFS step was the same as the classifier in the classification step.

D. Classification

Classification is a fundamental approach for the automatic identification of patterns. In this study, a support vector machine with linear (LINSVM) and radial basis function (RBFSVM) kernels, logistic regression, and linear discriminate analysis were used to ensure wider consistency and then to select the best classifier for identifying MDD. Data standardization based on the z-score transformation was performed on the training and testing sets to modify the unequal distributions of each feature. The hyperparameters of LINSVM, RBFSVM, LR, and LDA were optimized using the Bayesian optimizer.

E. Evaluation

In this study, the leave-one-subject-out method was employed to assess the classification performance of the proposed classifiers. In this procedure, we selected the characteristic data of one subject as the test set and the data of other subjects as the training set. Accuracy (ACC), sensitivity (SE), and specificity (SP) were used to investigate the overall classification performance. The sequential thresholding operation was conducted to optimize the proposed classifiers. We computed the ACC, SE, and SP under different threshold values (i.e., ACC_T, SE_T, and SP_T), which are defined as follows:

$$S_T[f(x)] = \begin{cases} 1 & \text{if } f(x) \geq T \\ 0 & else \end{cases} \tag{6}$$

$$\text{ACC}_T = \frac{\sum S_T[ACC(x)]}{HC_N + MDD_N} \tag{7}$$

$$\text{SE}_T = \frac{\sum S_T[SE(x)]}{MDD_N} \tag{8}$$

$$\text{SP}_T = \frac{\sum S_T[SP(x)]}{HC_N} \tag{9}$$

where $f(x)$ is the percentage of correctly classified individuals; T indicates threshold value; HC_N is the total number of HC individuals; and MDD_N is the total number of MDD patients.

IV. RESULTS

A. Demographic Characteristics

Table I summarizes the demographic information of the MDD and HC groups, along with statistical comparisons.
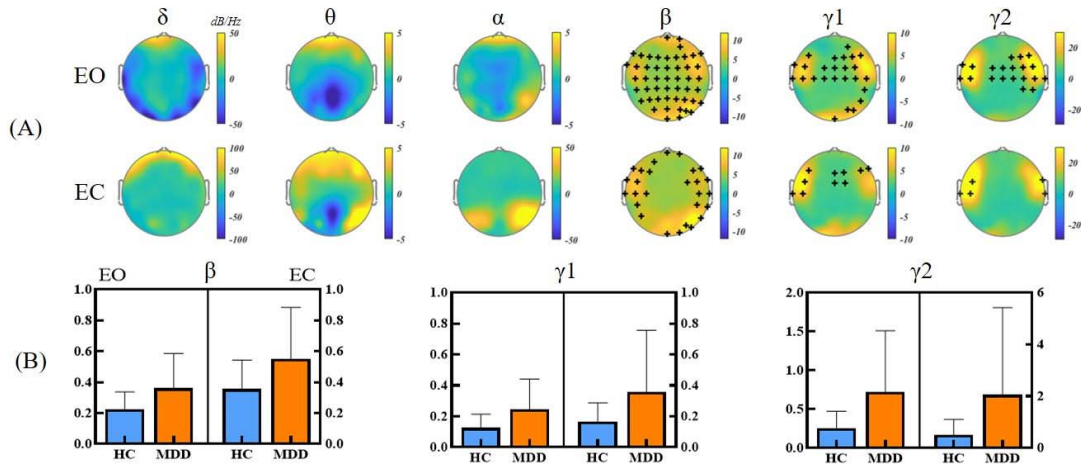
Fig. 3. The PSD difference values between the MDD and HC groups. (A) Topographic map of PSD difference values. Each subplot represents the PSD value of the MDD group minus that of the HC group. Each row represents a resting condition, that is, EO for 4 min and EC for 4 min. Each column represents a frequency band. The closer the color is to yellow, the higher are the brain activities of MDD patients compared to HC subjects, whereas the closer it is to blue, the lower are the brain activities of MDD patients. The black plus represent the channels that exhibited statistically significant differences (FDR, $p < 0.05$). (B) Bar plot of averaged PSD in the β, $\gamma 1$, and $\gamma 2$ bands in the channels with significant differences in the HC (blue) and the MDD (orange) groups. The left Y-axis represents the averaged PSD in the EO condition and the right Y-axis represents the averaged PSD in the EC condition.

TABLE I
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE
PARTICIPANTS ALONG WITH STATISTICAL COMPARISONS

	MDD	HC	χ^2/T/Z	*P*-value
Sex (Male / Female)	8 / 22	13 / 13	3.24	0.099
Age (Years)	27.13 ± 5.58	25.54 ± 1.58	29.81	0.143
Education (Years)	14.67 ± 3.08	16.12 ± 0.59	1.24	0.091
HAMD Score	21.26 ± 4.91	/		
YMRS Score	2.80 ± 2.02	/		

Values are mean ± SD unless otherwise noted. HAMD = the Hamilton Depression Scale; YMRS = the Young Mania Rating Scale.

There was no significant difference between the two groups in sex, as tested by chi-square analysis ($\chi^2_{(1)} = 3.24$, $p = 0.099$). Based on the results of the Kolmogorov–Smirnov test, the education level of MDD patients did not differ significantly from HC subjects ($Z = 1.24$, $p = 0.091$). There was no significant difference between the two groups in age ($T = 29.81$, $p = 0.143$). Overall, there were no statistical differences in sex, age, and education level between the MDD and the HC groups.

B. Spectrum Power

Figure 3(A) shows the topographic maps of the PSD difference values between the two groups in the δ, θ, α, β, $\gamma 1$, and $\gamma 2$ bands derived under the EO and EC conditions. Each subplot represents the PSD value of the MDD group minus that of the HC group. Differences between the two groups were clearly observed for all frequency bands, whereas the

degree of differences were diverse between the two conditions, indicating that the EO and EC conditions indeed affected the between-group variance, ultimately hindering the exploration of abnormal activities for depression. Concretely, in low-frequency bands, most notably in the θ band, the MDD group showed a reduction in the central parietal–occipital regions compared to the HC group. In contrast, in the high-frequency bands (i.e., β and γ bands), the brain activities in both the bilateral frontal and temporal lobes were more active for the MDD group and displayed lateralization. By performing the two-sample *t*-test, we found that the significant differences between the two groups were mainly concentrated in the β and γ bands. Specifically, the most prominent EEG activation for the MDD group was a global increase in the β band, along with a more regionally specific increase in the γ band (frontal, temporal, and central regions) in the EO condition relative to the HC subjects, demonstrating that MDD patients displayed more abnormal high-frequency oscillation in the anterior hemisphere when they remained eyes-open and awake.

C. LZC

LZC indicates the rate of occurrence of the new patterns in a time series. The larger the LZC, the greater is the probability of new sequence patterns, resulting in more complex dynamical behavior. Figure 4(A) illustrates the topographic maps of LZC difference values between the MDD and HC groups in each band between the EO and EC conditions. In order to determine the statistical differences in the complexity of EEG oscillations between the two groups, the two-sample *t*-test was utilized. We found that the significant differences of LZC between the two groups were concentrated in the α band (α-LZC) and concentrated mainly in the bilateral frontal and right parietal–occipital regions in the EO condition. The α-LZC values of the MDD group were larger than those of the
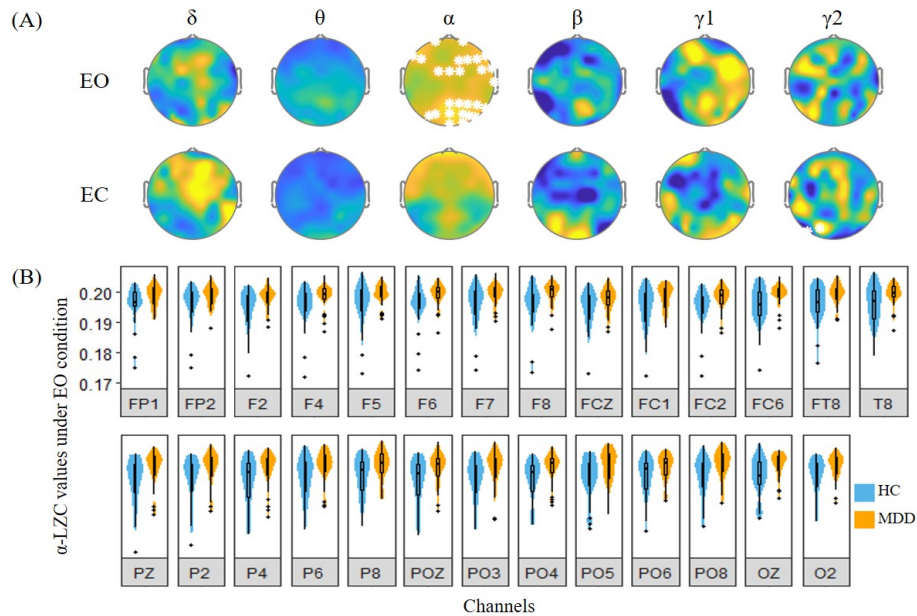
Fig. 4. The LZC values between the MDD and HC groups. (A) Topographic maps of LZC difference values of the MDD group minus that of the HC group. Each row represents a resting condition, that is, EO for 4 min and EC for 4 min. Each column represents a frequency band. The closer the color is to yellow, the more complex dynamical behavior there is in the MDD patients compared to HC subjects, whereas the closer it is to blue, the more complex dynamical behavior there is in the HC group compared to the MDD group. The small white stars represent the channels that exhibited statistically significant differences (FDR, $p < 0.05$). (B) Violin plot of α-LZC in the channels with significant differences in the HC (blue) and the MDD (orange) groups.
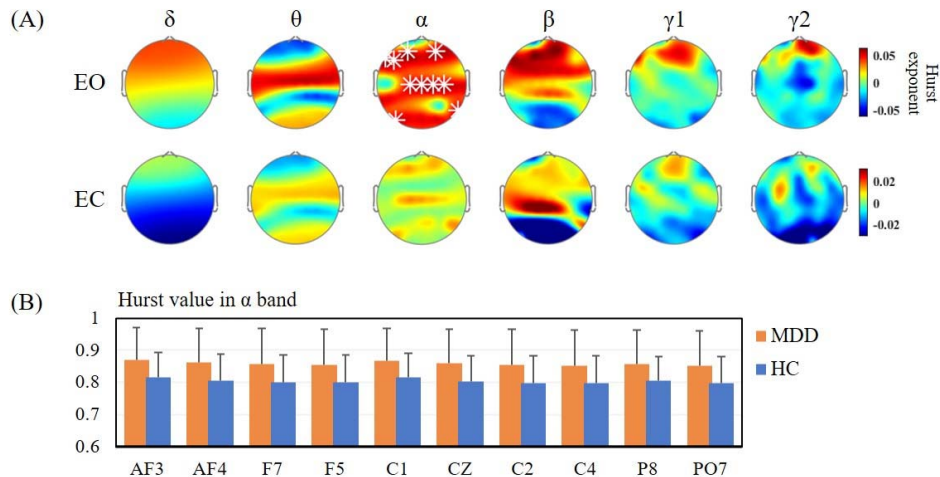

Fig. 5. The Hurst exponents between the MDD and HC groups. (A) Topographic maps of Hurst difference values of the MDD group minus that of the HC group. Each row represents a resting condition, that is, EO for 2 min and EC for 2 min. Each column represents a frequency band. The closer the color is to red, the larger is the scaling exponent of the MDD patients compared to the HC subjects, whereas the closer it is to blue, the lower is the scaling exponent of the MDD group compared to the HC group. The small white hexagons represent the channels that exhibited statistically significant differences (FDR, p < 0.05). (B) Bar plot of Hurst values in the α band in the channels with significant differences in the HC (blue) and the MDD (orange) groups.

HC group, with a narrower distribution (see Figure 4(B)), reflecting more complex and stable dynamical behavior of depressive patients compared with healthy controls. However, no significant differences were found in the EC condition.

D. Long-Range Time Correlations

By calculating the Hurst values in each band and channel for the MDD and HC groups in the EO and EC conditions, it was found that the Hurst values were greater than 0.5 and less

than 1 in each group, indicating that the two groups exhibited persistent LRTC of EEG oscillation. The spatial distribution of the Hurst values is presented in Figure 5(A). We found that in the EO condition, the Hurst values of the MDD group were much larger than those of the HC group and concentrated in the frontal and central regions. In contrast, in the EC condition, the Hurst values of the MDD group were smaller than those of the HC group, which were concentrated in the posterior parietal–occipital regions. Significantly different Hurst values

TABLE II
RESULTS OF CLASSIFICATION THROUGH THE SBFS ALGORITHM IN THE EO AND EC CONDITIONS

Feature Set	Classifier	EO			EC		
		ACC	SE	SP	ACC	SE	SP
Spectral [A]	LINSVM	**86.85%**	86.67%	87.06%	76.38%	74.85%	78.15%
	RBFSVM	74.84%	77.88%	71.33%	67.37%	65.15%	69.93%
	LR	75.97%	63.64%	90.21%	68.10%	53.79%	84.62%
	LDA	80.84%	72.12%	90.91%	68.83%	56.52%	83.04%
Nonlinear [B]	LINSVM	63.07%	71.97%	52.80%	56.66%	62.27%	50.17%
	RBFSVM	60.15%	64.70%	54.90%	57.06%	57.42%	56.64%
	LR	62.26%	62.58%	61.89%	56.57%	55.15%	58.22%
	LDA	61.77%	62.88%	60.49%	56.17%	54.84%	57.69%
Combined feature [C]	LINSVM	**89.04%**	89.55%	88.46%	75.49%	71.36%	80.24%
	RBFSVM	77.60%	82.73%	71.68%	70.37%	70.15%	70.63%
	LR	77.27%	68.94%	86.89%	70.94%	59.85%	83.74%
	LDA	82.63%	78.64%	87.24%	75.81%	66.97%	86.01%

Note. [A] The spectral feature set from β, γ1 and γ2 PSD in 60 channels.
[B] The nonlinear feature set from α-LZC and α-hurst values in 60 channels.
[C] The combined feature set comprising spectral and nonlinear feature sets.

were observed in the α band in the EO condition via the two-sample t-test. Differences between the two groups in the LRTC of α oscillation were observed in the frontal, central, and parieto-occipital channels. In addition, the Hurst values of the MDD patients in the α band with significant differences were larger than those of the HC subjects (see Figure 5(B)), suggesting that the EEG oscillations in the α band of depressive individuals exhibited more persistent tendency of LRTC in the EO condition. However, no significant differences were found in the EC condition.

E. Classification Results

To explore the separability of the spectral and nonlinear features extracted by the Welch, LZC, and DFA methods, continuous 2 min EO and 2 min EC resting data were selected. There were 24 samples (each sample from every 5 s) in each condition for every subject in this study. The first and last trials were removed to avoid the effects of the transition between open and closed eyes; that is, 22 samples were retained for each subject. Based on the statistical results, β, $\gamma 1$, and $\gamma 2$ bands were extracted as the characteristic frequency bands for the Welch method and α bands for the LZC and DFA methods. Significant features were further selected via the SBFS algorithm. Table II shows the numerical results of the average ACC, SE, and SP using different classifiers in the EO and EC conditions. As demonstrated in Table II, the EO condition had better performance from using the LINSVM classifier, with up to 86.85% and 89.04% for the spectral feature set and the combined feature set, respectively. We found that the classification performance of the spectral feature set was better than that of the nonlinear feature set, indicating that the β and γ powers would be more reliable than nonlinear features for

characterizing Rs-EEG activities. By comparing the results of the LINSVM, RBFSVM, LR, and LDA, it can be interpreted that the obtained results for the proposed classifiers were close and indicated an acceptable and robust performance.

Furthermore, we calculated the average ACC under different threshold values, as depicted in Figure 6(A). The threshold was set to a range from 0.50 to 1 with a step size of 0.05. The detailed calculation process is in Section III D. From figure 6(A), we noted that higher ACC was obtained for the EO condition compared with the EC condition using the proposed classifiers, irrespective of selecting the spectral or combined feature set. Specially, when the threshold was in the range of 0.50 to 0.70, relatively stable and high classification accuracy could be obtained. Therefore, 0.70 was selected as the threshold T to calculate the ACC_T, SE_T, and SP_T. As demonstrated in Figure 6(B), higher ACC_T, SE_T, and SP_T were obtained for the EO condition versus the EC condition with each proposed classifier. In the EO condition, the LINSVM classifier provided the best classification performance, with an average ACC_T of 89.29%, SE_T of 90.00%, and SP_T of 88.46% for the combined feature set. The second-best feature set for the classification of MDD and HC subjects based on EEG signals was the spectral feature set, with an average ACC_T of 83.93%, SE_T of 86.67%, and SP_T of 80.77%. These results demonstrate that the EO condition is the preferred one between the two resting conditions for identifying depression, and high-frequency spectral characteristics were more separable than low-frequency nonlinear characteristics.

V. DISCUSSION

MDD will be the greatest health burden on society—both economically and socially—by 2030. Therefore, there is an urgent need for objective and reliable biomarkers for early
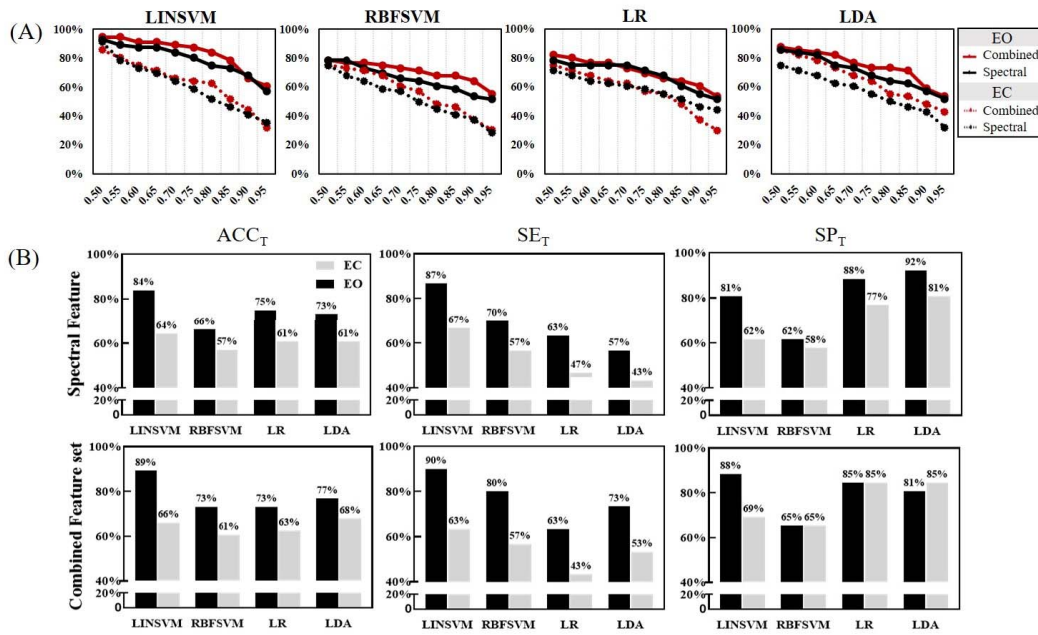
Fig. 6. Classification results of the LINSVM, RBFSVM, LR, and LDA classifiers. (A) The average ACC under different threshold values for different classifiers. In each subgraph, the solid line represents the classification results in the EO condition; the dotted line represents the classification results in the EC condition; the red indicates that the selected feature set is the combined feature set, the black indicates the selected feature set is the spectral feature set. (B) Bar plot of the ACC_T, SE_T, and SP_T achieved by the spectral feature set and combined feature sets using the LINSVM, RBFSVM, LR, and LDA classifiers when $T = 0.7$.

auxiliary diagnosis of MDD. Evidence supporting EEG abnormalities in depression has been well established in numerous studies. However, the consistency of these conclusions is poor, partly because they rarely consider the effects of the EO and EC states on the brain activation patterns. These conflicting results have therefore obfuscated our understanding of the pathologic mechanisms of MDD. There are only a few studies that comprehensively investigate data on the effects of different resting conditions in MDD. In this study, we presented the first systematic analysis of the effects of the EO and EC conditions by using traditional spectral and nonlinear dynamics methods. We found that the activities of high-frequency bands could be used as reliable indices for characterizing resting-state brain activities of MDD, and we recommend the EO condition for resting EEG studies, at least for patients with first-episode depression.

A. Studies of High-Frequency EEG Oscillations

Altered β and γ oscillations in MDD were found in our study, which is similar to the findings of Strelets *et al.* They compared the γ oscillations between HC subjects and MDD patients and found that the γ power was greater in the MDD group than in the HC group at rest, especially in the frontal and temporal regions [30]. Subsequent studies indicated γ oscillations in the prefrontal cortex may be a reliable marker for MDD, as the prefrontal cortex is heavily implicated in mood and emotional regulation [57]. Furthermore, Strelets *et al.* also found increased γ spectral power in the frontal regions during performance of the spatial imagination

test, further confirming the previous findings that task-induced activation patterns were incorporated in brain activation patterns at resting state [58], [59]. Moreover, γ oscillations are short-lived and emerge from the coordinated interactions of excitation and inhibition [60]. Some animal studies have suggested that MDD may be associated with an imbalanced excitation to inhibition ratio (E/I) of networks [19], [20]. Based on previous literature, our findings suggest that first-episode MDD patients also exhibit abnormal γ activation patterns in the frontal lobe, which may be associated with changes in the E/I. Jaworska *et al.* found that there is greater right frontal activation (less α power) and/or less left frontal activation in MDD in the EC condition [61], [62]. In other studies, MDD patients showed the opposite result when EO data were added into the analysis [63], [64]. Based on these inconsistent results in different resting conditions, we hypothesized that the poor consistency of the frontal α asymmetry of MDD might be caused by the EO and EC conditions [33], [34]. Indeed, by comparing the frontal asymmetry of the two groups, we found that there was a difference in the frontal α asymmetry of MDD in EO (0.032 ± 0.227, that is, higher right frontal α power) and EC conditions (-0.007 ± 0.157, that is, higher left frontal α power), but the difference was not significant.

In addition to the findings for high-frequency bands, the differences in the θ activities between the two groups were also found in the central parietal regions between the EO and EC conditions. Due to the fact θ oscillations are related to attention, we speculate that MDD patients may have attention defects at resting state, thereby associating with smaller activities in the θ band than healthy controls. Furthermore,

the amplitude of γ oscillation is modulated by slower oscillations, especially modulation by θ oscillation [65], [66]. It is also of great significance for future work to explore $\theta-\gamma$ coupling in the two resting conditions in first-episode MDD patients.

B. Long-Range Time Correlations of Depression

In line with previous research [21], we found significant increased LRTC in the α band in MDD patients relative to HC subjects, located at frontal, central, and parieto-occipital regions in this study. Differences in LRTC between the two groups suggested more persistent LRTC in MDD patients, indicating that MDD is characterized by changes in the temporal dynamics of resting-state neuronal oscillations [15]. It has been proved that α activities are related to top-down processing [67]. The activities of α oscillations have previously been implicated in MDD. Matti *et al.* supposed that altered θ and α LRTC during rest might relate to processes affecting mechanisms of cognitive control and emotion regulation in MDD patients [68], [69]. Furthermore, many studies have shown that γ oscillations are closely related to the change in E/I [20] and pointed out that θ and α oscillations help to maintain γ networks [66], [67]. Considering that LRTC can effectively respond to changes in the imbalance of the E/I of networks, coupled with the MDD-related findings in this study, we conjecture that increased α LRTC could play a role in this instability for first-episode MDD patients. Future work could test the connection between α LRTC and γ powers. In addition, a study on insomniacs found that individuals experiencing worse sleep quality tend to have stronger LRTC during eyes-open wakefulness [55]. Based on the literature, we speculate that the LRTC enhancement in MDD patients in our study may be associated with poor sleep quality. Further exploration of the relationship between sleep quality and LRTC is of great significance for the detection of specific symptoms of MDD.

The limitations of this study include the lack of correction for multiple comparisons across frequency bands and the sample size. Future studies in larger groups of depressive patients are needed to confirm and extend our findings. In addition, although there was no significant difference in the sex between the two groups, more male MDD patients should be recruited into subsequent studies to exclude the influence of sex on our results. Furthermore, longitudinal Rs-EEG assessment and correlation analysis between Rs-EEG and the clinical symptom scale in patients with MDD are helpful to better understand the disease progression of depressive patients and shed light on the physiological and pathological mechanisms of EEG oscillations in depression. It would also be important to investigate whether some of these resting EEG alterations could be used as prognostic and/or predictive indicators of treatment response.

VI. CONCLUSION

Exploring the effects of the EO and EC conditions on the separability of EEG biomarkers and understanding brain activities under different resting conditions is of great significance and necessity for depression diagnosis. This study was undertaken for the purpose of determining the better resting condition to provide more reliable estimates of altered brain activities in patients with first-episode depression and to identify sensitive and reliable EEG biomarkers for identifying depression. Traditional spectral and nonlinear methods were used to analyze EEG alterations in the EO and EC conditions. The LINSVM, RBFSVM, LR, and LDA classifiers were applied to verify the separability of EEG biomarkers. We found that the significant differences between the two groups in the EO condition were more prominent and representative in terms of spectrum, complexity, and scaling behavior. The EO condition had the best performance with LINSVM for the combined feature set, up to 89.29%, 90.00%, and 88.46% of accuracy, sensitivity, and specificity, respectively, when the threshold was set to 0.7. In addition, for the spectral feature set, the EO condition had the second-best performance with an average accuracy of 83.93%, sensitivity of 86.67%, and specificity of 80.77%. This suggests that there is more information about the altered EEG in depression in the EO resting condition compared to the EC condition. β and γ oscillations are candidates to serve as EEG biomarkers of first-episode depression recognition, which would provide a direction for follow-up research to continue the exploration of the electrophysiological mechanisms of depression.

CONFLICT OF INTEREST

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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