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ORIGINAL RESEARCH

Abnormalities in Electroencephalographic Microstates in Patients with Late-Life Depression

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Background: Late-life depression (LLD) is characterized by disrupted brain networks. Resting-state networks in the brain are composed of both stable and transient topological structures known as microstates, which reflect the dynamics of the neural activities. However, the specific pattern of EEG microstate in LLD remains unclear.

Methods: Resting-state EEG were recorded for 31 patients with episodic LLD (eLLD), 20 patients with remitted LLD (rLLD) and 32 healthy controls (HCs) using a 64-channel cap. The clinical data of the patients were collected and the 17-Item Hamilton Rating Scale for Depression (HAMD) was used for symptom assessment. Duration, occurrence, time coverage and syntax of the four microstate classes (A-D) were calculated. Group differences in EEG microstates and the relationship between microstates parameters and clinical features were analyzed.

Results: Compared with NC and patients with rLLD, patients with eLLD showed increased duration and time coverage of microstate class D. Besides, a decrease in occurrence of microstate C and transition probability between microstate B and C was observed. In addition, the time coverage of microstate D was positively correlated with the total score of HAMD, core symptoms, and miscellaneous items.

Conclusion: These findings suggest that disrupted EEG microstates may be associated with the pathophysiology of LLD and may serve as potential state markers for the monitoring of the disease.

Keywords: late-life depression, microstate, electroencephalogram, resting-state networks

Introduction

Late life depression (LLD) refers to major depressive disorder occurring in the older adults, characterized by chronic course, poor prognosis, and high recurrence rate.[1] As the most prevalent mental diseases, depression with an annual prevalence of 3.4% is one of the leading causes of the global burden of disease, ranking the 13th in Disability-adjusted life-years in 2019.[2] Unlike younger depressed patients, those with LLD often have more comorbidities and atypical clinical manifestations. LLD patients exhibit less prominent core symptoms and tend to experience cognitive impairment, physical symptoms and anhedonia,[3–5] which pose a challenge in accurately assessing the severity of the disorder, potentially leading to inappropriate therapy. Investigations into the underlying pathophysiological features of LLD may provide objective markers to enhance the evaluation of depressive severity.

Previous studies have shown that impaired global brain topology, disruption of synthesis and separation in brain functional networks might be an emblematic change of LLD.[6,7] Abnormalities in connectivity and interaction of the salience network, the default mode network, the cognitive control network were found in patients with LLD.[8–10]

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However, most of the available evidence comes from MRI studies. Restricted by the relatively low time resolution, MRI may fail to capture the rapidly changing dynamics of neural activities.

EEG records the neural electrical activity generated by the synchronous depolarization of the neuronal groups with high temporal resolution at the millisecond level. Given the consensus that altered brain oscillations and abnormal neural networks are core characteristics of various neuropsychiatric disease, EEG has been widely employed in studying brain networks in mental disorders.[11–14] Our previous research has identified abnormal functional connectivity in patients with LLD, and some studies have indicated that connectivity abnormalities can predict the treatment response in patients with depressive disorders.[15–17]

The resting-state EEG signal can be parceled out into different stable states referred as microstates, which rapidly transition to other microstates after remaining stable for 80–120 ms.[18] It is an effective means to study the spatial and temporal properties of resting-state networks.[19] Conventionally, microstates are categorized into four classes based on their topography. Class A exhibits a right frontal to left occipital orientation, class B exhibits a left frontal to right occipital orientation, class C has a prefrontal to occipital orientation, and class D shows a frontocentral to occipital orientation.[18] EEG-fMRI studies have identified microstates A, B, C, and D as corresponding to the auditory network, visual network, salience network, and attention network, separately.[19] Microstate is considered to be the cornerstone of spontaneous thinking.[20] It suggests that the rapid reorganization and adaptation of the brain's functional networks may be attributed to the scale-free dynamics observed.[21]

Microstates have been used in the study of many diseases.[22–24] Limited studies were conducted capitalizing on microstate to investigate patients with MDD.[25–28] However, the results of the studies were mixed. In most studies, abnormal duration, occurrence, and contribution of microstates were observed in patients with depression. One study included drug-naïve patients with MDD in the first episode showed an increase in the duration of microstate B, C, and D, as well as in the occurrence and contribution of microstate B, while another study of first-episode unmedicated MDD patients exhibited decreased duration of microstate D and increased duration of microstate A and B.[25] Apart from microstate D, Murphy et al reported a discrepancy in transition probability between remission and episode of depression.[29] In any case, microstates may potentially serve as an objective indicator of depressive state. However, few research has focused on LLD. Brain aging leads to various physiological, structural, functional and neurocognitive changes.[30] EEG microstates have been identified as age-related feature.[31] Therefore, it could be inferred that the pathophysiological alterations in LLD are different from those in MDD due to aging.

The aim of this study is to investigate the dysfunction of brain resting-state networks in LLD using EEG microstate analysis. Compared to those in healthy older individuals, it was assumed that microstate dynamics are disrupted in LLD based on the aforementioned evidence. Our study may enhance the understanding of the pathophysiology of LLD and offer novel insights into the treatment of LLD patients.

Methods

Participants

We recruited fifty-one patients with LLD from the Affiliated Brain Hospital of Guangzhou Medical University and community. Thirty-two elderly people from community in Guangzhou were recruited as healthy controls (HCs). Informed consent was signed by all participants. Approval of this study, which complies with the Declaration of Helsinki, was obtained from the Ethics Committee of The Affiliated Brain Hospital of Guangzhou Medical University.

The criteria for including patients with LLD were as follows: (1) age ≥60 years, (2) at least one episode of depression after 60 years; (3) meeting the diagnostic criteria for major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). (4) had normal visual and acoustic faculty. Diagnosis and clinical stage of LLD was confirmed by two clinicians from our hospital. Furthermore, patients with LLD were divided into two subgroups: 31 patients with episodic LLD (eLLD) and 20 patients with remitted LLD (rLLD). Episodic LLD was defined as a current episode. Remitted LLD was defined as past but no current diagnosis (remission) of LLD according to the the the Mini-International Neuropsychiatric Interview (M.I.N.I.).[32,33] HCs were also screened for psychiatric disorders using M.I.N.I. The exclusion criteria for both LLD and HCs were as follow: (1) presence of other mental diseases; (2) had brain organic diseases, history of brain trauma, or history of head injury resulting in a loss

of consciousness for >30 min; (3) presence of serious physical diseases; (4) had a history of substance abuse; (5) suffered from hypothyroidism.

Clinical Assessment

The demographic information and psychiatric history of the subjects were collected by a psychiatrist through interviews. The severity of depressive symptoms was assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17). Six factors subscores of HAMD were calculated by summing the HAMD item scores contained in each factor.[34] The six factors of the HAMD included in the analysis were: factor 1. "insomnia symptoms" (early insomnia, middle insomnia, late insomnia); factor 2. "severity" (feelings of guilt, suicide, insight); factor 3. "core symptoms" (depressed mood, work and activities, retardation); factor 4. "anxiety/hypochondriasis" (psychic anxiety, somatic anxiety, hypochondriasis); factor 5. "gastrointestinal symptoms/loss of weight" (gastrointestinal symptoms, loss of weight); and factor 6. "miscellaneous items" (agitation, general somatic symptoms, genital symptoms).

EEG Recording and Preprocessing

A 64-channel EGI net (Electrical Geodesic Inc., EGI) was used to record EEG data for a duration of 5 minutes with a sampling rate of 1000 Hz under the eyes-closed condition. The data processing was conducted using the EEGLAB toolbox in MATLAB R2021a.

We removed the redundant electrodes "E62" and "E63". The EEG data underwent band-pass filtering within the frequency range of 1 to 70 Hz, with a notch filter applied to eliminate power line interference. The data were segmented into epochs of 2000 ms duration.[27] We inspected the data by eyes to reject the bad epochs and interpolate bad channels. To eliminate non-physiological components, an independent component analysis (ICA) was conducted. The length of the included EEG data for analysis was at least 75 epochs.[35]

Microstate Analysis

MATLAB R2021a was used to conducted microstate analysis. The data underwent average referencing and were band-pass filtered in the range of 2–20Hz. We extracted the peaks of the global field power firstly. The topography that appeared at the peak of the global field power curve was then subjected to a modified k-means clustering algorithm in order to get the template maps. The number of replicates was set to 50 for clustering. The microstates classification was divided into 4 categories based on the most common classification.[36] For the four microstate classes, the following parameters were calculated: globally explained variance, duration, occurrence, coverage and transition probability. Duration represents the average duration of consecutive occurrences of a specific microstate class. Occurrence refers to the frequency of appearance of a particular microstate class per second. Time coverage indicates the percentage of cumulative time occupied by a certain microstate class. Transition probabilities between each pair of states were termed as microstate syntax.

Statistics

The one-way ANOVA and chi-square were used to compare general demographic information among three groups. The least significant difference (LSD) method was employed to identify significant differences in pairwise comparisons. To compare clinical data between eLLD group and rLLD group, an independent samples *t*-test was employed. A repeated-measures ANCOVA was conducted for each microstate parameter, with microstate classes (A–D) as a within-subject factor, group as a between-subject factor, and age, sex and years of education as controlling factors. When statistical significance was indicated in the repeated-measures ANCOVA, post-hoc univariate ANCOVA were conducted with the same covariates mentioned above. False discovery rates (FDR) correction was applied to these findings. For each pair of transition probabilities, differences among three groups were explored using univariate ANCOVA with the same covariate, corrected by FDR. For microstates revealing group differences, the partial correlation analysis was performed to investigate the association between EEG microstates and clinical characteristics controlling for the effects of age, sex and educational years in eLLD and rLLD patients, with FDR correction. Multiple linear regression analyses were employed to investigate the impact of microstate on depressive symptoms. Dependent variables included clinical features

significantly associated with microstates, independent variables included microstates parameters significantly associated with clinical features. A regression model was built, taking into account covariates such as age, sex, and years of education. A stepwise analysis approach was utilized for selecting independent variables, with a *p*-value of 0.05 for entry and 0.10 for removal. Each potential independent variable was evaluated for statistical significance when added to the model, and only the most significant variables were retained. This iterative process was repeated until achieving optimal results. Data analysis was conducted using SPSS 27 (IBM, USA), with a significance level set at 0.05. All statistical tests were two-tailed.

Results

Demographic and Clinical Characteristics

Table 1 shows the demographic and clinical characteristics. No significant difference was found in age or gender among groups ($p>0.05$). Patients with eLLD exhibited a lower level of education compared to the HCs group ($p = 0.005$), while there was no significant difference in educational years between the eLLD and the rLLD groups ($p>0.05$), as well as between the rLLD and the HCs groups ($p>0.05$). Additionally, there was no significant difference in the duration of disease, the number of episodes or the times of hospitalization between the eLLD and the rLLD groups ($p>0.05$).

Microstate Analysis

Figure 1 displays the topographical maps of the four microstate classes. Repeated-measures ANCOVAs yielded significant interactions between microstate class and group interaction for duration ($F = 3.462$, $p = 0.011$, $\eta^2 = 0.083$) and time coverage ($F = 2.914$, $p = 0.018$, $\eta^2 = 0.070$), as well as a microstate group interaction effect for duration ($F = 3.294$, $p = 0.042$, $\eta^2 = 0.079$) and occurrence ($F = 3.154$, $p = 0.048$, $\eta^2 = 0.076$) among the three groups. Post-hoc tests revealed that microstate C had decreased occurrence in patients with eLLD compared to patients with rLLD ($p = 0.003$) and HCs ($p = 0.040$). In addition, the eLLD group showed a significant increase in duration and time coverage of microstate D compared to the rLLD (duration D: $p = 0.002$; coverage D: $p = 0.002$) and HCs (duration D: $p = 0.028$; coverage D: $p = 0.037$) groups. (Figure 2, see also Table S1) Patients with eLLD were observed significantly reduced transition probabilities from classes B to C and from classes C to B compared to patients with rLLD (transition probability from B to C: $p = 0.004$; from C to B: $p = 0.001$) and HCs (transition probability from C to B: $p = 0.029$).

The Relationship Between EEG Microstate Parameters and Clinical Characters

Correlation analysis showed that Coverage D was associated with HAMD scores ($r = 0.444$, $p = 0.008$), core symptoms ($r = 0.489$, $p<0.001$), miscellaneous items ($r = 0.452$, $p = 0.006$). Duration D was associated with core symptoms ($r = 0.433$, $p = 0.024$). Transition probability from C to B was associated with core symptoms ($r = -0.433$, $p = 0.024$). No significant associations were observed between microstate D and other clinical indices, between the occurrence of microstate C and other clinical indices, as well as between other clinical indices and the transition probability between B and C. (Figure 3)

Table 1 Demographic and Clinical Characteristics of eLLD, rLLD and HCs

Variables	eLLD N=31	rLLD N=20	HCs N=32	F / χ^2 /t	*p*-value
Age	68.8±5.0	70.3±4.8	71.2±5.7	1.545	0.220
Gender(female/male)	20/11	17/3	20/12	3.294	0.193
Educational years	8.5±3.5	10.1±3.0	10.7±2.5	4.341	**0.016**
Duration of disease	148.5±168.7	118.1±133.8	–	0.695	0.491
HAMD scores	22.6±3.9	5.9±3.9	–	15.092	**<0.001**
Number of episodes	3.7±3.6	3.3±2.1	–	0.543	0.465
Times of hospitalization	1.4±1.3	0.9±1.3	–	0.003	0.958

Notes: Values of continuous variables are shown as mean ± standard deviation. Bold font indicates $p<0.05$.
Abbreviations: eLLD, episodic late life depression; rLLD, remitted late life depression; HCs, healthy controls; HAMD, Hamilton Rating Scale for Depression.

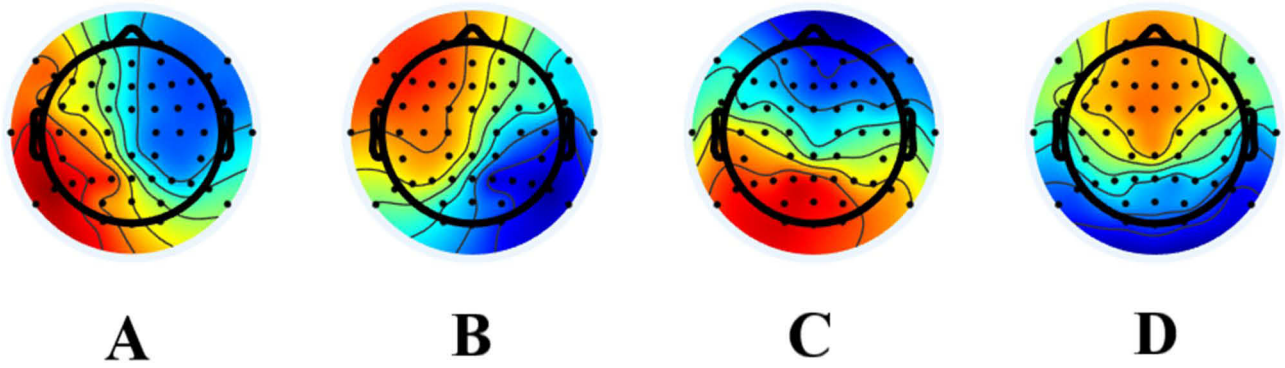

Figure 1 The topographical maps of the four microstate classes (**A**–**D**) estimated from resting state EEG of all participants.

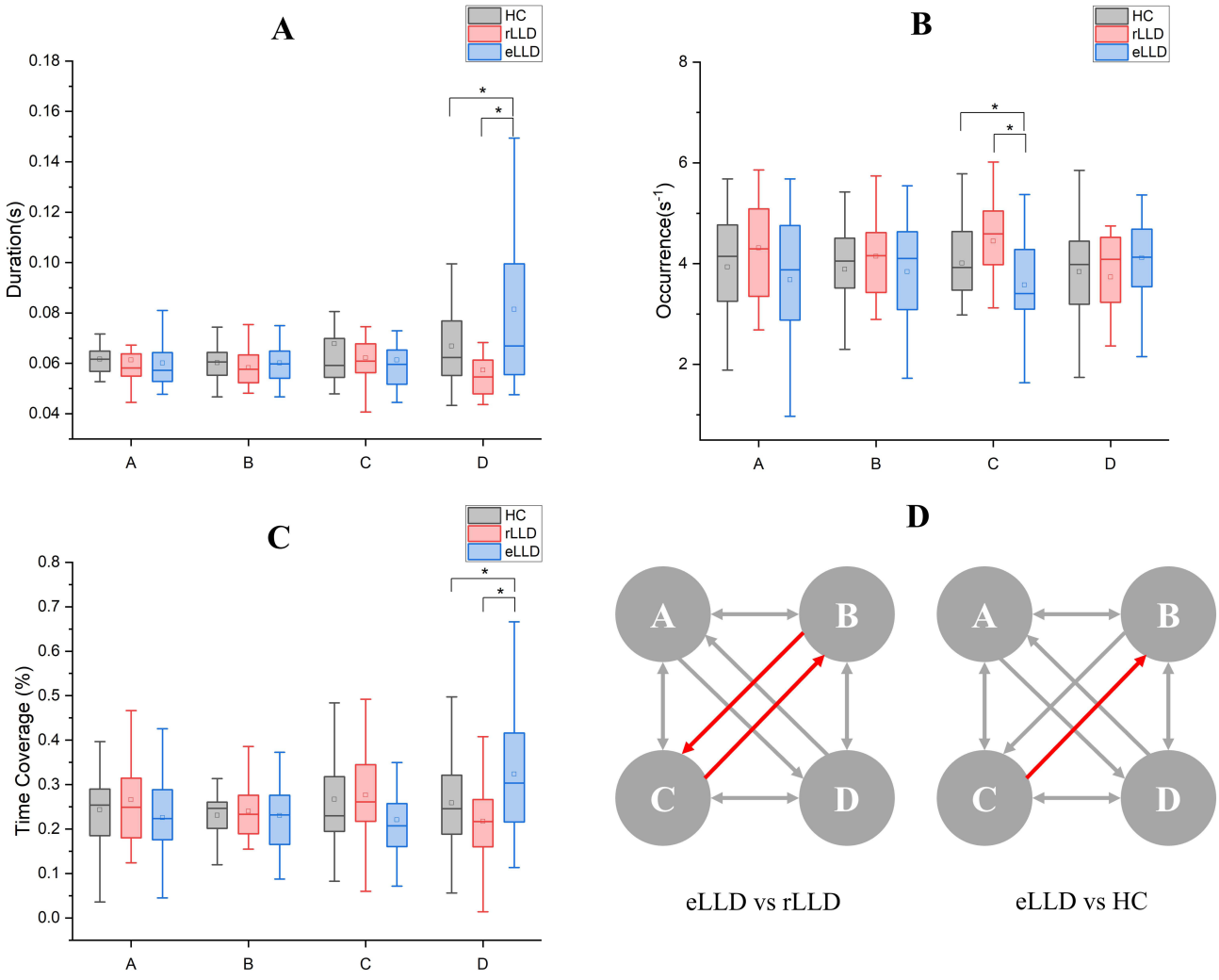

Figure 2 Results of the microstate analysis for eLLD, rLLD and HCs. (**A**) eLLD group exhibited increased duration of microstate D compared to the rLLD (p = 0.002) and HCs (p = 0.028) groups; (**B**) eLLD group exhibited decreased occurrence of microstate C compared to the rLLD (p = 0.003) and HCs (p = 0.040) groups; (**C**) eLLD group exhibited increased time coverage of microstate D compared to the rLLD (p = 0.002) and HCs (p = 0.037) groups. The parameters of each class are displayed from left to right. Gray icons indicate parameters of eLLD, Red icons indicate parameters of rLLD and blue icons indicate parameters of healthy controls. (**D**) The transition probabilities between microstate B and C were decrease in the eLLD group compared to the rLLD and HCs groups. Red arrows represent significant difference between groups while grey arrows represent no significant difference. * p-value ≤ 0.05.

Abbreviations: eLLD, patients with episodic LLD; rLLD, patients with remitted LLD; HCs, healthy controls.

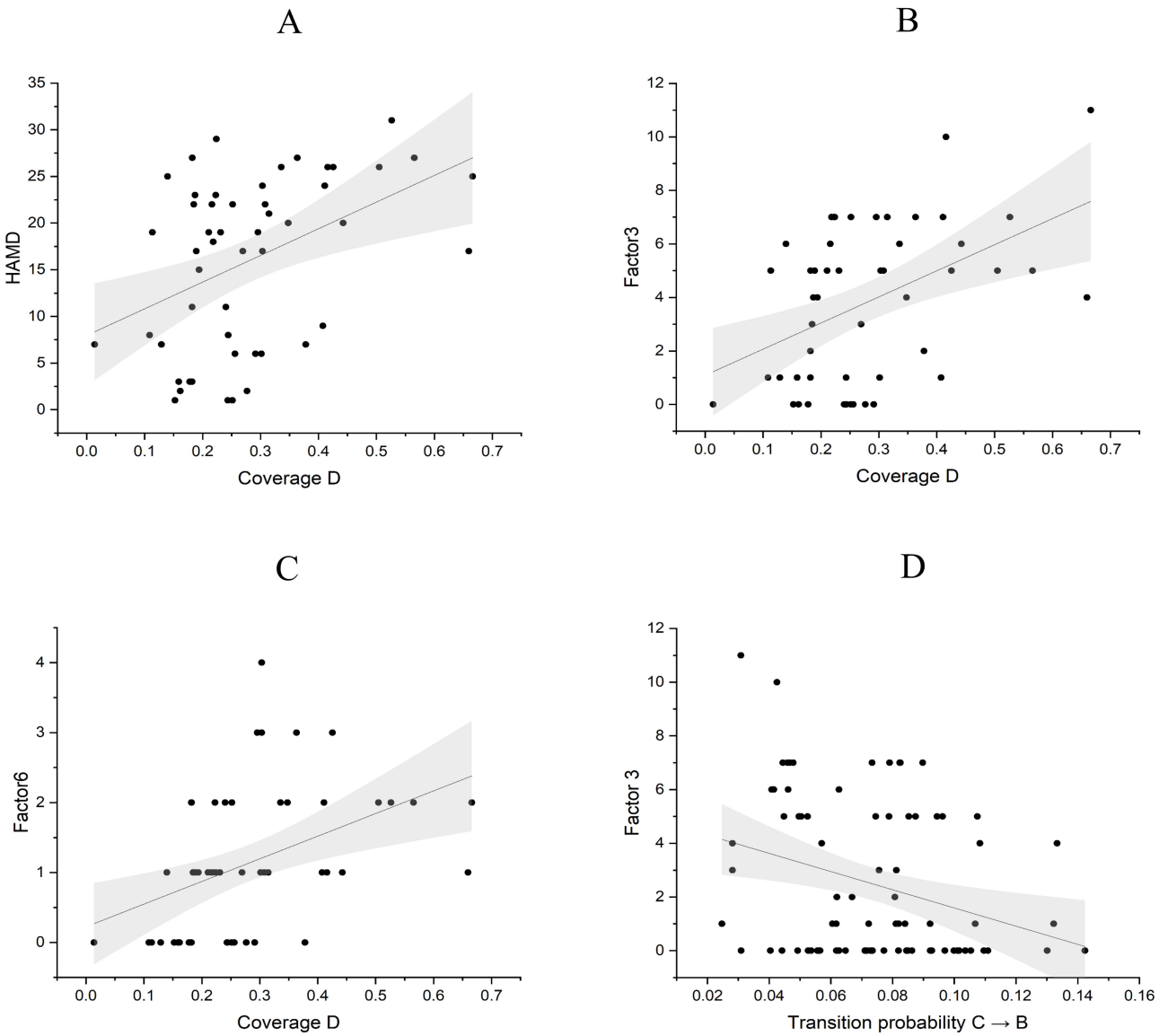

Figure 3 Correlation analysis for HAMD scores, factor 3 and factor 6. (**A**) Coverage of microstate D was associated with HAMD scores in patients with LLD (r = 0.444, p = 0.008), (**B**) Coverage of microstate D was associated with Factor 3 (core symptoms) in patients with LLD (r = 0.489, p<0.001); (**C**) Coverage of microstate D was associated with Factor 6 (miscellaneous items) in patients with LLD (r = 0.452, p = 0.006); (**D**) Transition probability from C to B and Factor 3 (core symptoms) was associated with in patients with LLD (r = −0.433, p = 0.024).
Abbreviations: LLD, Late-life depression; HAMD, Hamilton Rating Scale for Depression.

In linear regression with HAMD scores as the dependent variable, the coefficient for Coverage D (β = 0.426, t = 3.357, p = 0.002) was significant; In regression with core symptoms, the coefficient for Coverage D (β = 0.461, t = 3.801, p<0.001) was significant; In regression with miscellaneous items, the coefficient for Coverage D (β = 0.446, t = 3.349, p = 0.001) was significant. The aforementioned analyses were adjusted for age and years of education. (Table 2)

Discussion

To the best of our knowledge, this is the first study to investigate microstates in patients with LLD. In the case of eLLD, there was an observed increase in both the duration and contribution of microstate D, in comparison to rLLD and HCs. The results differ from previous studies on MDD, as several studies suggested a decrease in the duration and contribution of microstate D in MDD,[25,28,29] with one exception which reported an increase in the duration and contribution of microstate D as well as a reduction in the occurrence of microstate C in MDD.[28] There are likely several reasons for these discrepancies. For one thing, the temporal

Table 2 Regression Analysis for HAMD Scores, factor3 and factor 6

	Model			Variables	β	t	p
	R^2	F	p				
HAMD	0.268	4.212	**0.005**	Coverage D	0.426	3.357	**0.002**
				Age	−0.115	−0.903	0.371
				Sex	−0.159	−1.249	0.218
				Education	−0.201	−1.584	0.120
Factor 3	0.329	5.643	**0.001**	Coverage D	0.461	3.801	**<0.001**
				Age	−0.069	−0.564	0.575
				Sex	−0.315	−2.591	**0.013**
				Education	−0.112	−0.923	0.361
Factor 6	0.234	3.522	**0.014**	Coverage D	0.446	3.439	**0.001**
				Age	−0.209	−1.602	0.116
				Sex	−0.036	−0.274	0.785
				Education	−0.018	−0.137	0.892

Notes: Factor 3: core symptoms; factor 6: miscellaneous items. Bold font indicates $p<0.05$.
Abbreviation: HAMD, Hamilton Rating Scale for Depression.

features of EEG microstates exhibit age-related changes.[31] A neuroimaging study of depression showed that network efficiency decreased with age and was inversely correlated with depression severity.[37] A reduction in information processing speed among the elderly and a decrease in network efficiency have been documented.[38] Therefore, the abnormality of microstate D may indicate that the network efficiency of LLD decreases and the information processing speed slows down due to aging and disease.[39] For another, MDD and LLD have differences in frontoparietal network, dorsal attention network, and visual network.[40] The differences in neural networks may explain the increase of microstate B and reduction of microstate D in most previous studies on MDD, while we did not find an increase in microstate B but increased duration and contribution of microstate D in LLD. The neural basis related to attention allocation changes over time, and attentional control shifts rhythmically between nodes of the attention network, preventing process-time focusing on an event, which may be related to cognitive flexibility.[41] The increase in the duration and contribution of microstate D indicated that the dynamics of LLD microstate D was weakened, suggesting that there was an abnormality in the attention network and its rhythmicity was abnormal in LLD patients. This implied that patients with LLD had difficulties in resource allocation and impairment of cognitive flexibility.

In addition to microstate D, decreased occurrence of microstate C and reduced transition probability between microstate C and B were observed in eLLD compared to rLLD and HCs, which is thought to be associated with the disruption of salience network.[19] The salience network is responsible for detecting and filtering external stimuli.[42] It facilitates access to cognitive control resources upon detecting salient stimuli, regulating the dynamic switch between the default mode network-mediated self and inner world focus, and the externally-oriented, stimulus-related attention maintained by the frontoparietal network.[43,44] The deviant of occurrence of microstate C further supported the impaired allocation of cognitive resources in eLLD. The decrease of transition probability between microstate C and B implied the coded sequential activation of the neural components diminished in salience network and visual network.[18] This finding is in accord with a previous MRI study which showed a decrease in functional connectivity between the salience network and the visual network.[45] The changes in network dynamics observed between the visual and salience networks suggest a potential disruption in the integration of emotional processing and direct sensory experience.[46] This illustrates the absence of salient information selection in eLLD. In summary, our findings support impaired cognitive flexibility in eLLD.

There were several limitations in present study. Firstly, the sample size of the study was relatively small and the medication use was uncontrolled. Secondly, our study only used resting-state EEG data for analysis. Combining task-based and other detection methods could further explored the relationship between abnormal brain topology and clinical symptoms in LLD, as well as the underlying mechanism. Thirdly, our study was cross-sectional, and further longitudinal studies or neuromodulation protocol based on the observed microstates alterations are necessary to establish the causal association between abnormal neural networks and clinical symptoms in LLD. Fourthly, the absence of an independent validation dataset is a limitation of

our study. Additionally, future research can further use machine learning to validate the potential of microstate indicators in predicting depression symptoms at an individual level, thereby elucidating their clinical utility.

Conclusion

To summarize, patients with eLLD exhibited increased microstate class D of EEG. Furthermore, a positive correlation was found between microstate class D and depressive symptoms, especially core symptoms and miscellaneous items. Moreover, the presence of the atypical microstate D may indicate that the brain dysfunction is the underlying mechanism of LLD, which could be a potential indicator for tracing the symptom severity in patients with eLLD.

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Disclosure

The authors declare no conflicts of interest in this work.

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