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ORIGINAL ARTICLE

Observational Study

Abnormalities of electroencephalography microstates in patients with depression and their association with cognitive function

Rui-Jie Peng, Yu Fan, Jin Li, Feng Zhu, Qing Tian, Xiao-Bin Zhang

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Abstract

BACKGROUND

A growing number of recent studies have explored underlying activity in the brain by measuring electroencephalography (EEG) in people with depression. However, the consistency of findings on EEG microstates in patients with depression is poor, and few studies have reported the relationship between EEG microstates, cognitive scales, and depression severity scales.

AIM

To investigate the EEG microstate characteristics of patients with depression and their association with cognitive functions.

METHODS

A total of 24 patients diagnosed with depression and 32 healthy controls were included in this study using the Structured Clinical Interview for Disease for The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. We collected information relating to demographic and clinical characteristics, as well as data from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Chinese version) and EEG.

RESULTS

Compared with the controls, the duration, occurrence, and contribution of microstate C were significantly higher [depression (DEP): Duration 84.58 ± 24.35, occurrence 3.72 ± 0.56, contribution 30.39 ± 8.59; CON: Duration 72.77 ± 10.23, occurrence 3.41 ± 0.36, contribution 24.46 ± 4.66; Duration $F = 6.02$, $P = 0.049$; Occurrence $F = 6.19$, $P = 0.049$; Contribution $F = 10.82$, $P = 0.011$] while the duration, occurrence, and contribution of microstate D were significantly lower

(DEP: Duration 70.00 ± 15.92, occurrence 3.18 ± 0.71, contribution 22.48 ± 8.12; CON: Duration 85.46 ± 10.23, occurrence 3.54 ± 0.41, contribution 28.25 ± 5.85; Duration $F = 19.18$, $P < 0.001$; Occurrence $F = 5.79$, $P = 0.050$; Contribution $F = 9.41$, $P = 0.013$) in patients with depression. A positive correlation was observed between the visuospatial/constructional scores of the RBANS scale and the transition probability of microstate class C to B ($r = 0.405$, $P = 0.049$).

CONCLUSION

EEG microstate, especially C and D, is a possible biomarker in depression. Patients with depression had a more frequent transition from microstate C to B, which may relate to more negative rumination and visual processing.

Key Words: Depression; Electroencephalography; Microstates; Cognitive functions

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Core Tip: This study aims to explore electroencephalography microstates in patients with depression and the correlation between microstates and cognitive scales. Through statistical analyses, we found parameters of the microstate C were higher while microstate D were lower in patients with depression compared with the controls. A positive correlation was observed between the visuospatial/constructional scores and the transition probability of microstate C to B. Therefore, we speculate that microstates C and D, is a possible biomarker in depression. Patients with depression had a more frequent transition from microstate C to B, which may relate to more negative rumination and visual processing.

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INTRODUCTION

Depression is a chronic and debilitating disease that is characterized by depressed mood, diminished interests, and cognitive deficits manifested as low self-esteem, sleep disturbance, weight loss, and even disability[1,2]. In the Global Burden of Disease Study 2013 (GBD 2013), depression is the second-largest contributor to the burden of chronic disease as measured by years lived with disability[3]. Several characteristics of depression are consistent across countries, such as higher lifetime prevalence, lifelong chronic–recurrent persistence, and increased risk of early death due to somatic illness and suicide[4]. There is growing evidence that depression is associated with neural activity and connectivity[5], while our understanding of the neurobiology of depression continues to progress. However, there is still no definitive explanation for the pathophysiological mechanisms of the disease.

Electroencephalography (EEG), commonly used to study electrophysiological processes in the cerebral cortex, is capable of describing local and global neuronal activity in the brain neural networks[6]. Compared with other neuroimaging modalities such as functional magnetic resonance imaging (fMRI), EEG has the advantages of high temporal resolution, ease of measurement, and lower cost. Recently, a growing number of studies have attempted to explore possible abnormal potential activity in the brain neural networks of patients with depression by measuring EEG. For example, quantitative EEG was used to predict and monitor the response to depression treatment. Arns *et al*[7] found that depressed patients with low theta waves in the frontal cortex and the rostral anterior cingulate were more responsive to medication. Another study showed that those with increased quantitative EEG theta cordance had significant improvement in depressive symptoms after 6 weeks of repetitive transcranial magnetic stimulation (rTMS) treatment[8]. This suggests that changes in EEG theta cordance could be a potential clinical predictor of outcome of depression treatment.

In early studies based on resting-state EEG analyses, Lehmann *et al*[9] found that the alpha frequency band (8-12 Hz) of the EEG signal can be broken down into several quasi-stable states called EEG microstates, which can be recorded as four quasi-stable topographic maps to represent global brain activity[10], remaining stable for 80-120 ms and rapidly transitioning to the next microstate. Different information and data transmitted to the brain elicit different neurophysiological responses and correspond to individual EEG microstates. These four classical maps of EEG microstates are: (A) States associated with auditory processing; (B) States associated with visual processing; (C) States associated with cognitive control networks; and (D) States associated with dorsal attention networks[11]. EEG microstate analysis has been widely used in studies related to psychiatric disorders, showing schizophrenia[12-14], bipolar disorders[15,16], anxiety disorders [17], panic disorders[18], and insomnia[19]. For example, increases in microstate C and decreases in microstate D have been consistently identified as characteristic changes in individuals with schizophrenia. These microstates, C and D, have emerged as potential endophenotypes for schizophrenia[20]. The utilization of these microstates in the clinical diagnosis and treatment of schizophrenia has reached a significant level of consensus among various studies[21,22].

However, many studies found significant but less consistent results regarding EEG microstate features in patients with depression. Some studies found increased occurrence and contribution of microstate B and decreased occurrence and contribution of microstate D in patients with depression compared to healthy controls[23,24]. However, another study suggested that students with depression had lower duration of microstate C[25]. Qin *et al*[26] demonstrated a positive correlation between the occurrence of microstate B and Beck Depression Inventory-II (BDI-II) scores, and the occurrence of microstates D and E were negatively correlated with BDI-II scores. In contrast, several experimental studies have found no association between severity of depression and EEG microstate[23]. Lei *et al*[27] found that shorter durations of microstate D, higher frequencies of microstate C, and lower probabilities of transition from microstate D to B were associated with better treatment effects in patients with depression. Additionally, several studies have proposed that EEG microstate can predict the treatment outcomes of selective serotonin reuptake inhibitors (SSRI) or rTMS[27,28]. The discrepancy among the results of studies may be attributed to differences in the severity of depression or differences in microstate analysis methods. Therefore, there is a need to conduct a more comprehensive study of EEG microstates in patients with depression.

According to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), cognitive dysfunction is well established as a core diagnostic criterion of depression. Current research suggests that cognitive dysfunction reduces occupational productivity and interferes with social function in patients with depression[29]. In 2016, the United States Food and Drug Administration recommended cognitive symptoms as a target for intervention in the treatment of depressive disorder[30]. Thus, there is a need to emphasize the impairment of cognitive function in patients with and to include this in the diagnosis and treatment. A growing number of scientists are demonstrating that individual EEG microstates may correspond to specific mental states, which consistently influence the processing of and response to incoming information[31,32]. Taken together, we can collect data on global neuronal activity in the brain through EEG, quantify the cognitive cuts through neurocognitive assessment, and analyze multidimensional data in order to find biological markers that more accurately assess the condition of patients with depression.

We collected 128-lead resting-state EEG data from patients with depression and healthy controls to investigate their EEG microstate characteristics. The results were calibrated through statistical methods, attempting to find more realistic and reliable characterizations of EEG microstates. In addition, we also analyzed the correlation between EEG microstate characteristics and cognitive scales, which has rarely been studied before. Third, we correlated EEG microstate parameters with the Hamilton Depression Scale (HAMD) to figure out possible relationships between depression severity and EEG microstates.

MATERIALS AND METHODS

Participants

Participants were recruited from January 2016 to December 2018 at Suzhou Guangji Hospital, in adherence with the Helsinki Declaration. Written informed consent was obtained from all individuals, and the study received approval from the Ethics Committee of Suzhou Guangji Hospital. Demographic and clinical characteristics, as well as data from the repeatable battery for the assessment of neuropsychological status (RBANS; Chinese version)[33] and EEG, were collected from a sample of 24 patients diagnosed with depression (DEP) and 32 healthy controls (CON). Patients who exhibited stable depression were deemed suitable for inclusion. Each patient underwent an interview utilizing the Structured Clinical Interview for DSM Disorders (SCID) to ascertain their compliance with the criteria for a depressive episode. Control participants, who were in good health, possessed no prior psychiatric afflictions, had no immediate family members with psychiatric disorders, and had not previously utilized psychotropic medications. All participants, regardless of their depression status, underwent the SCID for diagnostic validation, as well as the HAMD to evaluate the extent of their depressive symptoms. All individuals classified with depression satisfied the inclusion criteria: (1) Age 18-60 years; (2) Right-handed; (3) All participants who were clinically stable did not have a history of neurological disorders or head trauma; and (4) None of the participants had undergone electroconvulsive therapy within the past 6 mo. Participants with a history of alcohol or drug dependence or abuse, with the exception of tobacco, were excluded from the study.

The CON group was comprised of individuals who were matched to the DEP group in terms of gender, age, and years of education.

Neurocognitive assessments

The neurocognitive functions of the participants were evaluated using the RBANS. RBANS is a standardized assessment tool that measures five specific cognitive domains, namely immediate memory (IMM), delayed memory (DEM), visuo-spatial/constructional (VC), attention (ATT), and language (LAN).

EEG recording and preprocessing

Participants were seated comfortably in a reclining chair and instructed to close their eyes and maintain a relaxed and quiet state for a duration of 3 min. The continuous EEG data were digitized at a sampling rate of 1000 Hz using the EGI EEG system (Electrical Geodesics, Eugene, OR, United States) with a 128-electrode HydroCelnet referenced to the vertex (Cz). Offline preprocessing of the EEG data was performed using the EEGLAB (v2021.1)[34] and HAPPE[35] toolboxes in MATLAB (Release 2022b; MathWorks). The raw EEG data were initially resampled to a sampling rate of 500 Hz. A band-pass filter with a range of 0.5-45 Hz was applied. Subsequently, the EEG data for each participant was preprocessed using the HAPPE toolkit. Following this, a manual inspection of the EEG data was conducted to confirm the removal of

artifacts. Lastly, all electrodes were re-referenced to an average reference.

Microstate analysis

A band-pass filtering ranging from 2 to 20 Hz was executed. Microstate analysis was conducted utilizing the EEGLAB microstate plugin[36]. The global field power was used to measure the collective alteration in potential across the electrode set, thereby indicating the electric field intensity throughout the brain at each moment. The atomize and agglomerate hierarchical clustering (AAHC) algorithm[37] was used to compute four optimal microstate topographies.

Cluster analyses were conducted on a series of EEGs at the individual level, referred to as first-level clustering. The clustering was performed at the group level, known as second-level clustering. And clusters were rearranged based on normative microstate template maps. This process involved clustering across all subjects to generate a comprehensive set of global maps representing all participants. Lastly, a new dataset was generated, and each temporal parameter of the microstate was extracted for subsequent statistical analysis. Figure 1 shows the topographic distributions of global maps. Based on earlier studies' spatial patterns[27,38], we classified the spatial patterns as microstates A/B/C/D. We used the duration, occurrence, contribution and transition probability of microstates as our parameters. Duration denoted the mean steady duration of a microstate; occurrence denoted the mean frequency of observation of each microstate; contribution denoted the proportion of the total time spent in each microstate; and transition probability denoted the proportion of all observed microstate transitions that went from X to Y.

Statistical analysis

Statistics were performed in RStudio (Version 2023.06.1, Boston, MA, United States) with R software (Version 4.3.1). The independent sample *t*-test, chi-square test and Wilcox Mann-Whitney test were conducted to evaluate potential differences in demographic and clinical characteristics between the DEP and CON groups. The analysis of covariance (ANCOVA, education was controlled) was conducted to calculate *P* value in RBANS score and EEG microstate features between the DEP and CON groups, and the false discovery rate (FDR) was calculated to adjust *P* values for multiple testing based on the Benjamini-Hochberg method[39]. $P < 0.05$ (two-tailed) was considered as indicative of statistical significance. Within the DEP group, Pearson correlation analysis were performed for neurocognitive RBANS score and EEG microstate parameters. To account for multiple testing, *P* values were calculated using a permutation test with 100000 replicates.

RESULTS

Demographic, clinical and neurocognitive RBANS characteristics

The demographic and primary clinical data include gender, age, years of education, HAMD score, duration of illness, and age at onset. Age and education were expressed as means and SDs, HAMD score, duration of illness and age at onset were expressed as median and range. The demographic and clinical characteristics of the DEP and CON groups are shown in Table 1. There were no significant differences in age or gender between the two groups. Only years of education and HAMD score showed significant differences in the two groups (education: $t = 2.056$, $P = 0.045$; HAMD score: $W = 83$, $P < 0.001$). ANCOVA and FDR were used to analyze participant RBANS characteristics, but no significant differences were found in the two groups (Table 2).

Differences in EEG microstate between the DEP and CON groups

The ANCOVA (education was controlled) and FDR results are shown in Figure 2 and Table 3. Regarding the duration of all four EEG microstates, the duration of microstate C (DEP: 84.58 ± 24.35; CON: 72.77 ± 10.23; $F = 6.02$, $P = 0.049$) in the DEP group was higher than in the CON group. The duration of microstate D (DEP: 70.0 ± 15.92; CON: 85.46 ± 10.23; $F = 19.18$, $P < 0.001$) in the DEP group was lower than in the CON group. The occurrence and contribution of microstate C (DEP: Occurrence 3.72 ± 0.56, contribution 30.39 ± 8.59; CON: Occurrence 3.41 ± 0.36, contribution 24.46 ± 4.66; Occurrence $F = 6.19$, $P = 0.049$; Contribution $F = 10.82$, $P = 0.011$) in the DEP group was significantly higher than in the CON group. The occurrence and contribution of microstate D (DEP: Occurrence 3.18 ± 0.71, contribution 22.48 ± 8.12; CON: Occurrence 3.54 ± 0.41, contribution 28.25 ± 5.85; Occurrence $F = 5.79$, $P = 0.050$; Contribution $F = 9.41$, $P = 0.013$) in the DEP group was significantly lower than in the CON group.

The result of EEG microstate transition probability (%) showed that the transition probability of class A to C (DEP: 9.17 ± 2.23; CON: 8.01 ± 1.42; $F = 5.94$, $P = 0.049$), class B to C (DEP: 9.18 ± 2.69; CON: 7.45 ± 1.68; $F = 8.58$, $P = 0.017$) and class C to B (DEP: 9.28 ± 2.89; CON: 7.39 ± 1.75; $F = 9.12$, $P = 0.015$) was significantly higher in the DEP group compared to the CON group. The transition probability of class A to D (DEP: 7.00 ± 2.43; CON: 8.93 ± 1.91; $F = 11.01$, $P = 0.011$) and class D to A (DEP: 7.08 ± 2.38; CON: 8.89 ± 1.91; $F = 9.95$, $P = 0.013$) was significantly lower in the DEP group than in the CON group. No statistically significant differences were found in other EEG microstate parameters.

Relationships among the EEG microstate parameters, HAMD score, and RBANS score in DEP group

Correlation analysis showed no significant correlation between the HAMD score and EEG microstate parameters in the DEP group. Considering the findings from EEG microstate analysis conducted on the DEP group, our attention was directed towards examining the relationship between microstate parameters and neurocognitive RBANS score. Pearson correlation analysis revealed a negative correlation between immediate memory scores and the frequency of microstate class A ($r = -0.406$, $P = 0.049$). Additionally, a positive correlation was observed between visuospatial/constructional

Table 1 Demographic and clinical characteristics of depression group and healthy control

Variables	DEP (*n* = 24)	CON (*n* = 32)	$\chi^2/t/W$	*P* value
Gender (female/male)	8/16	15/17	0.555	0.456[1]
Age (yr)	32.4 ± 11.3	33.8 ± 10.5	0.490	0.626[1]
Education (years of schooling)[a]	13.3 ± 2.8	14.8 ± 2.7	2.056	0.045[2]
HAMD score[c]	10 (0-23)	0 (0-6)	83	< 0.001[3]
Duration of illness (mo)	48.0 (24.5-195.0)			
Age at onset (yr)	25.5 (16.8- 27.3)			

[1]Indicates *P*-value for Chi-square test.
[2]Indicates *P*-value for independent sample *t*-test.
[3]Indicates *P*-value for Wilcox Mann–Whitney test.
[a]$P < 0.05$.
[c]$P < 0.001$.
mean ± SD are reported for age, education; Median (interquartile range) are reported duration of illness, age at onset, HAMD score. DEP: Depression group; CON: Healthy control group; HAMD: Hamilton Depression Scale.

Table 2 Neurocognitive RBANS score of depression group and healthy control

Variables	DEP (*n* = 24)	CON (*n* = 32)	*F*	*P* value[1]
RBANS score				
Immediate memory	85.92 ± 21.07	94.78 ± 15.57	3.559	0.145
Visuospatial/constructional	98.50 ± 17.92	94.44 ± 17.60	0.893	0.428
Language	92.92 ± 13.42	99.38 ± 14.23	3.204	0.167
Attention	104.54 ± 11.64	109.3 ± 11.74	2.755	0.196
Delayed memory	90.42 ± 18.13	94.25 ± 11.32	1.05	0.393
Total score	92.79 ± 17.66	97.78 ± 13.56	1.824	0.302

[1]Indicates *P* value for analysis of covariance, education was controlled, and false discovery rate was used to adjust *P* value.
mean ± SD are reported for all variables. DEP: Depression group; CON: Healthy control group.

scores and the transition probability of microstate class C to B ($r = 0.405$, $P = 0.049$). Nevertheless, no significant disparities were found in relation to other microstates. Subsequently, in order to mitigate the likelihood of erroneous positive results, a permutation test employing 100,000 random permutations was employed to ascertain the statistical significance of the two correlations. Notably, the correlation between the visuospatial/constructional score and the microstate transition probability from class C to B remained significant at $P < 0.050$ (Figure 3). Conversely, no significant correlation was observed between the immediate memory scores and the incidence of microstate class A.

DISCUSSION

This study sought to explore the dynamic activity of global brain resting-state networks (RSNs) among patients with depressive disorder and investigate their EEG microstate characteristics. This study showed significant differences in microstate analysis in the DEP group compared with the CON group, and EEG microstates can be characteristic indicators of depression. Especially, we showed that increased occurrence, duration, and contribution of microstate C and decreased occurrence, duration, and contribution of microstate D were depression characteristics. Another finding of our study was that patients with depression had a higher transition probability from C to B, which might be related to their cognitive function and visual processing.

EEG microstates in patients with depression

Our results indicate that the duration, occurrence, and contribution of microstate C increased while the duration, occurrence, and contribution of microstate D decreased. These results were generally consistent with previous studies. In a study exploring EEG microstates in adolescents with depression, the occurrence and contribution of microstate D were reduced compared with in healthy controls[23], which were also found among adults with depression[40]. Enhanced

Table 3 Electroencephalography microstate features of depression group and healthy control

Variables	DEP (*n* = 24)	CON (*n* = 32)	*F*	*P* value[1]
Duration (millisecond)				
Class A	70.01 ± 11.40	73.19 ± 7.35	1.70	0.314
Class B	72.20 ± 12.25	69.28 ± 6.37	1.38	0.36
Class C[a]	84.58 ± 24.35	72.77 ± 10.23	6.02	0.049
Class D[c]	70.00 ± 15.92	85.46 ± 10.23	19.18	< 0.001
Occurrence (Hz)				
Class A	3.30 ± 0.69	3.45 ± 0.41	1.13	0.393
Class B	3.36 ± 0.50	3.24 ± 0.25	1.31	0.363
Class C[a]	3.72 ± 0.56	3.41 ± 0.36	6.19	0.049
Class D[a]	3.18 ± 0.71	3.54 ± 0.41	5.79	0.050
Contribution (%)				
Class A	23.08 ± 7.06	25.25 ± 4.70	1.96	0.292
Class B	24.05 ± 5.68	22.04 ± 3.01	3.09	0.168
Class C[a]	30.39 ± 8.59	24.46 ± 4.66	10.82	0.011
Class D[a]	22.48 ± 8.12	28.25 ± 5.85	9.41	0.013
Transition probability (%)				
Class A to B	6.94 ± 1.82	7.22 ± 1.02	0.50	0.525
Class A to C[a]	9.17 ± 2.23	8.01 ± 1.42	5.94	0.049
Class A to D[a]	7.00 ± 2.43	8.93 ± 1.91	11.01	0.011
Class B to A	7.21 ± 1.88	7.55 ± 0.98	0.73	0.458
Class B to C[a]	9.18 ± 2.69	7.45 ± 1.68	8.58	0.017
Class B to D	7.16 ± 2.88	7.49 ± 1.31	0.34	0.578
Class C to A	8.83 ± 2.05	7.77 ± 1.41	5.40	0.057
Class C to B[a]	9.28 ± 2.89	7.39 ± 1.75	9.12	0.015
Class C to D	8.31 ± 2.31	8.60 ± 1.33	0.34	0.578
Class D to A[a]	7.08 ± 2.38	8.89 ± 1.91	9.95	0.013
Class D to B	7.30 ± 2.84	7.99 ± 1.54	1.38	0.360
Class D to C	8.08 ± 2.40	8.30 ± 1.20	0.21	0.650

[1]Indicates *P* value for analysis of covariance, education was controlled, and false discovery rate was used to adjust *P* value.
[a]$P < 0.05$.
[c]$P < 0.001$.
mean ± SD are reported for all variables. DEP: Depression group; CON: Healthy control group.

microstate D activity was found in the right superior parietal lobules, the right inferior parietal lobules, the right middle and superior frontal gyri[11,41], which was associated with the dorsal attention network. In a study combining fMRI and EEG to capture global brain activity, reduced microstate D associated with decreases in connectivity of the dorsal attention network may manifest as rumination and predict attention deficits among patients with depression[23,42]. Meanwhile, another study showed that duration of microstate C was significantly higher in patients with depression compared with the control group[43], which was also consistent with our results. However, some studies take different views; reduced duration of microstate C was found in students with depression[25]. Other studies found a result that we did not observe, which was the increased occurrence of microstate B[26,27].

There can be a number of possible reasons for these inconsistencies. Firstly, different frequency bands were studied; early experiments examined 8-12 Hz, but recently, most microstate studies were based on larger bandwidths such as 2-20 Hz or 1-40 Hz[32]. Secondly, the methods of analyzing EEG microstates varied, such as different clustering algorithms. Thirdly, the subjects included were different; for example, Liang's study[25] included college students with depressive symptoms and only screened the students with depression according to the Beck Depression Inventory-II (BDI-II) and

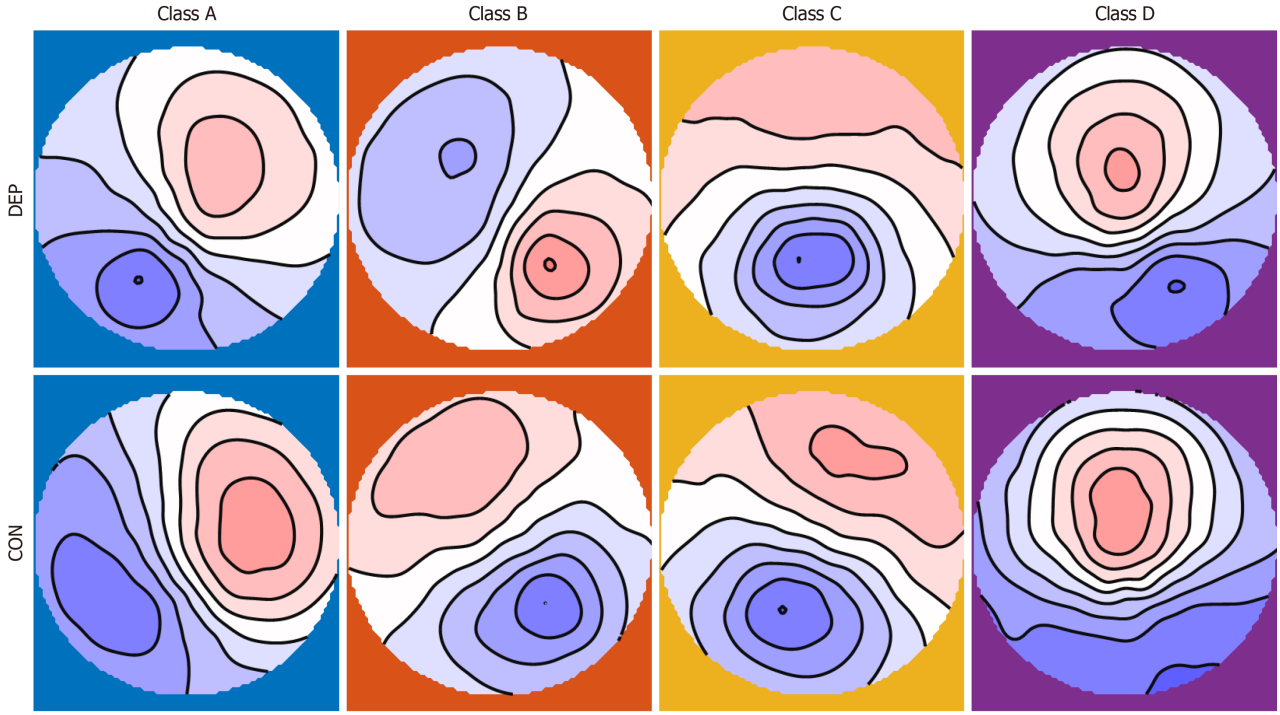

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Figure 1 Illustrates a comparison of scalp topographies between the depression group and healthy control group. According to previous literature, microstates are represented by the classes A to D. DEP: Depression group; CON: Healthy control group.

Depression Self-Rating Scale scores, but it did not fully meet the diagnostic criteria of the DSM-V. However, the decreased duration, occurrence, and contribution of microstate D have been found in most studies examining EEG microstates in patients with depression. We applied the FDR to adjust the *P* value to obtain more reliable results. Thus, possibly, microstate D is a potential biomarker for patients with depressive disorder.

From the transition probability among the EEG microstates, we found that the transition probability of microstates A to C, C to B, and B to C increased, while the transition probability of microstates A to D and D to A decreased. The fast transition probabilities among EEG microstates had a relationship with the quick switching in brain functional networks [44]. Patients with depression had significantly more transition from A to C, which explained the increase in microstate C among patients with depression compared with the controls. Some previous studies reported that microstate C was correlated with memory and rest recovery capabilities, and increased occurrence of microstate C and higher transition probability of A to C was related to the better therapeutic effect in patients with depression[27,42]. These results suggested that microstate C may be a protective factor and that the higher occurrence of microstate C was associated with better prognosis and treatment outcomes in depression. However, our study is a cross-sectional study, and in the future, we will follow up the EEG microstates of patients with depression after treatment to examine whether microstate C is an antidepressive factor.

Relationship between EEG microstates and cognitive function

Using RBANS, we found there were no significant differences in cognitive function among patients with depressive disorders compared to the controls, which is in contrast to the findings of previous studies[45-47]. The large discrepancy may be attributed to the following reasons. First, the subjects included were different in that the patients with depression in our study had lower HAMD scores (10.04 ± 8.06), whereas most of the other studies included patients with major depressive disorder, and thus the differences in cognitive dysfunction were not significant between our DEP and CON groups. Second, the tools of clinical and neuropsychological tests used to detect cognitive function were different. Our experiment used RBANS to detect cognitive functions, whereas other studies assessed them with the Sheehan Disability Scale[45], CogState Research Battery[46], or MATRICS Consensus Cognitive Battery[47], and different scales may produce different results.

From the EEG microstates, a significantly higher transition probability of microstates C to B was observed in patients with depression. Microstate B activity was found in the left and right occipital cortices (cuneus), including Brodmann areas 17 and 18 (primary visual cortex), the right insular cortex extending to the right claustrum, and the right frontal eye field[41], and was associated with visual processing[11]. Microstate C activity was found in the precuneus, posterior cingulate cortex, and left angular gyrus[41], and was associated with cognitive control networks[11]. In addition to this, from the RBANS scores of the DEP and CON groups in Table 2, patients with depression had a higher score of visuospatial/constructional compared with the CON group, which was the only item of the RBANS that scored higher than in the CON group, with all other items showing a downward trend. Furthermore, the increased transition probability of microstates C to B significantly correlated with the visuospatial/constructional of RBANS in Figure 3, so,

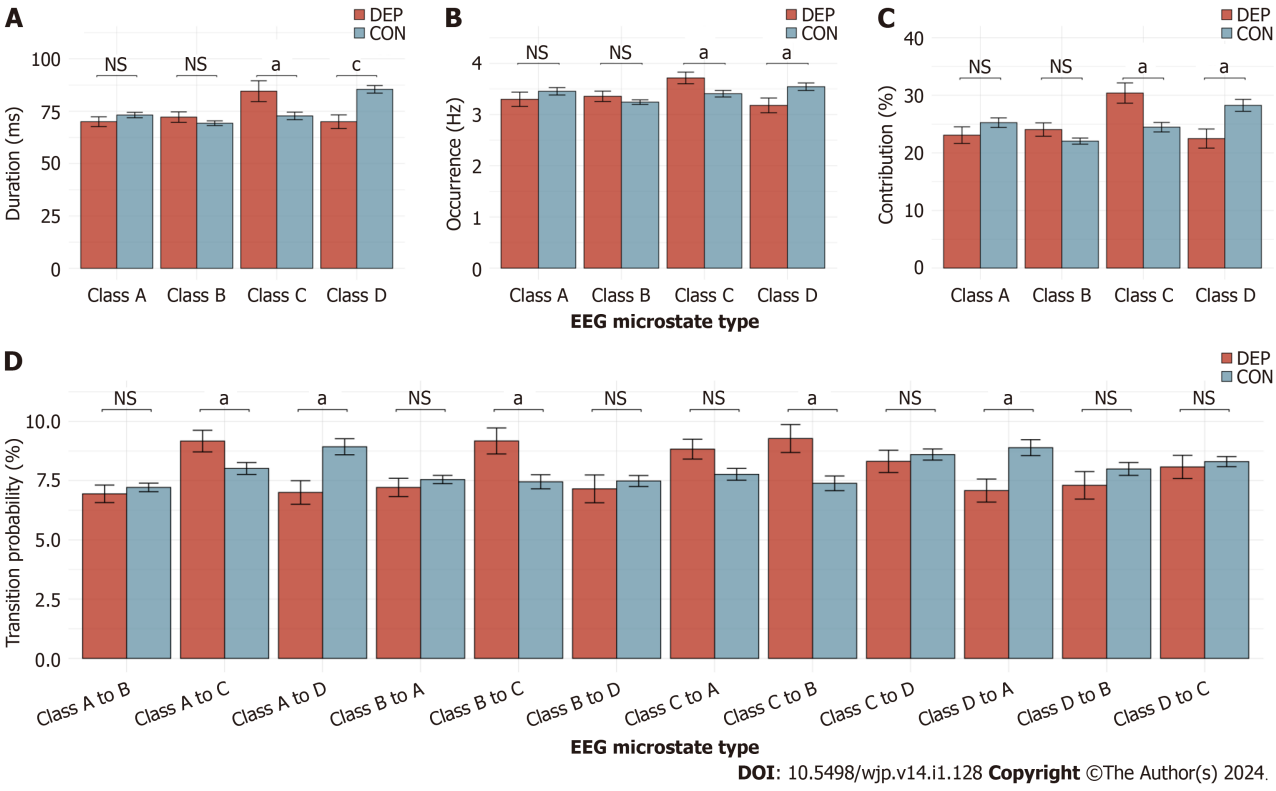

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Figure 2 Bar diagrams show the parameters of each microstate of the two groups. A: Duration; B: Occurrence; C: contribution. Horizontal coordinate axis represents four microstates A, B, C, and D; D: Transition probability; horizontal coordinate axis represents microstate transition type. $^{a}P < 0.05$; $^{c}P < 0.001$. DEP: Depression group; CON: Healthy control group; NS: Not significant.

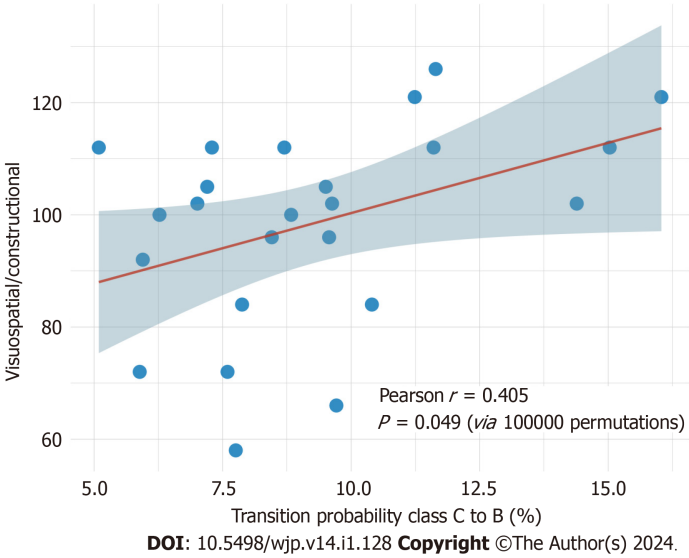

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Figure 3 Correlation between the repeatable battery for the assessment of neuropsychological status visuospatial/constructional function scores and transition probability microstate class C to class B in the depression group. *P* values were generated by permutation tests with 100000 replicates.

we were able to hypothesize that the increased transition probability of microstates C to B in patients with depression was related to more visual processing. Previous studies found that depression was associated with negative rumination [48], such as the constant recollection of replaying negative events in the mind, which involved visual processing[49], cognition[50], and the default mode network (DMN)[51], with visual processing being associated with microstate B and the activated regions of microstate C being part of the DMN. Consequently, the more frequent transition from C to B may imply that patients with depressive disorders had more frequent negative rumination as well as more and longer visual processing.

Correlations between EEG microstates and depressive severity

From the correlation analysis of HAMD and EEG microstates, our study did not identify a strong association between the severity of depression and EEG microstates, which was consistent with previous studies[23,27]. However, many studies have also found a strong relationship between the severity of depressive symptoms and EEG microstates. For example, some studies found that more severe depressive symptoms were positively correlated with microstate B and negatively correlated with microstate D[26,40], while other studies found that more severe depressive symptoms were associated with higher occurrence of microstate A[52]. Differences in results may be due to the following. First, different methodological approaches may have led to different conclusions regarding EEG microstate data in this and previous studies, such as different clustering algorithms applied and different numbers of maps recorded (4-6 types of maps were recorded in EEG microstate). Second, a variety of scales was used to assess the severity of depressive symptoms, including the Montgomery–Åsberg Depression Rating Scale, BDI-II, and HAMD.

CONCLUSION

we examined the temporal dynamics of resting-state EEG microstates in patients with depression and healthy controls. Our study demonstrated that, compared with controls, the occurrence, duration, and contribution of microstate C increased while the occurrence, duration, and contribution of microstate D decreased in patients with depression. Several alterations in EEG microstate transition probabilities were related to the fast switching in brain functional networks, including the increased transition probability of microstates A to C, C to B, and B to C, while the transition probability of microstates A to D and D to A decreased. In addition, we found that patients with depression had a more frequent transition from microstate C to B, which may be related to more negative rumination and visual processing. Therefore, EEG microstate analyzed the possible changes in neurons in the brain of patients with depression from the perspective of sub-second brain dynamics and was a possible biomarker in depression. In future clinical practice, comprehensive clinical examinations from multiple angles and dimensions should be performed to assess and diagnose depression.

This study had some limitations. First, the sample size was small, only 24 people were included in the DEP group and they only had mild or moderate depression. Subsequently, more studies with larger numbers of patients with depression and normal controls should be conducted to assess more accurately the relationship between depressive disorders and EEG microstates. Second, this study was only a cross-sectional study, and no longitudinal follow-up assessment was performed to explore the changes in EEG microstates after treatment. So, we will further perform a longitudinal interventional cohort study on therapy in the DEP group to find any possible associations between EEG microstates and prognosis through regular follow-up. Third, there was no sex difference between the two groups in our study, but other studies have found that there are differences in EEG microstates across age and sex[53]. In the future, we will study a broader age group and investigate possible sex differences in EEG microstates. Finally, future studies could combine EEG data with resting-state fMRI data from patients with depression to study brain neural network changes through both temporal and spatial dimensions in an integrated manner.

ARTICLE HIGHLIGHTS

Research background

Depression is a chronic and debilitating disease that is characterized by depressed mood, diminished interests, and cognitive deficits manifested as low self-esteem, sleep disturbance, weight loss, and even disability. Electroencephalography (EEG), commonly used to study electrophysiological processes in the cerebral cortex, is capable of describing local and global neuronal activity in the brain neural networks. Therefore, there is a need to conduct a more comprehensive study of EEG microstates in patients with depression.

Research motivation

The results were calibrated through statistical methods, attempting to find more realistic and reliable characterizations of EEG microstates. In addition, we also analyzed the correlation between EEG microstate characteristics and cognitive scales, which has rarely been studied before. Third, we correlated EEG microstate parameters with the Hamilton Depression Scale (HAMD) to figure out possible relationships between depression severity and EEG microstates.

Research objectives

This study was to investigate the EEG microstate characteristics of patients with depression and their association with cognitive functions. Our study demonstrated that, EEG microstate, especially C and D, is a possible biomarker in depression. In addition, we found that patients with depression had a more frequent transition from microstate C to B, which may be related to more negative rumination and visual processing. In future clinical practice, healthcare professionals can combine with clinical examination to assess and diagnose depression comprehensively from multiple angles and dimensions.

Research methods

Demographic and clinical characteristics, as well as data from the repeatable battery for the assessment of neuropsycho-

logical status (RBANS; Chinese version) and EEG, were collected from a sample of 24 patients diagnosed with depression (DEP) and 32 healthy controls (CON). Participants were seated comfortably in a reclining chair and instructed to close their eyes and maintain a relaxed and quiet state for a duration of 3 min. Microstate analysis was conducted utilizing the EEGLAB microstate plugin and the atomize and agglomerate hierarchical clustering algorithm was used to compute four optimal microstate topographies.

Research results

Our study found that years of education and HAMD score showed significant differences in the two groups (education: $t = 2.056$, $P = 0.045$; HAMD score: $W = 83$, $P < 0.001$). Compared with the controls, the duration, occurrence, and contribution of microstate C were significantly higher (duration $F = 6.02$, $P = 0.049$; Occurrence $F = 6.19$, $P = 0.049$; contribution $F = 10.82$, $P = 0.011$) while the duration, occurrence, and contribution of microstate D were significantly lower (duration $F = 19.18$, $P < 0.001$; Occurrence $F = 5.79$, $P = 0.050$; Contribution $F = 9.41$, $P = 0.013$) in depressed patients. Additionally, a positive correlation was observed between visuospatial/constructional scores and the transition probability of microstate class C to B ($r = 0.405$, $P = 0.049$).

Research conclusions

We examined the temporal dynamics of resting-state EEG microstates in patients with depression and healthy controls. EEG microstate analyzed the possible changes in neurons in the brain of patients with depression from the perspective of sub-second brain dynamics and was a possible biomarker (especially microstate C and D) in depression. Furthermore, the more frequent transition from microstate C to B, which may be related to more negative rumination and visual processing.

Research perspectives

In the future, more studies with larger numbers of patients with depression and normal controls should be conducted to assess more accurately the relationship between depressive disorders and electroencephalography EEG microstates. Furthermore, we will further perform a longitudinal interventional cohort study on therapy in the DEP group to find any possible associations between EEG microstates and prognosis through regular follow-up. Finally, future studies could combine EEG data with resting-state fMRI data from patients with depression to study brain neural network changes through both temporal and spatial dimensions in an integrated manner.

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Author contributions: Peng RJ and Fan Y were responsible for data collection, data curation, and writing original draft; Li J and Zhu F were involved in supervision and review; Tian Q and Zhang XB as co-corresponding author, participated in conceptualization, funding acquisition, supervision and editing; all authors reviewed the manuscript.

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