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The pro-inflammatory factors contribute to the EEG microstate abnormalities in patients with major depressive disorder

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ABSTRACT

Pro-inflammatory factors may be associated with abnormalities in functional brain networks, which may be a mechanism in the pathogenesis of major depressive disorder (MDD). Electroencephalogram (EEG) microstates reflect the functioning of brain networks. However, the relationship between pro-inflammatory factors and the microstate abnormalities in patients with MDD is poorly understood. 24 MDD patients and 24 age-and sex-matched healthy controls (HC) were recruited. Montgomery-Asberg Depression Rating Scale(MADRS) were assessed. Serum (interleukin- 2(IL- 2), tumor necrosis factor-α (TNF-α) and hs-C-reactive protein (CRP)and EEG data were collected. K-means clustering was performed to characterize different microstates. For each microstate, duration, occurrence and coverage were estimated. Four microstates (e.g. A, B, C, D) were characterized, MDD group showed lower duration, occurrence and coverage of microstate B and microstate D, while higher duration of microstate A and microstate C and levels of IL-2, TNF-α, hs-CRP than HC group. The duration, occurrence and coverage of microstate D were negatively correlated with levels of pro-inflammatory factors (IL-2, TNF- α and hs-CRP) (all $P < 0.05$). Serum pro-inflammatory induced the abnormalities of microstate D. Together, these findings add to the understanding of the pathophysiology of MDD and point to pro-inflammatory factors contribute to EEG microstate abnormalities in patients with MDD.

1. Introduction

Multiple lines of evidence implicate the involvement of long-term increase of inflammatory activity in major depressive disorder (MDD) pathogenesis (Herrman et al., 2022). According to recent meta-analyses, MDD is confirmed as a pro-inflammatory state, and levels of interleukin-2 (IL-2), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP) are significantly higher in MDD patients than in healthy people (Haapakoski et al., 2015; Horn et al., 2018; Osimo et al., 2020). Those like TNF-α that can gain access to the brain have been shown to cause depression-like behaviors. Pro-inflammatory factors have also been shown to affect neuronal functions through neuron growth/development and synaptic plasticity and their excessive increases can lead to impairment in various brain networks (Yirmiya and Goshen 2011; You et al., 2011; Calabrese et al., 2014).Those findings support the idea that pro-inflammatory signaling have a mechanistic role in the development and progression of MDD. More precisely, it is supposed that pro-inflammatory factors could be responsible for changes in functional brain networks and consequently for behavioral changes in MDD (Dionisie et al., 2021).

There have been few studies of inflammation-related changes in functional brain networks in MDD patients. Several studies have showed that pro-inflammatory factors are associated with altered connectivity in functional networks important for regulating aspects of emotion and cognition among younger populations (Felger et al., 2016; Lekander et al., 2016; Nusslock et al., 2019). Peripheral pro-inflammatory factors can interfere with neural circuit activity related to reward processing. A recent meta-analysis encompassing human experimental models of

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inflammation, clinical studies of hepatitis C patients receiving IFN-α treatment, and observational studies of community samples with variable blood levels of CRP, reported that inflammation-related changes were consistently co-localized to default mode network (DMN) and limbic functional networks (Kraynak et al., 2018). A study by (Conejero et al., 2019) using a social exclusion task found that IL-2 levels in MDD were positively correlated with activation levels in the right anterior cingulate cortex (ACC), insula and orbital-frontal-cortex (OFC) during the task (Conejero et al., 2019), suggesting that IL-2 can influence the functional activity of neural circuits that regulate emotion in patients. MDD itself has also been associated with changes in multiple large-scale cognitive networks. Numerous studies show decreased frontal cortex function and increased limbic system function in patients with MDD (Fischer et al., 2016), abnormalities in functional brain networks include hypoconnectivity within the frontoparietal network (Kaiser et al., 2015), the reward circuitry, centered around the ventral striatum (Satterthwaite et al., 2015). These Findings highlight the possibility that pro-inflammatory factors may contribute to the abnormalities in functional brain networks in MDD.

EEG research provides a window into these purported abnormalities (Lehmann et al., 1987). The temporal characteristics of these EEG microstates carry important information about mental processes which also are generated by distinct patterns of neural activity (Michel and Koenig 2018; Bréchet et al., 2019).Analysis of EEG microstates is a nascent field and microstates typically persist for tens of milliseconds before the brain enters another microstate (Michel and Koenig 2018). Combined fMRI-EEG imaging studies indicate that the neural assemblies generating microstates overlap with resting-state networks (RSNs) independently identified with fMRI(Britz et al., 2010a,b; Musso et al., 2010; Yuan et al., 2012). There were strong correlations between EEG-based microstates and fMRI studies with RSNs (Britz et al., 2010a,b; Musso et al., 2010; Yuan et al., 2018; Bréchet et al., 2019). There are increasing evidences that specific microstates link to distinct cognitive tasks or to differential components of DMN (Milz et al., 2017; Bréchet et al., 2019). One EEG source-imaging study found that all four canonical microstates are related to activity in the posterior cingulate cortex and that the neural correlates of microstates B to D incorporate other components of the DMN (Pascual-Marqui et al., 2014). Furthermore, source imaging results suggest that the DMN consists of several hubs that produce different EEG microstates through differential inhibition of alpha activity (Milz et al., 2017). Microstate A was related to neural activity in the auditory and insular cortices, while microstate B was related to activity in the visual and insular cortices (Custo et al., 2017). Even more advantageous is that microstate analysis enable us to reduce the multichannel EEG data into categories that correlate with distinct distributions of neural activity. Taken together, microstate analysis provides a powerful tool to probe functioning of brain networks in patients with MDD (Khanna et al., 2015).

To our knowledge, there have been no previous investigations evaluating association of pro-inflammatory factors with EEG microstate abnormalities of MDD patients in comparison with those in healthy controls (HC). To fill this gap in clinical guidance, we examined relationship between pro-inflammatory factors (IL-2, TNF-α, and hs-CRP) and microstate parameters (duration, occurrence and coverage) to determine the possible relationship between the pro-inflammatory signaling and functional brain networks in MDD patients.

2. Methods

2.1. Participants

Patients were recruited at Department of Physical & Mental Medicine, Guang'anmen Hospital of China Academy of Chinese Medical Sciences between Jan 2020 and Dec 2021. All Participants gave written informed consent in accordance with Declaration of Helsinki. The protocol was approved by the Ethics Committee of Guang'anmen Hospital of China Academy of Chinese Medical Sciences and registered with the China Clinical Trials Registry (ChiCTR2000029109).

Clinical characteristics, pro-inflammatory factors and EEG data were collected from 24 MDD patients and 24 HC participants. The MDD patients included in this study were first-episode drug-naïve participants. All MDD patients were interviewed using Chinese version of the Modified Structured Clinical Interview for ICD-10(SCID) patient version to ensure that they met the depressive episode criteria. Patients had the Montgomery–Åsberg Depression Rating Scale (MADRS) (Williams and Kobak 2008) scores between 12 and 30. Healthy control participants had no history of psychiatric illness, no first-degree relatives with psychiatric disorders, and no history of psychiatric medication use. All participants were administered the SCID to establish diagnosis and MADRS to assess depressive severity. All MDD participants met following inclusion criteria:

i. Aged 18–65 years;
ii. Right-handedness;
iii. No history of neurological illnesses or other severe diseases (e.g. malignant neoplasms, heart diseases, respiratory diseases and cerebrovascular diseases).
iv. No physical trauma, and No pregnancy or contraindications.

All patients were carefully monitored for safety (e.g. suicidality, significant worsening) during course of the study. We recruited 24 age- and sex-matched healthy control Participants using the ICD-10 criteria to ensure that they had no previous or current psychiatric disorders. Table 1 describes the detailed information of included MDD patients and HC participants.

2.2. Pro-inflammatory factors assessment

Screening pro-inflammatory factors were assessed by the Clinical Laboratory of Guang'anmen Hospital of China Academy of Chinese Medical Sciences. People who met the inclusion criteria and whose routine blood screening values were within normal limits were given an appointment for blood donation for the next day. After one fasting night except for water. All participants were admitted to the hospital and 6 mL of fasting venous blood was collected between 8:00 and 10:00 in the morning, and then centrifuged and stored in a refrigerator at −80 °C for examination. Serum pro-inflammatory factors TNF-α and IL-6 expression were measured by Enzyme-Linked Immunosorbent Assay (ELISA), while hs-CRP was measured by particle-enhanced immunoturbidimetry (ITM), and all data were recorded according to the instructions of the manufacturers (Boster Biotechnology Company, Wuhan, China).

2.3. EEG recording and pre-processing

All participants were asked to sit in a comfortable upright position in a dimlylit electrically shielded room. They were instructed to relax and keep their eyes closed for 5 min while remaining awake. Eyes-closed rest EEG data were recorded with 32-channel system (EGI System 400;

Table 1
Demographic characteristics of MDD and HC group.

	Patients with MDD	Healthy controls	χ^2/T value	*P* value
Gender(female/male)	13/11	15/9	0.024	0.877
Age(years)	44.7 ± 14.18	37.3 ± 13.4	0.536	0.089
Education(years)	14.4 ± 3.5	15.3 ± 2.5	0.136	0.342
IIIness duration (years)	29.0 ± 25.3	–	–	–
MADRS score	16.5 ± 2.9	2.0 ± 1.7	5.967	<0.001

The T-value is the statistical value of the *t*-test while the chi-square (χ2) value is the statistical value of the non-parametric test.

Electrical Geodesic Inc., OR, USA), a sampling rate of 1 kHz, and Cz as acquisition reference.

EEG data analysis was performed using MATLAB scripts (v.R2013b; MathWorks) and EEGLAB. The EEG was band-pass filtered between 1 and 40 Hz. The cleaned EEG recording was down-sampled to 125 Hz. We divided the EEG data into 2-s epochs referring to previous literature descriptions (Jia and Yu 2019). And previously identified noisy channels were interpolated using a three-dimensional spherical spline and re-referenced to average reference (Perrin et al., 1989). EEG data was reduced to 22 channels to remove muscular artifacts originating in neck and face and muscle artifacts were corrected by independent component analysis (ICA) (Winkler et al., 2015).

2.4. Microstate analyses

We used Cartool software to perform microstate analyses(Brunet et al., 2011). For each participant, we calculated global mean field power (GFP) across all electrodes. For microstate segmentation, we downsampled data by only including points where GFP had a local maximum (Murray et al., 2008). The data were then spatially filtered to enhance signal-to-noise ratio (Michel and Brunet 2019). The first step consisted of a k-means clustering performed at individual level. To select the optimal number of clusters, we performed the clustering with different numbers of k 1 to 12 initial clusters. In the second step, a second k-means clustering was performed at group level, clustering the concatenated individual topographies obtained in the previous step. For the second clustering, an initial number of k 5 to 15 clusters and 200 k-means initializations were set, which all were followed Cartool default settings for resting-state data(May et al., 2021). Finally, topographies were visually inspected and compared with topographies reported in the literature. For both groups, the first 4 topographies closely resembled the 4 well-known "canonical" microstates A to D reported previously and were labeled accordingly (A, B, C and D microstate which displayed in Fig. 1 for each group respectively)(Koenig et al., 2002; Khanna et al., 2015).

The spatial correlation across template maps between groups was analyzed with the scalp instantaneous topographic maps of each subject. In order to compare the differences of EEG microstates between MDD and HC group, we calculated duration, occurrence and coverage. Duration was average length of time a microstate lasted, occurrence was number of times that microstate occurred per second and coverage was the amount of the record covered by each microstate.

2.5. Statistical analysis

Statistical analysis was performed on Jamovi 2.2.5. Gender differences between groups were compared using the Chi-square test. Age, years of education, iIIness duration and MARDS scores, microstates (duration, occurrence and coverage) and the serum levels of IL-2, TNF-α and hs-CRP were compared using the independent sample *t*-test for MDD and HC group. Correlation analyses of microstate parameters with the levels of IL-2, TNF-α and hs-CRP was performed using Pearman's and Spearman's correlation. For all the above analyses, the significance level was set at $P = 0.05$.

3. Result

3.1. Definition four similar sets of microstates in MDD and HC group

In line with previous study, four microstates were identified (ie, microstate A, microstate B, microstate C, microstate D) both in MDD and HC group. They were Scalp topographies showed left posterior-right anterior orientation (microstate A), a right posterior-left anterior orientation (microstate B), an anterior-posterior orientation (microstate C), and a fronto-central maximum (microstate D), see Fig. 1. Total global explained variance of the 4 kinds of topographic map interpretations were all between 65% and 85%. The spatial correlations for topographies between MDD and HC groups was confirmed by high spatial correlations (microstate A: r = 0.99, B: r = 0.96, C: r = 0.93, D: r = 0.92).

3.2. Higher levels of pro-inflammatory factors in MDD

The serum levels of IL-2, TNF-α and hs-CRP of MDD group were higher than HC group ($t = 0.618$, $P < 0.001$; $t = 0.450$, P = 0.005; $t = 0.391$, $P = 0.014$). Correlation analysis of pro-inflammatory factors with clinical scales showed a significant positive correlation between IL-2 levels and MADRS scores (r = 0.620, $P = 0.001$).

3.3. Lower microstate B and D while higher microstate A and C in MDD

Regarding the duration of all four microstates, the duration of microstate B (MDD: 45.64 ± 3.371; HC: 48.51 ± 3.61; t = -2.852, P = 0.006) and D (MDD: 45.39 ± 3.764; HC: 54.85 ± 6.93; t = -5.874, $P <$ 0.001) of MDD group were lower than HC group, however, the duration of microstates A (MDD: 54.56 ± ; HC: 48.51 ± 3.61; $t = 5.732$, $P <$ 0.001) and C (MDD: 57.81 ± 6.40; HC: 50.18 ± 5.81; $t = 4.222$, $P <$ 0.001) were higher than HC group. The occurrence of microstates B (MDD: 3.90 ± 1.16; HC: 7.31 ± 1.15; $t = -10.208$, $P < 0.001$) and D (MDD: 4.61 ± 1.47; HC: 7.91 ± 1.66; $t = -7.292$, $P < 0.001$) of MDD group were significantly lower than HC group. The coverage of microstates B (MDD: 10.29 ± 4.00; HC: 21.22 ± 5.14; $t = -8.247$, $P < 0.001$) and D (MDD: 12.24 ± 4.79; HC: 27.03 ± 9.08; $t = -7.059$, $P < 0.001$) of

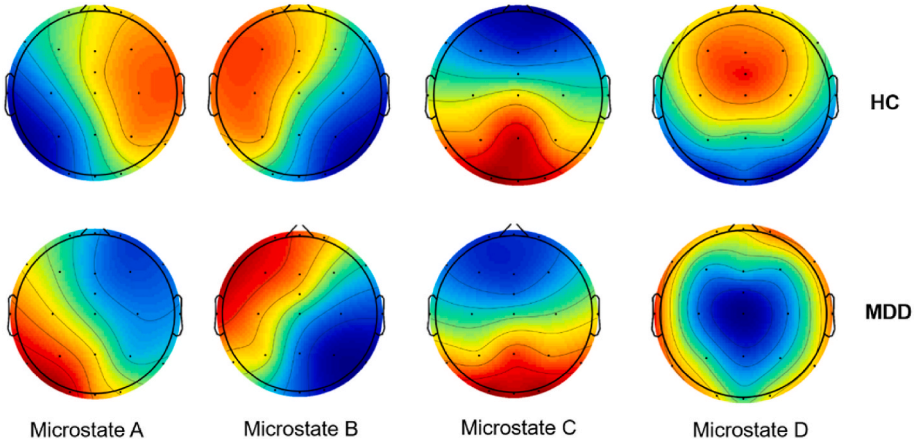

Fig. 1. Scalp topographies for MDD group (n = 24) compared with HC group (n = 24). Microstate topographies were defined for the entire mixed MDD group and HC separately. Microstates were labeled with the letters A to D according to previous literature.

MDD group were significantly lower than HC group. However, there were no significant differences of two groups in other microstates. The coverage of microstate D was significantly and negatively correlated with MADRS scores (r = −0.426, P = 0.038).

3.4. Relationships between the levels of pro-inflammatory factors and microstate parameters in MDD and HC group

Based on results of EEG microstate analysis in both groups of MDD and HC, we focused on correlation between microstate D and pro-inflammatory factors. For P-values of temporal measures, resampling-based FDR correction was performed in MATLAB across correlation analyses (3 inflammation markers x 3 state measures [duration, occurrence, coverage] x 2 groups [MDD, HC]), resulting in a correction for 18 statistical tests per rerun. Correlation analysis between microstate D parameters (duration, occurrence and coverage) and serum levels of pro-inflammatory factors (IL-2, TNF-α and hs-CRP) were estimated. The duration, occurrence and coverage of microstate D were all significantly negatively correlated with levels of inflammatory factors (IL-2, TNF-α and hs-CRP) in MDD group. However, there was no significant correlation between other microstates and levels of pro-inflammatory factors in MDD and HC group. see Fig. 2.

4. Discussion

We have shown that duration, occurrence and coverage of microstates D were negatively correlated with all serum levels of pro-inflammatory factors (IL-2,TNF- α and hs-CRP) in MDD group which was not found in HC group. We report similar microstate topographies (microstate A, microstate B, microstate C, microstate D) in HC and MDD group suggesting whether MDD or normal, the microstate topology is stable. And it also indicates that MDD patients do not appear in changes of brain structure(Mayberg 2003; Michel and Koenig 2018), but more abnormalities of functional brain networks. Next, duration, occurrence and coverage of microstate A, B, C and D were counted in this study. The results of study showed that for spatially mutually independent microstates, our results showed that duration, occurrence and coverage of microstate B and D were significantly lower, while duration of microstate A and C were significantly higher compared to HC group.

4.1. EEG microstates in MDD

Our results showed that duration, occurrence and coverage of microstate B and D were significantly lower, while duration of microstate A and C were significantly higher compared to HC group. There were strong correlations between EEG-based microstates and fMRI

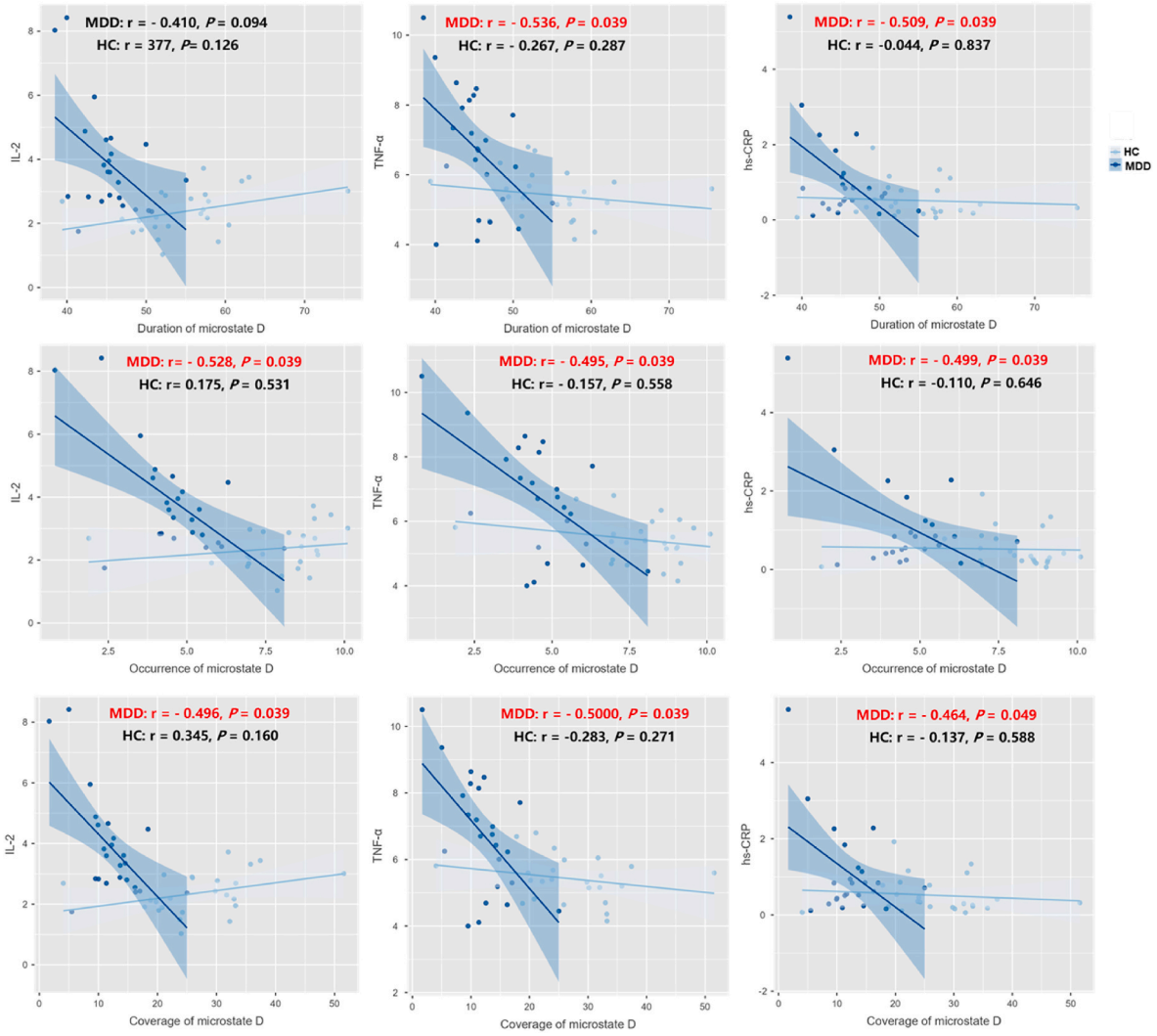

Fig. 2. Relationships between the levels of pro-inflammatory factors(IL-2, TNF-α and hs-CRP) and microstate D in MDD and HC group. Dark blue represents the MDD group(n = 24) and light blue represents HC group(n = 24). Red represents statistically significant after FDR correction. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

studies with RSNs(Britz et al., 2010a,b; Yuan et al., 2012, 2018).One study found that each microstate was related to RSNs: microstate A to the auditory network, B to the visual network, C to the salience network, and D to the attention network(Britz et al., 2010a,b).Using adaptive segmentation of resting state EEG in depressive patients, two early studies showed abnormal microstate topographies and reduced overall average microstate duration(Strik et al., 1995) but unchanged numbers of different microstates per second(Ihl and Brinkmeyer 1999). In a more recent study using a topographical atomize-agglomerate hierarchical clustering algorithm, abnormally increased overall microstate duration and decreased overall microstate occurrence per second were reported in treatment-resistant depression(Atluri et al., 2018). A recent study used k-means clustering method to estimate optimal set of topographies explaining EEG signal. There were no between-group differences in the temporal characteristics of microstates (Damborská et al., 2019).In agreement with Michael Murphy, we note a clear decrease in microstate D (duration, occurrence and coverage) emerged(Murphy et al., 2020).

Different methodological approaches might have, however, led to discrepant findings in terms of duration of microstates among the current and the four previous studies. The methodological differences include different frequency bands examined(Ihl and Brinkmeyer 1999), different clustering algorithms applied[], different numbers of maps used for backfitting to EEG(Atluri et al., 2018), and analyzing all data points or only those with the local maxima of the global field power (Atluri et al., 2018). Discrepant findings may also reflect pathophysiologic heterogeneity of MDD. Nevertheless, duration, occurrence and coverage of microstate B and D are potential biological markers for MDD patients.

4.2. Association of pro-inflammatory factors with EEG microstates in MDD

Previous work has demonstrated a robust relationship between inflammation, neurophysiological changes, and altered functional connectivity(Calabrese et al., 2014; Walker et al., 2020). Notably, our results suggest that serum pro-inflammatory factors are mainly associated with abnormalities of microstate D. However, to date, there have been no studies on association between pro-inflammatory factors and altered EEG microstates of patients with MDD. Pro-inflammatory factors have been shown to cross the blood-brain barrier, thereby interfering with various neurological functions such as neuroplasticity, neurotransmitter metabolism, neuroendocrinology and neuronal apoptosis, ultimately leading to MDD (Yirmiya and Goshen 2011). Due to the interoperability between the periphery and the centre, peripheral inflammatory factors can activate glial cells in brain, leading to a further inflammatory cascade(Kohler et al., 2016). A study (David et al., 2018) showed that post-mortem glial cell morphology and metabolism were altered in cingulate and hippocampus of MDD patients. This ultimately leads to neuroinflammation and neurodegeneration, resulting in emotional and cognitive impairment(Beurel et al., 2020). A recent study showed that dysconnectivity of a brain functional network was associated with blood inflammatory markers in MDD. Connections within this network were mainly between brain regions located in left insula/frontal operculum and posterior cingulate cortex, which were assigned to ventral attention and default mode canonical fMRI networks respectively(Aruldass et al., 2021). These studies suggest that inflammatory factors may affect structural and functional abnormalities in brain, leading to development of MDD while it still needs more research to further validate.

Decreased microstate D has also been reported in psychotic disorders suggesting a common pathophysiological process across affective and psychotic disorders(Rieger et al., 2016). Correlations of microstate D with resting-state functional brain networks have also been found in literature(Britz et al., 2010a,b). The previous study showed that microstate D was closely correlated with the Dorsal Attention Network (DAN) which is often seen as a conditioning network in the VN, especially in frontoparietal region(Britz et al., 2010a,b). Previous studies (Romeo et al., 2021) have also demonstrated moderating effect of DAN on VN. This process may be related to microstate D's proposed association with cognitive control and ability to attend to environmental stimuli and which may manifest as rumination in MDD or thought disorder in psychosis(Bréchet et al., 2019).Greater dynamic presence of frontoinsular-default network states (involving regions identified in our EEG data as microstates D was associated with more severe MDD in an adolescent patient sample(Bréchet et al., 2019).

While some, but not all, studies have found associations between elevated levels of pro-inflammatory factors and reduced DMN connectivity(Bréchet et al., 2019), other studies in younger samples have found that inflammation is associated with altered connectivity in limbic and ventral attention networks(Lekander et al., 2016). For example, Nusslock and colleagues recently demonstrated an association between higher circulating levels of pro-inflammatory factors and reduced connectivity within emotion regulation network (similar to our DAN) in two independent samples of adolescent and young adult participant(Nusslock et al., 2019). To sum up, this may mean that pro-inflammatory factors may be associated with microstate D which may interfere with abnormalities in the DAN of MDD patients. We again emphasize that our speculations require direct testing correlating pro-inflammatory factors with brain network changes. This is only an exploratory experiment and in-depth studies with large samples are still needed to replicate the phenomenon and the mechanisms behind.

4.3. Limitations

The current results should be interpreted within context of several limitations. First, inflammatory factors were measured at only one timepoint and may therefore be subject to random measurement error due to normal physiologic variability, potential occult medical illness, and other factors. Furthermore, future analyses should include a more comprehensive measure of inflammatory factors, including anti-inflammatory factors such as IL-10 and other widely used factors. Understanding cortical correlates of EEG microstates relies on source modeling techniques which have limited spatial resolution. Thus, we are unable to determine how inflammation may relate to connectivity within subcortical structures and within brainstem regions that are implicated in MDD and may be affected by inflammation. Lastly, as is the case with observational studies, the observed associations may be subject to residual confounding due to factors such as subclinical or unmeasured disease.

5. Conclusions

Taken together, the current study provides that pro-inflammatory factors may have potential effects on functional brain networks leading to MDD though future studies are needed to replicate these findings. We again emphasize that our speculations require direct testing correlating pro-inflammatory signaling with brain network changes, and future work would be complemented well with functional imaging to combine spatial and temporal precision in elucidating the EEG microstate correlates of pro-inflammatory signaling in MDD.

Author declaration

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with

respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from (drrongpj@163.com)

Declaration of competing interest

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Data availability

No data was used for the research described in the article.

Acknowledgments

Pei-Jing Rong and Ji-Liang Fang proposed the idea of article. Manuscript writing, data preprocessing, statistics and mapping were performed by Yan-nan Zhao. Patients were recruited and assessed by Jia-Kai He and Bao-Hui Jia. EEG data were collected by Jia-Kai He, Yan-Nan Zhao and Chun-Lei Guo. Pei-Jing Rong, Ji-Liang Fang, Yu Wang and Shao-Yuan Li supervised writing of the paper. Many thanks to Bin Hu, Hao Liu,Shuai-Zhang and Jin-Ling Zhang for guiding the statistical analysis. We are very grateful for Guo-Lei Zhang, Wei-Hang Zhai, Zi-Xuan Zhang and Yu Chen's recommendations for this article. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

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