QEEG indices are associated with inflammatory and metabolic risk factors in Parkinson's disease dementia: An observational study

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Summary

Background Quantitative electroencephalography (QEEG) is a reliable and non-invasive diagnostic tool to quantify cortical synaptic injury or loss in the clinical assessment of neurodegenerative diseases, and may be able to differentiate various types of dementia. We investigated if QEEG indices can differentiate Parkinson's Disease (PD) with nondementia (PD-ND) from PD with dementia (PDD), and to determine if QEEG indices correlate with inflammation and lipid metabolism markers in PD.

Methods This clinical study collected data between July 1, 2018 and July 1, 2021 in Zhujiang Hospital of Southern Medical University in China and data was analysed. A total of 125 individuals comprising of 31 PDD, 47 patients with PD-ND and 47 healthy controls were included. We calculated the absolute spectral power (ASP) of frequency bands and the slow-to-fast frequency ratios of specific brain regions. Plasma levels of hypersensitive C-reactive protein (Hs-CRP), superoxide dismutase (SOD), and high-density lipoprotein cholesterol (HDL-C) were measured and correlations with QEEG indices were examined.

Findings A significantly higher ASP of delta frequency especially in the frontal region was observed in patients with PDD compared to PD-ND (P=0.004) and controls (P=0.000). Decreased HDL-C (OR=0.186, P=0.030), and increased Hs-CRP (OR =2.856, P=0.015) were associated with PDD. Frontal-delta ASP was negatively correlated with plasma HDL-C (r=−0.353, P=0.000) and SOD (r=−0.322, P=0.001), and positively correlated with Hs-CRP (r=0.342, P=0.000).

Interpretation We highlight novel correlations between QEEG indices and inflammation and lipid metabolism markers in PD-ND and PDD. QEEG indices, HDL-C and Hs-CRP are potentially useful for the evaluation of PDD. Our current findings suggest that peripheral inflammation might contribute to the pathogenesis of cognitive impairment and EEG slowing in PDD. The mechanism underlying frontal-delta ASP and its correlation with neuroinflammatory and metabolic markers in PDD should be further investigated.

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Abbreviations: HDL-C, High-density lipoprotein cholesterol; Hs-CRP, Hypersensitive C-reactive protein

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Research in context

Evidence before this study

Quantitative Electroencephalogram (QEEG) is a reliable, noninvasive, and cost-effective diagnostic tool to evaluate cortical synaptic injury or loss in the clinical assessment on Parkinson's Disease (PD) including PD with nondementia (PD-ND) and PD with dementia (PDD); while inflammation markers and metabolic risk factors are potential predictors of PDD. Whether QEEG indices are correlated with inflammatory and lipid metabolism markers in PD is unknown. Here, we screened PubMed for previous studies published until Dec 1, 2021, using the terms ("QEEG") AND ("inflammation" or "hypersensitive C-reactive protein (Hs-CRP)" or "superoxide dismutase (SOD)" or "low-density lipoprotein cholesterol (LDL-C)" or "high-density lipoprotein cholesterol (HDL-C)" or "metabolic factors") in patients with PD; however, there has not been any published study that evaluated the association of QEEG indices with inflammation and lipid metabolism markers in PDD.

Added value of this study

In the study, a significantly higher EEG-slowing of delta frequency, especially in the frontal region, was observed in patients with PDD; while decreased HDL-C, and increased Hs-CRP were related to PDD. Frontal-delta power was negatively correlated with plasma HDL-C and SOD, and positively correlated with Hs-CRP. EEG slowing, which could be used to investigate the pathogenesis of PDD, was significantly associated with inflammatory and metabolic markers.

Implications of all the available evidence

To our knowledge, this is the first study to characterise the relationship between QEEG indices and inflammation and lipid metabolism markers in PD-ND and PDD. QEEG indices combined with HDL-C and Hs-CRP may be useful for the evaluation of PDD.

Introduction

Patients with Parkinson's disease (PD) can develop cognitive impairment or dementia, interfering with activities of daily living and increases disease burden. Various markers have been associated with PD and these may correlate with disease severity.[1,2] To date, there are no reliable objective markers for cognitive severity in PD with dementia (PDD).

Quantitative electroencephalography (QEEG), is a non-invasive, high temporal resolution, and objective diagnostic method that can provide a rapid evaluation of instantaneous neuronal and synaptic function and may be sensitive to early neurodegenerative changes. Several studies have suggested that QEEG features may distinguish dementia with Lewy bodies (DLB), PDD, and Alzheimer's disease (AD).[3] However, the utilization of QEEG to distinguish PDD from PD with non-dementia (PD-ND) and to differentiate PD-ND from healthy controls is unclear.

Recent studies have shown that inflammation and lipid metabolism in the circulation are involved in cognitive impairment in PDD.[4] High-sensitivity C-reactive protein (Hs-CRP) in the circulation is higher in patients with PD than in healthy controls (HCs).[5] A mate-analysis[6] reported that Hs-CRP is a marker of a proinflammatory state and may predict prognosis in PD. Other studies have indicated that Hs-CRP could enhance the permeability of the blood–brain barrier (BBB), through which the immune system mediates disease initiation and progression.[4,5] Lipids,[7] major component of cellular membranes, are essential for synaptogenesis. Several studies[4,8] have shown that abnormal lipid metabolism may contribute to PDD pathogenesis and lead to endolysosome and mitochondrial dysfunction, resulting in neuronal death in patients with PD. Cumulating evidence has shown that total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels are related to the severity and progression of PD.[4,9] However, a study demonstrated that there was no significant association between serum HDL-C and the risk of PD progression.[9] Whether there is any relationship between serum HDL-C and PDD needs to be further investigated.

Neuronal and synaptic loss are characteristic hallmarks of neurodegenerative diseases (such as PD and AD) and these lead to cognitive decline. EEG can capture the summative excitatory and inhibitory postsynaptic potentials, reflecting the activity and function of the brain.[10] Inflammation and lipid metabolism could influence the BBB integrity and participate in the activation of synaptic loss. One study[11] revealed that EEG activity, such as delta band power, is related to total phosphorylated α-synuclein in autopsy tissue in PD. Moreover, an experimental study[12] used vaccination to induce inflammation in healthy participants, which caused significant

alterations to task-related brain EEG activity, accompanied by cognitive impairment. Growing evidence demonstrated that inflammation and oxidative stress could influence the integrity of BBB, and participate in the pathophysiology of PD. One study demonstrated that the increased frontal theta power showed significant association with TNF-α in patients with mood disorders.[13] In a longitudinal cohort study of infants, Hs-CRP is significantly positively associated with QEEG-functional connectivity in the Beta band.[14] Whether inflammatory mediators are correlated with the EEG activity in patients with PD is unknown.

A previous study[5] found that an abnormal lipid profile was associated with damage of BBB, while HDL-C is associated with the BBB integrity. BBB dysfunction likely contributes to the pathophysiological process of PD. Moreover, our previous studies found HDL-C might be an important marker to assess the PD severity.[4] Interestingly, the ketogenic diet is an effective alternative therapy to control intractable seizures, especially in those with abnormal lipid profile. Qualitative and semiquantitative EEG evaluations showed an improvement in normal background activity or a decrease interictal epileptiform activity after the ketogenic diet in patients with epilepsy.[15] Whether lipid metabolism is related to the EEG activity in patients with PD remains largely unknown.

To address current gaps in knowledge, we investigated a detailed topographic map of EEG changes and QEEG parameters in individuals with PDD, PD-ND and HCs. In addition, we examined the associations between inflammation and lipid metabolism in PDD, and between QEEG features and the severity of cognition in PD (as measured by Mini-Mental State Examination (MMSE) scores and inflammation markers).

Methods

Ethics statement

We collected data from patients with PD with or without cognitive impairment between July 1, 2018 and July 1, 2021 in Zhujiang Hospital of Southern Medical University in China. This study was approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University and was conducted in accordance with the principles of the Helsinki Declaration revised in 1975 and the National Institutes of Health Policy and Guidelines for Human Individuals issued in 1999. All participants signed an informed consent form.

Patient selection

Pre-study calculation of the sample had performed to calculate the least required sample size prior to data collection using the samples size estimation formula for differences in means with power set as 80% with two-sided $\alpha = 0.05$. We collected 10 patients with PD-ND and 10 patients with PDD, and calculated the means and standard deviation of quantitative EEG delta power, respectively. The results showed that a sample size of 12 individuals per group is minimally needed to answer the research question.

All participants with PD fulfilled the Movement Disorder Society Clinical Diagnostic Criteria for idiopathic PD.[16] The exclusion criteria were as follows: (1) patients with incomplete data or artificial EEG; (2) patients with PD with major psychiatric disorders; (3) patients with PD with a history of cerebrovascular disease, head tumor or injury; (4) patients with PD with physical diseases, including liver or kidney disease, infection, tumors, or other critical diseases; and (5) patients with PD with abnormal EEG characteristics suggestive of epilepsy. Patients with PDD fulfilled the criteria for probable PDD as proposed by the Movement Disorder Society Task Force.[17] This is defined when there are at least two domains of cognitive impairment and severe enough to affect the patients' daily functioning. Cognitive domains included attention function, executive function, visuo-spatial function, Language, and memory function. We measured attention function with forward and backward digital test, executive function with phonetic verbal fluency, visuo-spatial function with the Clock Drawing Test, language, and memory function with recall test in MMSE. The HCs were recruited from the Medical Examination Centre of Zhujiang Hospital of Southern Medical University. We excluded individuals with epilepsy, psychiatric disorders, cerebrovascular disease, or individuals on medication. The study flow diagram was demonstrated in Figure 1.

A total of 125 individuals comprising of 31 patients with PDD, 47 PD-ND and 47 healthy controls were included. The evaluations of neurological examinations for all individuals were performed by experienced neurologists. All PD participants completed standard assessment measures as follows: an appropriate demography form, levodopa equivalent daily dose (LEDD), and the Unified Parkinson's Disease Rating Scale (UPDRS), including the UPDRS(I), UPDRS(II), and UPDRS (III) subscales, representing mentation, daily life, and motor function, respectively. We administered the UPDRS(I) to assess psychiatric dysfunction, while we administered the UPDRS(II), UPDRS(III), and H&Y subscales to assess the severity of motor dysfunction. The severity of cognitive decline was assessed with MMSE.

Venous blood samples for superoxide dismutase (SOD), uric acid (UA), cholesterol (Chol), blood glucose (GLU), Cystatin C (Cys C), HDL-C, LDL-C, Hs-CRP, erythrocyte sedimentation rate (ESR), neutrophil granulocyte (NEU%), lymphocyte (LYM%), and monocyte (MON%) detection were extracted from all individuals with PD in the study. The individuals' blood was taken in the morning under a fasting state, and all blood detections were repeated three times. All individuals underwent magnetic resonance imaging (3.0 T)

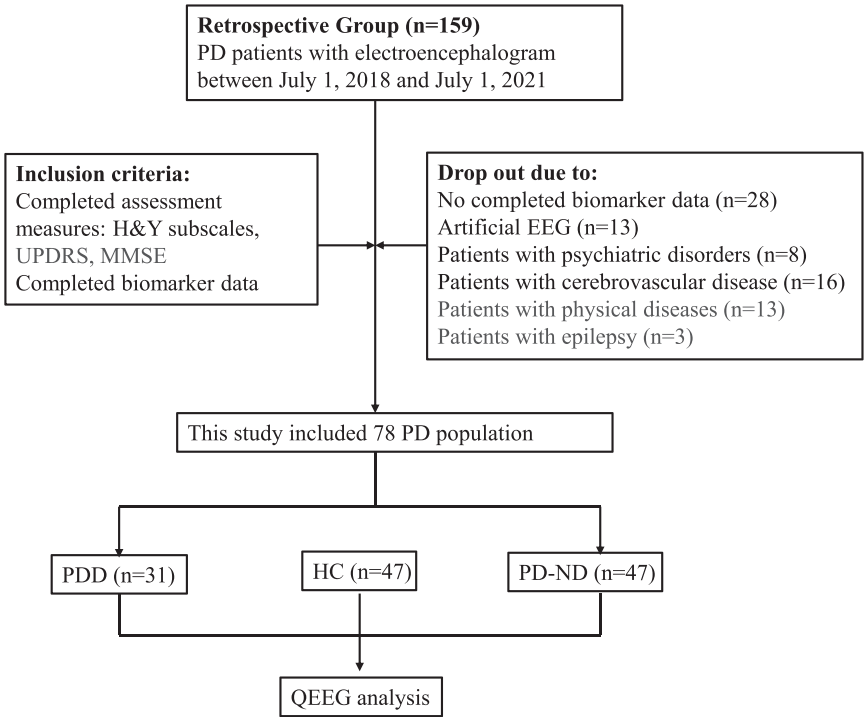

Figure 1. The study flow diagram.

PD, Parkinson' disease; H&Y, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; EEG, electroencephalography; PDD, PD with dementia; PD-ND, PD with non-dementia; HC, healthy control; QEEG, quantitative electroencephalography.

standard sequences to exclude nondegenerative causes of cognitive impairment.

EEG recording

Resting EEG was obtained as a continuous signal lasting 20 min in a dimly lit and silent room. According to the 10–20 International System, nineteen electrodes were positioned on all participants during relaxed wakefulness with eyes closed, comprising the Fp1, Fp2, F3, F4, Fz, F7, F8, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, and O2 electrodes.

Quantitative EEG analysis

Preprocessing of the resting EEG recordings was performed with EEGLAB toolbox version 13. Due to contamination of artifacts related to eye movements, the data for the Fp1 and Fp2 electrodes were not calculated. We used 1 Hz high-pass and 40 Hz low-pass filters to clean the EEG signal and applied a notch filter at 50 Hz. The records were then divided into 2-second time periods and checked for any remaining artifacts. The EEG containing large artifacts were deleted. The number of epochs available for analysis varied across individuals, ranging from 1 min to 3 min. The spectral absolute power (ASP) analysis of resting EEG data was experienced using fast Fourier transform analysis.

The ASP of the following common frequency bands was calculated: delta band (1–4 Hz), theta band (4–8 Hz), alpha band (8–13 Hz) and beta band (13–30 Hz). Then, the ratio of the slow-to-fast frequency, that is, [(delta + theta)/(alpha + beta)], was calculated, which was also called the spectral power ratio (SPR). The ASP and SPR could then be computed for each frequency band in global and specific brain regions, including frontal areas (F3, F4), central areas (C3, C4), temporal areas (T3, T4, T5, T6), parietal areas (P3, P4), and occipital areas. The global ASP was calculated based on the average of all electrodes. Finally, the dominant occipital frequency, called the average peak alpha rhythm frequency (6–13 Hz), was extracted from each subject in the O1 and O2 spectra obtained in the awake state.

Statistical analysis

IBM SPSS statistics 24.0 was used for statistical analysis. We measured skewness and kurtosis to determine normality. All continuous variables are expressed as the mean±standard deviation. Categorical variables are expressed as percentages. Among PDD, PD-ND and HCs, comparisons of sex, age and body mass index were conducted by chi-square test, one-way analyses of variance (ANOVA), or Mann–Whitney U-test, followed by Bonferroni post-hoc tests respectively. The Mann

−Whitney U-test was applied to compare the differences in MMSE score, H&Y stage, UPDRS(I-III) score, SOD, UA, Chol, HDL-C, GLU, Cys-C, LDL-C, Hs-CRP, ESR, NEU%, LYM%, and MON% between the PDD and PD-ND groups, depending on non-normality. We performed binary logistic regression to explore the potential risk factors in patients with PDD and PD-ND. Stepwise multiple logistic regression analysis (methods=stepwise, F-to-enter=0.05, F-to-remove=0.1) was performed to detect the independent influence of selected variables on patients with PDD. The selected variables included age, LEDD, HDL-C, GLU, Cys C, Hs-CRP, and ESR levels.

ASP was logarithmically transformed to achieve the homogeneity of variance and normally distributed data. Statistically significant differences in QEEG indices (including global delta ASP, global theta ASP, global alpha ASP, global beta ASP, frontal-delta ASP, frontal-theta ASP, frontal-alpha ASP, frontal-beta ASP, central-delta ASP, central-theta ASP, central-alpha ASP, central-beta ASP, temporal-delta ASP, temporal-theta ASP, temporal-alpha ASP, temporal-beta ASP, parietal-delta ASP, parietal-theta ASP, parietal-alpha ASP, parietal-beta ASP, occipital-delta ASP, occipital -theta ASP, occipital-alpha ASP, occipital-beta ASP, global SPR, frontal SPR, central SPR, temporal SPR, parietal SPR, and occipital SPR) in the PDD, PD-ND, and HC groups were assessed by one-way ANOVA, and then the Bonferroni method was used to adjust the significance level. Analyses of covariance (ANCOVAs) were applied to eliminate potential confounding effects of age on the significant indexes.

Linear correlations among the independent risk laboratory markers, QEEG indices, and severity of PD scales were explored using Spearman correlation analysis. A total of 5 variables were included in the correlation analysis (including frontal-delta power, MMSE, SOD, Hs-CRP, and HDL-C), and 10 pairwise comparisons were performed. According to Bonferroni test correction, $P<0.005$ should be considered meaningful, then the probability of cumulative type I error is 1-(1-0.005) ^10=0.0489. Thus, the cumulative probability of type I error is less than 0.05. We then performed receiver operator characteristic (ROC) curve analysis to measure the sensitivity and specificity of the QEEG indices and laboratory markers to predict PDD. P values less than 0.05 were considered significant. Considering age as the most potential confounder for QEEG analysis, we performed an age-adjusted ROC with STATA17.

Role of the funding source

There was no role of the funding in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the paper for publication. H.L.L, B.D, H.Z, and Q.W. have accessed and verified the data, and they were responsible for the decision to submit the manuscript for publication.

Results

Demographic characteristics and clinical manifestations of patients with PDD, patients with PD-ND, and HCs

This study included 31 patients with PDD (17 males [54.8%] and 14 females [45.2%]), 47 patients with PD-ND (21 males [44.7%] and 26 females [55.3%]), and 47 HCs (26 males [55.3%] and 21 females [44.7%]). Comparisons of sex were conducted by chi-square test followed by Bonferroni post-hoc tests. No significant difference was found among three groups (P=0.527) with no statistically significant difference detected in any of the pairwise comparisons (PDD vs PD-ND, P=1.000; PDD vs HC, P=1.000; PD-ND vs HC, P=1.000, Table 1). All enrolled patients were Asian. The mean ages of the PDD, PD-ND and HC groups were 71.1±7.0, 62.4±8.0, 63.9±8.6 years, respectively. The mean age of patients with PDD was higher than that of patients with PD-ND (P=0.000), but not than HCs (P=0.054). Sex-matched and age-matched healthy controls were included in the study (Table 1**).** The clinical characteristics, including PD duration (P=0.03), H&Y stage (P=0.02), LEDD (P=0.007), and UPDRS(I) (P=0.001), UPDRS(II) (P=0.001), UPDRS(III) (P=0.003), and MMSE scores (P=0.000), in patients with PDD were significantly higher than those in patients with PD-ND. The demographic and clinical characteristics, plus laboratory markers of patients with PD and controls are described in Table 1.

Comparisons of plasma markers between the PDD group and the PD-ND group

After the Mann−Whitney U test, significant differences were observed in plasma HDL-C (P=0.002), GLU (P=0.013), Cys-C (P=0.003), Hs-CRP (P=0.001), and ESR levels (P=0.006) between the PDD group and the PD-ND group, while no differences were found in serum SOD(P=0.379), UA (P=0.050), Chol (P=0.379, LDL-C (P=0.569), NEU% (P=0.061), MON% (P=0.153) and LYM% (P=0.084). Binary logistic regression was applied to evaluate the association between the significant markers and PDD. The results revealed that lower levels of HDL-C (OR= 0.186, P=0.030) and high levels of Hs-CRP (OR =2.856, P=0.015) were significant associated with for PDD but not for PD-ND. The results strengthened the clinical evidence that PD is accompanied by an inflammatory response, as shown in Table 2.

QEEG analysis

Various QEEG indices were shown in Table 3. We compared the global ASP of different frequency bands in different groups. With age as a covariant, ANCOVAs demonstrated significant interactions among groups in the delta band (P=0.000). However, there was no significant difference in global ASP among the three groups in the theta (P=0.054), alpha (P=0.573), and beta bands

Characteristics	PDD (*N*=31) A	PD-ND (*N*=47) B	Controls (*N*=47) C	*P*-value
Sex				0.527; A=B=C[a]
Male	17 (54.8%)	21 (44.7%)	26 (55.3%)	
Female	14 (45.2%)	26 (55.3%)	21 (44.7%)	
Age, y	71.1 (7.0)	62.4 (8.0)	66.4 (9.3)	0.000***; A>B[b]
BMI	22.2 (3.3)	22.8 (2.1)	23.1 (3.3)	0.694; A=B=C[c]
PD duration, y	5.4 (3.5)	4.1 (3.9)		0.030*
H&Y stage	2.7 (0.8)	2.3 (0.7)		0.020*
LEDD, mg	618.9 (199.8)	506.9 (154.7)		0.007**
UPDRS (I)	4.7 (2.7)	2.6 (1.9)		0.001**
UPDRS (II)	15.8 (5.7)	11.1 (5.6)		0.001**
UPDRS (III)	29.7 (11.3)	22.1 (8.4)		0.003**
MMSE	23.6 (2.4)	27.4 (1.6)		0.000***
Laboratory mean (SD)				
SOD (KU/L)	143.5 (23.8)	150.1 (20.1)		0.379
UA (umol /L)	336.3 (101.2)	296.6 (72.5)		0.050
Chol (mmol/L)	4.3 (1.2)	4.5 (1.2)		0.327
HDL-C (mmol/L)	1.2 (0.3)	1.5 (0.6)		0.002**
LDL-C (mmol/L)	2.4 (0.9)	2.7 (0.9)		0.569
GLU (mmol/L)	6.0 (2.3)	5.2 (1.7)		0.013*
Cys C (mg/L)	1.1 (0.2)	0.9 (0.1)		0.003**
Hs-CRP (mg/L)	4.6 (8.1)	0.7 (0.6)		0.001**
ESR	30.5 (23.9)	18.1 (12.7)		0.006**
NEU%	60.2 (12.3)	56.4 (10.2)		0.061
LYM%	29.2 (10.9)	32.1 (8.8)		0.084
MON%	7.2 (1.7)	8.0 (2.8)		0.153

***Table 1*: Baseline characteristic of study population.**

Abbreviations: PDD, Parkinson's disease with dementia; PD-ND, Parkinson's disease with non-dementia; BMI, Body mass index; LEDD, levodopa equivalent daily dose; H&Y stage, Hoehn and Yahr staging; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; SOD, Superoxide dismutase; UA, Uric acid; Chol, Cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; GLU: blood glucose; Cys C, Cystatin C; Hs-CRP, Hypersensitive C-reactive protein; ESR, Erythrocyte sedimentation rate; NEU, Neutrophile granulocyte; LYM, Lymphocytes; MON, Monocyte.

[a] Chi-square test followed by Bonferroni post-hoc tests, and no significant difference was detected in any of the pairwise comparisons.

[b] One-way ANOVA followed by Bonferroni post-hoc tests.

[c] Mann–Whitney U-test followed by Bonferroni post-hoc tests. Other comparisons of variables between PDD and PD-ND was performed by Mann-Whitney U-test.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

(P=0.723). The global region was then classified into five parts: frontal, central, temporal, parietal, and occipital brain regions. Comparing the SPR of the global brain, patients with PDD had a higher ratio than patients with PD-ND (P=0.033) and HCs (P=0.000). In specific regions, a significant difference in SPR was observed in every brain region (Figure 2A). We compared every regional ASP in the delta, theta, alpha, and beta bands in each group. In the delta band, the PDD group had higher power than the PD-ND group and HCs in all specific regions (Figure 2B), while the PDD group had higher power than the PD-ND group and HCs only in the frontal, central, and temporal regions in the theta band. Differences in the ASP of the delta (Figure 3A) and theta (Figure. 3B) bands among groups were demonstrated in the regional distribution by topographic map. According to the P value, frontal-delta power (P=0.000) was the dominantly significant marker in QEEG. No significant differences were observed in the alpha and beta bands in any brain region. patients with PDD revealed a lower level of occipital alpha peak frequency than both patients with PD-ND and HCs (8.9 ± 0.9; 9.3 ± 0.8; 9.5 ± 0.5, respectively; Figure. 2C). Peak frequency of electrode O1 (Figure 3C) and electrode O2 (Figure 3D) in PDD, PD-ND, and HC was showed with cures.

Correlation among QEEG indices, disease severity, and plasma metabolic and inflammatory markers

Since frontal-delta ASP was the dominant marker in patients with PDD, it was chosen as the prominent indicator of EEG slowing. Spearman's rank correlation was performed among frontal-delta ASP, MMSE, SOD,

Variable	OR	
	Adjusted OR (95%CI)	*P* value
Age (years)	1.206 (1.090−1.334)	0.001**
LEDD (mg)	1.002 (0.998−1.006)	0.333
UPDRS (III)	1.015 (0.926−1.113)	0.704
HDL-C (mmol/L)	0.186 (0.038−0.904)	0.030*
GLU (mmol/L)	1.212 (0.945−1.555)	0.052
Cys C (mg/L)	1.028 (0.992−1.065)	0.131
Hs-CRP (mg/L)	2.856 (1.226−6.650)	0.015*
ESR	1.019 (0.972−1.068)	0.445

***Table 2*: Binary logistic regression of possible variables associated with PDD.**

Abbreviations: PDD, Parkinson's disease with dementia; LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale; HDL-C, High-density lipoprotein cholesterol; GLU: blood glucose; Cys C, Cystatin C; Hs-CRP, Hypersensitive C-reactive protein; ESR, Erythrocyte sedimentation rate. Higher age (*P*=0.001), relatively lower levels of HDL-C (*P*=0.030) and higher Hs-CRP (*P*=0.015) were independently associated factors of PDD.

* *P*<0.05.

** *P* < 0.01.

HDL-C, and Hs-CRP measurements (Table 4, Figure 4). We found that frontal-delta ASP was negatively correlated with MMSE scores (Figure 4A), HDL-C (Figire 4**B**), and SOD (Figure 4C) but positively correlated with Hs-CRP (Figure 4D).

ROC curves for QEEG indices, HDL-C, and Hs-CRP in the diagnosis of PDD

We conducted ROC curve analyses to explore whether frontal-delta ASP, HDL-C, or Hs-CRP might offer potential discrimination of PDD and PD-ND before adjusted age (Figure 5A). The areas under the curves (AUC) for frontal-delta ASP was 0.726 (95% CI= 0.629 −0.823, *P*=0.000), with a sensitivity of 77.8%, a specificity of 68.5%, and a cutoff of 1.688. The AUCs for HDL-C and Hs-CRP to discriminate between PDD and PD-ND were 0.703 and 0.709, respectively. The Youden index was 0.389 for HDL-C, and 0.359 for Hs-CRP. Moreover, we performed an ROC analysis for the

QEEG indices	PDD (*N* = 31) A	PD-ND (*N*=47) B	Controls (*N*=47) C	*P*-value[a]	F	Adjusted for age *P*-value
Global spectral power of frequency (log)						
Delta	1.69 (0.02)	1.68 (0.01)	1.67 (0.02)	0.000 A>B, A>C	8.498	0.000***
						A>B (*P*=0.014)
						A>C (*P*=0.000)
Theta	1.66 (0.03)	1.65 (0.02)	1.65 (0.02)	0.054		
Alpha	1.64 (0.03)	1.63 (0.02)	1.64 (0.03)	0.573		
Beta	1.57 (0.03)	1.57 (0.02)	1.57 (0.03)	0.723		
Absolute power (log) of regions in brain						
Frontal-delta	1.69 (0.02)	1.68 (0.01)	1.67 (0.01)	0.000 A>B, A>C	13.128	0.000***
						A>B (*P*=0.004)
						A>C (*P*=0.000)
Frontal-theta	1.66 (0.02)	1.65 (0.25)	1.64 (0.02)	0.007 A>B, A>C	5.989	0.003**
						A>B (*P*=0.015)
						A>C (*P*=0.004)
Frontal-alpha	1.63 (0.03)	1.62 (0.02)	1.63 (0.03)	0.569		
				0.350		
Frontal-beta	1.56 (0.03)	1.56 (0.02)	1.56 (0.03)	0.873		
Central-delta	1.68 (0.02)	1.66 (0.01)	1.66 (0.02)	0.000 A>B, A>C	8.585	0.000***
						A>B (*P*=0.006)
						A>C (*P*=0.007)
Central -theta	1.65 (0.03)	1.64 (0.02)	1.64 (0.02)	0.036 A>C	3.565	0.031*
						A>C (*P*=0.038)
Central -alpha	1.63 (0.03)	1.62 (0.03)	1.63 (0.03)	0.501		
Central -beta	1.56 (0.04)	1.56 (0.3)	1.56 (0.03)	0.976		
Temporal-delta	1.68 (0.02)	1.66 (0.01)	1.67 (0.01)	0.001 A>B, A>C	7.773	0.001**
						A>B (*P*=0.023)
						A>C (*P*=0.001)
Temporal -theta	1.66 (0.03)	1.64 (0.02)	1.64 (0.02)	0.015 A>B, A>C	4.330	0.015*
						A>B (*P*=0.044)
						A>C (*P*=0.018)
Temporal -alpha	1.64 (0.03)	1.63 (0.02)	1.64 (0.02)	0.358		
Temporal -beta	1.57 (0.03)	1.57 (0.02)	1.57 (0.03)	0.968		

Table 3 *(Continued)*

QEEG indices	PDD (*N* = 31) A	PD-ND (*N*=47) B	Controls (*N*=47) C	*P*-value[a]	F	Adjusted for age *P*-value
Parietal-delta	1.69 (0.03)	1.67 (0.01)	1.67 (0.02)	0.000 A>B, A>C	9.534	0.000***
						A>B (*P*=0.008)
						A>C (*P*=0.000)
Parietal -theta	1.66 (0.03)	1.65 (0.03)	1.65 (0.03)	0.112		
Parietal -alpha	1.64 (0.03)	1.64 (0.03)	1.64 (0.03)	0.753		
Parietal -beta	1.56 (0.03)	1.57 (0.02)	1.57 (0.04)	0.360		
Occipital-delta	1.70 (0.02)	1.69 (0.02)	1.68 (0.02)	0.003 A>C	5.674	0.004**
						A>C (*P*=0.004)
Occipital -theta	1.68 (0.03)	1.68 (0.02)	1.68 (0.03)	0.861		
Occipital -alpha	1.66 (0.03)	1.67 (0.02)	1.67 (0.03)	0.477		
Occipital -beta	1.58 (0.03)	1.60 (0.02)	1.59 (0.03)	0.108		
slow-to-fast frequencies ratio (%) in different regions						
Frontal	1.20 (0.07)	1.17 (0.04)	1.14 (0.05)	0.001	6.445	0.002**
				A>B, A>C		A>B (*P*=0.040)
						A>C (*P*=0.001)
Central	1.17 (0.07)	1.14 (0.04)	1.13 (0.05)	0.005	4.891	0.009**
				A>B, A>C		A>B (*P*=0.050)
						A>C (*P*=0.008)
Temporal	1.16 (0.06)	1.13 (0.04)	1.12 (0.04)	0.001	7.557	0.001**
				A>B, A>C		A>B (*P*=0.044)
						A>C (*P*=0.000)
Parietal	1.18 (0.08)	1.13 (0.05)	1.11 (0.05)	0.000	9.614	0.000***
				A>B, A>C		A>B (*P*=0.020)
						A>C (*P*=0.000)
Occipital	1.16 (0.07)	1.11 (0.04)	1.09 (0.04)	0.000	11.479	0.000***
				A>B, A>C		A>B (*P*=0.011)
						A>C (*P*=0.029)
Global	1.18 (0.07)	1.15 (0.04)	1.13 (0.04)	0.000	8.107	0.000***
				A>B, A>C		A>B (*P*=0.033)
						A>C (*P*=0.000)

***Table 3*: Various quantitative electroencephalography indices in different groups.**
Abbreviations: QEEG, quantitative electroencephalography; PDD, Parkinson's disease with dementia; PD-ND, Parkinson's disease with non-dementia. A comparison of variables of QEEG indices among PDD, PD-ND, and healthy controls was performed by [a] Bonferroni post-hoc tests. With age as a covariant, ANCOVAs demonstrated significant interactions among groups. *$P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

combination of frontal-delta ASP, HDL-C, and Hs-CRP in the discrimination of PDD and PD-ND. The AUC for the combination was 0.806 (95% CI=0.728–0.885, *P*=0.000), with a sensitivity of 77.3% and specificity of 75.3%. ROC curve analysis adjusted age (Figure 5B) was used to measure the AUC of the QEEG indices and laboratory markers to predict PDD. The AUC was 0.747 for frontal-delta power (blue curve), 0.771 for Hs-PCR (orange curve) and 0.712 for HDL-C (green curve). The AUC was 0.801 for the combination of frontal-delta power, Hs-PCR, and HDL-C (red curve).

Discussion

In our study, we demonstrated that decreased HDL-C, and increased Hs-CRP were correlated with PDD but not for PD-ND. We found that a significantly higher global ASP of delta frequency and global SPR in PDDs than in patients with PD-ND and HCs, especially in the frontal brain region. Moreover, a significantly lower occipital alpha peak frequency was found in PDD. However, no significant differences in QEEG indices were found between patients with PD-ND and controls. We also found that EEG slowing showed a negative correlation with SOD but a positive correlation with HDL-C and Hs-CRP.

Cumulated evidence indicates that inflammation and metabolic dysfunction play crucial roles in the pathophysiological process of PD. Hs-CRP is a part of the nonspecific acute-stage response to inflammation or tissue damage, acts as a potential biomarker reflecting the inflammatory activity of various diseases, and might be regulated by interleukin-6.[18] Previous studies have revealed that Hs-CRP levels increase significantly

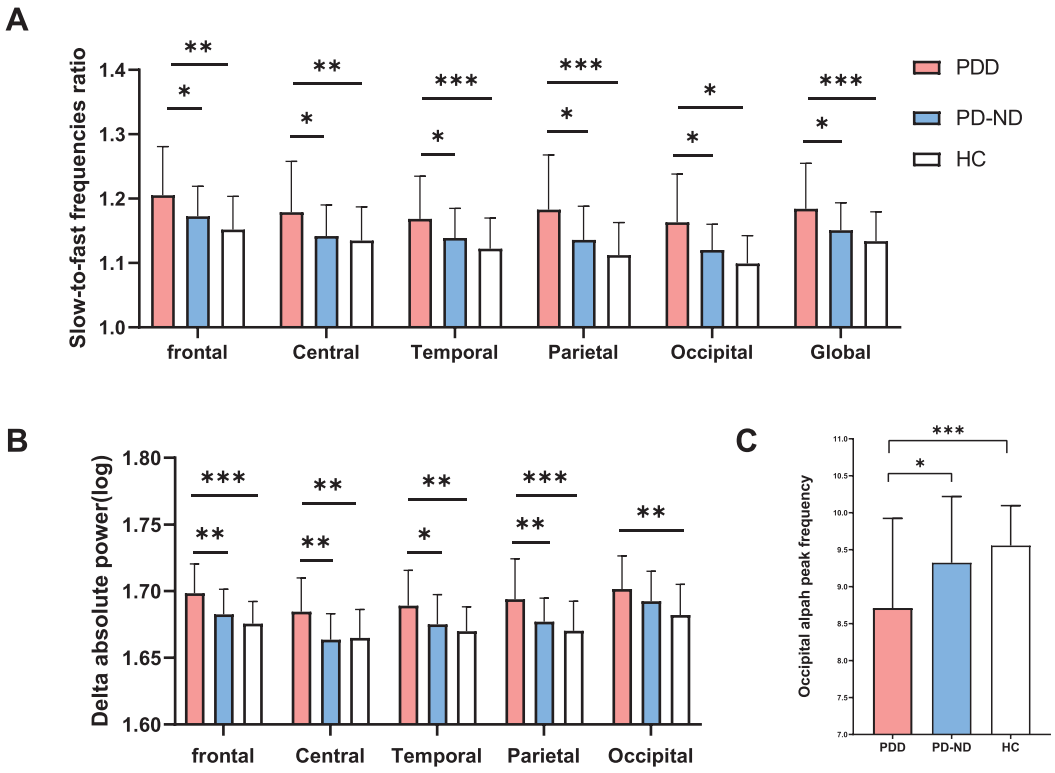

Figure 2. patients with PDD showed more EEG slowing in QEEG.

(A): Comparison of slow-to-fast frequency ratios of specific brain regions in patients with PDD, patients with PD-ND, and controls.

(B): Delta absolute spectral power of specific brain regions in different populations.

(C): Comparison of background rhythm frequency (Hz).

Bonferroni post hoc tests: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. PD, Parkinson's disease; EEG, electroencephalography; QEEG, quantitative electroencephalography; PDD, PD with dementia; PD-ND, PD with non-dementia.

during PD and are negatively correlated with Montreal Cognitive Assessment (MoCA).[19] The Hs-CRP level was correlated with PDD, suggesting that the Hs-CRP level might be an important indicator for evaluating the severity of PD, especially in cognitive impairment. Another study showed that there was a causal relationship between dyslipidemia and BBB damage.[20] Some large-scale prospective studies demonstrated that Hs-CRP or CRP was associated with chronic inflammation, and was predictive of cognitive decline and dementia.[21] Immune dysregulation may play an important role in the pathogenesis of PD.[5] Evidence showed that patients with PD showed alterations in peripheral plasma markers of immune function, including leukocyte differential counts and Hs-CRP or CRP.[4,6,22,23] A meta-analysis showed that patients with PD had higher peripheral blood concentrations of interleukin-6 (IL-6), tumor necrosis factor, IL-2, IL-10, and CRP, demonstrating the inflammatory response related to PD progression.[6] CRP is not only a good biomarker of chronic inflammation, but also a measure of the pathological process in PD.[24] Our study was designed to test the correlation of easy to measure common systemic inflammatory and metabolic markers with neurophysiologic and cognitive measures in PD. Hs-CRP was chosen not just because it has been used as a marker of chronic inflammation in PD, but it is also a routine blood test in hospitals in most countries, easily available and non-expensive. While Hs-CRP level is a generic measure of inflammation, several studies have shown that they are useful for screening and monitoring response to treatment in various neurological diseases such as stroke, dementia, and others.[5,21,23] As such, we think that our

Variable	Frontal-delta	
	r	p
MMSE	-0.344	0.000***
HDL-C (mmol/L)	-0.353	0.000***
Hs-CRP (mg/L)	0.342	0.000***
SOD (KU/L)	-0.322	0.001**

***Table 4*: Correlation analysis of all variables in patients with PD.**

Abbreviations: PD, Parkinson's disease; MMSE, Mini-Mental State Examination; HDL-C, High-density lipoprotein cholesterol; Hs-CRP, Hypersensitive C-reactive protein; SOD, Superoxide dismutase. r: Spearman's rank correlation coefficient.

** $P < 0.01$,

*** $P < 0.001$.

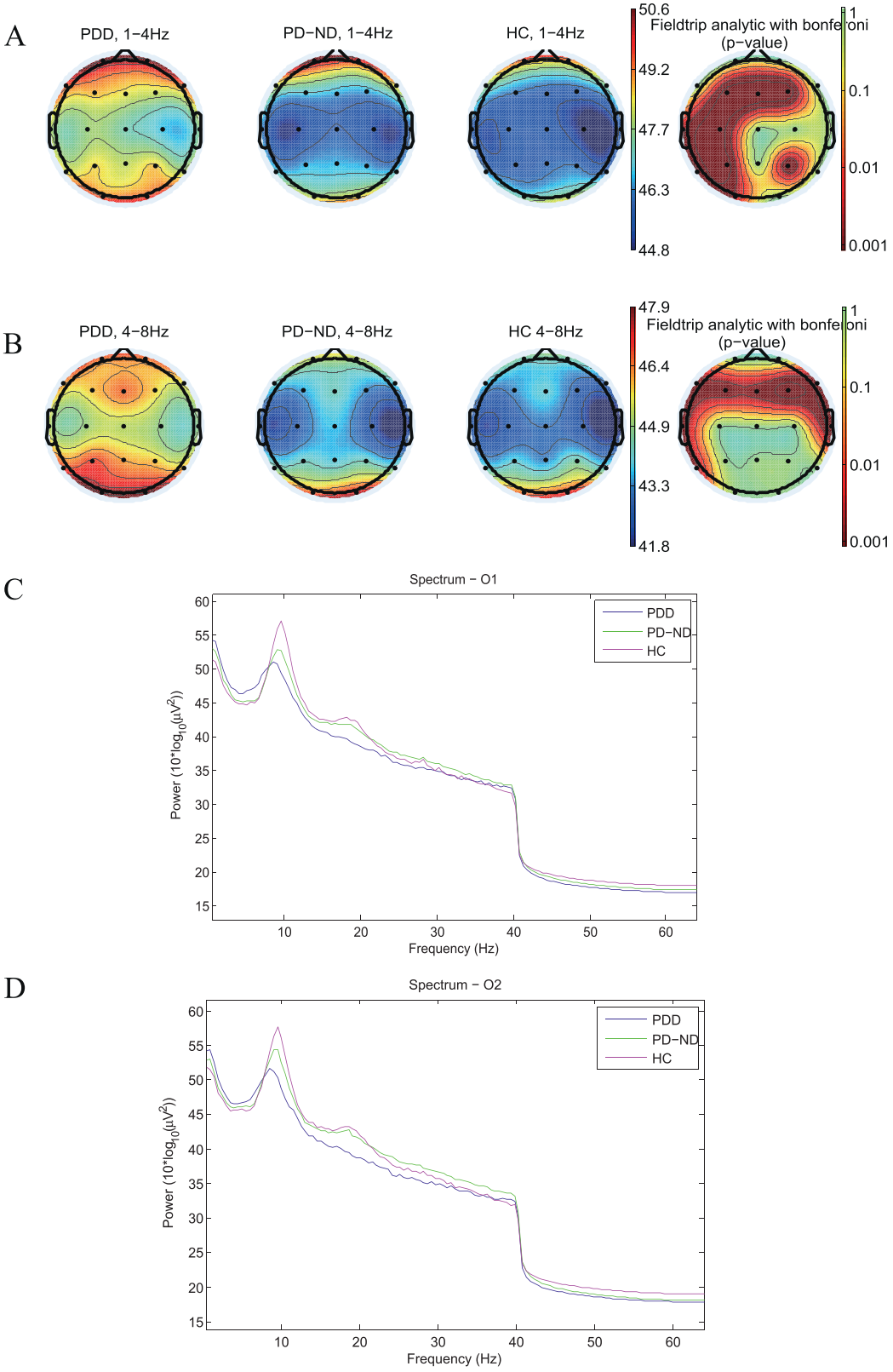

Figure 3. **Absolute spectral power of frequency bands on regional distribution showed with topographic map and peak frequency of occipital derivation showed with cures in different groups.**

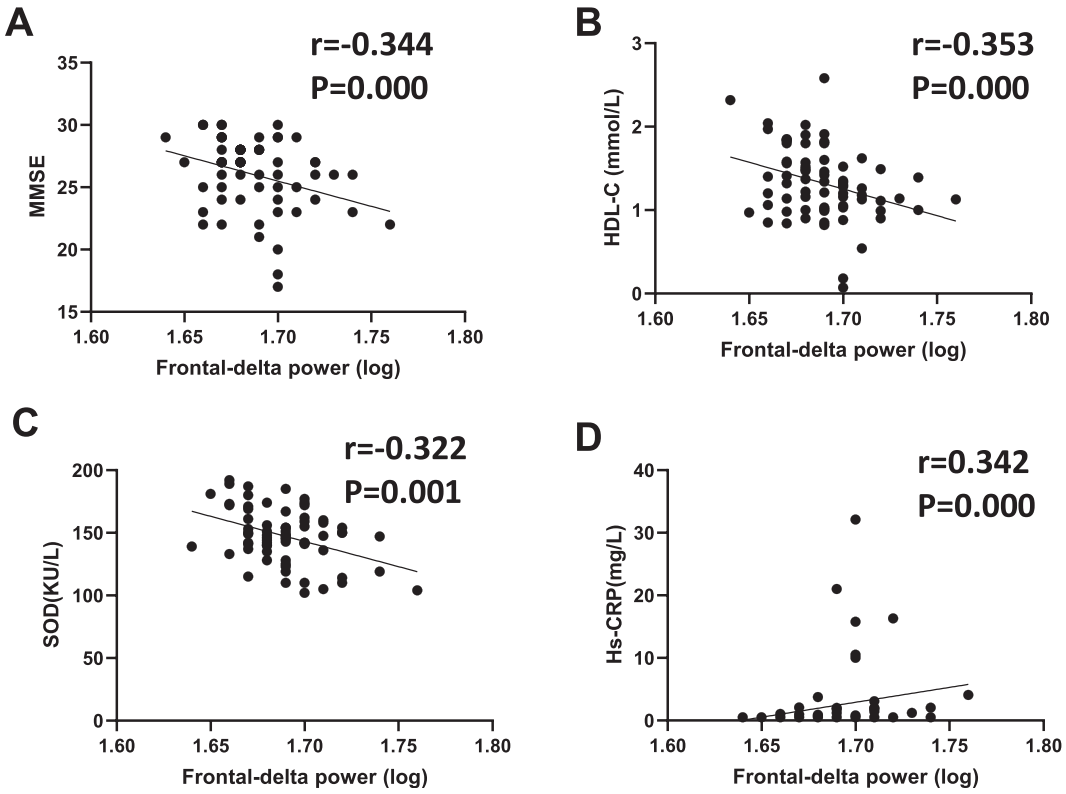

Figure 4. Correlation analysis among QEEG indices, disease severity, plasma metabolic and inflammation markers.

(A): A significant negative correlation was found between frontal-delta power and MMSE scores in patients with PD. (B): A significant negative correlation was found between frontal-delta power and HDL-C in patients with PD. (C): A significant negative correlation was found between frontal-delta power and SOD in patients with PD. (D): A significant positive correlation was found between frontal-delta power and Hs-CRP in patients with PD. $P<0.005$ means significant.

QEEG, quantitative electroencephalography; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; HDL-C, high-density lipoprotein cholesterol; SOD, superoxide dismutase; Hs-CRP, hypersensitive C-reactive protein.

findings highlighting the utility of common blood biomarkers in PD will be clinically useful. Ideally, we could have analyzed additional more neuro specific markers (such as neurofilament light chain) to see if these also yield similar results. However, some of these tests will need special equipment for more accurate measurement and are more costly.

Plasma HDL-C was the lipid most related to the integrity of the BBB. Previous studies[25] have found that total Chol, HDL-C, and LDL-C were significantly different in patients with PD compared to HCs, while some studies presented a controversial result for HDL-C with the future risk of PD.[9] Interestingly, in our study, we found that decreased HDL-C was correlated with PDD, which indicated that HDL-C may be a potential risk factor for PDD.

There is increasing evidence to suggest that lipid metabolism and generic inflammatory markers in the circulation play important roles in the pathogenesis of PDD. Novel therapeutic approaches are being investigated with the intention of influencing pathways leading to neuronal death. The exploration on the lipid and inflammation dysregulation in dementia and its translational implications in the PDD treatment and prevention offers promising options for the disease. One previous study reported that statins could reduce risk of

(A): Comparison of delta (1−4 Hz) absolute spectral power of specific brain regions in patients with PDD, patients with PD-ND, and controls revealed a significant increase in patients with PDD in almost all specific regions, especially in the frontal region. However, no significant differences were found between patients with PD-ND and controls; (B): Comparison of theta (4−8 Hz) absolute spectral power of specific brain regions presented a significant difference in patients with PDD only in the frontal, central, and temporal regions. Patients with PDD showed the lowest peak frequency at the left occipital electrode O1 (C) and right occipital electrode O2 (D), followed by patients with PD-ND and HCs.

PD, Parkinson's disease; PDD, PD with dementia; PD-ND, PD with non-dementia.

A

QEEG and laboratory indices	AUC	Cut-off value	P value	95%CI	Sensitivity	Specificity
Frontal-delta power	0.726	1.68	0.000	0.629-0.823	0.778	0.685
Hs-CPR	0.709	1.13	0.000	0.607-0.811	0.455	0.904
HLD-C	0.703	1.56	0.000	0.611-0.795	0.411	0.970
Combined factors*	0.806	0.32	0.000	0.728-0.885	0.773	0.753

B

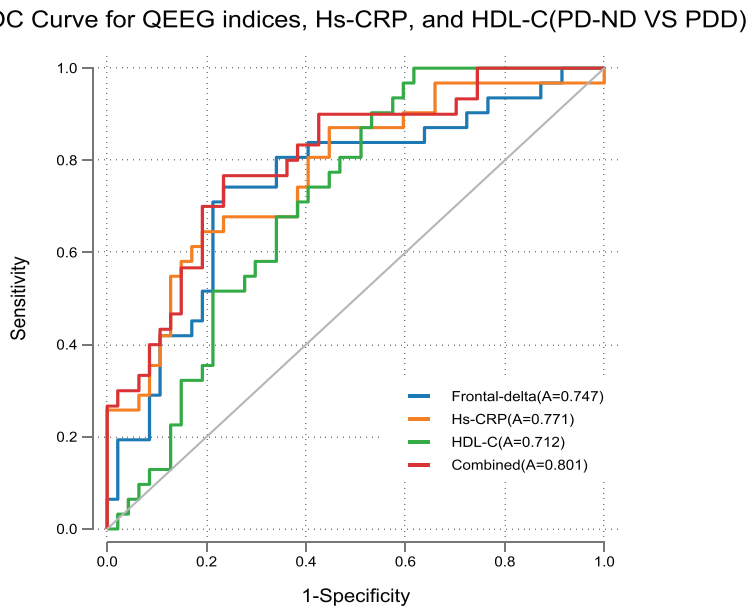

Figure 5. ROC curves for the evaluation of the utility of QEEG and laboratory characteristics for the discrimination of PDD and PD-ND.

A: Detail data of ROC curves of QEEG and laboratory characteristics for the discrimination of PD-ND and PDD before adjusted age. *: combination of frontal-delta power, Hs-CRP, and HDL-C.

B: The ROC curve analysis was used to measure the AUC of the QEEG indices and laboratory markers to predict PDD adjusted age. The AUC was 0.747 for frontal-delta power (blue curve), 0.771 for Hs-PCR (orange curve) and 0.712 for HDL-C (green curve). The AUC was 0.801 for the combination of frontal-delta power, Hs-PCR, and HDL-C (red curve). A, area under the curves. P, *P* value.

ROC, receiver operating characteristic; QEEG, quantitative electroencephalography; PDD, PD with dementia; PD-ND, PD with non-dementia; Hs-CRP, hypersensitive C-reactive protein; HDL-C, high-density lipoprotein cholesterol; AUC, areas under the curves.

neurodegeneration by interfering with Aβ metabolism.[26] However, further systematic analysis demonstrated that statins have no benefit on the primary outcome measures of MMSE for patients with dementia.[27] There is also no evidence for the efficacy of omega-3 polyunsaturated fatty acids omega (PUFA) supplements in the treatment of mild to moderate PDD. Polyphenols may modulate inflammatory and reactive oxygen species (factors that can result in amyloid dysfunction)[28] and improve phentotype in several experimental models of PD. Consumption of dietary flavonoids was also associated with lower PD risk in humans.[29] In addition, transcranial magnetic stimulation (TMS) may potential be helpful in cognitive disorders and dementia, including PDD.[30]

QEEG indices provide a wealth of information and comprise a new method that is developing rapidly in modern neuroscience. EEG is a dynamic method to evaluate the synaptic function of cortical pyramidal neurons, which can capture the sum of excitatory and inhibitory postsynaptic potentials within millisecond time resolution on a macroscopic spatial scale. Consequently, QEEG

techniques could identify abnormal patterns of cortical activation through power spectral analysis. A study demonstrated that QEEG can provide an in vivo approximation of α-Syn in the PD cortex.[11] Previous studies[3] have shown that a slowing EEG is associated with overall cognitive impairment, manifested in AD, DLB and PDD. We found consistent results, reflecting EEG slowing, such as increased delta power, a higher slow-to-fast frequency ratio and a decreased dominant occipital frequency, in the PDD group compared to the PD-ND and HC groups. Moreover, we explored differences in EEG slowing in different brain regions and found significantly slower delta EEG in all regions and slower theta EEG in frontal, central, and temporal regions. Interestingly, of the total brain regions, the frontal region was the dominant region. A previous study[31] showed that altered levels of neuro-metabolism on magnetic resonance (MRI) spectroscopic imaging in the frontal lobe are good indicators for predicting the severity and progression of PD, which may precede the clinical manifestations of these diseases. A review of the neuroimaging literature supports the view that functional MRI shows frontal lobe abnormalities in PDD.[32] In addition, the relatively low metabolism of the frontal cortex may be one of the reasons for the decline in cognitive function in PD. The frontal lobe of positron emission tomography is consistent with the frontal region of EEG, suggesting that EEG deceleration in the frontal region is a sensitive and useful marker of cognitive deterioration at the individual level.

In the present study, there was no significant difference among the three groups in the alpha and beta bands in any specific regions. Studies have revealed that beta band power changes are associated with dyskinesias, such as freezing gait, while abnormalities in delta or theta band power are related to worsening cognitive deficits in patients with PD.[33] The results for the alpha band are controversial. Previous studies reported that patients with PDD might present an increasing delta band, with or without a decreasing alpha band.[34] In the present study, the average alpha band power did not present a difference among groups, suggesting that the delta band was more significant in predicting cognitive decline than the alpha band. No significant differences were detected in EEG slowing between patients with PD-ND and controls, which was consistent with most previous results.[33] In addition, EEG slowing could be observed in the early stage of PD with dementia, especially in early PD with sleep behavioral disorder,[35] suggesting that EEG slowing is a sensitive marker to predict cognitive impairment in PD.

EEG slowing is associated with severe cholinergic deficits and synaptic dysfunction and might be a biomarker to quantify synapse damage and loss in the brain.[36] Moreover, studies have demonstrated that lipid abnormalities and immune activation contribute to BBB impairment, synapse damage and neuronal loss, leading to cognitive decline in PD.[5] This result raises questions about the potential pathophysiological association of lipids, inflammation, and PD EEG slowdown. We explored the correlation of QEEG indices, HDL-C, and Hs-CRP with PD severity. Interestingly, we noticed that EEG slowing revealed a negative correlation with HDL-C and SOD, and a positive correlation with Hs-CRP, suggesting that lipid and inflammation participates in the pathogenesis of EEG slowing in PDD. Moreover, we revealed that EEG slowing was negatively correlated with SOD. As a systemic inflammatory mediator, SOD can catalyse the conversion of superoxide free radicals to hydrogen peroxide. Studies[5] have demonstrated that excessive neuroinflammation can affect the integrity of the BBB and trigger or promote the development of various neurological disorders, including PD. Further studies are needed to confirm these results.

In the long-term, up to 90% patients with PD would develop to PDD as the disease progresses. Moreover, the patients with an older age at diagnosis generally develop dementia more quickly, while having a shorter duration of disease.[37] The mean age of patients with PDD was higher than that of patients with PD-ND and HCs in the study, which was consistent with previous data.[4,5] Our ROC curve analysis results show that QEEG indices, HDL-C and Hs-CRP have appropriate sensitivity and specificity in distinguishing patients with PDD and those with PD-ND, adjusted with age. Obviously, QEEG indices showed more pronounced discrimination than HDL-C or Hs-CRP, suggesting that EEG could be a useful and potential detector of PDD. Considering the relationship of dementia with EEG indices, inflammation, and lipid metabolism, we aimed to determine whether the combination of QEEG indices, HDL-C, and Hs-CRP can be applied to distinguish PDD from patients with PD-ND, and to evaluate cognitive severity. Finally, we showed that the combination of QEEG indices, HDL-C, and Hs-CRP presented better discriminatory capacity for PDD, with a good AUC of 0.806 and higher sensitivity (77.3%) and specificity (75.3%) than each marker alone, suggesting the use of the combination of markers to predict PDD.

Our study has some inherent limitations. First, ours is a single centre study with a modest number of participants and used a retrospective design. Second, we do not have longitudinal data to evaluate the association between EEG indices and biomarkers over time. Third, Hs-CRP is a routine blood test in hospitals in most countries, easily available and non-expensive. While Hs-CRP level is a generic measure of inflammation, several studies have shown that they are useful for screening and monitoring response to treatment in various neurological diseases.[5] However, Hs-CRP is not a specific neuroinflammatory marker but a circulating-inflammatory marker, and hence we cannot draw conclusions on the effects on specific neuroinflammatory pathways. Serum neurofilament light chain or glial fibrillary acidic protein measurements may be useful. Fourth, MMSE

has been shown to be highly accurate to detect patients with cognitive impairment. However, MMSE alone cannot capture the discriminative differences in cognitive domains like in a full neuropsychological test. However, our key strength includes an analysis of a comprehensive topographic map of EEG changes in patients with PDD. In addition, we examined the correlations of the inflammatory and metabolic indicators with EEG slowing in patients with PDD.

We highlight novel correlations between QEEG indices and inflammation and lipid metabolism markers in PD-ND and PDD. QEEG indices, combined with HDL-C and Hs-CRP are potentially useful for the evaluation of PDD. We showed a correlation between generic inflammatory markers and EEG indices in specific subset of patients (PDD). Our current findings suggest that peripheral inflammation might contribute to the pathogenesis of cognitive impairment and EEG slowing in PDD. The mechanism underlying frontal-delta ASP and its correlation with neuro-inflammatory and other metabolic markers in PDD should be further investigated.

Contributors

Conceived and designed the study: H.L.L, B.D, H.Z, Z. H.W, S.Z.Z, E.K.T and Q.W. Performed the study: H.L. L, B.D, H.Z, Y.H.C, Z.H.W, G.M.W, H.T.W, J P. X., Z. D.Z and Q.W. Revised the paper for intellectual content: Z.D.Z, E.K.T, H.T.W, X.J.P, and S.Z.Z. Data statistics and analysis: H.L.L, B.D, H.Z, and Q.W. Wrote the paper: H.L.L, Z.D.Z, E.K.T and Q.W. All authors read and approved the final manuscript. H.L.L, B.D, H.Z, and Q.W. have accessed and verified the data. H.L.L, B. D, H.Z, and Q.W. were responsible for the decision to submit the manuscript for publication.

Data sharing statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declaration of interests

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101615.

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