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# Analysis of Brain Functional Network Based on EEG Signals for Early-Stage Parkinson's Disease Detection

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This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by the Ethics Committee of Tianjin Medical University General Hospital, China.

**ABSTRACT** The early diagnosis of Parkinson's disease (PD) has always been a difficult problem to be solved clinically. At present, there is no clinical auxiliary diagnostic index for reference. We attempted to extract potential biomarkers for early PD from the currently used scalp EEG detection methods in clinical practice. We calculated the phase synchronization index to quantify the synchrony of EEG channels in various frequency bands (delta, theta, alpha and beta bands) of early PD. The results showed that the synchronization of early PD in the delta band was significantly lower than the healthy level, and the brain region reflecting the lower synchronization was located in the temporal lobe, the posterior temporal lobe, the parietal lobe (the posterior center) and the occipital lobe. Moreover, this lower synchronicity is consistent with weaker brain functional connections. Besides, by constructing functional brain network, the graph theoretic topological features of each frequency band of early PD are presented. We have found that early PD has characteristics of small world network in the delta and beta bands, and functional integration and separation characteristics of brain network in early PD are significantly abnormal in the delta, theta, alpha and beta bands. These results indicate that early PD has significant pathological changes from the perspective of brain function network analysis, and its characteristics can be described by multiple features, which may provide auxiliary guidance for the clinical diagnosis of early PD, and also provide theoretical support for the brain function changes of early PD.

**INDEX TERMS** Parkinson's disease, brain functional network, frequency variability.

## I. INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disorder without pathologic treatment, characterized by motor symptoms (resting tremor, bradykinesia, rigidity and abnormal gait) and non-motor symptoms (depression, anxiety, cognitive decline, etc.) [1]–[3]. Patients usually need to seek

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treatment after 50 to 80% of the Substantia Nigra pars compacta (SNc) has been destroyed [4]. This suggests that the destructive process of SNc begins several years before the diagnosis of the early stage of PD, and with the progressive development of the disease course, the PD patient will gradually lose the corresponding function, and then reach the stage of disability. Therefore, early-stage clinical diagnosis plays a key role in the control of the progression of PD and the delay of its disabling stage. However, due to the

diverse clinical symptoms of early PD and the absence of reliable clinical biomarkers at present, it has been difficult to diagnose early PD accurately [5]. In consequence, it is an urgent problem to find out the significant biomarker of early PD, and the reliable biomarker will be an excellent auxiliary index to reduce the clinical misdiagnosis rate. Neuroscience deems that the human brain is a network with functional (synchronization of neural activity) and anatomical (neural synapses) connections [14], during these, functional brain connectivity presents the temporal dependence of neuronal activity between two brain regions anatomically separated or not [16], and it also refers to the neural co-activities of different brain areas to reflect the transient interaction between two specific regions in the human brain [15]. What's more, studies [17], [18] have shown that functional network plays an important role in explaining the brain function and activities. In recent years, there has been an increase number of studies investigating the changes of network structure and functional connections in PD [6]–[9]. Several studies of functional magnetic resonance imaging (fMRI) have shown abnormal functional connectivity patterns between and within the nodes of major networks including the default mode, sensorimotor, executive-attention, and salience networks in PD (for a meta-analysis see [10]). Similarly, the brain has been studied as a complex network based on EEG signals, which can reflect the dynamic interaction between different regions of the brain by constructing and analyzing the local and global characteristics of the network composed of nodes and edges [11], [12]. Suo *et al.* found the configurations of brain functional network in PD were correlated to the severity of the disease [13]. Besides, other researchers have used graph theory to study the entire brain functional network, and these studies would be useful as a possible marker for the evaluation of PD associated with mild cognitive impairment (MCI) [14], [19]. During the clinical brain imaging techniques, electroencephalogram (EEG) has the advantages of higher temporal resolution, lower cost, stronger repeatability, and can study the oscillation of the cerebral networks non-invasively [20]–[22]. Theoretically, EEG can reflect functional markers of synaptic and neuronal integrity, and it is sensitive to the subtle alterations in brain activities prior to structural changes in neurodegenerative diseases such as PD [23]. This study is the first work to explore the characteristics of spontaneous brain activities in early PD by quantitative analysis of multi-channel EEG signals. Firstly, we used PLI method to quantify the whole brain of EEG signals in early PD and the phase synchronization between each pair of channels. Then, the brain functional network was reconstructed based on PLI matrix, and graph theory indicators were extracted to explore the characteristic attributes of the whole brain functional connectivity in early PD. Finally, the characteristics of spontaneous brain activity in early PD were analyzed, and the role of these characteristics as an auxiliary for the clinical diagnosis of early PD was prospected.

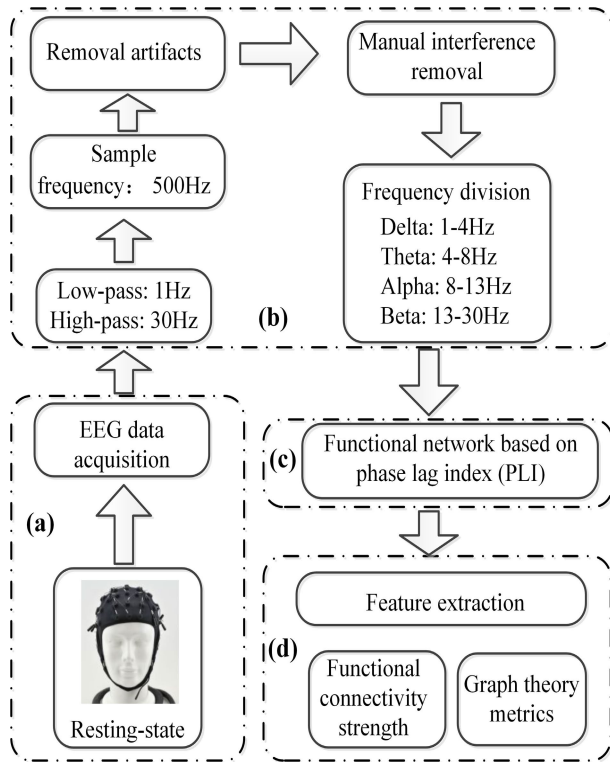
## II. MATERIALS AND METHODS

### A. SUBJECTS

We recruited 29 patients with early-stage of PD from the department of Neurology of Tianjin Medical University (20 female patients: aged range of 53-74, average age of 62 years old; 9 male patients: aged range of 52-74, average age of 63 years old). All of the patients had been diagnosed as primary PD with  $3.2 \pm 2.5$  years' disease duration, and they had been off medication for more than 12h before collecting EEG. In addition, 22 gender-matched and age-matched healthy subjects with no history of psychiatric or neurological illness were recruited as the control group (11 females, aged of 54-70, average age of 62; 11 males, aged of 51-74, average age of 65). There is no history of mental illness and cerebrovascular disease in normal control group and no significant difference between the two groups in gender, age or education level. This study is approved by the Ethics Committee of Tianjin Medical University General Hospital, China. In addition, written consent is provided by all subjects or their legal representatives after full understanding of the study purpose and study procedures.

### B. EEG RECORDING AND PREPROCESSING

Fig.1 presents all of the steps of the EEG signal analysis. The subjects were asked to sit comfortably in a low-light environment, with their eyes closed and awake. We placed 19 Ag-AgCl electrodes on the scalp, including channels Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz according to the international standard 10-20 system. Four additional channels were placed to record left and right electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG) signals of subjects during the collection process. All the EEG preprocessing steps were performed in MATLAB 2018a. Firstly, EEG signals were processed by a 1–45 Hz band-pass zero-phase shift filter, so as to filter out the 50 Hz power frequency interference and ensure the phase information of the original signal remains unchanged. Then fast Independent Component Analysis (fastICA) was used to remove artifacts. FastICA algorithm decomposed 19-channel EEG signals into IC components that are statistically independent of each other through a hybrid matrix. Then we analyzed the correlation between the extracted IC components and the EOG, EMG and ECG signals. The IC component whose absolute value of correlation coefficient is greater than 0.5 is considered as component that has strong correlation with a certain artifact signal. We zeroed out these IC components (PD group:  $0.6207 \pm 0.7277$ ; HC group:  $1.0455 \pm 1.0450$ ) and multiplied them by the resulting mixture matrix to obtain the EEG signals with the artifacts removed. Finally, the manual screen was used to remove some large noise interference signals which were difficult to be filtered by filtering and fastICA method. Finally, we used "eegfiltfft" tool package in eeglab toolbox to filter the signal into four sub-bands delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz), and beta (13-30Hz).



**FIGURE 1.** A flowchart structure about materials and methods. (a) EEG data acquisition. (b) EEG signal preprocessing steps. (c) Construction of functional connectivity network based on phase lag index (PLI). (d) Graph theory analysis.

**C. FUNCTIONAL CONNECTIVITY NETWORK**

The synchronous activity of brain neurons represented the transmission of information in the brain. The phase lag index (PLI) was a method to quantify the phase synchronization level between two time series. In the field of nonlinear dynamics, Stam *et al.* [24] first proposed the phase lag index and quickly used it to describe the degree of phase synchronization between two time series signals. In this study, PLI was used to describe the phase synchronization level between electrodes of EEG signals and constructed brain functional networks. It can be used to reflect the degree of synchronous oscillation of EEG signals in different brain regions and to indicate the correlation between different brain regions. The formula was as follows:

$$PLI = |\langle \text{sign} [\Delta\phi(t_k)] \rangle|, \quad k = 1, 2, \dots, N \quad (1)$$

where  $\Delta\phi(t_k)$  represented the asymmetry of the phase difference distribution of the two signals in time  $t_k$ .

The functional connection matrix based on PLI algorithm is fully weighted. The application of topological filtering transforms a fully-weighted network into a sparser weighted network, which is often used to visualize the brain connectivity distribution. We adopt proportional threshold method as a topology filtering technique in this part before visualizing the functional brain networks. This method “thresholds” the connectivity matrix by preserving

a proportion  $p$  ( $0 < p < 1$ ) of the strongest weights. The threshold value of sample proportion is defined as 0.3 in our study to ensure that there are no isolated nodes in the network. All other weights are set to 0.

**D. GRAPH THEORY METRIC**

Brain functional network is a mathematical representation of the real complex system of the brain. In mathematics, we used the term “graph” to describe a network. In graph theory analysis, graph theory parameters could well describe the functional state of the network, such as the information transmission rate between different nodes, the clustering ability of local areas in the network, the importance of different nodes in information exchange, and so on. The following parameters could be used to describe the topology of the functional network. The following parameters are calculated based on the fully weighted functional connection matrix obtained by PLI.

The clustering coefficient represented the degree of functional separation of the network [25]. It was used to quantify the ability to form small communities within a network. The clustering coefficient of each node in the network was defined as the number of connecting edges that actually existed with this node in its neighborhood divided by the maximum number of connecting edges that may exist. Its calculation formula was as follows:

$$C_p = \frac{\sum_{q,h=1}^N a_{pq}a_{qh}a_{hp}}{k_p(k_p - 1)} \quad (2)$$

where  $a_{pq}$ ,  $a_{qh}$  and  $a_{hp}$  represented an edge that was adjacent to node  $p$ .  $k_p$  was the degree of the node  $p$ . The clustering coefficient of the global network was defined as the average of the clustering coefficients of all nodes, and its calculation formula was:

$$C = \frac{1}{N} \sum_{p=1}^N C_p \quad (3)$$

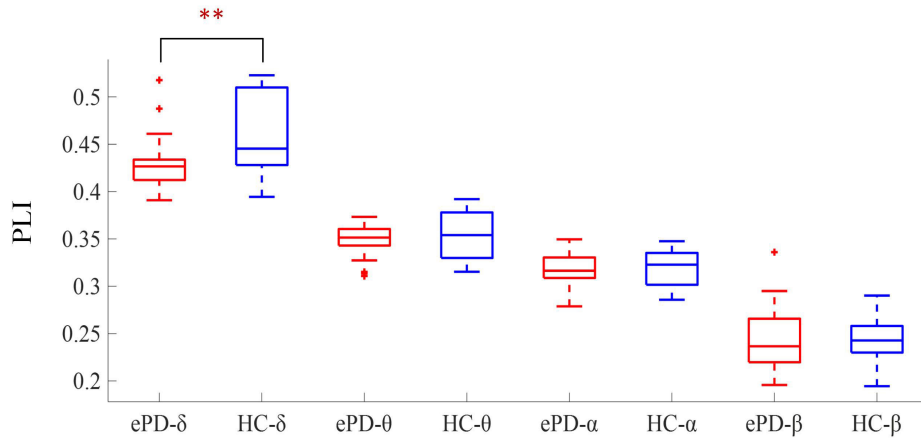
For an adjacency matrix  $a$  with  $N$  nodes, node  $p$  and node  $q$  were connected to form edges.

The network shortest path length can evaluate the aggregation ability of the network. It represented the integration of the graph and the speed at which information was transmitted over the network. The arithmetic average of the shortest path length of all nodes in the network was taken as the shortest path length of the global network, and the formula was:

$$L = \frac{1}{N(N - 1)} \sum_{p,q=1}^N l_{pq} \quad (4)$$

where  $l_{pq}$  was defined as the shortest path length between nodes  $p$  and  $q$ .

Global efficiency was used to quantify whether the network was efficient in processing and transmitting information. The lower the global efficiency was, the higher the cost the network would pay for information interaction [26].



**FIGURE 2. Intergroup differences of PLI of the synchronization matrix between early PD and healthy control (HC) in delta, theta, alpha and beta bands.**

It described the global characteristics of the network, and the formula was:

$$G_e = \frac{1}{N(N-1)} \sum_{p \neq q \in N} \frac{1}{l_{pq}} \quad (5)$$

Local efficiency was used to measure the efficiency of local information processing and transmission of the network, and it also implied whether the network had a certain defense capability against external supply [27]. The local efficiency formula of node  $p$  was as follows:

$$L_e(p) = \frac{1}{k_p(k_p-1)} \sum_{p \neq q \in N} \frac{1}{l_{pq}} \quad (6)$$

And the local efficiency of the network could be deduced as follows:

$$L_e = \frac{1}{N} \sum_{p \in N} L_e(p) \quad (7)$$

**E. STATISTICAL ANALYSIS**

The one-way analysis of Variance (ANOVA) was used to evaluate statistical differences between early-PD group and HC group in delta, theta, alpha and beta bands. And multiple correction tests were performed. The index P, calculated from the mean and variance of characteristic parameters in each state, represents the significance of differences between groups. In order to control type error caused by multiple comparisons of multiple sub-bands or electrodes, we used false discovery rate (FDR) to correct the results. For the parameters extracted in this paper, we assumed that  $p < 0.05$  (\*) and  $p < 0.01$  (\*\*) indicates the level of significant difference of different degrees.

**III. RESULTS**

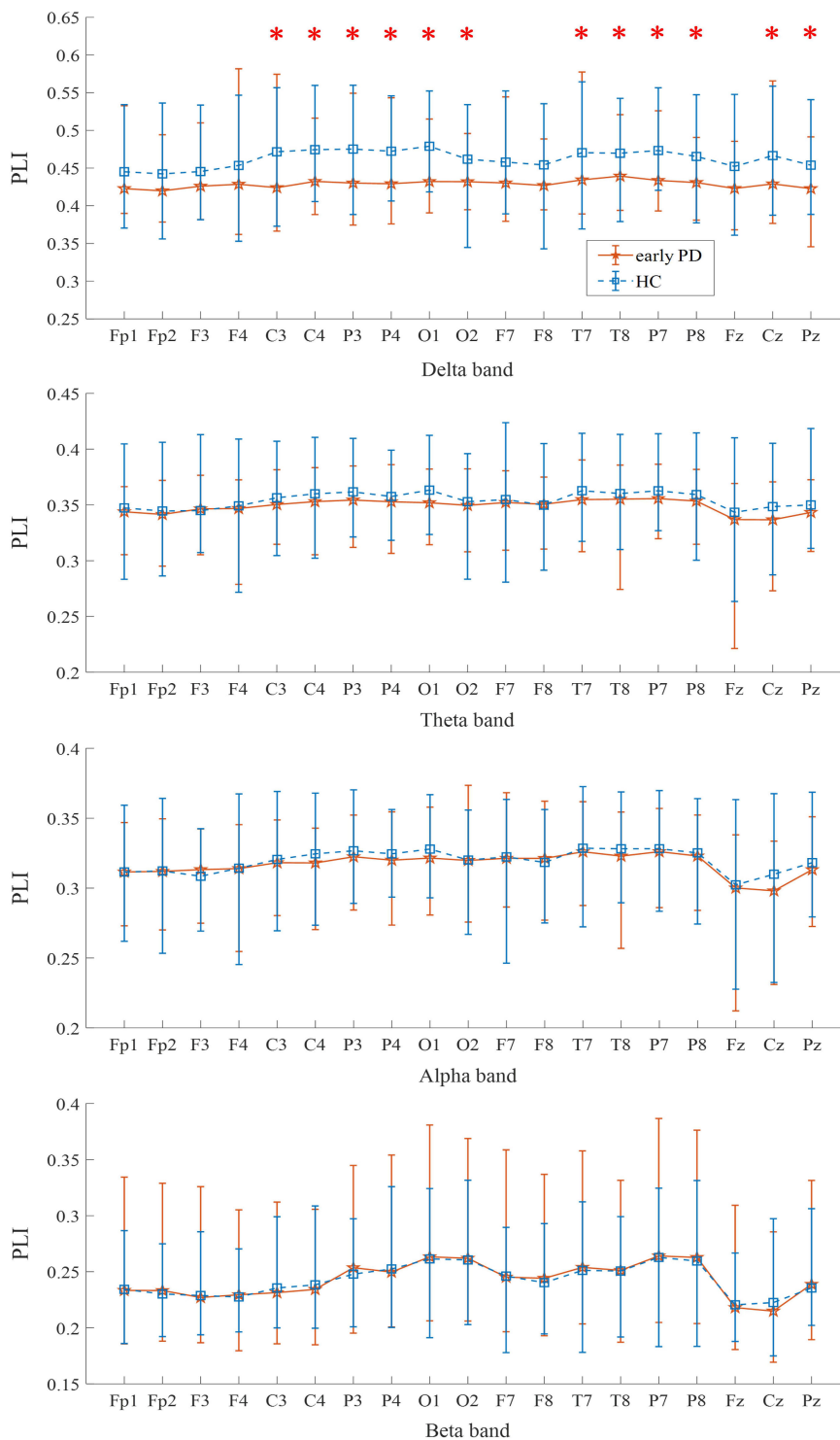
In order to study whether the synchronization level of brain activity in patients with early PD has a state that is typically different from the healthy level, we calculated the

average parameters of PLI-based synchronization matrix of 29 patients with early PD and 22 HC subjects respectively. As shown in Fig.2 and Table 1, the mean values of resting state whole brain PLI (rs-hb PLI) of early PD at all studied frequency bands was lower than healthy levels. Particularly, the statistical analysis shows that the rs-hb PLI of delta band under the early PD state is significantly lower than that of the healthy state with  $p < 0.01$ , and their mean values and the corresponding variance are 0.4288 (0.0254) and 0.4623 (0.0432), respectively. It is evident that the synchronization level of early PD in the delta band is lower than healthy level, indicating that there is abnormal synchronization of brain activity in early PD.

Fig.3 shows the PLI of the individual electrode in the resting state between early PD group and the HC group in four frequency bands. As shown in Fig.3, in the delta band, the PLI value of each channel of PD is lower than that of the healthy level, among which the PLI values of channel C3, C4, P3, P4, O1, O2, F7, F8, P7, P8, Cz, and Pz are significantly reduced ( $p < 0.01$ ), while the PLI values of PD in other frequency bands are not significantly different from that of the healthy level.

These channels with significant differences between the PD group and the HC group in the delta band are shown in Fig.4. The red solid circles represent channels with significant differences, and the yellow solid circles represent no significant differences. These results demonstrate that in the delta band, the synchronization strength in early PD is significantly weaker than in HC, especially in the cerebral central region (channels C3, C4, Cz), the medial-temporal lobe (channels T7, T8), the posterior temporal lobe (channels P7, P8), the parietal lobe (the posterior center) (channels P3, P4, Pz), and the occipital lobe (channels O1, O2).

In order to supplement the analytical perspectives in addition to the whole-brain and synchrony index of each channel, we reconstructed weighted functional connectivity of the brain in the early PD state and the healthy



**FIGURE 3.** Intergroup differences of PLI of each single electrode in four frequency bands between early PD group and HC group. The \* in red indicates the p value less than 0.01.

state, respectively. We averaged all the weighted functional connectivity matrices of two groups respectively. Fig.5 shows the functional connectivity matrices of all the frequency bands between early PD group and HC group, where the

edges represent the PLI values and the nodes correspond to EEG channels. Then we applied proportional thresholding (here, the threshold value is defined as 0.3) to fully-weighted functional connection matrices that averaged in group level.



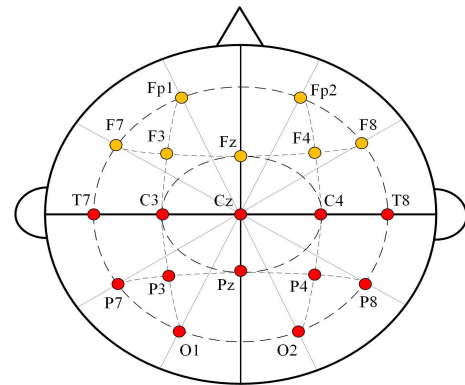
**TABLE 1. The PLI of the whole brain in each frequency band.**

	$\delta$ (mean, S. D.)	$\theta$ (mean, S. D.)	$\alpha$ (mean, S. D.)	$\beta$ (mean, S. D.)
Early PD	0.4288 ± 0.0254	0.3489 ± 0.0162	0.3170 ± 0.0159	0.2424 ± 0.0318
HC	0.4623 ± 0.0432	0.3542 ± 0.0246	0.3196 ± 0.0205	0.2426 ± 0.0230
p-value	<b>0.0011</b>	0.3630	0.6108	0.9778

The functional brain network was shown in Fig.6. Clearly there were significant differences in brain functional connectivity patterns between the early PD group and the HC group. In the all different frequency bands, some new functional connectivities appeared (marked in yellow solid line) in the early PD group, while some another disappeared (marked in black dotted line) compared to the HC group in the whole brain. For example, there was no connectivity between Fp1 and Fp2 in the HC group in delta, theta and alpha band while early PD group existed (yellow solid lines), and there was no connectivity between T7 and C3 in the early PD group in delta band while HC group existed (black dotted lines). Besides, in delta frequency band, all the functional connectivities of early PD group were stronger than those of HC group (Fig. 6(a)). As shown in Fig. 6 (b), most functional connectivities were enhanced and a small amount of these connectivities were weakened in the early PD group in the whole brain in theta frequency band. On the contrary, most of the functional connectivities were weakened in the left brain of early PD, and the unique functional connectivities in the early PD group compared to HC group were mainly distributed between the left and right brain in the alpha band as shown in Fig. 6 (c). In the beta frequency band, the functional connectivities of left-right brain were enhanced in the early PD group, while functional connectivities in the left brain were significantly reduced as shown in Fig. 6 (d).

The pathological changes in functional connectivity in PD patients are consistent with the abnormality of synchronization in each lead. For channels such as C4, P3, P4, O1, O2, T7, T8, P7, and P8, PLI values of the early-PD were significantly reduced in the delta band (Fig.3). Combine the results of Fig.3 and Fig.5, the results of the average functional connectivity matrix indicate that the connectivity strength of these electrodes with difference significantly to other brain regions is also weaker than HC group on average. At the same time, their functional connectivity with other channels has also become stronger (Fig.6). No significant characteristics of the cerebral activities in early-PD were found in other frequency bands.

Furthermore, four graph derived features including clustering coefficient (C), shortest path length (L), local efficiency (Le), and global efficiency (Ge) of all the frequency bands between early-PD group and HC group were extracted from the respective corresponding functional brain networks. One-way ANOVA analysis was applied to compare the characteristic distribution of the four features of the functional brain network among these frequency bands between the two groups.



**FIGURE 4. The brain regions of resting state PLI in the delta band that have significant differences between the early PD patients and HC subjects. The red solid circles indicate channels with significant statistical differences, while the yellow solid circles indicate channels with no statistical differences.**

As shown in Fig.7 (a), the clustering coefficients of all frequency bands (including the delta, theta, alpha and beta bands) in early-PD group are significantly higher than those in HC group with  $p < 0.01$ . Besides, as we can find in Fig.7 (b), the values of shortest path length of theta and alpha bands in early-PD group are significantly higher than those in healthy subjects with  $p < 0.01$ . What's more, the local efficiency and global efficiency of the early-PD group are significantly stronger than those of the HC in delta, alpha, and beta bands with  $p < 0.01$  as shown in Fig.7 (c) (d). These statistical analyses have shown that there are significance differences among specific frequency bands in the brain network structure between early-PD patients and healthy subjects, which illustrated that patients with early PD have abnormal characteristic brain activity in specific frequency bands.

**IV. DISCUSSION**

In this paper, the methods of phase synchronization, complex network and graph theory were used to analyze the multichannel EEG signals of the patients with early-PD to reveal the characteristics of the brain network and the cerebral activities at the state of early-PD without medication. The results showed that the features of the brain functional network of early-PD were unified and significantly different from the healthy level, and the graph theory derived features set based on the brain functional network could be used as an appropriate marker to assist in the diagnosis of early PD.

We used the values of PLI to quantify the synchronization of pair-wire channels. It was found that whole-brain synchronization in the delta band in early PD was significantly lower

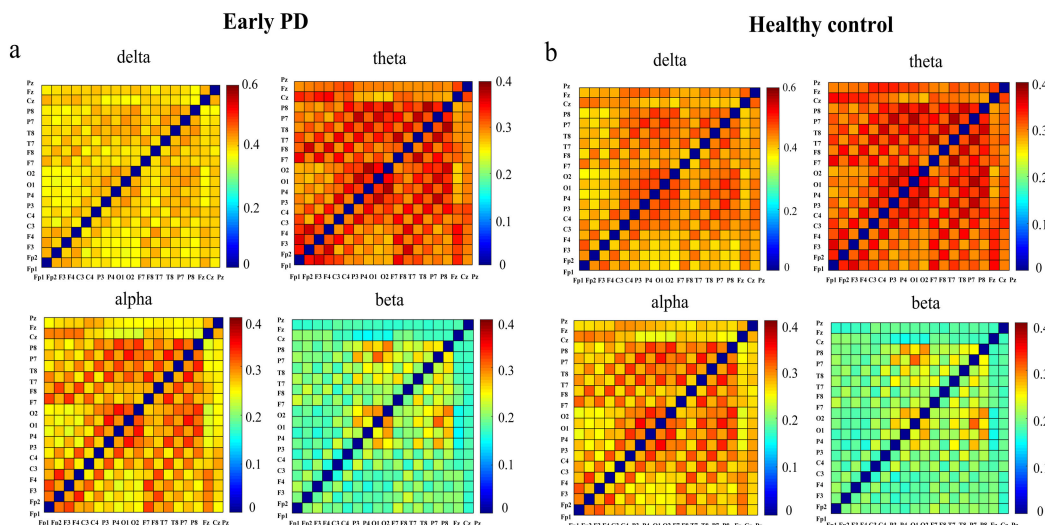


FIGURE 5. Functional connectivity matrix in all the frequency bands between early PD (a) and HC (b) groups.

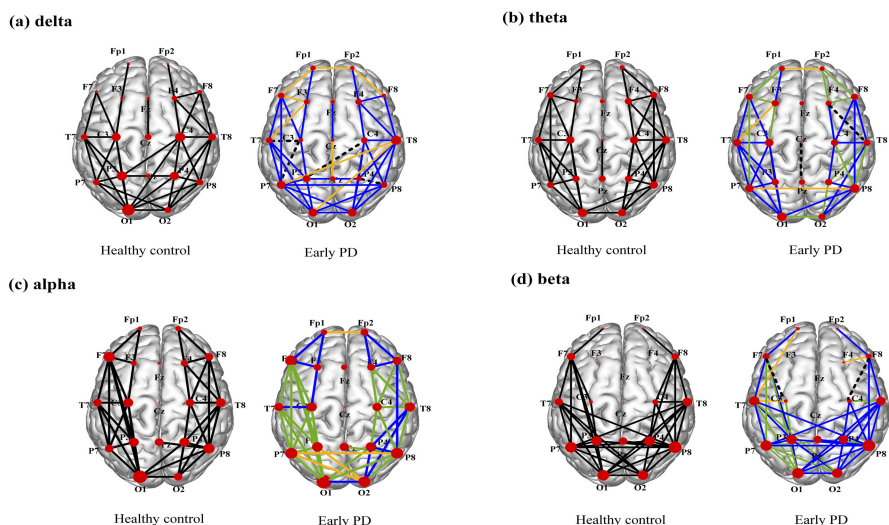
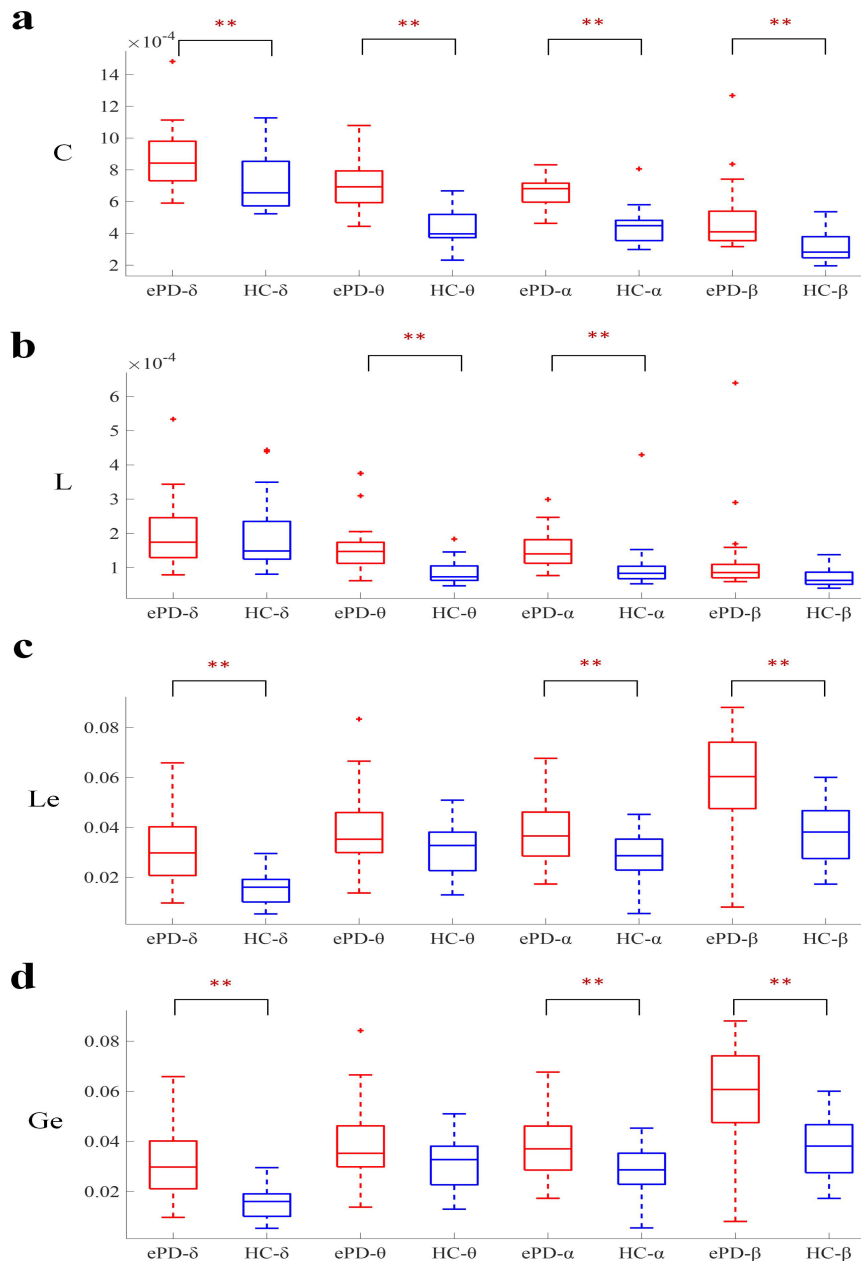


FIGURE 6. Corresponding brain functional networks between early PD and HC groups in four different frequency bands: (a) delta; (b) theta; (c) alpha; (d) beta. The size of the node represented the number of the functional connectivity (degree) of the corresponding channel. The differences of functional connectivity between the two groups in each frequency band were shown by using lines with different colors and line-types. Yellow solid lines denoted the connectivity that only existed in early PD. Black dotted lines denoted the connectivity that did not exist in early PD but existed in HC. Blue solid lines denoted the connectivity in early PD was stronger than HC, while green solid lines denoted the connectivity in early PD was smaller than HC.

than the healthy level. In the delta band, the synchronization strength in the bilateral posterior temporal, parietal and occipital lobes are significantly reduced in early PD group compared to the healthy level. Suarez *et al.* found that compared to non-demented PD, PD with dementia (PDD) was characterized by lower intertemporal synchronization strength in delta [28]. Compared to PD patients, PDD patients had lower mean PLI values in the fronto-temporal and parieto-temporo-occipital areas of the delta [29]. These findings are similar to the abnormalities in early PD, and we speculated that the synchronization intensity of delta frequency band forewarns the abnormal changes in the cognition level of early PD as reflected by the state of the brain network. Besides, the PLI matrices in the delta band showed that the

functional connectivity of early PD is significantly lower than the healthy level at the same brain regions. Related to this, there is a study that shows that patients with PD have reduced gray matter (GM) volume in brain regions, including the left temporal lobe, left middle temporal, middle temporal gyrus, parietal lobe, postcentral gyrus, left inferior parietal, left medial frontal gyrus, supplement motor area [7], and this finding was also backed up by other investigations [30], [31]. The location of atrophy in PD GM volume found in these studies is consistent with our findings on the scalp EEG, which suggests that the synchronous decrease of EEG signals and the function connectivity reduce in such regions in the delta band in the early stage of PD may reflect the area and level of atrophy in the brain GM.



**FIGURE 7.** The graph theory features of early-PD group and HC group in  $\delta$ ,  $\theta$ ,  $\alpha$ ,  $\beta$  bands with a, b, c, and d representing clustering coefficient, shortest path length, local efficiency, and global efficiency respectively. The parentheses marked with \*\* indicate a significant difference ( $p < 0.01$  with FDR corrected) between the groups in which the parameter is located.

Moreover, the brain network features were extracted by using graph theory analysis, and we have calculated the clustering coefficient, shortest path length, local efficiency, and global efficiency respectively. It can be seen that most of the network properties of early-PD were significantly higher than those of HC. Compared with random networks, small world networks (SWNs) have higher clustering coefficient and shorter path length [32], [33]. They deliver information more efficiently and meet competing demands for integration and separation of functions [34], [35]. We can find that in the theta and alpha bands, early PD has the higher clustering coefficient and longer path length, therefore, it can be

inferred that in these particular frequency bands, the brain of early PD doesn't have a representative characteristic of SWN. One study has found that the abnormal path length in the theta band is associated with deterioration of global cognitive function, while an exception in the shortest path length in the alpha band is associated with deterioration of motor function [36]. In addition, in delta and beta bands, there are higher clustering coefficient and normal path length in early PD. The clustering coefficient is used to quantify the ability to form small communities within a network [25]. These findings indicate that in the delta and beta bands of early PD, the brain network has an abnormally enhanced



degree of small module aggregation. What is also interesting is that, in the delta, alpha and beta bands, both local and global efficiency are relatively improved. This phenomenon indicates that early PD has a higher information transmission efficiency than healthy person in these frequency bands. This abnormal increase in information transmission ability is reflected in the process of information interaction between single brain region and other brain regions, and it also exists in the global brain. Some studies have observed that excessive synchronization between the basal ganglia, cortex and muscles leads to the phenomena similar to our findings [37], [41], [42]. This activity can be partially reversed by deep brain stimulation and levodopa, and its presence is associated with motor retardation in Parkinson's disease [38]. It has been suggested that dysfunctional basal ganglia subcortical input compensates for this increased network efficiency [39]. Another study suggests that this increased integration occurs in networks with higher energy costs and may therefore put the network under stress [40], and these source factors may be the internal reasons that lead to various clinical symptoms in early PD. Such specific brain network characteristics may reveal the specific brain activity of early PD. These findings may have important potential implications for the diagnosis of early-PD, even in the pre-symptomatic phase, as well as for tracking disease progression.

In our study, we explored the static functional connectivity patterns of brain network in early PD but ignored the dynamic characteristics of the brain network. Dynamic functional connectivity may provide more information about brain function in early PD. Besides, we didn't apply surrogate analysis to detect significant connections but follow a fully-weighted connectivity analysis. Topological filtering technique such as Minimum-cost spanning trees can be used for exploring the dynamic functional connectivity of brain networks in early PD in the next work.

## V. CONCLUSION

In early PD, there was a significant decrease in brain synchronization and functional connectivity in the delta band, and the most significant brain regions were located in bilateral posterior temporal lobe, parietal lobe and occipital lobe. Interestingly, this lower synchronicity is consistent with weaker brain functional connections. Such early PD abnormalities may serve as an early warning of cognitive decline in PD patients. What's more, there are significance differences among specific frequency bands in the brain network structure between early PD patients and healthy subjects. Such specific brain network characteristics may reveal the specific brain activity of early PD. The graph theory derived features set based on the brain functional network could be used as an appropriate marker to assist in the diagnosis of early PD.

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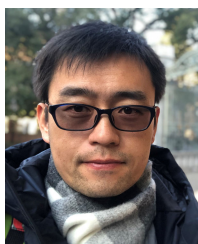
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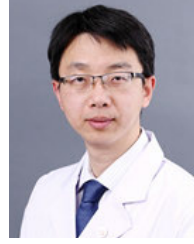
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