Title: A Study Over Brain Connectivity Network of Parkinson's Patients, Using Nonparametric Bayesian Model

Running title: Brain Connectivity Network of Parkinson's Patients

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Abstract

Introduction: Parkinson's disease is a neurodegenerative disease that disrupts functional brain networks. Many neurodegenerative disorders are associated with changes in brain communication patterns. Resting-state functional connectivity studies can distinguish the topological structure of Parkinson's patients from healthy individuals by analyzing patterns between different regions of the brain. Accordingly, the present study aimed to determine the brain topological features and functional connectivity in patients with Parkinson's disease, using a Bayesian approach.

Method: The data of this study were downloaded from the open neuro site. These data include "Resting-State Functional MRI" (rs-fMRI) of 11 healthy individuals and 11 Parkinson's patients with mean ages of 64.36 and 63.73, respectively. An advanced nonparametric Bayesian model was used to evaluate topological characteristics, including clustering of brain regions and correlation coefficient of the clusters. The significance of functional relationships based on each edge between the two groups was examined through false discovery rate (FDR) and network-based statistics (NBS) methods.

Results: Brain connectivity results showed a major difference in terms of the number of regions in each cluster and the correlation coefficient between the patient and healthy groups. The largest clusters in the patient and control groups were 26 and 53 regions, respectively, with clustering correlation values of 0.36 and 0.26. Although there are 15 common areas across the two clusters, the intensity of the functional relationship between these areas was different in the two groups. Moreover, using NBS and FDR methods, no significant difference was observed for each edge between the patient and healthy groups ($p\text{-value} > 0.05$).

Conclusion: The results of this study show a different topological configuration of the brain network between the patient and healthy groups, indicating changes in the functional relationship between a set of areas of the brain.

Keywords: Parkinson's Disease, Functional Brain Imaging, fMRI, Bayesian Method.

Introduction

Parkinson's is a chronic neurological system disorder that affects the dopaminergic, noradrenergic, cholinergic, and serotonergic systems. It is the most common age-related neurological disease next to Alzheimer's, with a prevalence of about 0.5 to 1 percent in the age range of 69-65 and 1 to 3 percent in people over 80 (Ahmadou et al., 2019; Nussbaum & Ellis, 2003). The risk factors for Parkinson's disease (PD) are generally unknown, and old age, environmental factors, and genetic factors increase the risk of developing the disease (Kouli et al., 2018; Reeve et al., 2014). The clinical signs of Parkinson's are characterized by motor and non-motor symptoms. Motor symptoms include rigidity, bradykinesia, akinesia, abnormal posture, and resting tremor. Non-motor symptoms such as autonomic, sleep, olfactory, psychiatric (depression, psychosis, hallucination, anxiety, and impulse control), and cognitive disorders are essential factors in patients' disabilities that are referred to as the mechanisms of the initial stages of Parkinson's diagnosis. Since cognitive and psychiatric disorders can reduce the daily function and quality of life of patients with PD, non-motor symptoms are of high clinical importance (Błaszczyk, 2016; Martinez-Martin et al., 2011; Pellicano et al., 2007; Han et al., 2018; Painous & Marti, 2020). Among the psychiatric disorders, particularly depression and anxiety have been determined as risk factors for PD. The literature has also displayed that the underlying effects of depression and anxiety can appear many years before the incidence of motor symptoms (Behari et al., 2001; Bower et al., 2010; Lin et al., 2014; Shiba et al., 2000).

Resting-state functional connectivity (rsFC) studies are used to examine the pathophysiology of neurodegenerative disorders, including Parkinson's. These studies use non-invasive functional magnetic resonance imaging (fMRI) to distinguish distinct patterns of brain connectivity between healthy and diseased individuals. Since many neurological disorders are associated with altered topological patterns of brain connectivity, rsFC studies can detect connections between different brain areas by recognizing this topological structure. Topology is defined as the study of features that describe how brain areas are arranged based on their interconnections. The use of these studies in Parkinson's patients is important as it provides helpful information about functional and morphological changes, including motor and non-motor functions (S. Chen et al., 2020; Markošová et al., 2008; Stoessl, 2009; Tuovinen et al., 2018). In this regard, several studies have indicated alterations of brain connectivity in PD patients with cognitive disorders. For example, Gorges et al. assessed the brain connectivity networks using seed-based analyses. Compared with the control subjects, PD patients

decreased functional communication within some regions of the default mode network (DMN). Baggio et al. reported decreased FC in PD patients between the dorsal attention network and right frontoinsula areas using independent component analysis (Amboni et al., 2015; Baggio et al., 2015; B. Chen et al., 2017; Gorges et al., 2015).

Functional connectivity (FC) is determined based on the correlation patterns, using statistical methods such as Pearson correlation coefficient, mutual information, and partial correlation coefficient (Kim & Pan, 2015; Smith et al., 2011; Xiong et al., 1999). Moreover, there are other statistical methods for inferring functional relationships, including clustering models, multivariate models, graphical Lasso models, and Bayesian models (Baumgartner et al., 2000; Cribben et al., 2012; Hyvärinen & Oja, 2000; Patel et al., 2006a, 2006b; Varoquaux et al., 2010).

Functional communication data at rest faces significant challenges: 1) the existence of correlations between the connectivity edges that are related to the features of the topological network. 2) The high number of parameters in the covariance matrix, specifically if the number of regions-of-interest (ROIs) is high. Although many functional studies have been performed on Parkinson's disease data, the analysis of functional correlation data without considering these characteristics does not seem appropriate. Accordingly, in this study, considering the characteristics of functional relationship data, the advanced nonparametric Bayesian model introduced by Chen et al. was used to evaluate the topological network structure in Parkinson's patients (S. Chen et al., 2018).

Materials and methods

1. Data acquisition

The resting-state fMRI data were obtained from the Open fMRI dataset with the document ID ds000245. The scans acquisition protocol was obtained as follows: TR = 2500ms, TE = 30ms, 39 transverse slices with inter-slice interval = 0.5 mm and thickness = 3 mm, FOV = 192 mm, matrix size = 64×64 , flip angle = 80° . Resting-state fMRI scans were obtained for 8 minutes with eyes closed. T1-weighted images had a total time of 349 seconds.

2. Data processing

Pre-processing of resting-state fMRI scans was performed using FSL software version 6.0.1. The first five volumes of each time course were removed due to the correction of the initial image inhomogeneity and the adaptation of individuals to the surrounding conditions; hence, a

total of 193 volumes per person was considered. Images were normalized with a voxel resolution of $2 * 2 * 2 \text{ mm}^3$, and for smoothing, a Gaussian filter with 6 mm FWHM was used. Then, the pre-processed images were divided into 90 desired areas, according to atlas AAL, using WFU Pickatlas toolbox in MATLAB R2019b software (Tzourio-Mazoyer et al., 2002). Fisher's Z-transformed correlations were considered as the measurement index of the edges.

3. Statistical analysis

Statistical inference of brain functional connectivity was performed in two stages:

Step 1: A nonparametric Bayesian model was used to evaluate the topological structure of the brain network. To assess the network properties, including determining the number of clusters of brain regions and the correlation coefficient of clusters, first, the residual matrix $R^o_{N \times E}$ was calculated as follows:

$$R^o_{N \times E} = Y_{N \times E} - X_N^T \hat{\beta}_{p \times E}$$

$Y_{N \times E}$ is the E-th sample Fisher's Z transformed correlation for the N-th of the subject ($1, \dots, N$). Each subject has $V = 90$ areas and $E = \binom{90}{2} = 4005$ edges. X_n^T is the design matrix of p-covariates and $\hat{\beta}_{p \times E}$ is the parameters estimation linking the covariates to the response.

Suppose $Y^N_{1 \times E} \sim MVN(X_N^T \beta_{p \times E}, \Lambda_{E \times E})$, $\Lambda_{E \times E}$ represent the correlation matrix between regions of the brain. This matrix is a function of network structure and correlation parameters $\rho = (\rho_0, \rho_1, \dots, \rho_k)$.

The network topological structure-based correlation matrix is defined as follows:

$$\Lambda_{e_{i,j} \times e_{i',j'}} = \begin{cases} \rho_k, & \text{if } \omega_i = \omega_j = \omega_{i'} = \omega_{j'} = C_k \\ \rho_0, & \text{otherwise} \end{cases}$$

$\Lambda_{e_{i,j} \times e_{i',j'}}$ is an entry of the matrix $\Lambda_{E \times E}$ which is based on the correlation between the edges $e_{i,j}$ (correlation between regions i and $j, i \neq j$) and $e_{i',j'}$. $\omega_i = C_k$ is considered as an indicator variable, based on whether region i belongs to the cluster k or not. If a pair of edges are in a cluster then it can be assumed that $e_{i,j} \cong e_{i',j'}$:

$$e_{i,j} \cong e_{i',j'} \quad (e_{i,j} \in C_k, e_{i',j'} \in C_k) \quad \text{if and only if } \omega_i = \omega_j = \omega_{i'} = \omega_{j'} = C_k$$

Finally, the posterior distributions ρ and ω are obtained, using the Markov Monte Carlo chain (MCMC) with 5000 iterations.

Step 2: To compare the pairwise association of 90 regions, the number of univariate tests is as high as $\binom{90}{2} = 4005$. Considering multiple comparisons, the network-based statistics (NBS) and false discovery rate (FDR) were performed to assess any significant pairwise connections between the patient and healthy groups. The NBS method uses a permutation test to examine the cluster difference of edges with a predefined threshold across the two groups. The FDR method examines the significant individual level of each edge in the two groups. P-value <0.05 was considered as a significant level. The analysis was performed through the NBS Connectome package in MATLAB software.

Results

Resting-state fMRI data were included 11 Parkinson's patients (six male) and 11 healthy individuals (six male), matched on sex ratio. The mean age was 64.36 years for the PD group and 63.73 years for the healthy group, in which, in terms of age distribution (p-value = 0.83), there was no significant difference between the two groups.

Estimation of the number of clusters and their correlation coefficient was performed using a nonparametric Bayesian model to consider the specific characteristics of functional relationship data. According to what was previously explained in the theory of this model: 1) the regions within each cluster have a considerable functional relationship with each other and 2) the correlation coefficient of each cluster expresses the degree of pairwise correlation of regions within the cluster. Figure 1 shows the mean Fisher's Z-transformed correlations of brain regions in both diseased and healthy groups.

The areas in the diagram are arranged according to their placement in the clusters. The more correlated edges had a higher mean value in each cluster, indicating the correct detection of clustering by the nonparametric Bayesian model. Figure 2 shows a clustering of areas of the brain. The brain network regions of the two groups were divided into six clusters and identified by the same color.

Table 1 shows the names of the areas in each cluster and the estimation of the correlation between the clusters by groups. The largest cluster in the patient and the healthy group has 26 and 53 areas, respectively. Common areas of these clusters include right superior frontal gyrus (orbital part), left inferior frontal gyrus (orbital part), left olfactory cortex, right olfactory cortex, left middle frontal gyrus (orbital part), right middle frontal gyrus (orbital part), left gyrus rectus, right gyrus rectus, left anterior cingulate and paracingulate gyri, right amygdala,

left pallidum, right pallidum, left temporal pole(superior), left Temporal pole(middle), right inferior temporal gyrus.

Although the clusters have common areas, the correlation between these areas is different in the two groups of sick and healthy. The correlation of this cluster was 0.36 in the patient group and 0.26 in the control group, which indicates that the relationship between the regions of this cluster in the patient group is stronger than that of the control group. The correlation coefficient results in clusters five and six also show stronger regional connectivity in the patient group. The correlation coefficients of the second, third and fourth clusters in the patient group are 0.35, 0.30, and 0.47, respectively, which shows weaker regional connectivity of these clusters than their respective clusters in the control group.

To evaluate the cluster performance of the edges, the NBS method was used with the following settings: $t = 3.1$, permutations = 5000, component size = "extent". The results of this method did not show a statistically significant difference between the edges in the two groups of patients and healthy, which was similar to the results of the FDR method, with the p-value of the tests being greater than 0.05.

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Figure 1: Mean brain connectivity matrix of individuals (a) Control group (b) Parkinson's patients group.

Figure 2: Clustering of brain regions in each group (a) control group (b) Parkinson's patients group.

Table 1: Brain regions in each cluster by group

Cluster	Control subjects		PD subjects	
	Label	correlation	Label	correlation
1	PreCG.L, ORBsup.R, IFGoperc.L, IFGoperc.R, ORBinf.L, ROL.L, ROL.R, OLF.L, OLF.R, ORBsupmed.L, ORBsupmed.R, REC.L, REC.R, INS.L, INS.R, ACG.L, DCG.L, DCG.R, HIP.R, Amygdala_R, LING.R, SOG.L, SOG.R, MOG.L, MOG.R, IOG.R, FFG.L, FFG.R, PoCG.L, PoCG.R, SPG.L, SPG.R, IPL.L, IPL.R, SMG.L, SMG.R, ANG.R, PCL.L, CAU.L, CAU.R, PUT.L, PUT.R, PAL.L, PAL.R, HES.L, HES.R, STG.L, STG.R, TPOsup.L, MTG.L, MTG.R, TPOmid.L, ITG.R	0.26	ORBsup.L, ORBsup.R, ORBmid.L, ORBmid.R, ORBinf.L, ORBinf.R, OLF.L, OLF.R, SFGmed.L, SFGmed.R, ORBsupmed.L, ORBsupmed.R, REC.L, REC.R, ACG.L, PHG.L, PHG.R, PAL.L, PAL.R, TPOsup.L, TPOsup.R, TPOmid.L, TPOmid.R, ITG.L, ITG.R	0.36
2	PreCG.R, SFGdor.L, SFGdor.R, MFG.L, MFG.R, IFGtriang.L, SMA.L, SMA.R, SFGmed.L, SFGmed.R, ANG.L, PCL.R	0.45	IFGoperc.R, ROL.L, ROL.R, INS.L, INS.R, DCG.L, DCG.R, PCG.L, PCG.R, HIP.L, HIP.R, LING.L, IOG.L, FFG.L, FFG.R, , PUT.L, PUT.R, HES.L, HES.R, STG.L, STG.R, MTG.L, MTG.R	0.35
3	ORBsup.L, ORBmid.L, ORBmid.R, ORBinf.R, PHG.L, PHG.R, TPOsup.R, TPOmid.R, ITG.L	0.40	IFGoperc.L, CAL.R, CUN.L, CUN.R, LING.R, SOG.L, SOG.R, MOG.L, MOG.R, SPG.L, IPL.L, IPL.R, SMG.L, SMG.R, ANG.L, ANG.R, PCUN.L, PCUN.R, PCL.L, THA.L	0.30
4	CAL.L, CAL.R, CUN.L, CUN.R, LING.L, PCUN.L, PCUN.R	0.62	PreCG.L, PreCG.R, SFGdor.L, SFGdor.R, MFG.L, MFG.R, SMA.L, SMA.R, PoCG.L, PoCG.R	0.47

5	PCG.L, PCG.R, HIP.L, IOG.L, THA.L, THA.R	0.31	IFGtriang.R, ACG.R, CAU.L, CAU.R, THA.R	0.43
6	IFGtriang.R, ACG.R, AMYG.L	0.13	IFGtriang.L, CAL.L, SPG.R, PCL.R	0.30

Label: Abbreviation of the names of the desired areas (ROIs). More details about the names of the areas are available in the appendix.

Discussion

This study used a nonparametric Bayesian method to evaluate brain connectivity between Parkinson's and healthy groups. Different areas were assigned to clusters based on the similarity between these areas and variation from conventional clustering methods. Previous models often consider the structure of the dependence between the edges based on the spatial closeness, which depends on the characteristics of the topological network. Still, biologically, the correct structures of the topological network are not limited to being spatially adjacent, so it does not seem appropriate to use them. The nonparametric Bayesian model does the clustering of the brain regions based on the correlation between edges based on topological features.

According to the nonparametric Bayesian model, brain regions in both groups were divided into six clusters. Although there were common regions between the two groups of patients and healthy in each cluster, the intensity of the functional relationship between these regions differed in the two groups. In addition, the connectivity of some clusters in the control group was higher, while several clusters showed stronger functional connectivity in the patient group. In this regard, Chen et al. used a new statistical method to study the network topology of brain connectivity in Parkinson's patients. In this study, the control group in the occipital and inferior temporal lobes had more substantial connections with the superior temporal lobes and insular than the patient group. However, the control group showed a weaker functional relationship than the patient group in several areas, including the insular right or superior frontal gyrus orbital (S. Chen et al., 2020).

Another study on brain connectivity in people with Parkinson's disease showed a decrease in functional communication between the amygdala and the inferior parietal lobule, lingual gyrus and fusiform gyrus associated with the severity of hyposmia, and cognitive performance. In

this study, Parkinson's patients in canonical networks such as high visual, primarily visual, executive control, visuospatial, salience, and default mode networks had a more functional relationship with areas outside these canonical networks than the control group (Yoneyama et al., 2018). Also, a study on whole-brain analysis of PDs with visual hallucinations showed that the disease-related effects influence the resting-state functional connectivity of posterior and paracentral brain regions (Hepp et al., 2017).

In the present study, decreased FC was identified in the medial superior frontal gyrus and the precuneus gyrus (both as critical parts of DMN) with some brain regions in PD patients. These alterations can affect cognitive processes such as visuo-spatial attention and episodic memory retrieval. The findings seem to be consistent with other research, which found different aspects of reduction connectivity in the DMN across PD patients (Shin et al., 2016).

In general the present study results show that there are fundamental differences between the two groups of patients and healthy in terms of areas in each cluster and their correlation coefficient. These results could provide a better understanding of the topological mechanism of Parkinson's disease. The findings of this study are in line with the results of several studies that show changes in the topological characteristics of Parkinson's patients (Engels et al., 2018; Huang et al., 2019; Prajapati & Emerson, 2020; Shine et al., 2019). Sang et al. examined the brain topology network of Parkinson's patients receiving antiparkinson therapy. This study reported changes in the topological organization of these patients and showed that anti-Parkinson therapy could affect the effectiveness of the brain network ineffectively relieving Parkinson's clinical symptoms (Sang et al., 2015).

A total of 4005 univariate tests are needed to compare pairwise connectivity of 90 brain regions. In evaluating the significance of the connections between these areas, multiple comparison methods of FDR and NBS were used, but no significant relationship was found across the two groups. However, as previously reported, there were different topological features in the two groups. In this regard, Heidari et al. also examined the functional communication characteristics of Parkinson's patients using variance components linear modeling. In this study, a decrease in the functional association of 10 pairs of ROIs was observed in Parkinson's patients. However, considering the multiple comparison test, the functional relationship of each couple of regions was not significantly different between the two groups (Heidari et al., 2019).

Limitations

A limitation of this study is that the number of subjects in the patient and control groups was relatively small. Although the Bayesian nonparametric model addressed shortcomings in FC data, the power of analysis could be improved in a larger sample size. Therefore, considering future studies with an increased sample size will help better understand the underlying brain connectivity network in Parkinson's disease. The other factor is hardware limitations which required high computational time to analyze multi-subject fMRI data.

Conclusion

Given that rsFc studies identify communication patterns associated with phenotypes of neurological diseases, appropriate statistical tests to estimate the correlation patterns of FC data are of utmost importance. This study investigated the brain connectivity of Parkinson's patients using an advanced nonparametric Bayesian model. The results of this model indicate that the characteristics of the brain functional network topology in Parkinson's patients are different from the control group.

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