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ORIGINAL RESEARCH

Functional Connectivity Network Analysis in Brain Regions using Resting State-fMRI data with Parkinson's disease

Serve Heidari [1], Nasrin Borumandnia [2], Naghmeh Khadembashi [3], Hamid Alavimajd [4]

[1] Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3] English Language Department, school of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [4] Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence to: Alavimajd H, Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Qods Square, Tajrish, Tehran, Iran.
tel: +982122707347, +989121483687; e-mail: alavimajd@sbmu.ac.ir

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Abstract

OBJECTIVE: Investigating the functional connectivity (FC) in different regions of the brain with functional Magnetic Resonance Imaging (fMRI) method has proved to be useful for identifying patterns of neurological disorders. The present study aimed to investigate changes in the brain network between patients with Parkinson's Disorder and healthy people. The gender effect is also examined for these changes.
MATERIALS AND METHODS: Scan data from 15 Parkinson's patients including 6 males and 9 females and 15 healthy subjects, including 7 males and 8 females were analyzed using variance components model after pre-processing. In addition to the comparison between the patient and the healthy group, they were also analyzed based on gender segregation.
RESULTS: There were significant correlations among the 11 pairs of regions over the patient and the control group in the general form, with a *p*-value below 0.05. A significant difference was found merely in 1 pair of cases for patient and control group of females, while 16 pairs of regions were significantly different among males.
CONCLUSION: The results indicate that there is a clear difference between the FC changes of various regions of the brain in males compared to females with Parkinson's disease. In the FC study of each pair of regions in male patients compared to the control group, a decrease of FC correlations strength was experienced in many of the regions while in some other regions, an increase was witnessed. This change in FC was not significant in female group.

Abbreviations:
Functional connectivity (FC); functional Magnetic Resonance Imaging (fMRI).

Introduction

Neural activity in the brain causes changes in blood volume and oxygenation, as well as brain blood flow (Hashemi *et al.* 2012). The fMRI imaging science uses

sensitive techniques for such changes, such as the use of visual paradigms and motor stimuli in a non-invasive state, without the need to inject a radioisotope or other drug agents to image and produce tomographic maps of activity the human brain deals (Wolbarst & Hendee 2006). Imaging in the case where the person is immobile on the scanner and no stimulus is applied to him is also one of the methods of imaging fMRI, first described by Biswal *et al.* (1995). In recent years, this kind of imaging and its data have been considered as a baseline or control in the understanding of more complex neural systems (Lv *et al.* 2018). Based on resting imaging studies to date, various methods including the use of general linear regression model (Friston *et al.* 1994), independent component analysis (McKeown *et al.* 1998), mixture modeling (Hartvig & Jensen 2000), autoregressive spatial models (Smith *et al.* 2004) and Bayesian approaches have been present (Luo & Puthusserypady 2007). One of the issues discussed in the fMRI reviews is the subject of investigating the functional connectivity which examines the time correlations instead of examining anatomical correlations in the course of physiological neural activity between the two brain sites (Friston et al 1993). Since the FC in different brain regions, even during rest periods are dynamic (which changes over time), challenges in interpreting the information provided to researchers, making computations and statistical estimates have become more difficult and complex (Fox *et al.* 2005). So far, many studies have been conducted to investigate various neurological diseases, including Alzheimer's disease, Parkinson's disease, sleep disturbances, reading disorder, underestimation and prophylaxis, stuttering, etc., using rs-fMRI data, and there are many ways to deal with and solve the computational problems ahead. For example, Fuqing Zhou *et al.* in a study using voxel-mirrored homotopic connectivity (VMHC), investigated FC in patients with chronic sleep disorder (Zhou *et al.* 2018). Yang *et al.* showed the relationship between cerebellar-cortical and basal ganglia-thalamocortical networks in patients with growing stomach upset through Seed-to-voxel analysis (Yang *et al.* 2016). A study by Rui Li *et al.* was conducted using an independent component analysis and Bayesian network to examine FC in patients with Alzheimer's disease (Li *et al.* 2013). The model of variance components by Fiecas *et al.* was used to investigate the FC between resting state data between two groups including people with Dyslexia disease and healthy people (control), since time correlation between BOLD signals and heterogeneity between individuals as two components of the error in the model, compared with other studies gives more accurate statistical inference, and has a higher statistical power in terms of similar methods (Fiecas *et al.* 2017). In this paper, following the studies carried out by Fiecas *et al.* and using the variance components model of similarity or non-similarity of functional dynamic connectivity, networks in the resting state between patients with Parkinson's disease and healthy subjects is compared. Parkinson's disease (shaking palsy) was first identified by Dr. James Parkinson in 1817(Ahmadou *et al.* 2019; Parkinson 1817). This disease, after the Alzheimer's disease is the second most commonly diagnosed neurological disorder associated with age in the world, with about 7 to 10 million people worldwide suffering from it; its relative risk in males is reported to be about 1.5 times higher than in females (Elbaz *et al.* 2002). Although the incidence of this disease and newly diagnosed cases increases with age, about 4% of people are diagnosed before the age of 50. The disease has a tremendous clinical impact on patients, their families, and their caregivers, and will reduce the quality of life to a great extent (Hanamsagar & Bilbo 2016).

Materials and methods

Statistical Inference Based on Variance Two-Components Model

To examine the strength of gender-specific relationship between Parkinson's disease and healthy subjects in different brain regions, variance components model was used in the following sequence: once for all subjects, once for healthy and diseased female separately and once for the healthy and diseased male separately. For the N individual sample, consider a network of p's region of interest (ROI). In order to examine the functional connectivity, at first the simple correlations between the time series of each ROI is calculated. For each person, the number of pairwise correlations calculated between the regions is equal to $q=\binom{p}{2}$ and a network consists of N vector of q variables, which calculates each vector of pairwise correlations for each individual.

$Y=(r_{11},\ldots,r_{q1},r_{12},\ldots,r_{q2},r_{1N},\ldots,r_{qN})$ shows the vector of the correlation coefficients for each individual which in which r_{ij} is defined as the i_{th} correlation factor in the j-th individual. The model consists of two components of the error, in which the first error term is ε with the mean vector 0 and the covariance matrix Σ which, in fact is calculating the temporal autocorrelation of the time series of each pair of ROIs in each person. Furthermore, the second error phrase, ψ, with the mean vector 0 and the covariance matrix Ψ, controls heterogeneity between individuals. The model is defined as follows:

$$Y= X\beta + \varepsilon + \psi$$

In the referenced article, it also determines how the parameters are estimated in detail (Fiecas *et al.* 2017).

Database

The data used in this study was resting imaging of 15 patients with Parkinson's disease and 15 healthy controls. The patient group included 6 males and 9 females, and the control group included 7 males and 8 females. The model once in general and once by gender, examines the strength of the FC in the areas between

the patient and the control group. The data has been downloaded from the open fMRI databases with the accession number ds000245. The total time of scan for the T1-weighted is 349 seconds and the number of scans done per person is 198. Scans of resting state fMRI (8 minutes, closed eyes) are obtained. (TR = 2.5 seconds, TE = 30 ms, 39 cross sections with a gap of 0.5-1 mm and a thickness of 3 mm, FOV = 192 mm, 64 × 64 dimensional matrix, flip angle = 80 °). MRI scan is done. The pre-processing of data was done using MATLAB software and the spm12 toolbox and out of 198 scans for each sample person, the first five scans were eliminated to correct the initial imbalance. For each person, 193 functional rest scans were first realigned for the average functional image. Then, the structural images of the samples were co-registered. Images were then normalized with voxel resolution of 2*2*2 mm^3 and using an 8mm FWHM Gaussian Filter, a smoothing step was performed. Moreover, using the toolbox of WRU Pick-atlas and TDlobes of HUMAN ATLAS, 12 (ROIs) were selected and the time series of each ROI was extracted by averaging the series of its voxels. The pairwise correlation between the time series of all ROIs was computed afterwards, which included a total of 66 pairs. ROIs and their numbers are shown in Table 1.

Tab. 1. ROIs and their numberset

Number	Region of interest
1	Cerebellum Anterior Lobe
2	Cerebellum Posterior Lobe
3	Frontal Lobe
4	Frontal-Temporal Space
5	Limbic Lobe
6	Medulla
7	Midbrain
8	Occipital Lobe
9	Parietal Lobe
10	Pons
11	Sub-lobar
12	Temporal Lobe

Results

The matrix of correlation coefficients for all individuals by group separation is shown in (Fig. 1-3), which shows that this correlation is once in general (Fig. 1), once for female in two groups (Fig. 2) and once for Male are examined in two groups (Fig. 3) which, according to the figures, both in general and in isolation from both male and female, all correlations are positive and close to one. The variance component model can also be used to investigate the similarity of FC networks with resting data for Parkinson's patients and healthy people. FC was considered between each pair of ROIs in this study. The results are shown once in general (Fig. 4) and once in a gender breakdown (Figure 5-6). With q = 66

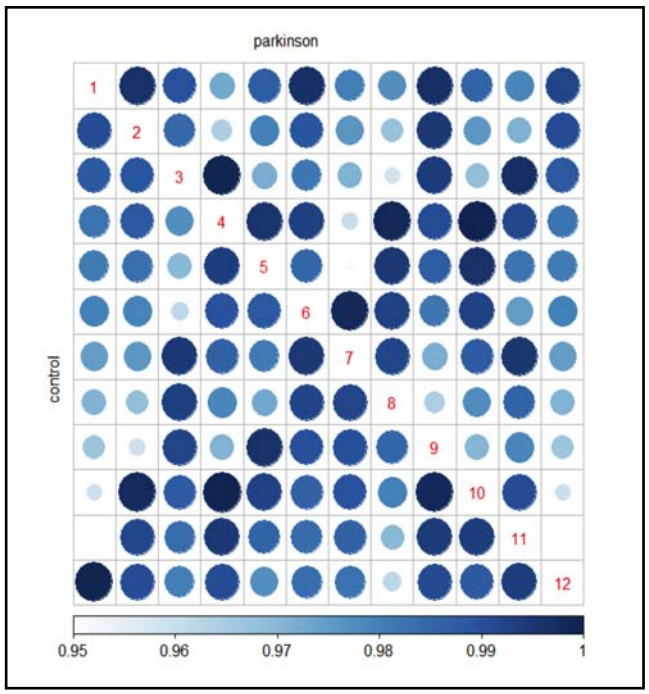

Fig. 1. The correlation matrix averaged across all subjects within each of the two groups. The upper triangle is the correlation matrix for the Parkinson group, and the lower triangle is the correlation matrix for the control group.

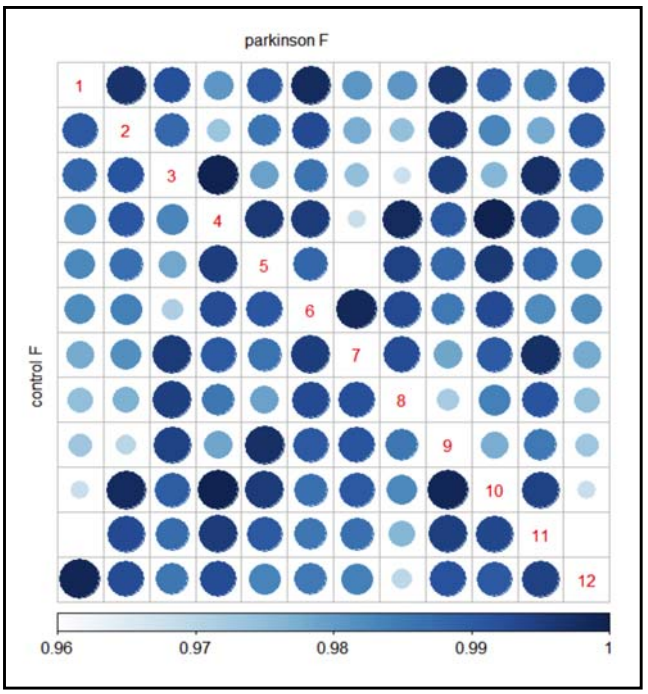

Fig. 2. The correlation matrix averaged across female subjects within each of the two groups. The upper triangle is the correlation matrix for the Parkinson group, and the lower triangle is the correlation matrix for the control group.

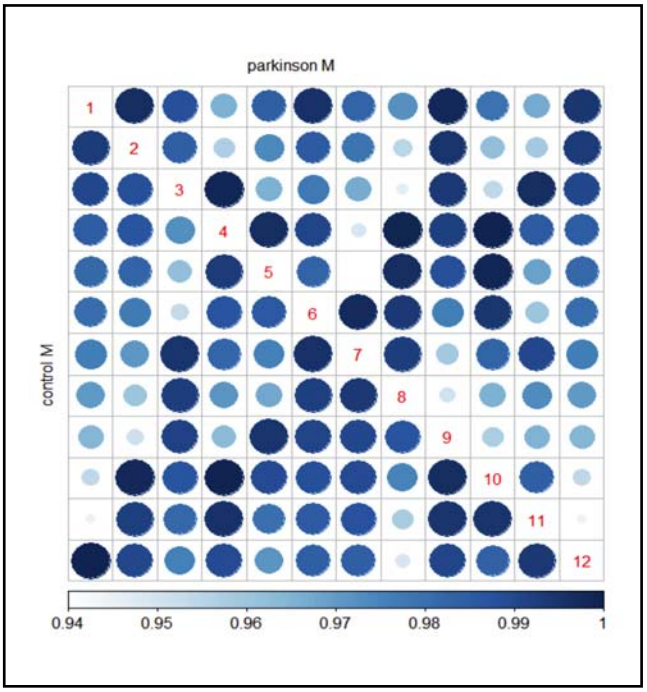

Fig. 3. The correlation matrix averaged across male subjects within each of the two groups. The upper triangle is the correlation matrix for the Parkinson group, and the lower triangle is the correlation matrix for the control group.

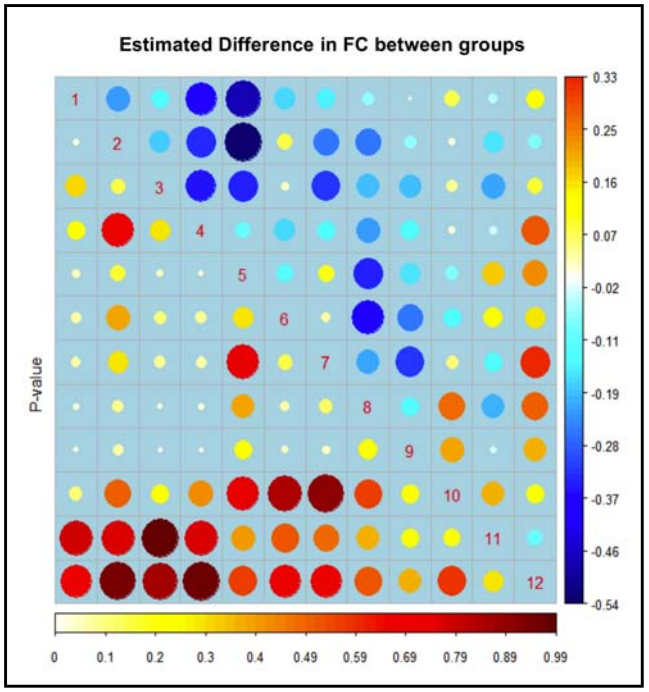

Fig. 4. Upper triangle: The estimated difference in FC between the two groups for each pair of ROIs across all subjects.Lower triangle: The *p*-value associated with the pairwise tests for no difference in FC between the two groups.

pairs of ROI in each of the three comparisons, the test at α level with αε (0.1) and in this paper α = 0.05 shows that in general, 11 pairs of areas with *p*-value below 0.05 have a significant difference which was reduced in 10 pairs of these areas and in one pair, small increase in FC for the Parkinson's group. These areas are as follows:

ROIs 1 and 2 (*p*-value=0.023, difference of - 0.221),
ROIs 3 and 5 (*p*-value=0.047, difference of -0.340),
ROIs 4 and 5 (*p*-value=0.024, difference of - 0.090),
ROIs 1 and 8 (*p*-value=0.031, difference of- 0.057),
ROIs 3 and 8 (*p*-value = 0.024, difference of -0.195),
ROIs 4 and 8 (*p*-value = 0.03, difference of -w 0.220),
ROIs 1 and 9 (*p*-value = 0.011, difference of 0.047),
ROIs 3 and 9 (*p*-value = 0.015, difference of -0.185),
ROIs 4 and 9 (*p*-value = 0.018, difference of -0.136),
ROIs 6 and 9 (*p*-value = 0.032, difference of -0.260),
ROIs 7 and 9 (*p*-value = 0.043, difference of- 0.324),

According to Fig. 5, in the comparison of healthy and patient females, at a level of α =0.05, only one pair of areas (1 and 2) with (*p*-value = 0.01, difference -0.322) had a significant difference, with a decrease in FC for the patient group. Nonetheless, compared to healthy male patients (Fig. 6), unlike females, the results were significant in 16 pairs of areas, indicating 12 pairs decrease and 4 pairs increase in FC for the patient group. The results are as follows:

ROIs 2 and 3 (*p*-value = 0.031, difference -0.032),
ROIs 3 and 5 (*p*-value = 0.028, difference of -0.240),
ROIs 4 and 5 (*p*-value = 0.030, difference of 0.410),
ROIs 3 and 6 (*p*-value = 0.045, difference of 0.072),
ROIs 3 and 7 (*p*-value = 0.04, difference of -0.670),
ROIs 2 and 8 (*p*-value = 0.22, difference of -0.422),
ROIs 3 and 8 (*p*-value = 0.013, difference of -0.333),
ROIs 4 and 8 (*p*-value = 0.014, difference of -0.384),
ROIs 6 and 8 (*p*-value = 0.04, difference of -0.797),
ROIs 7 and 8 (*p*-value = 0.044, difference of -0.238),
ROIs 1 and 9 (*p*-value = 0.025, difference of 0.405),
ROIs 2 and 9 (*p*-value = 0.012, difference of 0.391),
ROIs 3 and 9 (*p*-value = 0.004, difference of -0.276),
ROIs 4 and 9 (*p*-value = 0.007, difference of -0.179),
ROIs 6 and 9 (*p*-value = 0.018, difference of -0.439),
ROIs 7 and 9 (*p*-value = 0.24, difference of -0.612),

However, in order to correct the *p*-value, False Discovery Rate (FDR) method was used for multiple comparison (Genovese *et al.* 2002). Therefore, after correction of *p*-value, the differences between FC networks in the patient group and the control as general, as well as by gender were not statistically significant. Nonetheless, as shown in the figures above, *p*-value in the male's group are quite different from female group, showing a much lower percentage, which can be attributed to the effect of gender in Parkinson's disease.

Discussion

This paper looked at the similarity or disparity of FC networks between patients with Parkinson's disease compared to healthy people using the variance com-

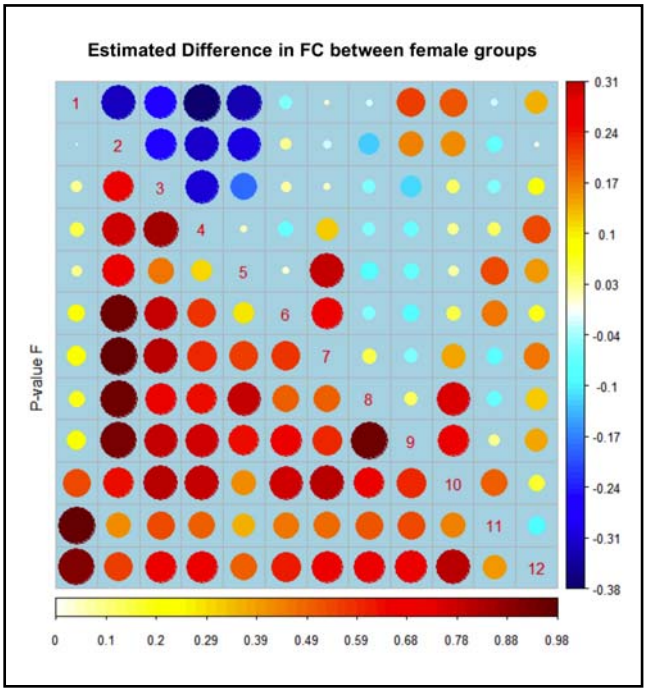

Fig. 5. Upper triangle: The estimated difference in FC between the two groups for each pair of ROIs in female subjects. Lower triangle: The *p*-value associated with the pairwise tests for no difference in FC between the two groups.

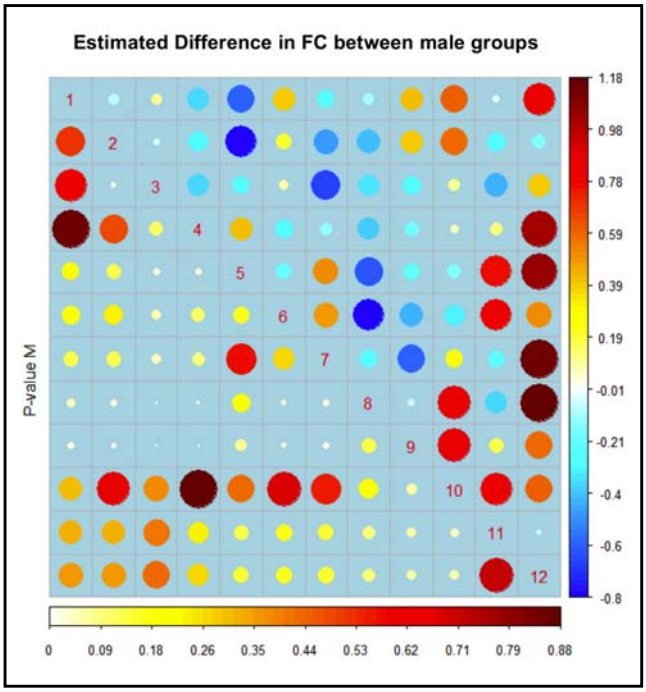

Fig. 6. Upper triangle: The estimated difference in FC between the two groups for each pair of ROIs in male subjects. Lower triangle: The *p*-value associated with the pairwise tests for no difference in FC between the two groups.

ponent model introduced by Fiecas et al in 2017. And since the model controls the temporal autocorrelation and heterogeneity between individuals, the results have a higher statistical power than those of the same tests. Here, in addition to studying the disease in general, the hypothesis was analyzed between the patient group and the control group by gender. The results showed that FC power in 11 pairs of areas had a significant difference between the patient and the control group. In the female group, this difference was observed in one pair of areas, but for males, 16 pairs of areas had a significant difference in terms of FC power between the two groups. However, the results manifested that after the correction of *p*-value by the FDR method, there is no significant difference between FC networks in the patient group and control group either in general or by gender but as noted in the results, *p*-values for males are clearly smaller than females in several pairs of areas. Our results are consistent with the previous studies that have been using meta-analysis methods to examine the differences in the prevalence of Parkinson's disease among males and females, with Parkinson's disease significantly at higher risk for males compared to Females. This is happening for various reasons such as head injury, nerve protection by estrogen, genetic risk factors, and so on (Wooten *et al.* 2004). A study by Hepp D *et al.* in 2017 on patients with visual hallucinating (VH) and Parkinson's disease using resting data on FC networks shows the effect of Parkinson's disease on posterior and paracentral: when combined with visual hallucinating, it may reduce the overall performance of the network (Hepp *et al.* 2017). In 2014, ChunYan Luo *et al.* with resting data and using the voxel-mirrored homotopic connectivity (VMHC) approach, compared the performance of the intergenspheric patient with Parkinson's disease and healthy subjects, and showed that FC between the hematopoietic brain regions in Parkinson's patients are harmed (Luo *et al.* 2015). Liviu Badea *et al.* reviewed resting scans for 27 Parkinson's patients and 16 healthy subjects, with a double-scan for each individual, and found that functional heterogeneity of the disease was a major reason for the lack of repeatability of FC changes in various research studies this disease in resting state (Badea *et al.* 2017). In the paper of Fiecas *et al.* (2017), the results of the comparison of FC between dyslexia patients and healthy subjects are similar to those in this paper. As mentioned above, in the variance component model, two error expressions to control the temporal autocorrelation of the time series and heterogeneity between individuals have been entered, which increases the statistical power, compared to similar methods for multiple comparisons, such as the Hotelling T^2 test and the aSPU test (Fiecas *et al.* 2017).

Conclusion

An analysis of the FC between genders in the present work is very helpful in understanding the differences within FC networks among patients with Parkinson's disease compared with healthy people because these differences in clinical reviews have reduced the error

rate and increased combating power against this disease. Since the model of variance components uses all time course, there are a lot of computing challenges to use more ROI, since with an increase in the number of regions, the parameters in the model show significant growth. The paper addresses the computational challenges and also ways to upgrade the proposed model.

Conflict of Interests

The authors declare no conflict of interest in this study.

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