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The Diagnosis of Parkinson's disease Based on Human Brain Imaging

Abstract

Parkinson's disease (PD) is a neurodegenerative condition in which the lowered levels of the neurotransmitter "dopamine" and a sort of neurotransmission changes in the basal ganglia are supposed to play key roles in movement problems and symptoms. In recent years, the structural brain networks (SBNs)-based diagnosis of PD has been sought-after by many researchers due to an uptick in the prevalence of PD and the development of innovative brain imaging techniques. This study aims to diagnose PD by analyzing the data obtained from "resting-state functional magnetic resonance imaging" (rs-fMRI). The proposed algorithm explores the differences between "healthy individuals" and "PD patients" based on statistical data and cross-correlation assessments. In this algorithm, after pre-processing the images and creating the time series of the 16 brain regions, the features of these regions are extracted and the best attribute for each stage is chosen by analysis of variance (ANOVA) at $p<0.05$. The feature matrix consists of a group of features picked from time-series statistical data and cross-correlation analyses between the affected PD brain's regions. In this study, the simulation results indicate a specificity of 97% and a sensitivity of 100% in diagnosing PD using the artificial neural network (ANN) classifier.

Keywords: *Parkinson's disease (DP); Magnetic resonance imaging (MRI); Functional imaging (FI); Brain functional connectivity.*

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Introduction

Parkinson's disease (PD) is caused by the degeneration of nerve cells that secret and release the neurotransmitter "dopamine". A rise in the ratio of acetylcholine (ACh) to dopamine in the basal ganglia (BG) of the brain causes tumor symptoms, stiffness (rigidity) of the limbs and muscles, and slow movement (bradykinesia) [1]. The causes of PD are not yet known. However, the most important symptoms of PD are slowness of movements (bradykinesia), stiffness (rigidity) of hands and feet, experiencing tremors in hands or feet during resting, and disturbed normal body position(s) (i.e., the patient's neck and trunk are bent, while hands do not move normally during walking). Overall, PD is diagnosed by the physician based on the manifested signs and symptoms [2].

PD is well characterized by a notable reduction in the level of the neurotransmitter "dopamine", where the level of dopamine is gradually decreasing over several years before signs and symptoms manifest. Treatment of PD is based on dopamine replacement in the brain through a process known as "dopamine replacement therapy (DRT)". Physiotherapy, occupational therapy, and speech therapy can be practiced in some phases of the treatment, but their efficiency is far less than that of administrated drugs. The reason for utilizing these techniques is to keep the body active and assist the patient in organizing the daily tasks. There is currently no definitive cure for PD, but early diagnosis can greatly help to prevent the progress and occurrence of symptoms [3]. Accordingly, functional imaging techniques are used for prompt diagnosis and to hinder disease progression using preventive treatments.[4]

In recent years, image processing techniques have broadly contributed to various fields of medicine to foster the timely identification and treatment of diseases (e.g., PD) in which "time" is a key factor in diagnosis[5]. Research shows that using novel computer-based technologies such as image processing has effectively facilitated the processes involved in PD diagnosis. For this, recent studies have employed various image processing methods, where improving the associated algorithms is desperately in demand.[7]

The ability to visualize the structures involved in specific brain functions is now conceivable via functional magnetic resonance imaging (fMRI). fMRI is a non-invasive technique that provides images of brain activities by detecting small changes in the signals related to blood oxygen levels. Such a direct visualization of brain functions enhances our understanding of brain activities, neurological conditions, and neurological risk factors.[8] fMRI relies on alternative imaging of the brain during activity and rest. The images taken are then digitally subtracted and the result of this processing demonstrates the physiological brain function as a result of changes in blood flow in the brain [9].

fMRI resembles MRI with slight differences in principles and nature. Indeed, fMRI images and the recorded signals of changes in the blood level of oxygen allow us to non-invasively understand and monitor various activities of the brain.[10] The fMRI system has broad applications in the recognition of neural activities. The brain's response to the experiments can be assessed through the obtained fMRI signals and images. Various studies concerning the "blood-oxygen-level-dependent (BOLD)" signal indicate a non-linear correlation between the applied stimulation and the response received from the neurons [11].

In their study using fMRI images, Tessitore et al. reported a declined resting-state network connectivity in the default

mode network (DMN) in patients with PD. The DMN is a large-scale brain network that includes "regions exhibiting strongly correlated activities" but these regions are separate from other brain networks. They supposed that disruption in brain connectivity may cause cognitive problems in PD patients [12].

By extracting the brain's resting state network (RSN) from fMRI images and using graph theory, Wu et al. found a reduction in the functional connectivity of the networks in the left putamen, the supporting motor area, and the anterior frontal cortex, and a rise in the functional connectivity of the networks in the cerebellum, the primary motor cortex, and the left parietal cortex in PD patients compared to healthy ones [13]. In another study, Amboni et al. reported that the decreased connectivity in the RSN of the frontal and parietal regions is correlated with the reduction of cognitive parameters in PD patients [14]. Likewise, Onu et al. revealed changes in the connectivity of the RSN and the sensorimotor and attentional networks in patients with PD [15].

Despite numerous studies investigating changes in the brain's RSN in PD patients, research is still ongoing utilizing various methods due to the controversial reports on the brain's RSN in these patients. This study analyzes statistical features and time-series cross-correlations to investigate the RSN of the data set.[16-17]

It is currently possible to partially detect the activity of the brain's various parts and the connection between its different areas from functional images before the clinical symptoms manifest. Thus, fMRI evaluating the brain's function in PD patients and comparing the results with those obtained from healthy individuals are supposed to foster our ability to control and prevent disease progression in cases of timely and early diagnoses. This study aims to achieve the early diagnosis of PD by comparing the findings of various studies and utilizing a straightforward method to easily and promptly diagnose the disease.

Research Methodology

The data were obtained from the website of the Parkinson's Progression Markers Initiative (PPMI), which gathers information from numerous researchers and participants to identify PD-progression biomarkers for PD treatment. From 2015 to 2018, over 140 research projects have utilized the data from the PPMI's website, mostly for identifying disease treatment methods.

The rs-fMRI data set comprised 18 people with PD and 18 healthy individuals. The healthy individuals were age- and gender-corresponded to those with PD. All the participants were in a resting position during the experiments and were asked to be entirely relaxed and close their eyes without falling asleep. Patients were allowed to take their usual daily medication during the experiments. All the analyses were performed in MATLAB using SPM (*statistical parametric mapping*), REX, and protocol toolboxes. The images were first pre-processed in MATLAB using the SPM toolbox. SPM is designed to analyze the sequence of brain imaging data. The sequences might be a series of images from different groups or a time series of the same subject. The current version of SPM is designed for fMRI, PET, SPECT, EEG, and MEG analyses.

REX is a toolbox developed to extract time series of desired brain regions from fMRI images. In this toolbox, pre-processed functional images are first chosen as the source. Next, 16 time series are extracted for each participant by choosing 16 different regions. The time series can be extracted based on the mean image voxels in each area, their sum, measuring the median of voxels, counting positive voxels, and or finding the maximum and minimum of voxels. All these features can be adjusted in the toolbox settings.

After pre-processing and converting the images into time series using the above toolboxes, the next step is to investigate the time series and extract features. Then, ANOVA is utilized to choose the best feature after the features were extracted in the previous step. After that, the feature matrix is created using ANOVA at $p<0.05$. Ultimately, the disease is diagnosed using this matrix and with the help of ANN. This study employs perceptron neural network (PNN) due to its easy usage and application and well-established functioning, as reported in the literature.

Figure 1 illustrates the analysis steps.

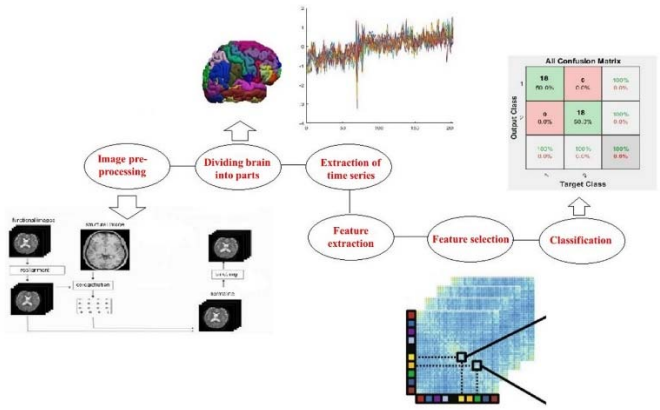


Figure 1. Analysis steps

The images need to be pre-processed before final processing and analyses. First, the images with the extension ".nii.gz" should be recalled to allow using them in the SPM toolbox. The next step is to process each series of structural images. Each series of these images includes 1) a 3D "176×240×256" image and 2) functional images (including 210 3D "68×66×40" images for each person). For this, five images are first removed from the images to remove the effects

exerted by the instability of the scanner's magnetic moments. Then, the data are pre-processed into steps discussed in the following.

Time correction

In this step, the discrepancy in time between different slices of the image is corrected. Notably, all a "given brain volume" is scanned alternately over a determined period. Thus, the "time correction" step allows for putting consecutive scans together. As a result of this, the whole brain volume will seem to be scanned at one moment. Time correction of the slices is performed using the phase shift of the time series in the Fourier space. At this stage, all the images are put in a given time unit volume, while having TR=2.4 s, 68 slices, and one slice as reference.

Correction of head movements

The head movement alters the angle of the image at the time of imaging. At this stage, all the movements and changes in the imaging angle are corrected using "the six rigid-body parameters" and the "least squares method". Likewise, all the images are aligned so that each voxel now belongs to only one point of the brain. The first image selected by the user is considered a reference and all the other images are aligned with this reference image. The correction parameters are saved in a text file and used to create a general linear model (GLM). In this step, 205 functional images are sorted and rearranged. Then, the "image averaging" process is done by stacking the series of functional images for use in the next steps.

Registration

Image registration is the process of overlaying images taken from different angles to create a more complete image. In SPM, "rigid body registration" is used to register the functional images into the structural images. This process allows us to accurately investigate brain function using more detailed and accurate data obtained from structural images. In this stage, the functional images are aligned with the "averaged image" of the structural images saved in the previous stage to maximize mutual data in both functional and structural images and increase the quality of the images.

Segmentation

At this stage, the structural images are segmented into 1) grey matter, 2) white matter, and 3) cerebrospinal fluid. The multiplication of the mask correlated with these bias-corrected areas in the functional images allows for the extraction of the corresponding functional areas. The gray matter is used to extract time series (Figure 2).

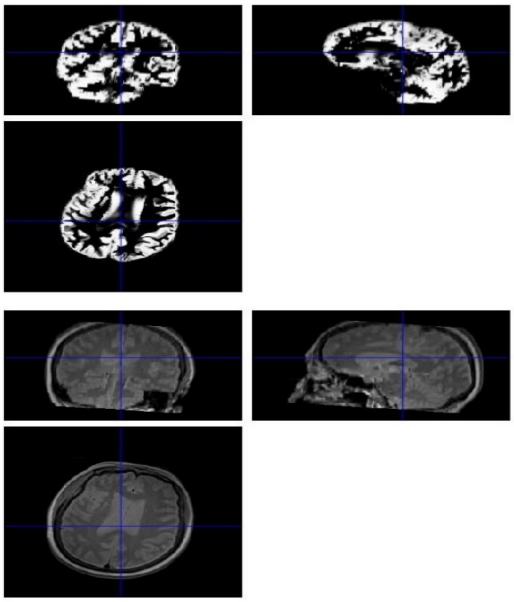


Figure 2. Segmentation of structural images

Normalization

Since the brain's volume and size differ from one person to another, the brain images of various persons need to be matched to a single atlas to allow for the investigation of all the persons against each other. For this, the functional images of each person are normalized to the structural images of the same person. The high-resolution images are then transferred to the standard atlas space of the Montreal Neurological Institute-Hospital (MNI) to allow the analysis of all the images registered in the same volume.

Smoothing

The last step is to avoid image bricking by applying the spatial Gaussian function on the image and moving forward. Images are smoothed by applying a low-pass filter in the spatial dimension of the data. This is achieved by the convolution of a spatial window with a kernel function having an adjustable FWHM parameter while having FWHM=6.

Conversion of fMRI data into time series

After the pre-processing phase and separating different areas, each area is converted into a time series. By averaging the voxels of each area in each photo, we reach a point where the time series is formed from the sequence of these points.

A sequence of random variables sampled at fixed time intervals is referred to as a time series or a random event in a given period. Indeed, a time series is a set of statistical data collected at equal and regular intervals. Overall, various statistical features of image voxels (e.g., average voxels, the sum of voxels, the median of voxels in an area, the number of positive voxels, or maximum and minimum voxels in an area)

are used to convert functional images into time series and analyze brain function using this sequence. In this study, time series were extracted and investigated based on the average of voxels and the count of positive voxels in an area. This way, 16 "time series" were extracted for each person from eight regions of the brain (i.e., caudate nucleus, cerebellum, hippocampus, thalamus, postfrontal cortex, pallidum, putamen, and motor cortex in two hemispheres). Since the extracted time series are not in the same domain and have dc, all the time series were normalized and placed in the same interval to allow placing the series in the same domain (Figure 3).

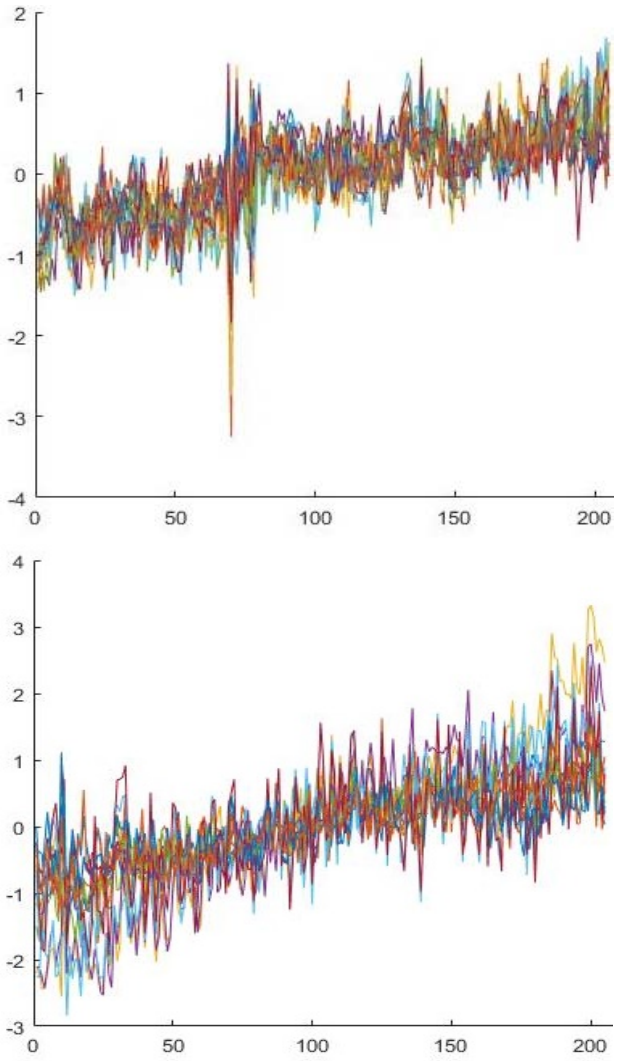


Figure 3. A) An example of the time series of 16 normalized areas for a healthy person. B) An example of the time series of 16 normalized areas for a patient with PD

Results

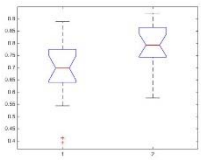
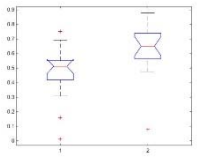
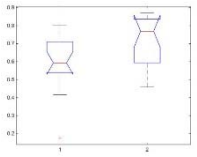
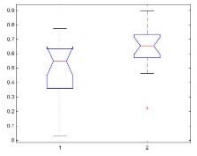
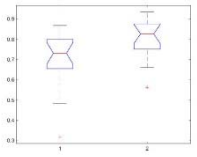
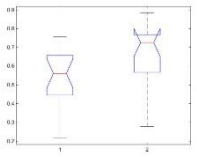
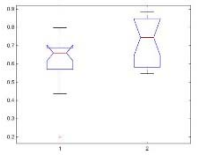
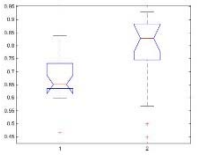
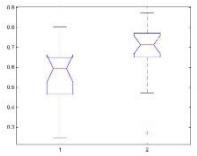
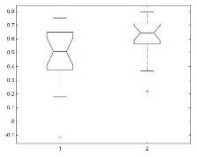
The correlation of each area in the left and right hemispheres of the brain was investigated with ANOVA to identify the difference between a healthy person and a patient with PD. For this, a 64×36 matrix of the extracted features was created for healthy and sick persons. The difference between the sick and healthy individuals was observed in the motor cortex area, concerning eight features at $p<0.05$. The matrix for the selected feature is 8×36.

In Table 1, the horizontal column represents 16 regions of the brain, where numbers 1 to 8 represent healthy individuals and numbers 9 to 16 represent patients with PD.

In the second stage of analyzing the statistical features, 16 "time series" were extracted for each person, where each time series contains 7 extracted statistical features. Thus, each person has 112 features, and the matrix of this stage is 36×112. The time series for each region of the brain of healthy participants were compared with those for patients with PD using ANOVA at $p<0.03$. As a result, 7 features were selected and a feature matrix was 7×36. These seven features are the standard deviation (SD) of the time series of the left hippocampus region, the minimum of the left hippocampus time series, the median of the left hippocampus time series, the median of the right caudate nucleus, the median of the right prefrontal cortex, the minimum of the left thalamus, and the median of the right motor cortex. These features exhibit the greatest difference between healthy individuals and patients with PD.

Table 1. The areas exhibiting the greatest differences in functional correlations between healthy individuals and patients with PD

No.	Areas with differences in functional correlations between healthy individuals and patients with PD	p-value	ANOVA

1	Cerebellum_L ←→ PFC_L	0.0108	
2	PFC_L←→ Pallidum_R	0.0164	
3	Hippocampus_R←→ PFC_L	0.0167	
4	PFC_R ←→ Pallidum_R	0.0193	
5	Cerebellum_R ←→PFC_L	0.0214	
6	Cerebellum_L ←→ Pallidum_R	0.0219	
7	Hippocampus_R ←→ Pallidum_R	0.0235	
8	Cerebellum_R ←→Hippocampus_R	0.0235	
9	Cerebellum_R ←→ Pallidum_R	0.0244	
10	Caudate_R ←→ PFC_l	0.0252	

Cross-correlation analysis

The cross-correlation between the time series of each area and 16 other areas was investigated. The cross-correlation between different areas was considered as a 256×36 feature matrix. After investigating this matrix by ANOVA at $p<0.05$, the areas exhibiting the greatest difference in functional correlations are given in Table 1 in descending order, with the relevant 10×36 feature matrix. p-value and ANOVA diagrams are represented in columns 3 and 5, respectively. The ANOVA and the function of each area are given and investigated in the following sections.

Correlation between the prefrontal cortex and the cerebellum

The first significant difference is in the functional correlations between the prefrontal cortex and the cerebellum. The cerebellum is critically involved in motor movement regulation and balance control. When the cerebellum loses its connection with other parts of the brain, particularly the prefrontal cortex and then the BG, signs of slowness and stiffness manifest in the movements of the affected person (Figure 4).

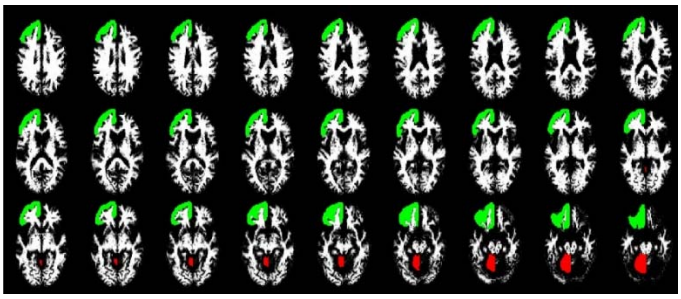


Figure 4. A graphical illustration of the brain's two regions, i.e., the cerebellum (in red) and PFC (in green).

Cross-correlation between the prefrontal cortex and pallidum

The next "two areas" which lose the functional connection with each other are the BG and the prefrontal cortex. Figure 5 represents the ANOVA for functional correlations between healthy individuals and patients with PD, as well as the graphical visualization of the two regions.

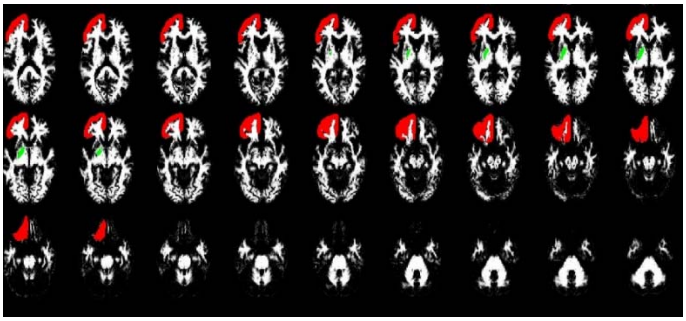


Figure 5. A graphical illustration of the brain's two regions, i.e., the prefrontal cortex (in red) and pallidum (in green).

Cross-correlation between the prefrontal cortex and caudate nucleus

The caudate nucleus is a part of the BG and its connection with other parts of the brain is disrupted in PD. The connection of this area with the prefrontal cortex (which is the center of balance and social relations) is reduced in patients with PD (Figure 6).

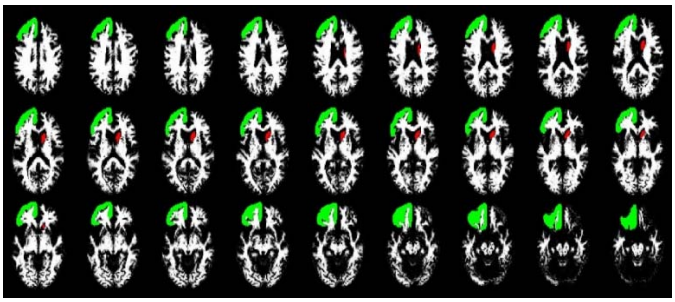


Figure 6. A graphical illustration of the brain's two regions, i.e., the caudate nucleus (in red) and PFC (in green).

Correlation between cerebellum and pallidum

The pallidum is the next part of the BG and its connection with the cerebellum was significantly reduced, leading to diminished uptake of dopamine and thereby disease symptoms (Figure 7).

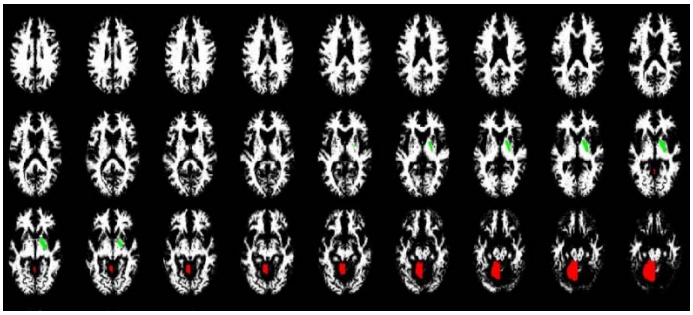


Figure 7. A graphical illustration of the brain's two regions, i.e., the cerebellum (in red) and pallidum (in green).

Correlation between cerebellum and hippocampus

The connection between the hippocampus of the brain's two hemispheres is different in patients with PD than in healthy individuals. Again, the functional connection of this part with the cerebellum is reduced (Figure 8).

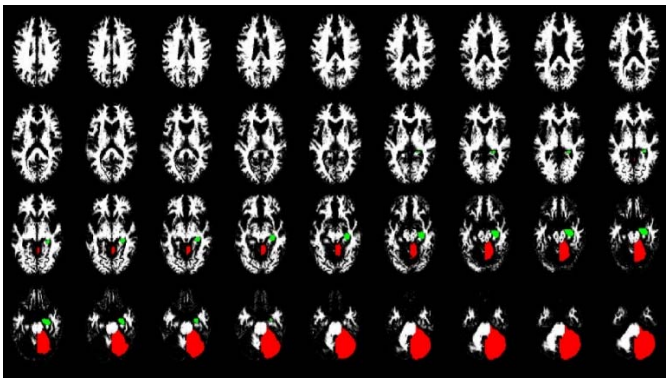


Figure 8. A graphical illustration of the brain's two regions, i.e., the cerebellum (in red) and hippocampus (in green).

Correlation between the prefrontal cortex and hippocampus

The hippocampus is embedded deep in the center of the brain. In PD, memory is disturbed following a reduction in the functional connection of this part of the brain with the prefrontal cortex and the pallidum (Figure 9).

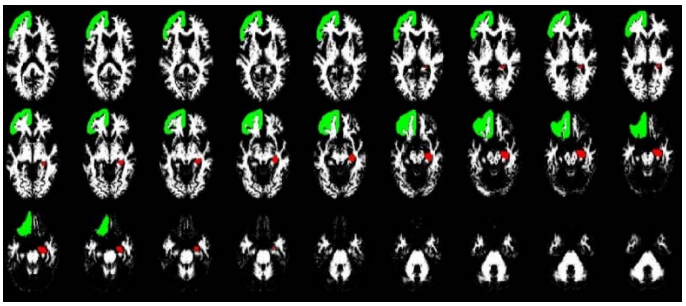


Figure 9. A graphical illustration of the brain's two regions, i.e., the hippocampus (in red) and prefrontal cortex (in green).

Correlation between the pallidum and hippocampus

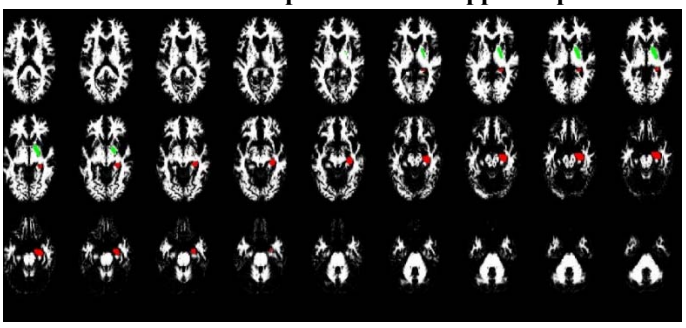


Figure 10. A graphical illustration of the brain's two regions, i.e., the hippocampus (in red) and the pallidum (in green).

In the second stage, the time series extracted by counting the positive voxels of the images of each brain part is used for extracting better features and accessing more accurate results. Likewise, the cross-correlation is performed to analyze the correlation between the time series of each region and 16 other regions. Then, such an effect of the cross-correlation between different brain areas is considered as a 256×36 feature matrix.

Ultimately, all the selected features are gathered in a 28×36 feature matrix (Table 2).

Table 2. The dimensions of the matrix of features extracted and selected with p-value

Feature extraction method		Dimensions of the matrix of obtained features	Dimensions of the matrix of selected features (with p-value)
Investigating the statistical features of the time series for healthy individuals and PD patients	Investigating the correlation of these features between the brain's two hemispheres	64×36	8×36
	Investigating the features between the two groups	112×36	7×36
Calculating the cross-correlation between the brain's areas in healthy individuals and PD patients	Using the time series extracted with the mean of voxels	256×36	10×36
	Using the time series extracted by counting the positive voxels	256×36	3×36

Neural network implementation and construction

In this study, the features extracted and selected from the fMRI images of 18 healthy individuals and 18 patients with PD are arranged into a 28×36 matrix (number of data: 36; number of selected features: 28).

After creating the feature and target matrixes and using them as the input of the neural network, a neural network was selected containing 10 intermediate layers, 70% of the data for testing, 10% of the data for training, and 10% of the data for investigating the correctness.

For evaluating the overall result, it is crucial to calculate both sensitivity and specificity values. Sensitivity (true positive rate) refers to a proportion of positive cases that the test correctly labels as positive. The specificity (true negative rate) refers to a proportion of negative cases that the test correctly labels as negative.

- True Positive: A PD patient is correctly diagnosed as the patient.
- False positive: A healthy individual is mistakenly diagnosed as a patient with PD.
- True Negative: A healthy individual is correctly diagnosed as healthy.

- False Negative: A patient with PD is mistakenly diagnosed as healthy.

Sensitivity is obtained by dividing true positives by the sum of true positives and false negatives.

$$Sensitivity = \frac{number\ of\ true\ positives}{number\ of\ true\ positives + number\ of\ false\ negatives}$$

Specificity is obtained by dividing the true negatives by the sum of the true negatives and false positives.

$$Specificity = \frac{number\ of\ true\ negatives}{number\ of\ true\ negatives + number\ of\ false\ positives}$$

Table 3 summarizes the neural network results in detail. The network is iterated 10 times and the final result is expressed by averaging all the 10 results obtained. The second column shows the number of data that are correctly recognized as positive at each stage of the training. As demonstrated, the network has correctly recognized 17.6 images of the patient on average. The third column presents false positives. On average, less than one patient's data has been incorrectly diagnosed as healthy. Columns 3 and 4 present true negatives and false negatives, respectively. As shown, about 17.6 healthy data are correctly diagnosed as healthy, and only less than one healthy data has been incorrectly categorized in the patient group. The columns related to the sensitivity (94%) and the specificity (97.2%) show the correctness of the diagnosis of healthy individuals and patients with PD. The last column (epoche) shows that the network is trained after 39.5 stages of weighting on average.

Table 3. Iteration of the network training and the obtained results

Training orders	TP	FP	TN	FN	Sensitivity "TP/(TP+FN)"	Specificity "TN/(TN+FP)"	Epoch
1	18	0	17	1	100	97.2	33
2	18	0	17	0	100	100	38
3	18	0	17	1	100	97.2	34
4	18	0	17	1	100	97.2	38
5	18	0	18	0	100	10	38
6	18	0	17	1	100	97.2	19
7	18	0	18	0	100	100	38
8	18	0	18	0	100	100	38
9	16	2	16	2	60	88.9	10
10	16	2	18	0	80	94.4	9
Average	17.6	0.4	17.4	0.6	94	97.21	39.5

Figure 11. Confusion with the training in the first iteration

Figure 11 shows the network's performance in each stage. For example, in the training stage, all the selected data have been trained correctly. Similarly, all the data have been accurately investigated in the accuracy stage, which is done along with the training. However, in the testing phase, one of the four data is incorrectly diagnosed, where a patient with PD is incorrectly diagnosed as healthy.

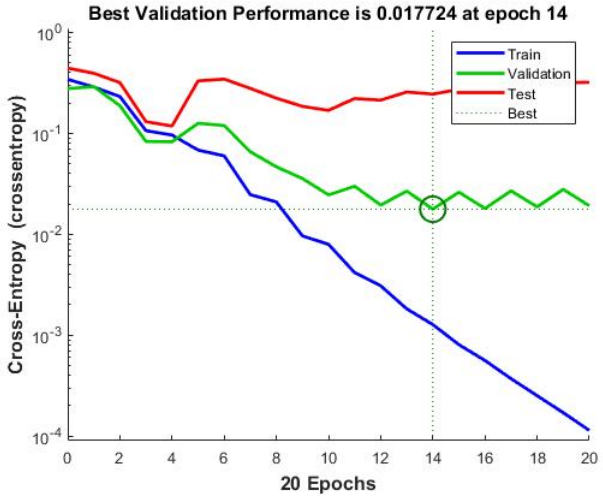


Figure 12. The performance graph

In Figure 12, the horizontal axis denotes the number of iterations, and the vertical axis denotes the mean squared error. As shown, the best performance of the function is obtained in the 14th iteration.

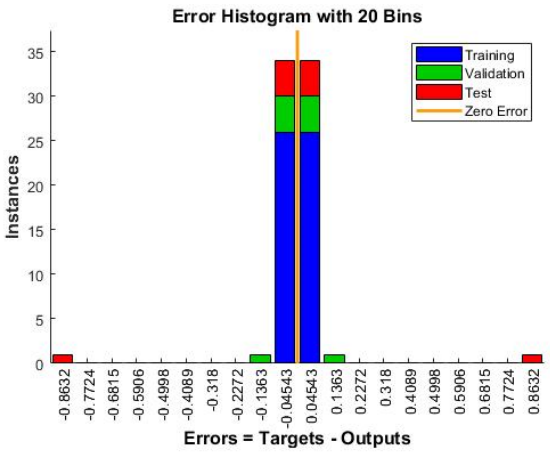


Figure 13. Error histogram

Figure 13 depicts the degree to which the errors belong to each stage. As shown, the highest degree of error belongs to the test phase.

As illustrated, the method proposed in this study and the combination of features allows us to differentiate patients with PD from healthy individuals using fMRI images, as supported by a specificity of 97% and a sensitivity of 100% in diagnosing PD.

Conclusion

This study aimed to diagnose patients with PD by processing brain images. fMRI is widely used in the recognition of neural activities. The data obtained from this method are more accessible and cheaper than those obtained from the functional imaging of the brain. Hence, this study was conducted based on data obtained from fMRI.

Overall, brain imaging is performed under "stimulated" and "resting" states. Since recent attempts have targeted the resting state of the brain where the performance of each brain area is only connected to the same area and not due to compensating for the lack of performance of other areas, this study used the data obtained from the resting state. For this, data from 18 healthy individuals and 18 patients with PD were utilized.

The images were first pre-processed. Eight brain areas of each brain's hemisphere were considered and the time series were extracted for each person. In the next step, each time series was investigated by extracting the statistical features of each series and the connections between the series. The neural network was then trained with selected features. Ultimately, a specificity of 97.21% was obtained for differentiating PD patients from healthy individuals.

The following findings were obtained based on the selected features in each stage of feature extraction:

1. The greatest difference between PD patients and healthy individuals in terms of the ratio of the features of time series was observed in the motor cortex area, compared to other areas.
2. Seven features including the standard deviation of the time series of the left hippocampus region, the minimum of the left hippocampus time series, the median of the left hippocampus time series, the median of the right caudate nucleus, the median of the right prefrontal cortex, the minimum of the left thalamus, and the median of the right motor cortex exhibited the greatest differences between healthy individuals and patients with PD.
3. The communication areas disturbed in PD include the connection between the prefrontal cortex and the cerebellum, the pallidum, the caudate nucleus, and the hippocampus, the connections between the hippocampus and the cerebellum and the pallidum, as well as the connection between the cerebellum and the pallidum.

The strengths of this research include the simplicity and rapidity of the proposed method, its ability to investigate communications between the two hemispheres of the brain, and the high level of accuracy and sensitivity of the method compared to other similar studies. For example, in 2018 and 2019 studies, Salama Mustafa et al. investigated multiple assessment features and classification methods to enhance PD diagnosis and achieved diagnoses up to 91% and 89% using neural networks and the decision tree, respectively. In a similar 2018 study entitled "*Automated Classification of Resting-State fMRI Networks using Machine Learning Algorithms*", Pinardi et al. reported that the highest rate of diagnosis is 89.4%.

Thinking that this study only used time series features for analyses, future studies are recommended to use frequency features of time series to achieve higher accuracy and sensitivity. Likewise, concerning the various therapies administrated tailored to different stages of the disease progression and the damage caused to different brain areas, future research is hoped to investigate the disease progression in affected patients and to classify patients based on the damage to different brain areas.

Ethics Statement: Treat those with whom we work and those we serve with civility and consideration. Actively strive to merit the respect, trust, and confidence of colleagues, customers, and the public.

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