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Betweenness Centrality in Resting-State Functional Networks Distinguishes Parkinson's Disease

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***Abstract*— The goal of this paper is to use graph theory network measures derived from non-invasive electroencephalography (EEG) to develop neural decoders that can differentiate Parkinson's disease (PD) patients from healthy controls (HC). EEG signals from 27 patients and 27 demographically matched controls from New Mexico were analyzed by estimating their functional networks. Data recorded from the patients during ON and OFF levodopa sessions were included in the analysis for comparison. We used betweenness centrality of estimated functional networks to classify the HC and PD groups. The classifiers were evaluated using leave-one-out cross-validation. We observed that the PD patients (on and off medication) could be distinguished from healthy controls with 89% accuracy – approximately 4% higher than the state-of-the-art on the same dataset. This work shows that brain network analysis using extracranial resting-state EEG can discover patterns of interactions indicative of PD. This approach can also be extended to other neurological disorders.**

I. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that predominately affects dopamine-producing ("dopaminergic") neurons in a specific area of the brain called substantia nigra, which impacts communication pathways of the brain. PD affects the lives of more than 10 million people worldwide and is expected to become more prevalent in the future [1]. The main symptoms of PD are tremor, muscle stiffness, bradykinesia (slowness of movement), unstable posture, balance and gait abnormalities, and dysphonia (voice disorders). Non-motor symptoms can range from mild cognitive impairment (MCI) to dementia.

Diagnosis of PD remains complicated, especially in patients without severe symptoms. Accuracy of gold-standard clinical diagnosis is only about 80% and has not improved in the last 30 years [2]. Considering that most PD patients develop dementia in 15-20 years, there is an urgent need to identify biomarkers for early diagnosis, monitor disease progression, and establish efficacious therapies. It is established that cognitive dysfunction in neurological disorders can be described as aberrant patterns of interactions between neural elements in a large-scale brain network [3]–[6]. We hypothesize that network analysis may hold the key to understanding the electrophysiological basis of PD.

Although functional network analysis of Parkinson's was addressed in past literature, majority of these studies are limited to functional magnetic resonance imaging (fMRI) [7]–[10]. Scalp EEG is optimal for clinical, commercial, and research purposes because of its non-invasive nature and wide availability. More importantly, EEG can sample neural activity at 100–1000x higher time resolution than fMRI, making it more suitable to assess temporal dynamics. Previous EEG research on Parkinson's was focused on spectral features, or event-related potentials [11]–[15]. However, these approaches do not consider simultaneous interactions between multiple brain areas, i.e., EEG network functional connectivity.

This paper presents a functional network analysis to decode scalp EEG signals and detect node centrality modulations indicative of PD. Recent studies demonstrated statistical differences in network measures such as node centrality between PD patients and healthy controls [16]–[19]. Here, we present perhaps the first EEG-based machine learning analysis that utilizes node centrality features to differentiate between Parkinson's patients and healthy controls to the best of our knowledge.

The rest of the paper is organized as follows. Section II describes the data and methods. Section III presents the results. The results are discussed in Section IV. Section V concludes the paper.

II. Materials and Methods

A. Data

The data analyzed in this paper were reported in previous studies [11], [20], [21], and can be downloaded from https://narayanan.lab.uiowa.edu/article/datasets. The data included scalp EEG recordings from 27 patients with PD who were recruited from the Albuquerque, New Mexico community and an equal number of demographically matched (sex and age) controls. All participants were evaluated using Mini-Mental State Exam (MMSE) and achieved a score above 26. The PD and control groups did not differ on any education or premorbid intelligence measurements. All procedures were approved by the University of New Mexico Office of the Institutional Review Board, and the participants were paid $20/hour. Each PD patient visited the lab twice: on medication (PD-ON) and off medication (PD-OFF). In the PD-OFF phase, the patients took their most recent dose of dopaminergic medicines at least 12 hours before the experiment.

The EEG was recorded from Ag/AgCl electrodes with a sampling rate of 500 Hz on a 64-channel Brain Vision system. The signals were referenced to the 'CPz' channel, resulting in 63 timeseries. The original dataset consisted of two one-minute segments per subject: eyes-open and closed

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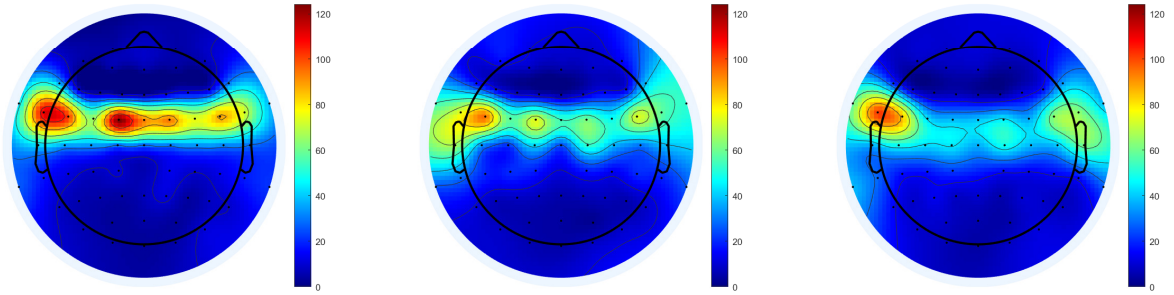


(a) Healthy controls (HC) (b) Parkinson's– on medication (PD-ON) (c) Parkinson's– off medication (PD-OFF)

Fig. 1: Scalp topographical maps of average betweenness centrality.

conditions. This analysis uses resting-state EEG signals of one-minute duration recorded under the eyes-open condition. Power line noise and its harmonics were removed using 6th order IIR filters.

B. Feature Extraction Using Network Analysis

Functional Networks were constructed by computing absolute Pearson's correlation coefficient between all pairs of channels. In this case, each EEG channel is a node. Therefore, an edge with high connectivity displays a strong correlation between the interacting channels. Since a value between 0 and 1 represents each connection, these are weighted-undirected networks.

For each subject, the one-minute recording was divided into 11 30-second segments with 90% overlap. Functional networks for each of the 11 segments were computed. The final representative network was the mean of these 11 networks. The mean networks were considered to minimize the effects of non-stationarity.

The node centrality of a given node measures its importance within the network. We compute three node centrality metrics: betweenness centrality, node degree, and eigenvector centrality. Betweenness centrality measures the extent to which a given node falls in the shortest path between any two other nodes [22]. Node degree quantifies the number of connections to a node. Eigenvector centrality is a measure of the influence a node has on a network and was found to be linked to firing rates of neurons [23]. The node centrality values were used as features for classification.

Fig. 1 shows the two-dimensional scalp topographic maps depicting the average betweenness centrality of nodes in the three groups: healthy controls (HC), PD-ON, and PD-OFF. All three scalp maps were plotted on the same scale for comparison. We observe that the betweenness centrality in HC is higher in the mid-frontal region compared to PD-ON and PD-OFF.

C. Feature Selection and Classification

Naive Bayes classifiers with Gaussian kernel were trained to differentiate PD patients from healthy controls. The classifiers were modeled separately for PD-ON and PD-OFF patients. For single-channel classification, the betweenness centrality of a single node was used as the input feature. For multi-channel classification, sequential forward feature selection was employed to select the optimal features/channels. That is, we first start with an empty candidate set. In each iteration, a new feature is sequentially added to the set to minimize classification error. The process is stopped when the accuracy cannot be improved further [4], [24].

The classifiers were evaluated using leave-one-subject-out cross-validation. The cross-validation prevents overestimating the accuracy due to over-fitting of training data and ensures the models were evaluated on all subjects.

III. Results

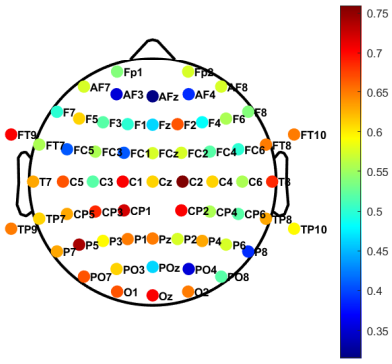
A. Single-Channel Classification

Fig. 2(a) and Fig. 2(b) depict single-channel classification performance for HC vs. PD-ON and HC vs. PD-OFF, respectively. Each value is the mean cross-validation accuracy. The best HC vs. PD-ON accuracy was 75.93% for channel C2. For HC vs. PD-OFF, the highest accuracy of 79.63% was attained by channel PO7.

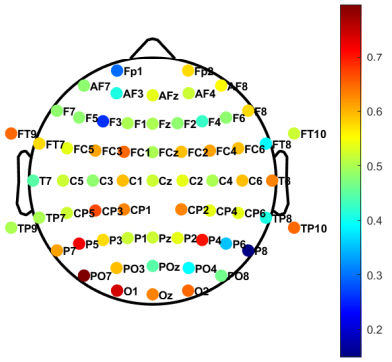
B. Multi-Channel Classification

The results presented here are based on Naive Bayes classifiers with Gaussian kernels. We observed that these models performed the best with minimal overfitting compared with other machine learning models such as support vector machines, linear discriminant analysis, and decision trees. The receiver operating characteristic (ROC) curves comparing the three node-centrality measures are depicted in Fig. 3. ROC curve can be used to evaluate the performance of binary classifiers. The higher the area under the ROC curve (AUC), the better the models distinguish between the two classes. The plots illustrate that betweenness centrality differentiates the healthy subjects from PD patients, with the highest AUC in PD-ON and PD-OFF conditions. The betweenness centrality-based classifiers achieved an AUC of 91.63% and 88.6% for HC vs. PD-ON and PD-OFF, respectively.

The individual classification results are presented in Table I. It can be observed that betweenness centrality (BC) outperforms node degree (ND) and eigenvector centrality (EC) in both cases. For HC vs. PD-ON, the accuracy, sensitivity,

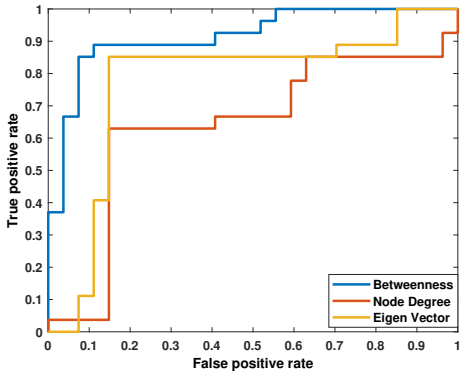


(a) Healthy controls vs. PD-ON

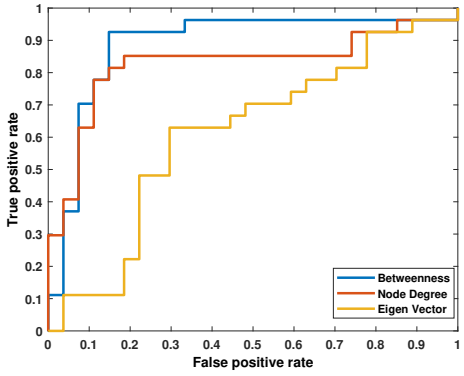


(b) Healthy controls vs. PD-OFF

Fig. 2: Single-channel classification performance comparison.



(a) Healthy controls vs. PD-ON



(b) Healthy controls vs. PD-OFF

Fig. 3: Receiver operating characteristic (ROC) curves comparison between 3 node centrality measures.

and specificity were 88.9% each. Betweenness centrality of nodes represented by EEG electrodes FT9, PO5 and PO7 were the most discriminatory between the two classes. In the case of HC vs. PD-OFF, the accuracy, sensitivity, and specificity were 88.89%, 92.59%, and 88.6%, respectively. Betweenness centralities of P5, PO7 and PO3 were chosen as the optimal features for HC vs. PD-OFF.

IV. Discussion

There is a growing consensus in modern neuroscience that human brain function is encoded as complex small-world networks. In other words, functional brain networks contain a combination of dense local connectivity and sparse yet efficient long-distance (global) connectivity. Some nodes are more important (hub nodes) than other as a result of this small-worldness. This node importance can be measured using node centrality metrics such as betweenness centrality. Our work showed that betweenness centrality differentiates PD patients from age-matched controls. We also show that this effect is independent of the patients' medication status. Besides PD, modulated betweenness centrality has been also implicated in other neurological disorders such as Alzheimer's, Schizophrenia and Epilepsy [3], [25]–[27].

Our method achieved higher leave-one-out cross-validation accuracy (88.9%) than the state-of-the-art (85.2%) on this dataset [11]. The decoders in [11] are based on spectral properties of individual channels but do not take into account the interactions between the channels. One limitation of the proposed approach is that the neural activity is recorded from the scalp. Scalp EEG is typically affected by confounding factors such as volume conduction. Also, compared to fMRI, EEG has a lower spatial resolution, making it difficult to localize the source of the activity. However, the proposed approach is amenable to real-time applications since it only requires 1-minute resting-state EEG recordings. All existing methods use longer recordings or employ computationally complex algorithms like deep learning [11], [14], [28]. Also, PD-ON scalp plots in Fig. 1 appear closer to HC than PD-OFF, leading to a higher accuracy for HC vs. PD-OFF. We attribute this to the fact that the data consists of resting state activity, which does not account for any motor symptoms usually affected by medication.

V. Conclusion

This work demonstrates that metrics like betweenness centrality can measure how functional networks encode PD. We employed graph analysis to develop neural classifiers that

TABLE I: Leave-one-subject-out cross validation results summary for HC vs. PD classification. Sensitivity and specificity represent the healthy control and PD accuracies, respectively. Random label-assignment would result in a baseline accuracy of 50%.

Classifier	HC vs. PD-ON			HC vs. PD-OFF			HC vs. PD (ON+OFF)
Features	BC	ND	EC	BC	ND	EC	LEAPD [11]
Accuracy(%)	88.9	74.1	83.3	88.9	83.3	63	85.2
Sensitivity(%)	88.9	63	85.2	92.6	77.8	63	88.9
Specificity(%)	88.9	85.2	81.5	88.2	88.9	63	81.5
AUC(%)	91.6	63.92	77.2	88.6	82.7	61.2	93.8

Abbreviations: HC=Healthy controls, PD=Parkinson's disease, BC = Betweenness centrality, ND=Node degree, EC=Eigenvector centrality, LEAPD=Linear-predictive-coding EEG Algorithm for PD [11]

accurately separate PD patients from healthy age-matched controls regardless of their medication status. Such decoders can assist clinicians as a cost-effective diagnostic tool, crucial for prognostic and therapeutic purposes. These decoders can also be used to find biomarkers of PD for developing interventional therapies such as adaptive deep-brain stimulation or transcranial direct-current stimulation [29]. Future research will be directed towards causal network analysis and validating the approach on multiple datasets [30]. Also, methods to attenuate the effects of volume conduction such as spatial filters or source-level connectivity can be explored.

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