



Altered functional network topology correlates with clinical measures in very early-stage, drug-naïve Parkinson's disease

Karthik Sreenivasan^a, Virendra Mishra^a, Christopher Bird^a, Xiaowei Zhuang^a, Zhengshi Yang^a, Dietmar Cordes^{a,b}, Ryan R. Walsh^{c,*}

^a Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, 89106, USA

^b University of Colorado, Boulder, CO, 80309, USA

^c Muhammad Ali Parkinson Center at Barrow Neurological Institute, Phoenix, AZ, USA

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ABSTRACT

Introduction: The aim of the study was to identify abnormalities of whole-brain network functional organization and their relation to clinical measures in a well-characterized, multi-site cohort of very early-stage, drug-naïve Parkinson's Disease (PD) patients.

Methods: Functional-MRI data for 16 healthy controls and 20 very early-stage, drug-naïve patients with PD were obtained from the Parkinson's Progression Markers Initiative database after controlling for strict inclusion/exclusion imaging criteria. Connectivity between regions of interest was estimated using Pearson's correlation between averaged time-series, and subsequently a connectivity matrix was obtained for each subject. These connectivity matrices were then used in an unbiased, whole-brain graph theoretical approach to investigate the functional connectome and its correlation with disease severity in very early PD.

Results: The current study revealed altered network topology which correlated with multiple clinical measures in very early drug-naïve PD. Decreased functional segregation and integration (both globally and locally) were evident in PD. Importantly, our results demonstrated that most of the cortical regions hypothesized to be involved early in PD manifested decreased graph theoretical measures, despite utilizing a whole-brain analytic approach that is free from prior assumptions regarding cortical region involvement.

Conclusion: Graph theoretical investigation of very early drug-naïve PD revealed disrupted topological organization. These findings are evident in a stringently homogeneous group of very early-stage, medication-naïve, and non-tremor dominant PD patients by using a whole-brain unbiased approach. These results provide an important unbiased and rigorously controlled baseline for understanding further studies of PD functional connectivity investigating response to treatment, symptom development, and disease progression.

1. Introduction

Parkinson's Disease is a progressive neurodegenerative movement disorder, characterized by advancing motor and non-motor symptoms [1]. While motoric symptoms related to PD are classically associated with loss of dopamine producing neurons in the substantia nigra [2], PD pathology also involves many other cortical and sub-cortical brain regions [3,4]. Functional MRI (fMRI) techniques have provided useful insights into functional connectivity (FC) changes in PD involving these widely distributed brain regions. Altered connectivity has been reported between the basal ganglia (mostly striatum) and multiple cortical and sub-cortical regions using resting-state fMRI (rs-fMRI)

throughout different stages of PD [4–6].

Although these studies have identified brain network changes in PD, the results are often varying given the inherent clinical and pathological heterogeneity of PD combined with differing experimental and analytic approaches [3,4]. Furthermore, the confounding influence of multiple factors including medication status, disease duration, PD subtype, a priori model and analytic assumptions, and cohort differences make it difficult to generalize findings from PD fMRI studies. Recent advances in application of graph theoretical approaches to fMRI data have allowed unbiased, whole brain alternatives to characterize connectivity at both global and local levels, providing useful information about topological organization of the brain in health and disease [7–9]. Graph

* Corresponding author. Department of Neurology, Muhammad Ali Parkinson Center, Barrow Neurological Institute, 240 W. Thomas Road Ste 301, Phoenix, AZ, 85013, USA.

E-mail address: Ryan.Walsh@BarrowNeuro.org (R.R. Walsh).

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Table 1
Studies that investigated network topology in drug naïve patients with PD.

Authors/year		Sreenivasan K., et al. (Current study)	Luo.C.Y. et al. [13]	Hou. Y. et al. [14].	
Number of subjects		20 PD patients	47 PD patients	20 PD patients	
		16 healthy controls	47 healthy controls	20 healthy controls	
Multisite		Yes	No	No	
Stage of disease		Very early stage drug naïve	Early stage drug naïve	Relatively early stage drug naïve	
		UPDRS-III 16.15 ± 7.79	UPDRS-III 22.32 ± 9.47	UPDRS-III 20.55 ± 9.18	
		H&Y stage (1:2:3) 9:10:1	H&Y stage 22:25:0	H&Y stage 4:12:4	
		Disease duration 1.03 ± 1.12 yrs	Disease duration 1.37 ± 0.79 yrs	Disease duration 2.44 ± 2.50 yrs	
Network	Global efficiency	Reduced in PD	Not different	Not different	
	Local efficiency	Reduced in PD	Reduced in PD	Not different	
	Strength	Reduced in PD	–	–	
	Small world	Reduced in PD	–	–	
	Clustering coefficient	Reduced in PD	Reduced in PD	Not different	
		Negatively correlated with Disease duration			
Regional	Path length	Greater in PD	Not different	Not different	
	Global efficiency	Not different	–	Altered in PD	
				Negatively correlated with UPDRS III score	
	Local efficiency	Reduced in PD	–	–	
	Clustering coefficient		Positively correlated with SBR		
			Reduced in PD	–	–
			Positively correlated with SBR		
	Path length	Greater in PD	–	–	
Nodal strength	Not different	Reduced in PD	Altered in PD		
Betweenness	Reduced in PD	–	Altered in PD		

theoretical analyses of rs-fMRI data studies have revealed disrupted networks in PD [10–14].

While Luo et al. [13] and Hou et al. [14] have reported altered topology of brain function in drug naïve patients with PD (Table 1), this has not been validated in a well characterized, rigorously homogeneous, multi-site cohort of very early-stage, drug naïve patients with PD to the best of our knowledge. It is important to establish such baseline topological network dysfunction in newly diagnosed and unmedicated PD, which in turn will aid not only the understanding of network pathophysiology very early in disease (particularly as it relates to symptom severity) but also will establish a baseline to inform longitudinal tracking of topological dysfunction throughout the disease course. This baseline is vital in developing an imaging-based assay to improve PD diagnosis, track symptom development, and understand response to treatment. Thus, we applied an unbiased, whole-brain, data-driven graph theoretical approach to rs-fMRI data from the Parkinson's Progression Markers Initiative database (PPMI) database to establish a rigorously controlled baseline of network topology in PD very early in disease and prior to use of PD medications.

2. Materials and methods

2.1. Participants

Data used in the preparation of this article were obtained from the PPMI database. The PPMI study was approved by the Institutional Review Board of all the participating sites and written informed consent was obtained from all the participants by the site investigators. The PPMI is a large-scale, landmark, multi-site study that recruits de novo PD patients and age-matched healthy controls among other cohorts to identify biomarkers of PD progression. For up-to-date information on the study, visit www.ppmi-info.org. fMRI data sets acquired between 2011 and 2015 were downloaded in 2017 through a standard application process from the PPMI website. Inclusion criteria for this study were: (i) recent diagnosis of PD meeting all diagnostic criteria; (ii) absence of treatment for PD; and (iii) available rs-fMRI images (for both PD patients and controls). Patients with a diagnosis of dementia were excluded from the analysis. In addition, patients with tremor-dominant PD were excluded from the study to maintain a homogenous group of PD patients and avoid the confound of tremor in MRI scanning: motor severity score was calculated using Modified Unified Parkinson's Disease-Related Score (UPDRS)-III [15], and a subscale for tremor was

defined based on tremor at rest along with action or postural tremor of the hands [16,17]. A patient was considered tremor-dominant if the summed limb UPDRS-III tremor score was ≥ 4 with at least one limb scoring 2 [16–18]. These stringent criteria reduced the cohorts to 20 PD (11 Male (M); age: 56.39 (11.18) years (mean (SD)); education: 17.25 (2.36); handedness: 16/4/0 (right/left/ambidextrous)) and 16 controls (13 Male (M); age: 63.38 (9.99) years; education: 16.94 (2.67); handedness: 13/2/1).

2.2. MRI acquisition

Imaging parameters were identical across all PPMI sites, and are briefly detailed here: data were acquired on 3 T MRI scanners. High resolution (1 mm³) structural images were acquired using a T1-weighted gradient echo 3D MP-RAGE sequence (TR = 2300 ms, TE = 2.98 ms). Functional scans were acquired using gradient-echo T2*-weighted echo planar imaging (EPI), optimized for blood oxygen level dependent (BOLD) contrast (TR = 2400 ms, TE = 25 ms, voxel size = 3.3 mm³).

2.3. fMRI preprocessing

The first 5 time frames (12sec) were removed to allow the MR signal to achieve T1 equilibrium. Time frames were slice-time corrected and realigned to the mean echo-planar image in SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>), further co-registered to the subject T1 space, and then normalized to the standard MNI-152 2 mm-template using ANTs software (<http://stnava.github.io/ANTs/>). Furthermore, 24 motion parameters, along with WM and CSF signals (3-mm cubes centered at MNI (26,-12, 35) and (19,-33, 18) [19]), were regressed out from each dataset. rs-fMRI data were further spatially smoothed using an 8 mm 3D-Gaussian filter. All voxel time courses were band pass filtered (0.008Hz < f < 0.1Hz) to emphasize low-frequency correlations in the resting-state, and variance normalized.

2.4. Connectivity and network analysis

In order to analyze whole-brain connectivity in PD, ninety different regions of interest (ROIs) were identified based on the AAL atlas [20]. Average time series were extracted from these regions for all participants. The time series were extracted from only those voxels within the ROIs intersecting with the individual subjects' fMRI image to ensure

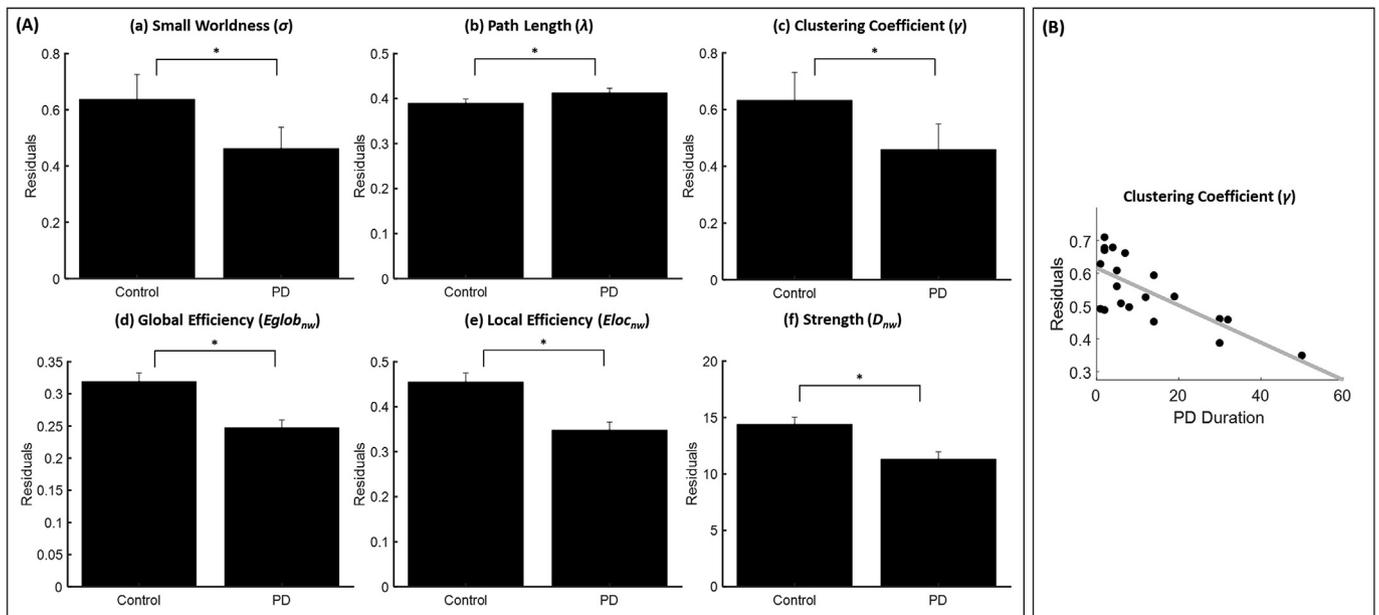


Fig. 1. Reduced global network integration and segregation in PD when compared to controls, and their relationship to clinical variables. **A.** Mean gender, age, handedness, years of education and site adjusted area under the curve (AUC) for (a) Small worldness (σ) (b) Path length (λ) (c) Clustering coefficient (γ) (d) Global efficiency ($E_{g_{nw}}$) (e) Local efficiency ($E_{l_{nw}}$) and (f) Strength (D_{nw}) for both controls and PD. * indicates statistical significance. **B.** The right panel indicates the relationship between overall network clustering coefficient and disease duration.

that the zero intensity voxels were excluded and to ensure high signal intensity. Edges represent interactions between brain regions (nodes) which are defined by the temporal correlation between each paired node. Pearson correlation coefficient between the time series for each pair of ROIs was calculated and a 90×90 correlation matrix was obtained for each subject.

The topological properties of functional networks were investigated by graph theoretical analysis using custom Matlab® scripts and GREYNA [21]. The correlation matrices obtained for each participant were thresholded into a set of weighted graphs (i.e. networks) to ensure that the networks being compared had the same number of nodes and edges in order to determine unbiased between-group differences in network organization [22]. A threshold range of $0.10 < S < 0.50$ with an interval of 0.01 was applied to each connectivity matrix. The lower limit was chosen such that there are no nodes which are isolated from the rest of the network, and the upper limit was chosen such that the contribution of spurious correlations is strongly suppressed. Only positive r values were used for the analysis [10]. At each sparsity threshold S , we calculated global and nodal network parameters: (1) network strength (D_{nw} , D_{nodal}), (2) small-world parameters (including weighted clustering coefficient (C), weighted characteristic path length (L), normalized weighted clustering coefficient (γ), and normalized weighted characteristic path length (λ)), (3) efficiency measures (E_{glob} , E_{loc}) and (4) betweenness centrality (B). In particular, small-worldness (σ) of the graph is defined as a ratio between γ and λ , and for a network to be small-world, $\sigma > 1$; $\gamma \gg 1$ and $\lambda = 1$ [23,24], which represents efficient network segregation and network integration [25]. Small world measures, network strength, betweenness centrality, and efficiency measures are metrics that were utilized to provide insight into the network characteristics of the functional brain network (please see supplementary material for detailed descriptions of each of the graph theory measures).

2.5. Statistical analysis

Chi-square (χ^2) test was used to test the significance of categorical demographic variables and the Mann-Whitney U test was used to check the statistical significance of continuous demographic and clinical

variables as well as head motion. Significance was established at $p < 0.05$.

Two sample t-tests were used to determine significant group differences in graph-based metrics. All AUC values were normally distributed, and this was tested using the Kolmogorov-Smirnov test. Linear regression analyses were performed to investigate the relationship between the network metrics significantly different between the groups and clinical variables (disease duration, UPDRS III score, and striatal binding ratios (SBR)). The SBR values (putamen and caudate) for PD patients were downloaded from the PPMI website, and for the purpose of our study the SBR was averaged across all regions. Significance was established at Bonferroni corrected $p < 0.05$. Each participant's age, gender, years of education, handedness, and scanner site were used as covariates of no interest. Please note that in all figure plots the y-axis shows the mean gender, age, handedness, years of education, and site adjusted area under the curve (AUC) values.

3. Results

3.1. Demographics

None of the demographics such as gender, age, years of education, or handedness were significantly different between the groups. The PD cohort was very early in motoric disease course: mean disease duration was 1.03 ± 1.12 years, and mean modified UPDRS-III score was 16.15 ± 7.79 . For motion calculation, root-mean-square (RMS) head motion was computed for every subject. Importantly, all subjects had less than one voxel size RMS head motion and this was not significantly different between the PD and NC groups.

3.2. Topological differences between PD and controls

The graph theory analysis results showed that both PD and controls demonstrated a small world organization ($\sigma > 1$), but by comparing the integrated AUC values at the network level we found that controls had significantly greater σ , γ , D_{nw} , $E_{g_{nw}}$, $E_{l_{nw}}$ and shorter λ when compared to PD (Fig. 1A). The γ was negatively associated with duration of disease (Fig. 1B). Overall the PD subjects showed decreased

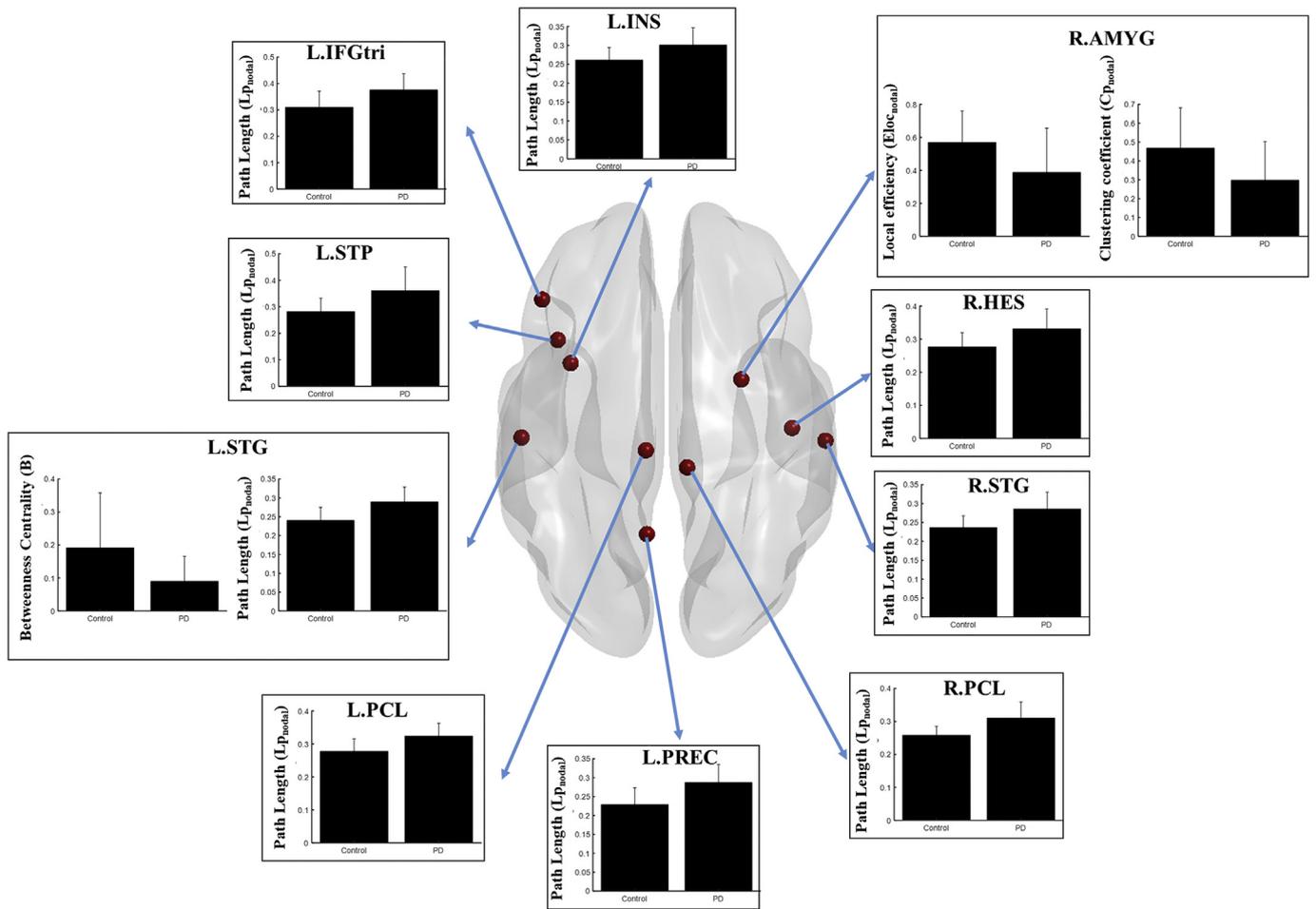


Fig. 2. Altered nodal network metrics in PD when compared to controls. Nodes with significantly different network properties in PD and controls are overlaid on MNI brain. The altered network metrics are shown within each of the small blocks. The bar denotes the mean gender, age, handedness, years of education and site adjusted area under the curve (AUC) and the error bar is the standard deviation.

segregation and integration of functional networks, and this was associated with duration of disease.

In addition to whole-brain network differences, there were also regional differences in network metrics between the two groups (Fig. 2). In particular, nine nodes were identified to have significantly greater L_{nodal} in PD: one node had significantly greater C_{nodal} and $Eloc_{nodal}$ in controls, and one node had significantly greater B in controls (Fig. 2).

Only the nodal metrics (C_{nodal} and $Eloc_{nodal}$) of the supramarginal gyrus and the nodal metrics ($Eloc_{nodal}$) of the middle frontal gyrus were positively related to the SBR in the PD patients when assessing the relationship between the different nodal network metrics and SBR (Fig. 3).

4. Discussion

The key findings of this study were: 1) integration and segregation of network connectivity are both impaired in regions known to be pathologically involved in PD, despite the lack of prior assumptions or modeling in this study; 2) altered network metrics are correlated with disease duration and SBR; and 3) these findings are evident in a well characterized, rigorously homogeneous, multi-site cohort of very early-stage, drug naïve patients with PD, and as such establish a network topology baseline in early PD.

Previous studies have shown that functional connections of brain networks are structured in a well-organized small-world manner theorized to be responsible for efficient local information processing and

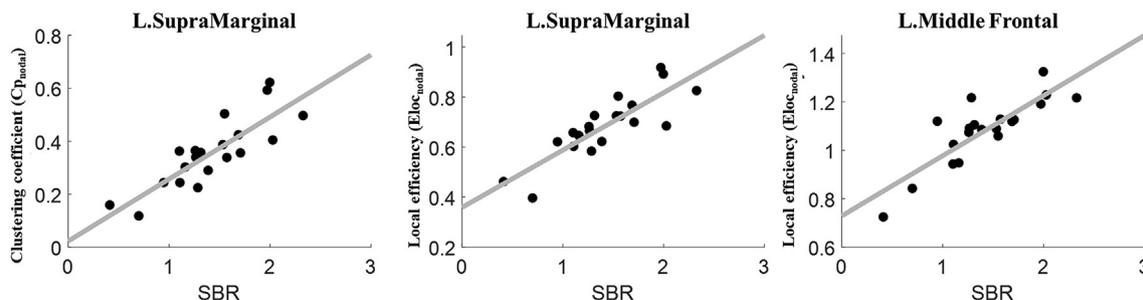


Fig. 3. Nodal network metrics in PD and their relationship to SBR. The relationship between the clustering coefficient and path length of left supramarginal gyrus and local efficiency of left middle frontal gyrus, and SBR are shown respectively.

efficient long-distance connectivity, both of which are important to ensure a high level of segregation and integration of information within the overall network [8,9]. The local inter-connectivity in the network can be measured by γ and $Eloc$, while the global functional integration is commonly measured using λ and Eg . Specifically, small-world organization reflects an optimized, healthy brain network organization and a disturbance of this balance could be in turn associated with differences in functioning of the brain in healthy and diseased states. In the present study, using both global and nodal network metrics including small-world and network efficiency measures, we found that there is a shift in the optimal topological organization of functional networks in patients with PD when compared to controls.

Our results show that both controls and PD maintain a small world organization of brain networks ($\sigma > 1$). Despite both groups showing small-world topology, however, the local segregation and global integration was significantly reduced in patients with PD when compared to controls: PD displayed reduced overall σ , γ , Eg_{nw} , $Eloc_{nw}$ and D_{nw} and increased λ when compared to controls. Decreased values of both γ and $Eloc$ indicate a loss in optimal modular information processing (functional segregation) in PD patients, whereas the increase in λ and decrease in Eg_{nw} indicate inefficient overall information routing (functional integration). In addition, and of particular importance, the normalized clustering coefficient was significantly correlated with disease duration suggesting a functional-pathology relationship between network dysfunction and manifestation of the disease over time (i.e. pathophysiological relevance of network dysfunction).

Contrary to our results, Luo et al. [13] found no difference in global efficiency but did show reduced local efficiency and Hou et al. [14] found no difference in any global network metrics between controls and very early stage drug naïve PD patients using a similar approach (Table 1). Different PD symptoms could be a result of different pathophysiology in this inherently heterogeneous disease [26], and as a result could reflect distinct topological organization. Furthermore, the PD cohort utilized in the present study was stringently characterized and homogeneous in terms of symptoms unlike the group of PD patients used in Luo et al. [13]. In addition, this study's patient population was non-tremor-predominant by design in an effort to ensure cohort homogeneity and reduce the potential confound of head movement as well. While Hou et al. [14] had a homogeneous group of PD patients, they were further along the course of the disease based on both H & Y stage (2 ± 0.65) and disease duration (2.44 ± 2.50 yrs). As mentioned earlier, we speculate that difference in stage of disease likely influences differences in topological network organization, particularly given the correlation between network topology and disease duration identified in this study.

In addition to overall network metrics, several regions showed reduced and significantly altered nodal characteristics in PD when compared to controls. Lp_{nodal} was the primary nodal characteristic affected in many of the nodes (e.g. left insula, left and right superior temporal gyrus, left and right paracentral lobule, left superior temporal pole), with higher path length evident in PD when compared to controls. Many of these nodes spatially overlapped with regions of decreased connectivity in PD, where cortical involvement has been hypothesized to include temporal mesocortex early in disease, progressing to higher order sensory association and prefrontal regions and eventually affecting premotor as well as primary sensory and motor regions [27]. The increased path length indicates a high wiring cost in the functional networks of PD patients, which is hypothesized to lead to inefficient network integration. Interestingly, our results showed that most of the cortical regions hypothesized to be involved early in PD manifested decreased regional measures, despite our unbiased whole-brain approach free from a priori assumption. For example, left superior temporal gyrus showed altered betweenness centrality and both left and right STG demonstrated altered path length. The reduced functional integration of these nodes is in agreement with an earlier study showing anteromedial temporal lobe changes in drug naïve early stage PD

patients [28]. Another region in the proximity of the temporal lobe, the amygdala, also showed reduced network segregation (C_{nodal} and $Eloc_{nodal}$) in PD. The amygdala, in addition to being crucial for emotional processing, is also recognized to be integral in a variety of cognitive functions including attention, perception, and explicit memory [29], and previous studies have shown that the amygdala is implicated in the neuropathology of PD [30]. Furthermore, the nodal characteristics of the left supramarginal gyrus and the left middle frontal gyrus were significantly related to SBR as well, lending credence to the pathophysiological relevance of this finding in PD.

In addition to investigating topological properties, we also compared functional connectivity values between the two groups. Fisher's r -to- z transformation was applied to the connectivity (correlation matrix) matrix of each individual subject to improve the normality of the correlation coefficients. Two sample t-tests were used to determine significant group differences in FC. While there was a trend of overall reduced functional connectivity in PD with a large effect size (Cohen's $d > 0.8$), this did not survive multiple comparisons correction and therefore these data were not reported. One possible explanation for this is the very early stage of disease and unmedicated status for the PD cohort in this study: pathologic network function may not yet be manifest to drive symptom development at a whole brain level, but with progression of disease network dysfunction including these regions could subsequently develop. In summary, the present study demonstrates pathologic functional integration and segregation in very early drug naïve PD including a loss of small-world characteristics and an early shift away from optimal topological organization in PD, and these findings were correlated with disease duration and SBR values. The sum of these results suggests that pathophysiologically relevant altered topological organization is detectable using this method in very early stage PD, establishing a baseline for further development of a graph theoretical approach as an imaging based biomarker in longitudinal studies of PD.

A major strength of our study is the use of a multi-site cohort of well-characterized PD patients from the PPMI data base with a well-matched control sample, including very early stage and drug naïve PD patients. To the best of our knowledge, this is the first study to use such a multi-site cohort to investigate network topology in drug naïve very early stage PD. Large, multi-site studies using fMRI data present an opportunity to obtain a very well characterized and representative cohort by pooling data, which is critical given the inherent clinical and pathological heterogeneity of PD. The present PD cohort is stringently homogeneous, as they are all cognitively intact, very early stage, medication naïve, and non-tremor dominant PD patients. Furthermore, stringent control for head movement and other imaging parameters homogenized the PD cohort and limited spurious variables. Despite working with this highly controlled and limited sample the results shown survived strict statistical analyses, bolstering the statistical and pathophysiological significance of our findings. While several studies have investigated functional connectivity and network organization in PD, the findings reported are disparate and the cause of such disparate findings could be due to the heterogeneous nature of the disease as well as the functional and anatomical variation present within each individual and study. Therefore it is important to establish a baseline of brain network dysfunction in the very early stages of disease, which in turn will aid not only the understanding of network pathophysiology but could potentially be integral in development of longitudinal tracking of the course PD.

There are, however, limitations to this study. In the present study, 90 regions of interest were chosen according to the AAL atlas emphasizing a whole-brain unbiased analytic approach. As a result, small structures, such as striatal subregions and other subcortical structures which can demonstrate pathological changes in PD, were not included in this study. Therefore, studies using different brain parcellation strategies are needed to validate the findings of our study and identify the most consistent topological organization of brain networks in very

early stage drug naive PD patients using a standardized parcellation scheme. In addition, while the graph theory measures used in our study provide information about functional network topology, to develop a comprehensive model of baseline topological network dysfunction future studies need to investigate community structure (modularity), synchronization, and network robustness as well. The sample size used in this study was small mainly due to stringent imaging criteria and to maintain a well-matched, stringently homogeneous, cognitively intact, very early stage, medication naive, and non-tremor dominant PD cohort. Our findings need to be validated with larger PD samples adhering to the same stringent criteria to maintain a relatively homogenous group of subjects, while endeavoring to respect the inherent heterogeneity of the disease. This may allow the detection of functional connectivity differences that were not observed in the current study. Lastly, it will be important to track longitudinal functional network changes over the duration of PD as well as determine specific medication effects on the same stringently controlled and standardized graph theory approach, and these studies are ongoing.

Our results provide an unbiased, whole brain description of network topology in very early stage de novo unmedicated PD, which provides an important baseline for understanding further studies of PD functional connectivity investigating response to treatment, symptom development, and disease progression. In turn, this should help enable development of a clinically useful and standardized in vivo assay in PD, an important unmet need in the field.

Author contributions

(1) A. Conception and design of the study, B. Acquisition of data, C. Analysis and interpretation of data, (2) A. Drafting the article, B. Revising it critically for important intellectual content, (3) Final approval of the version to be submitted.

K.S.: 1C, 2A, 2B, 3.

V.M.: 1C, 2B, 3.

C.B.: 1C, 2B, 3.

X.Z.: 1C, 2B, 3.

Z.Y.: 1C, 2B, 3.

D.C.: 1A, 1C, 2B, 3.

R.R.W.: 1A, 1C, 2B, 3.

Declarations

No competing financial interests exist relevant for this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2019.02.001>.

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