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Research article

Large-scale cortical volume correlation networks reveal disrupted small world patterns in Parkinson's disease

Qiong Wu[a], Yang Gao[a], Ai-Shi Liu[a], Li-Zhi Xie[b], Long Qian[c], Xiao-Guang Yang[a,*]

[a] Department of Radiology, The Affiliated Hospital of Inner Mongolia Medical College, Hohhot 010050, China
[b] GE Healthcare, MR Research China, 100088, Beijing, China
[c] Center for MRI Research, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, 100871, China

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ABSTRACT

To date, the most frequently reported neuroimaging biomarkers in Parkinson's disease (PD) are direct brain imaging measurements focusing on local disrupted regions. However, the notion that PD is related to abnormal functional and structural connectivity has received support in the past few years. Here, we employed graph theory to analyze the structural co-variance networks derived from 50 PD patients and 48 normal controls (NC). Then, the small world properties of brain networks were assessed in the structural networks that were constructed based on cortical volume data. Our results showed that both the PD and NC groups had a small world architecture in brain structural networks. However, the PD patients had a higher characteristic path length and clustering coefficients compared with the NC group. With regard to the nodal centrality, 11 regions, including 3 association cortices, 5 paralimbic cortices, and 3 subcortical regions were identified as hubs in the PD group. In contrast, 10 regions, including 7 association cortical regions, 2 paralimbic cortical regions, and the primary motor cortex region, were identified as hubs. Moreover, the regional centrality was profoundly affected in PD patients, including decreased nodal centrality in the right inferior occipital gyrus and the middle temporal gyrus and increased nodal centrality in the right amygdala, the left caudate and the superior temporal gyrus. In addition, the structural cortical network of PD showed reduced topological stability for targeted attacks. Together, this study shows that the coordinated patterns of cortical volume network are widely altered in PD patients with a decrease in the efficiency of parallel information processing. These changes provide structural evidence to support the concept that the core pathophysiology of PD is associated with disruptive alterations in the coordination of large-scale brain networks that underlie high-level cognition.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder caused mainly by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta projecting to the striatum. The dysfunction of the cortico-striatal-thalamic-cortical loops is believed to lead to the hallmark motor features of PD including tremor, akinesia and rigor [1,2]. Although the exact mechanism underlying the pathophysiology of PD is unknown, increasing evidences have suggested that it could be associated with abnormal cortical morphology and connectivity involving a widespread of brain regions [3,4]. Quantitative analysis of the morphological changes of the cerebral cortex provides a potential informative way of uncovering the pathological derivations in PD. Using voxel-based morphometry (VBM) method, previous studies observed statistically significant gray matter volume reduction in multiple brain regions in PD patients [5–7]. Although such univariate analysis could highlight the roles played by each brain region in the pathogenesis in PD, it does not allow us to evaluate the interaction or functional integration among brain regions.

Recently, large-scale brain network analysis has been demonstrated to reveal the associations between the cognitive performance or psychiatric brain disorders and topological organization of brain networks, which is typically achieved through all major modalities of magnetic resonance imaging (MRI) and neurophysiological data acquisition from both functional and structural perspectives [8,9]. These methods can not only provide powerful modes to detect subtle differences in brain organization [8,10], but also bring new insights into relevant network parameters that have profound effects on the dynamic performances of a network, such as the local efficiency and the global efficiency, against pathological attacks of the disease [11]. Under this framework, structural MRI is applied to investigate the topological organization of brain covariance networks in this current research. Quantitative

* Corresponding author at: Affiliated Hospital of Inner Mongolia Medical College, Hohhot, 010050, China.
E-mail address: xiaoguang1121@126.com (X.-G. Yang).

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investigations of the structural covariance of cortical volume in PD patients might contribute more to the understanding of this disorder than conventional VBM analysis.

Studies that performed brain network analysis on PD were focused in the domain of functional connectivity measured by fMRI or magnetoencephalography (MEG) [12–16], while the topological profiles of structural covariance network at the whole brain level are yet to be investigated in PD patients. Based on wavelet correlation, Skidmore and his colleagues [16] observed reduced global and nodal efficiencies in PD patients. By assessing the whole brain functional connectivity, a recent study identified altered topological parameters at global, intermediate and local levels in PD patients [13]. Further, a longitudinal magnetoencephalography (MEG) study [15] observed lower local clustering with preserved path length in the delta frequency band in PD patients. Although one study had delineated the topological patterns of brain networks from the prospective of structural covariance network, both the method of the network constructing and the disease stages of the cohorts of PD patients were different with the current study [17]. Particularly, the structural covariance networks were constructed using cortical thickness [4,5], and the PD patients with and without mild cognitive impairment (MCI) were investigated in that study.

In order to investigate whether the structural covariance network derived from cortical volume is also changed in PD patients, in the current study, large-scale structural covariance networks were constructed for 48 PD patients and 50 normal controls (NC). Network topological properties, such as path length, clustering coefficient, normalized path length and normalized clustering coefficient, were computed and compared between the two groups. Regional nodal characteristics of brain networks were also assessed to investigate the differences of the regional topological profiles in both PD and NC groups. Moreover, to assess the resilience of cortical volume networks in PD patients against random failures and targeted attacks, network robustness was utilized to evaluate the stability of this network. To our knowledge, the present study is the first to explore the topological alterations of cortical volume based network in patients with PD, seeking to use the volume based connectivity network properties as an evaluation criterion.

2. Methods and materials

2.1. Participants

The study was approved by the Medical Research Ethical Committee of the Affiliated Hospital of Inner Mongolia Medical College Hospital. All patients were recruited from The Affiliated Hospital of Inner Mongolia Medical College (Hohhot, China), and written informed consents were obtained from all subject prior to MRI scanning. 50 patients (24 males) with idiopathic PD and 48 age- and gender-matched NC (25 males) were recruited ($P > 0.05$). All the subjects were right-handed. The selection of PD patients followed the criteria of UK Parkinson's Disease Society Brain Bank for idiopathic PD [18]. Subjects with Mini-Mental State Examination (MMSE) scores < 24 were also excluded. Clinical tests and MRI scans were performed to exclude acute physical illness, primary neurological illness, and other major psychiatric illness, such as brain tumor, stoke or dementia. NC group were interviewed to confirm that they had no history of neurological disorder or psychiatric illness, and no gross abnormality was observed from their brain MRI images (Table 1). For each PD patient, all psychometric and neurologic evaluations were conducted during a practically defined "on" state. The stage of the disease was evaluated by the Hoehn and Yahr (H & Y) staging scale [19]; motor disability was evaluated using the Unified Parkinson's Disease Rating Scale motor part III (UPDRS III) [20]; and the global cognitive function was evaluated using MMSE score [21].

Table 1
Demographic and neuropsychological characteristics of all subjects.

	NC (n = 50) Mean ± SD	PD (n = 48) Mean ± SD	P value
Age(years)	57.74 ± 5.56	57.64 ± 7.00	0.973*
Education(years)	11.61 ± 4.95	10.83 ± 3.29	0.647*
Gender(M/F)	24/26	25/23	0.791*
MMSE	29.00 ± 2.33	28.60 ± 1.69	0.330*
UPDRS III	NA	26.21 ± 13.44	NA
H & Y	NA	1.63 ± 0.54	NA
Disease Duration	NA	6.28 ± 3.35	NA

Values are represented as the mean ± SD. For comparisons of demographics, *P values are obtained using two sample *t*-test; $P < 0.05$ was considered significant. NA: not applicable. F = female; M = male; PD = Parkinson's disease; UPDRS III = Unified Parkinson's Disease Rating Scale motor part III; SD = standard deviation.

2.2. MRI data acquisition, image preprocessing and network construction

MR images were acquired on a 3.0-T MR system (Discovery MR750, General Electric, Milwaukee, WI, USA) and images were analyzed with VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8/) in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). After performing VBM analysis, the next step is to construct the brain graph G with N nodes and K edges. In the current study, we used the former 90 ROIs from the common AAL atlas (Table 2), extracted by WFU PickAtlas Toolbox [21], as the graph nodes [7,23,24]. Cortical volumes were calculated by masking the 90 ROIs with the individually modulated and normalized GM images and then extracting the average volume within each ROI using the REX code (http://web.mit.edu/swg/software.htm). Afterwards, the association matrix and the corresponding binary adjacency of each group were generated, see Supplementary Material (SM) for detailed information.

2.3. Network analysis

To describe the global topological profiles and small world architectures, clustering coefficient (Cp), characteristic path length (Lp), Lambda and Gamma were computed, see SM for detailed information

Table 2
Cortical and subcortical regions of interest defined in the study.

Index	Region	Abbr.	Index	Region	Abbr.
(1,2)	Amygdala	AMYG	(47,48).	Occipital_Mid	MOG
(3,4)	Angular	ANG	(49,50)	Occipital_Sup	SOG
(5,6)	Calcarine	CALC	(51,52)	Olfactory	OFB
(7,8)	Caudate	CN	(53,54)	Pallidum	PLD
(9,10)	Cingulum_Ant	ACC	(55,56)	Paracentral_Lobule	PCL
(11,12)	Cingulum_Mid	MCC	(57,58)	Parahippocampal	PHIP
(13,14)	Cingulum_Post	PCC	(59,60)	Parietal_Inf	IPL
(15,16)	Cuneus	CUN	(61,62)	Parietal_Sup	SPL
(17,18)	Frontal_Inf_Oper	IFOp	(63,64)	Postcentral	PoCG
(19,20)	Frontal_Inf_Orb	IFOr	(65,66)	Precentral	PrCG
(21,22)	Frontal_Inf_Tri	IFTr	(67,68)	Precuneus	PCUN
(23,24)	Frontal_Med_Orb	MedFOr	(69,70)	Putamen	PUT
(25,26)	Frontal_Mid	MFG	(71,72)	Rectus	REC
(27,28)	Frontal_Mid_Orb	MFOr	(73,74)	Rolandic_Oper	RLN
(29,30)	Frontal_Sup	SFG	(75,76)	Supp_Motor_Area	SMA
(31,32)	Frontal_Sup_Medial	MedSF	(77,78)	SupraMarginal	SMG
(33,34)	Frontal_Sup_Orb	SFOr	(79,80)	Temporal_Inf	ITG
(35,36)	Fusiform	FG	(81,82)	Temporal_Mid	MTG
(37,38)	Heschel	HSHL	(83,84)	Temporal_Pole_Mid	MTP
(39,40)	Hippocampus	HIPP	(85,86)	Temporal_Pole_Sup	STP
(41,42)	Insula	INS	(87,88)	Temporal_Sup	STG
(43,44)	Lingual	LNG	(89,90)	Thalamus	THL
(45,46)	Occipital_Inf	IOG			

The regions are presented according to a prior template obtained from an AAL atlas; odd numbers represent the corresponding brain regions in left hemisphere, and even numbers denote the specific brain regions in right hemisphere. AAL: automated anatomical labelling.