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Possible association between cerebral white matter atrophy and impaired performance of activities of daily living in patients with Parkinson's disease

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Abstract

Introduction: *The contribution of brain abnormalities in patients with Parkinson's disease (PD) to impaired functional status remains uncertain. Our study assessed whether global and regional brain structural abnormalities are associated with impaired performance of activities of daily living (ADL) in PD patients.*

Material and methods: *A retrospective analysis was conducted of 46 patients with PD, recruited prospectively from a movement disorder clinic. Motor impairment and disability were assessed using the Hoehn and Yahr (H-Y) scale and Unified Parkinson's Disease Rating Scale Part III (UPDRS-III). Cognitive status was evaluated with Montreal Cognitive Assessment (MoCA). The performance of ADL was indexed by the sum score of the Physical Self-Maintenance Scale (PSMS) and Lawton Instrumental ADL scale. Brain magnetic resonance imaging (MRI) was performed to assess white matter hyperintensities and medial temporal lobe atrophy (MTLA). Global brain atrophy, indexed by the relative grey matter volume (RGM), relative white matter volume (RWM) and average cortical thickness of the whole brain, was quantified by voxel-based morphometry (VBM).*

Results: *The ADL score (where higher scores indicate poorer performance) negatively correlated with RWM (where greater volume indicates less severe atrophy; $r = -0.41$, $p = 0.004$) and RGM (where greater volume indicates less severe atrophy; $r = -0.43$, $p = 0.003$) but not with the average cortical thickness ($r = -0.16$, $p = 0.29$). With ADL score as the dependent variable in a linear regression model, H-Y stage and RWM significantly correlated with the ADL score after adjusting for age and MoCA score, and together accounted for 51% of the variance therein. RGM was not significantly correlated with the ADL score after adjusting for age and MoCA score.*

Conclusions: *Cerebral white matter atrophy may be associated with the performance of ADL in patients with PD, indicating an important role of white matter impairment in their functional status.*

Key words: *Parkinson's disease, activities of daily living, voxel-based morphometry.*

Introduction

Parkinson's disease (PD) is a chronic disorder characterized by motor and non-motor symptoms [19], in association with the progressive degeneration of dopamine-producing cells in brain structures including the substantia nigra [29]. With disease progression, PD patients tend to show decreased ability to perform activities of daily living (ADL), such as walking, talking, and swallowing, as well as simple tasks like bathing and dressing [21]. In fact, ADL limitations may appear in the early stage of PD [18]. Patients with advanced-

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stage PD, particularly those with a balance disorder [32,33], show more severe impairment in the performance of ADL, and gradually lose their independence [20]. The treatment of patients with PD is focused on improving symptoms and the capacity for ADL. Therefore, assessment of the ADL of patients with PD is mandatory when evaluating the effectiveness of both symptomatic and potentially disease-modifying treatments.

Previous studies have shown that both motor and non-motor symptoms, including depression, apathy, cognitive impairment and decreased motor function, can affect the quality of life of patients with PD [8,13,24]. Some researchers have posited that the burden imposed by non-motor symptoms, such as neuropsychiatric disorders, cognitive impairment and fatigue, may exceed that of motor symptoms [1]. PD patients often exhibit slight structural abnormalities, such as brain atrophy, although brain magnetic resonance imaging (MRI) is not specifically used for the diagnosis of PD. In patients with PD, frontal and temporal lobe atrophy is associated with cognitive impairment [2,27], suggesting that changes in brain structure may be involved in some of the non-motor symptoms of PD.

However, to our knowledge, few studies have focused on the association between ADL and brain abnormalities in PD patients. Brain MRI provides comprehensive information on structural changes in the brain, including global and regional brain atrophy, lacunes, white matter hyperintensities (WMHs) and enlarged perivascular spaces (EPVS). Voxel-based morphometry (VBM) is used to quantify the grey and white matter of the whole brain. Prior findings using VBM indicate that grey and white matter atrophy is associated with depression in patients with PD, and affects their quality of life [11,22]. However, the contribution of brain abnormalities to the functional status of PD patients remains uncertain. Therefore, this study explored clinical and MRI correlates of ADL in patients with PD. We hypothesized that brain MRI abnormalities may partly explain the impaired ADL performance seen in patients with PD.

Material and methods

Participants and setting

We performed a retrospective analysis of data from a prospective registration study of PD patients seen at a movement disorder clinic in the Department of Neurology of Dongguan People's Hospital (DGPH) between 1 August 2018 and 30 December 2019. DGPH, which is the largest public tertiary hospital in Dongguan City, is located in the south of China.

The criteria for patient inclusion were as follows: 1) diagnosis of idiopathic PD established according to the current United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria [15]; 2) aged 18-80 years; 3) underwent brain MRI examination with three-dimensional T1-weighted imaging (3D-T1WI); and 4) sufficiently stable to complete the clinical assessment.

The exclusion criteria were as follows: 1) incomplete clinical data; 2) poor-quality brain images compromising quantitative MRI measurements; 3) diagnosed with dementia or psychosis; and 4) comorbid severe impairment of vital organic functions or malignant tumour.

The study protocol was approved by the Ethics Committee of DGPH. Consent was obtained from all subjects in accordance with the Declaration of Helsinki.

Data collection and neurological and psychiatric assessments

Each PD patient included in the study underwent a clinical evaluation by three neurologists (ZHL, XLF and YKC) trained in the diagnosis of movement disorders. The patient information collected included age, gender, age of onset, disease duration, education level, family history, presence of motor fluctuations and dyskinesia, and current medications. Impairment in daily activities was assessed using the Unified Parkinson's Disease Rating Scale Part II (UPDRS-II). Motor impairment and disability were assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) and Hoehn and Yahr (H-Y) scale. All patients affected by motor fluctuations were examined during the "on" period. Levodopa-related complications (dyskinesia and motor fluctuations) were evaluated using the Unified Parkinson's Disease Rating Scale Part IV (UPDRS-IV). Non-motor symptoms were evaluated using the Non-Motor Symptoms Scale (NMSS) [5]. NMSS subscores were obtained to assess non-motor symptoms associated with ADL, such as constipation, pain and genitourinary problems (item 21 assesses constipation, items 22-26 assess genitourinary problems and item 27 assesses pain).

The following assessments were performed by a neurologist (ZHL) with training in the performance of neuropsychological assessments: 1) Chinese versions of the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) to evaluate cognitive function [12,28]; 2) Chinese versions of the Hamilton Depression Scale (HAM-D) scale to evaluate depressive symptoms [16] and Hamilton Anxiety Scale (HAM-A) to evaluate anxiety symptoms [17]; 3) Chinese version of the Fatigue Severity Scale (FSS) to quantify fatigue [23]; 4) the Pittsburgh Sleep Quality Index (PSQI) to evaluate the severity of sleep disorders [4]; and 5) an ADL scale composed of the Physical Self-Maintenance

Scale (PSMS) and Lawton Instrumental ADL (IADL) scale, to measure functional capacity [25]. The ADL scale comprises six items assessing self-maintenance and eight evaluating instrumental activities (ability to use a telephone, go shopping, prepare food, perform housekeeping duties, do the laundry, travel, manage medications and handle finances). The total ADL score is calculated by summing the scores for all items; the maximum score is 56. Higher scores indicate less ability to perform ADL. The ADL scale has been validated and used in PD patients [8].

MRI assessment

VBM parameter settings

All brain T1W MRI scans were performed with a 3.0 T system (Sonata; Siemens Medical, Erlangen, Germany). A whole-brain structural phase gradient echo image was collected, and the sagittal image was used as a reference. With the thalamus as the centre of the layer, the scanning baseline is parallel to the anterior and posterior joint lines. The scanning parameters were as follows: repetition time/echo time/excitation = 7.6/3.3/1, field of view = 240 mm, slice thickness = 2 mm, matrix = 256 × 256, and voxel size = 0.93 × 0.93 × 2.2 mm^3. In total, 72 transverse axial images covering the whole brain were acquired.

VBM data processing

All data were processed by a trained neurologist (ZHL) using the CAT12 tool of SPM8 Statistical Parametric Mapping software (http://www.fil.ion.ucl.ac.uk/spm) and MATLAB R2008A (MathWorks Inc., Natick, MA, USA). The brain MRI gradient echo T1W images of all patients were spatially standardized into an identical three-dimensional space, and high-resolution brain structural images with high grey-white matter contrast were segmented into grey matter, white matter and cerebrospinal fluid. The volumes of grey matter and white matter, and the average cerebral cortex thickness, were quantified. The relative grey matter volume (RGM), relative white matter volume (RWM) and average cortical thickness were extracted from the whole-brain index report generated by the statistical software.

WMHs and medial temporal lobe atrophy (MTLA) assessment

Two neurologists (ZHL and YKC) blinded to the clinical information and assessment results of each patient assessed the following MRI variables:

The severity of WMHs was graded using the four-point scale of Fazekas *et al*. [10]. Periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs) were scored separately on fluid-attenuated inversion recovery (FLAIR) images.

MTLA was evaluated using Scheltens' scale [31]. The severity of the MTLA on coronal MRI sections was rated on a scale ranging from 0 (*no atrophy*) to 4 (*severe atrophy*).

Interrater reliability tests were performed on 20 patients (ZHL). The interrater agreement values for the MRI measurements ranged from *good* to *excellent* (WMH, kappa = 0.78, MTLA, kappa = 0.82). To confirm the interrater agreement, another trained neurologist (YKC) re-evaluated the MRI images of all 20 cases; the interrater agreement was again *good* to *excellent* (WMH, kappa = 0.73, MTLA, kappa = 0.78).

Statistical analysis

All statistical analyses were performed using SPSS software (ver. 22.0; **SPSS** Inc., Chicago, IL, USA). The relationships between variables of interest and ADL scores were analysed by Pearson and Spearman correlation (for normally distributed data and non-normally distributed or categorical data, respectively). Variables significantly related to ADL ($p < 0.05$) were entered into a separate multiple linear regression analysis as independent variables; ADL was the dependent variable. Multicollinearity between independent variables (defined as a correlation coefficient ≥ 0.6) was tested. The significance was set at 0.05 (two-sided).

Results

Our analysis included data from 55 patients who met the inclusion and exclusion criteria. We excluded nine patients who lacked MRI data, and there were no significant differences in major clinical features between the included and excluded PD patients (Table I). Thus, the data of 46 cases were finally analysed, comprising 25 men (54.3%) and 21 women (45.7%) with a mean age of 63.9 years; the mean age of onset was 61.4 years and the mean disease duration was 2 years. The average ADL score was 21.2. The clinical features of the subjects are shown in Table II.

The results of bivariate correlation analyses between ADL scores and clinical and imaging variables are shown in Table III. In the entire cohort, ADL scores (where higher scores indicate poorer performance of ADL) negatively correlated with RWM ($r = –0.41$, $p = 0.004$) and RGM ($r = –0.43$, $p = 0.003$) but not with average cortical thickness ($r = –0.16$, $p = 0.29$). Additionally, age, age of onset, H-Y stage, and UPDRS-II, UPDRS-III, NMSS and MoCA scores correlated with ADL ($p < 0.01$). Similar to the ADL score, the UPDRS-II and UPDRS-III scores were highly correlated with H-Y stage ($r = 0.78$, $p < 0.001$ and $r = 0.79$, $p < 0.001$, respectively). Thus, they were not

Table I. Comparison of major sociodemographic and clinical characteristics of included and excluded Parkinson's disease (PD) patients

Variables	Whole sample (n = 55)	Included sample (n = 46)	Excluded sample (n = 9)	$T/\chi^2/Z$	P
Age, mean ±SD*	63.5 ±10.1	63.9 ±10.4	61.8 ±9.0	0.570	0.571
Sex (female), *n* (%)+	27 (49.1)	21 (45.7)	6 (66.7)	0.018	0.893
Age of onset, mean ±SD*	60.7 ±10.6	61.4 ±10.7	57.3 ±10.3	1.056	0.296
Disease duration, median (25Q-75Q)#	2.0 (1.0-3.0)	2.0 (0.9-3.0)	4.0 (1.3-8.0)	–1.664	0.096
H-Y stage, median (25Q-75Q)#	2.5 (2.0-3.0)	2.5 (2.0–3.0)	2.0 (1.5-3.0)	–0.106	0.916

**t-test, +χ^2 test, #Mann-Whitney U test; H-Y – Hoehn and Yahr scale.*

Table II. Basic demographic, clinical, and MRI characteristics of the study sample

Variables	The whole sample, N = 46, mean ±SD/median (25Q-75Q)/n (%)
Age	63.9 ±10.4
Sex (female)	21 (45.7)
Age of onset	61.4 ±10.7
Disease duration	2.0 (0.9-3.0)
Hypertension	15 (32.6)
Diabetes mellitus	4 (8.7)
History of stroke	1 (2.2)
Family history of PD	2 (4.3)
H-Y stage	2.5 (2.0-3.0)
Symptom fluctuation	7 (15.2)
Use of madopar	18 (39.1)
Use of ropinirole	1 (2.2)
Use of pramipexole	1 (2.2)
Assessments	
UPDRS-II	11.5 ±4.2
UPDRS-III	28.2 ±12.5
HAM-D	14.9 ±6.3
HAM-A	16.8 ±6.3
FSS	40.5 ±11.2
PSQI	9.8 ±4.6
NMSS	68.4 ±36.3
Sub-score of NMSS	
Constipation	3.0 (1.0-6.0)
Genitourinary symptoms	10.0 (4.8-13.5)
Pain	0.0 (0.0-0.0)
MMSE	27.5 ±2.7
MoCA	22.7 ±4.4
Cortical atrophy	
MTLA-total	2.0 (1.0-4.0)
PVH	2.0 (1.0-2.0)
DWMH	1.0 (0.0-2.0)
RWM	35.0 ±3.0
RGM	34.9 ±3.9
Average cortical thickness	2.1 ±0.1

H-Y – Hoehn and Yahr scale, MMSE – Mini-Mental State Examination, MoCA – Montreal Cognitive Assessment, UPDRS-II – Unified Parkinson's Disease Rating Scale total score, part II, UPDRS-III – UDPRS total score, part III, HAM-D – Hamilton Depression Scale, HAM-A – Hamilton Anxiety Scale, FSS – Fatigue Severity Scale, PSQI – Pittsburgh Sleep Quality Index, NMSS – non-motor symptoms, PD – Parkinson's disease, MTLA-total – medial temporal lobe atrophy, total score, PVH – periventricular hyperintensities, DWMH – deep white matter hyperintensities, RWM – relative white matter volume, RGM – relative grey matter volume

included in the linear regression models as independent variables. We constructed three linear regression models to explore the associations between quantitative brain atrophy variables (RGM, RWM and average cortical thickness) and the ADL score; age, H-Y stage and the NMSS and MoCA scores were also entered into the models.

In the linear regression model, higher H-Y stage and lower RWM were significantly associated with a higher ADL score after adjusting for age and the MoCA score, and these accounted for 51% of the variance in the ADL score (Table IV). RGM and average cortical thickness were not significantly correlated with the ADL score after adjusting for age and the MoCA score.

Discussion

In this study, MRI showed that lower RWM, which indicates more severe cerebral white matter atrophy, was associated with poorer performance of ADL in patients with PD. To the best of our knowledge, this finding has not been reported previously.

Table III. Correlations between demographic, clinical, and MRI characteristics and activities of daily living (ADL)

Variables	ADL	
	r	*p*
Age*	0.50	< 0.001
Sex (female), *n* (%)	–0.20	0.19
Age of onset*	0.44	0.002
Disease duration*	0.22	0.15
Hypertension	0.06	0.68
Diabetes mellitus	0.25	0.09
History of stroke	0.25	0.09
Family history of PD	–0.15	0.33
H-Y stage	0.70	< 0.001
Symptom fluctuation	0.26	0.08
Use of madopar	0.23	0.12
Use of ropinirole	0.25	0.09
Use of pramipexole	0.24	0.11
Assessments		
UPDRS-II*	0.78	< 0.001
UPDRS-III*	0.64	< 0.001
HAM-D	0.26	0.08
HAM-A	0.13	0.40
FSS	0.33	0.03
PSQI	0.09	0.56
NMSS*	0.53	< 0.001
Subscore of NMSS		
Constipation	0.27	0.07
Genitourinary symptoms	0.26	0.08
Pain	0.25	0.09
MMSE	–0.15	0.09
MoCA	–0.37	0.01
Cortical atrophy		
MTLA-total	0.21	0.16
PVH	0.40	0.005
DWMH	0.47	0.001
RWM	–0.41	0.004
RGM	–0.43	0.003
Average cortical thickness	–0.16	0.29

**Pearson correlation, otherwise Spearman correlation.*
H-Y – Hoehn and Yahr scale, MMSE – Mini-Mental State Examination, MoCA – Montreal Cognitive Assessment, UPDRS-II – Unified Parkinson's Disease Rating Scale total score, part II, UPDRS-III – UDPRS total score, part III, HAM-D – Hamilton Depression Scale, HAM-A – Hamilton Anxiety Scale, FSS – Fatigue Severity Scale, PSQI – Pittsburgh Sleep Quality Index, NMSS – non-motor symptoms, PD – Parkinson's disease, MTLA-total – medial temporal lobe atrophy, total score, PVH – periventricular hyperintensities, DWMH – deep white matter hyperintensities, RWM – relative white matter volume, RGM – relative grey matter volume

Table IV. Factors associated with activities of daily living (ADL)

Independent variables	Dependent variables		
	ADL		
	β (95% CI)	*P*	Adjusted R^2
Model 1			
H-Y stage	4.71 (2.94-6.48)	< 0.001	0.37
RWM	–0.71 (–1.10–-0.32)	0.001	0.14
Age	–0.07 (–0.28-0.20)	0.78	–
NMSS	0.23 (–0.01-0.08)	0.06	–
MoCA	0.11 (–0.29-0.48)	0.45	–
Model 2			
H-Y stage	4.28 (2.34-6.21)	< 0.001	0.37
Age	0.19 (0.06-0.33)	0.006	0.10
RGM	–0.02 (–0.63-0.57)	0.98	–
NMSS	0.18 (–0.02-0.08)	0.18	–
MoCA	0.08 (–0.27-0.50)	0.45	–
Model 3			
H-Y stage	4.28 (2.34-6.21)	< 0.001	0.37
Age	0.19 (0.06-0.33)	0.006	0.10
Average cortical thickness	0.17 (–3.83-24.27)	0.15	–
NMSS	0.15 (–0.02-0.07)	0.18	–
MoCA	0.06 (–0.31-0.47)	0.45	–

H-Y – Hoehn and Yahr scale, MoCA – Montreal Cognitive Assessment, NMSS – non-motor symptoms, RWM – relative white matter volume, RGM – relative grey matter volume

Voxel-based morphometry provides accurate measures of the volumes of grey and white matter, and the average cerebral cortex thickness, as quantitative indices of global brain atrophy. We found that RWM was inversely correlated with the ADL score in PD patients, indicating the important role of white matter impairment in the functional status seen in this group. Cerebral white matter atrophy disrupts pathways involved in functional connectivity in the white matter fibre bundle. Previous studies found that the severity of WMHs was significantly correlated with the total UPDRS score in vascular Parkinsonism patients [6], which suggests that disruption of cortico-subcortical circuits may lead to impaired ADL and motor performance. Lesions in subcortical white matter influence the function of the frontal lobes, and disruption of frontal-subcortical circuits leads to action execution dysfunction [34]; in turn, this impairs ADL. Thus, the integrity of brain networks and structures merits further research in the context of PD patients with ADL impairment. No correlation between RGM and ADL was observed in our PD patients. Neuronal cell death is characterized by subsequent atrophy of grey matter [30]. White matter changes, which reflect axonal degeneration and myelin damage, may be more pertinent to the early stages of PD [3]. Therefore, grey matter atrophy may appear later

in PD patients with impaired ADL. One study found that the UPDRS-III score was correlated with the thickness of the cortex in PD patients [14], suggesting that cortical thickness may play a role in the poor ADL performance seen in PD. However, this was not observed in our study, possibly because most of the cases were in the early stage of PD.

Consistent with a previous study [26], we found that the H-Y stage was the most significant indicator of ADL performance in patients with PD. The H-Y stage reflects the severity of PD and motor impairment; the higher the H-Y stage, the worse the motor function and ADL performance. The NMSS and ADL scores were not significantly correlated in our study, different from previous investigations on depression and cognitive impairment [35,36]. The NMSS is not specifically designed for evaluating non-motor symptoms; we distinguished among different types of non-motor symptoms, but we did not find any associations with the ADL score. A scale specifically designed to assess the severity of different non-motor symptoms is needed. Furthermore, the MoCA and ADL scores of our PD patients were not significantly associated. A study of PD patients without dementia showed that cognitive function was associated with ADL performance [8]. ADL deficits due to cognitive impairment are an essential component of the diagnosis of PD with dementia (PDD) [9]. The PDD group in a previous study had significantly poorer basic ADL performance scores compared with the PD group [7]. The ADL scale covers instrumental ADL, which are related to cognitive function. Prospective studies are needed to determine the relationships between impairments in specific cognitive domains and ADL.

The main strengths of this study were as follows: we analysed complete clinical data, and we used accurate and comprehensive neuroimaging parameters to quantify global brain atrophy (including grey and white matter volumes and cortical thickness). However, the study also had a number of limitations. First, because of the cross-sectional design, the associations between ADL and PD features observed herein should be considered preliminary. Second, we only assessed global, as opposed to local, cortical thickness and grey and white matter atrophy in brain lobes. Third, the sample size was small, which might have reduced the likelihood of finding associations between the factors of interest and ADL score. Finally, the standardization of anatomical MRI images using SPM8 may have affected the measurements to some extent. In future studies, we will compare patients with healthy controls.

Conclusions

In this study, PD staging and cerebral white matter atrophy were associated with the ADL scores of patients with PD. This suggests that the deterioration in the ability to perform ADL seen in PD has a multifactorial origin, with cerebral white matter atrophy potentially playing a key role. Cerebral white matter atrophy may lead to more rapid deterioration in the performance of ADL in PD patients; close follow-up of such patients is required. Prospective studies with larger sample sizes focusing on the white matter fibre bundle are warranted to identify risk factors for poor ADL performance in patients with PD.

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Disclosure

The authors report no conflict of interest.

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