

Cognitive Performance is Associated with Altered Cerebral Hemodynamics Assessed by Transcranial Ultrasound in Parkinson's Disease

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Purpose: Cognitive impairment (CI) is a common but debilitating non-motor symptom in Parkinson's disease (PD). Although cerebrovascular functions are related to cognitive performance in healthy individuals, such a relation in PD remains elusive. This study aims to assess the association between cerebrovascular function and cognitive performance in PD individuals.

Patients and Methods: Two-hundred-and-one PD individuals were retrospectively included. They were subsequently divided into two groups: PD with normal cognition (PD-NC) and PD with CI (PD-CI). Cerebral hemodynamic characteristics of the middle cerebral arteries were assessed by transcranial ultrasound. The association between scores in each cognitive domain and cerebral hemodynamic parameters was further analyzed using regression analyses. Additionally, a binary logistic regression model with backward stepwise procedure was applied to build the model for discriminating CI in PD individuals. An independent dataset of additional 46 PD individuals was used further.

Results: The PD-CI group showed a relatively lower end-diastolic blood flow velocity (EDV, $p < 0.05$) and a higher resistive index (RI, $p < 0.05$) compared to the PD-NC group. RI showed significant associations with the memory item score of Montreal Cognitive Assessment ($p < 0.05$). A model combining clinical and hemodynamic variables was established with optimal efficiency (area under the curve, AUC = 0.651). Further replication of the model in an independent dataset yielded a great consistency (AUC = 0.704).

Conclusion: In our study, cerebrovascular functions were significantly associated with the cognitive performance in PD individuals, especially with the memory task. The established model was effective in identifying CI in PD individuals, which might be a potentially useful tool to screen the cognitive decline in PD individuals at an early stage of the disease. Further studies with larger sample sizes in different populations are warranted.

Keywords: Parkinson's disease, cognitive impairment, transcranial ultrasound, resistive index

Introduction

Although Parkinson's disease (PD) is mainly characterized by motor symptoms, cognitive impairment (CI) in PD can develop at an early stage or even precede the development of motor symptoms with a high prevalence and considerably reduces patients' quality of life.¹⁻³ Large cross-sectional cohorts have unveiled that the prevalence rate of mild cognitive impairment (MCI) is 20.3~64.3%,^{4,5} and approximately 20% of PD individuals with MCI will convert to dementia within three years.⁶ 83% of PD individuals will end up with dementia after 20 years of follow-up, which poses enormous challenges for families and society.⁷

Several studies showed that vascular pathologies frequently occurred in PD individuals, which may contribute to the development of CI.^{8,9} Additionally, a growing body of studies has shed light on the importance of modifiable vascular risk factors on cognitive decline in PD.^{10–12} Therefore, exploring cerebrovascular hemodynamic changes in PD individuals with CI is of vital importance.

Transcranial ultrasound is a commonly used method for disease assessment in PD. Previous studies revealed that PD individuals with cognitive deficits exhibited the enlarged third ventricle¹³ and enhanced substantia nigra echogenicity.¹⁴ Researchers have also found that cerebral small-vessel disease is associated with cognitive decline and motor deterioration in PD.^{15,16} PD patients with vascular risk factors or vascular comorbidities tend to have higher rates of CI, postural instability, and some other non-motor symptoms.¹⁰ However, few studies have demonstrated the relationship between cognitive dysfunctions and cerebrovascular characteristics in PD.

Transcranial ultrasound is a non-invasive and economical tool with accuracy for measuring cerebral hemodynamics in major cerebral arteries.¹⁷ The present study aims to delineate the potential associations between CI in PD individuals and cerebrovascular features. Furthermore, we investigated the relationship between each cognitive domain score of the cognitive assessments and cerebral hemodynamic parameters. Finally, a model for differentiating CI in PD was constructed with logistic regression analyses, and further replication of the model was conducted using an independent dataset.

Methods

Subjects

Two hundred and seventy PD individuals, who fulfilled either the 2015 Movement Disorder Society clinical diagnostic criteria¹⁸ or UK Brain Bank criteria for PD,¹⁹ were recruited consecutively from the Department of Neurology of the Second Affiliated Hospital of Soochow University (Suzhou, China) from April 2012 to May 2019. Thirty-one individuals were excluded from the study due to the insufficient bone window. Six individuals with major depressive symptoms, as assessed by the Hamilton Depression Rating Scale (HAM-D), were excluded.²⁰ All participants went through magnetic resonance imaging on a 3.0-T scanner (Achieva, Philips Healthcare, Best, the Netherlands) and 21 participants with extended white matter lesions were also excluded. Individuals with a medical history of stroke were not enrolled in this study. Eleven PD individuals at an advanced stage with poor compliance were also excluded from the study. In total, a total of 201 individuals were included in the study. In the replication stage, additional 60 PD individuals were recruited to validate our model. Eleven of 60 individuals were excluded due to depressive symptoms, and 3 were excluded because of insufficient bone window. This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University. Data were collected after written informed consent was obtained from all participants.

Clinical Assessment

Motor symptoms were evaluated with Unified Parkinson's Disease Rating Scale (UPDRS) Part III in the "on" state.²¹ Disease severity was assessed with a modified Hoehn & Yahr (H&Y) scale in the "off" state.²² Levodopa equivalent doses (LEDs) of prescribed dopaminergic medications were calculated as previously described.²³ Cognitive performance was assessed by the Mini-Mental State Examination (MMSE)²⁴ and Montreal Cognitive Assessment (MoCA, Beijing version).²⁵ Participants were divided into two groups based on MoCA scores:²⁶ PD with normal cognition (PD-NC) and PD with CI (PD-CI). HAM-D was used for the evaluation of depression in PD individuals.²⁰ All evaluations were performed by trained movement-disorder neurologists who were blinded to the diagnosis of the patients.

Transcranial Ultrasound

Transcranial ultrasound was conducted by our experienced ultrasound practitioners within one week after clinical assessments. The individuals were examined in the supine position. The brain was insonated through the bilateral temporal acoustic bone window in the orbitomeatal line using a transducer (Acuson Sequoia 512, Siemens, Erlangen, Germany) with an emitting frequency of 2 MHz, a wall filter of 150 Hz, and a Doppler angle of 48°. ^{27,28} Blood flow

velocities of the middle cerebral arteries (MCAs), including peak systolic velocity (PSV) and end-diastolic velocity (EDV), were obtained at the depth of 52 to 64 mm, where the hemodynamic signals were the most stable.²⁸ Resistive indexes (RIs) were calculated automatically by the internal algorithm according to the formula $RI = (PSV - EDV) / PSV$.²⁷ The angle of the transducer was varied when needed. These parameters were obtained bilaterally over at least 10 cardiac cycles after a 30s stable period with a clear signal. Transcranial ultrasound was performed in a darkened room by the same experienced clinician who was blinded to the individuals' clinical status to eliminate any bias in the examination results.

Statistical Analysis

All statistical analyses were conducted with IBM SPSS Statistics, version 25.0, 64-bit (IBM Corporation, Armonk, NY, USA). Normality tests were verified using Kolmogorov–Smirnov test or Shapiro–Wilk's test. Quantitative data were compared using Student's *t*-test if normally distributed or non-parametric Mann–Whitney *U*-test if not normally distributed. Categorical variables were compared using chi-square test. Unary linear regression was used to assess the association between scores of specific cognitive domains and cerebral hemodynamic parameters. A binary logistic regression model with backward stepwise procedure was applied to build the model for discriminating CI. Hosmer–Lemeshow test was performed to assess the goodness of fit in logistic regression analyses. Areas under the curves (AUCs) were calculated to estimate the efficiency of our model. All the statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant.

Results

Demographics

In total, 201 PD individuals were included in the study. Of them, 147 were male. The average age was 61.99 ± 10.04 years, and the mean disease duration was 47.46 ± 39.80 months. The mean age at onset was 57.99 ± 10.25 years. No statistically significant difference regarding demographics was found between the PD-NC and PD-CI groups (Table 1).

Cerebral Hemodynamics Were Associated with Cognitive Performance in PD Individuals

We calculated the maximum, minimum and average values of PSV, EDV and RI of bilateral MCAs, and compared these values between the PD-NC and PD-CI groups (Table 2). There was no statistically significant difference between the two groups regarding all the PSV parameters. However, the maximum, minimum and average EDV values were significantly lower in the PD-CI group than in the PD-NC group ($p = 0.008$ for maximum, $p = 0.032$ for minimum and $p = 0.008$ for

Table 1 Demographic Characteristics of PD Individuals with/Without Cognitive Impairment

	PD-NC (n = 101)	PD-CI (n = 100)	<i>p</i>
Gender (male, %)	71 (70.3%)	76 (76.0%)	0.427
Age (years, $\bar{x} \pm SD$)	61.07 ± 10.94	62.92 ± 9.00	0.374
Disease duration (years, $\bar{x} \pm SD$)	47.11 ± 39.82	47.81 ± 39.97	0.871
Age at onset (years, $\bar{x} \pm SD$)	57.08 ± 11.05	58.91 ± 9.34	0.384
Education (years, $\bar{x} \pm SD$)	9.18 ± 5.37	9.53 ± 3.06	0.732
LED (mg, $\bar{x} \pm SD$)	379.54 ± 236.99	430.41 ± 243.83	0.077
UPDRS-III ($\bar{x} \pm SD$)	19.89 ± 10.51	23.10 ± 11.27	0.053
MMSE ($\bar{x} \pm SD$)	27.79 ± 2.64	25.66 ± 4.01	<0.001***
MoCA ($\bar{x} \pm SD$)	24.64 ± 3.74	18.69 ± 4.68	<0.001***

Note: ***Denotes $p < 0.001$.

Abbreviations: PD, Parkinson's Disease; PD-NC, Parkinson's Disease with Normal Cognition; PD-CI, Parkinson's Disease with Cognitive Impairment; SD, Standard Deviation; LED, Levodopa Equivalent Dose; UPDRS-III, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

Table 2 Cerebral Hemodynamic Parameters in PD Patients with/Without Cognitive Impairment

	PD-NC (n = 101)	PD-CI (n = 100)	p
Maximum PSV ($\bar{x} \pm SD$)	89.59 \pm 22.20	84.27 \pm 19.91	0.133
Minimum PSV ($\bar{x} \pm SD$)	75.11 \pm 19.28	71.90 \pm 18.74	0.236
Average PSV ($\bar{x} \pm SD$)	82.35 \pm 19.82	78.09 \pm 18.58	0.162
Maximum EDV ($\bar{x} \pm SD$)	39.27 \pm 12.75	35.12 \pm 9.08	0.008**
minimum EDV ($\bar{x} \pm SD$)	31.57 \pm 10.50	28.62 \pm 7.81	0.032*
Average EDV ($\bar{x} \pm SD$)	35.42 \pm 11.09	31.87 \pm 7.97	0.008**
Maximum RI ($\bar{x} \pm SD$)	0.60 \pm 0.07	0.61 \pm 0.06	0.070
Minimum RI ($\bar{x} \pm SD$)	0.55 \pm 0.06	0.56 \pm 0.06	0.026*
Average RI ($\bar{x} \pm SD$)	0.57 \pm 0.07	0.59 \pm 0.06	0.031*

Notes: Maximum refers to the maximum value of the both sides, minimum refers to the minimum value of the both sides, average refers to the average value of the both sides (eg, "maximum PSV" means the maximum value of the peak systolic blood flow velocity in either left middle cerebral artery or right middle cerebral artery). *Denotes $p < 0.05$, **Denotes $p < 0.01$.

Abbreviations: PD, Parkinson's Disease; PD-NC, Parkinson's Disease with Normal Cognition; PD-CI, Parkinson's Disease with Cognitive Impairment; PSV, Peak Systolic Velocity of blood flow in middle cerebral artery; EDV, End Diastolic Velocity of blood flow in middle cerebral artery; RI, Resistive Index.

average, respectively) (Table 2). Additionally, the PD-CI group showed a significantly higher minimum and average RI than the PD-NC group ($p = 0.026$ for minimum, $p = 0.031$ for average, respectively) (Table 2).

Cerebral Hemodynamics Were Associated with Short-Term Memory in PD Individuals

For cognitive domains, all item scores were poorer in the PD-CI group, while the most significant difference was in the memory task (delayed recall) score (Supplementary Material 1). Negative correlations were observed between RI and memory task score of MoCA ($p = 0.002$ for minimum RI of the both sides; $p = 0.003$ for average) (Table 3). However, there was no association between RI and other cognitive domains assessed with MoCA (Table 3).

There was no statistically significant difference between EDV values and each cognitive domain evaluated with MoCA in PD individuals (Table 4). However, a potentially positive correlation was observed between the memory task score of MoCA and average EDV, albeit without reaching statistical significance ($p = 0.068$ for average bottom velocity) (Table 4).

Development and Validation of the Model in Identifying Cognitive Impairment in PD Individuals

We used the five hemodynamic parameters, respectively, as independent predictors for CI but yielded limited effectiveness (Figure 1). We then developed a model using binary logistic regression analyses for discriminating CI in PD individuals. Additionally, the stepwise (backward) logistic regression procedure was applied to exclude covariates with less significance or collinearity (Table 5). Finally, the model exhibited acceptable goodness of fit (Hosmer-Lemeshow, $p > 0.05$) with an AUC of 0.651 (95% CI 0.576–0.727) (Figure 2). Further validation of this model on an additional independent dataset of 46 PD individuals yielded optimal efficiency with an AUC of 0.704 (95% CI 0.551–0.858) (Figure 3).

Discussion

In this study, we evaluated the association between cerebrovascular functions assessed by transcranial Doppler (TCD) and cognitive performance in PD individuals. Our findings showed that PD individuals with cognitive impairment exhibited significantly lower EDV values and higher RI values compared to the PD-NC group. Furthermore, our study showed an inverse correlation between RI and memory index score of MoCA in PD individuals. Additionally, a model combining the clinical and hemodynamic parameters was constructed for discriminating CI in PD.

Table 3 Unary Linear Regression Analyses Between RI and 7 Independent Cognitive Domains of MoCA in PD Patients

Cognitive Domains		Visuospatial/Executive	Naming	Attention	Language	Abstraction	Memory	Orientation
Minimum RI	B	0.508	0.981	0.444	0.478	1.139	-6.046	-1.482
	p	0.745	0.273	0.763	0.680	0.203	0.002**	0.167
	95% CI for B	-2.569 to 3.586	-0.778 to 2.740	-2.458 to 3.347	-1.806 to 2.762	-0.619 to 2.896	-9.784 to -2.307	-3.587 to 0.623
Average RI	B	1.085	1.266	0.400	0.505	1.046	-5.797	-1.108
	p	0.491	0.160	0.788	0.666	0.246	0.003**	0.306
	95% CI for B	-2.015 to 4.184	-0.504 to 3.037	-2.526 to 3.327	-1.798 to 2.807	-0.727 to 2.819	-9.575 to -2.019	-3.235 to 1.019

Note: **Denotes $p < 0.01$.

Abbreviations: RI, Resistive Index; MoCA, Montreal Cognitive Assessment; PD, Parkinson's Disease; CI, Confidence interval; B, regression coefficient.

Table 4 Unary Linear Regression Analyses Between EDV and 7 Independent Cognitive Domains of MoCA in PD Individuals

Cognitive Domains		Visuospatial/Executive	Naming	Attention	Language	Abstraction	Memory	Orientation
Maximum EDV	B	0.003	−0.003	0.002	0.009	−0.004	0.019	0.006
	p	0.696	0.583	0.789	0.169	0.461	0.08	0.344
	95% CI for B	−0.014 to 0.021	−0.013 to 0.007	−0.014 to 0.018	−0.004 to 0.022	−0.014 to 0.006	−0.002 to 0.040	−0.006 to 0.017
Minimum EDV	B	0.002	0.001	0.009	0.012	−0.005	0.022	0.007
	p	0.84	0.931	0.384	0.123	0.441	0.086	0.301
	95% CI for B	−0.019 to 0.023	−0.011 to 0.012	−0.011 to 0.028	−0.003 to 0.027	−0.017 to 0.007	−0.003 to 0.048	−0.007 to 0.022
Average EDV	B	0.003	−0.002	0.005	0.011	−0.005	0.023	0.007
	p	0.749	0.785	0.569	0.127	0.429	0.068	0.3
	95% CI for B	−0.017 to 0.023	−0.013 to 0.010	−0.013 to 0.024	−0.003 to 0.026	−0.016 to 0.007	−0.002 to 0.047	−0.006 to 0.021

Abbreviations: EDV, End-Diastolic Velocity of blood flow in middle cerebral artery; MoCA, Montreal Cognitive Assessment; PD, Parkinson’s Disease; CI, Confidence Interval; B, regression coefficient.

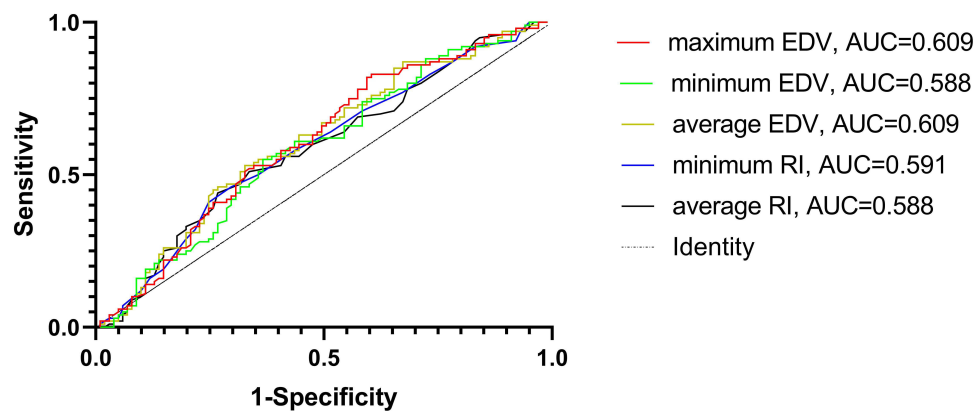


Figure 1 The Receiver operating characteristic plots using five hemodynamic parameters respectively as independent predictors for CI.

Abbreviation: CI, cognitive impairment.

Our study demonstrated that the PD-CI group exhibited lower EDV values than the PD-NC group, while there was no significant difference in PSV parameters between the two groups. The different changes in EDV and PSV reflect increased blood flow velocity variability. The alteration of blood flow velocity variability might be a cause or consequence of cognitive impairments related to vascular pathology or neuropathology. In fact, it remains elusive whether the result is secondary to the decreased metabolic demand in PD individuals with cognitive deficits or whether the altered variation in blood flow velocity leads to the recurrent and chronic cerebral hypoperfusion, which further causes neuronal damage or dysfunction in vulnerable areas like the hippocampus, thereby causing cognitive decline in PD. However, the latter one, also known as the vascular hypothesis, is supported by longitudinal studies showing that increasing volume of white matter hyperintensities was associated with a performance decline in cognitive tests in the healthy elderly.^{29,30} Of note, previous research has provided other potential mechanisms responsible for the cognitive decline in PD, including energy deficiency in neurons,^{31,32} free radical mediated injury,^{33–36} synaptic changes^{37–40} and microinfarcts.^{41,42}

Meanwhile, some studies reported that the autonomic denervation associated with parkinsonism further led to compromised vascular autoregulatory capacity.⁴³ Therefore, our findings may support the hypothesis that the decreased capacity of cerebrovascular autoregulation could lead to cognitive decline through cerebral hypoperfusion in PD.

Table 5 Binary Logistic Regression Analyses of Cognitive Impairment in 201 PD Individuals

	Regression Coefficient	<i>p</i>	Exp(B)	95% CI
Age	−0.087	0.129	0.92	0.82 to 1.03
Age at onset	0.081	0.132	1.08	0.98 to 1.21
Education	0.026	0.453	1.03	0.96 to 1.10
LED	0.001	0.274	1.00	1.00 to 1.00
UPDRS-III	0.017	0.335	1.02	0.98 to 1.05
H&Y stage	0.319	0.295	1.38	0.76 to 2.50
Maximum EDV	−0.022	0.640	0.98	0.89 to 1.07
Average EDV	−0.003	0.957	1.00	0.90 to 1.11
Minimum RI	2.552	0.402	12.83	0.03 to 4994.86
Constant	−1.359	0.500	0.26	

Note: Maximum refers to the maximum value of the both sides, minimum refers to the minimum value of the both sides, average refers to the average value of the both sides (eg, “maximum EDV” means the maximum value of the end-diastolic blood flow velocity in either left middle cerebral artery or right middle cerebral artery).

Abbreviations: PD, Parkinson’s Disease; LED, Levodopa Equivalent Dose; UPDRS-III, Unified Parkinson’s Disease Rating Scale; H&Y stage, Hoehn and Yahr stage; EDV, End Diastolic Velocity of blood flow in middle cerebral artery; RI, Resistive Index.

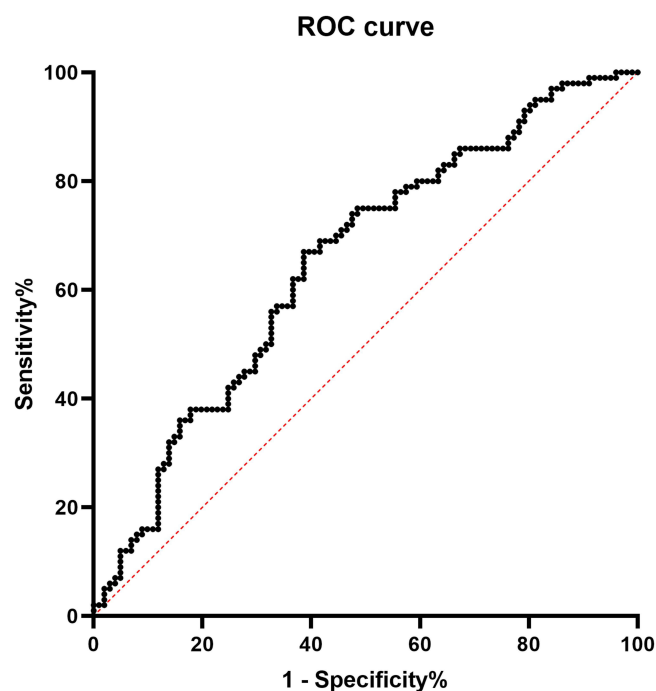


Figure 2 The Receiver operating characteristic plots based on logistic regression analyses of cognition impairment in 201 PD. AUC = 0.651 [95% CI = 0.576 to 0.727], $p < 0.001$.

Abbreviations: PD, Parkinson's disease; AUC, area under the curve.

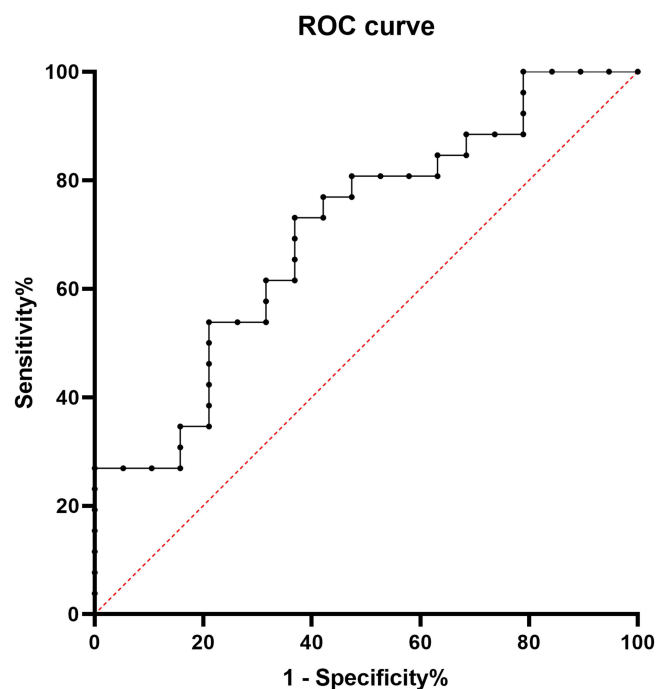


Figure 3 The Receiver operating characteristic plots of validation of the model for discriminating cognition impairment in 46 PD. AUC = 0.704 [95% CI = 0.551 to 0.858], $p = 0.020$.

Abbreviations: PD, Parkinson's disease; AUC, area under the curve.

Our investigation showed that RI values in the PD-CI group were significantly higher than those in the PD-NC group. RI, a conclusive parameter that incorporates systolic and diastolic blood flow velocities, represents the stiffness of arterial vessel walls and vascular compliance or responsiveness to dilatory stimulation in the microvascular bed.^{27,44} With the increase in peripheral resistance as implicated by higher RI, the EDV values should show a decline theoretically, which is consistent with our findings. RI can be a proxy marker for hypoperfusion that causes neuronal damage or dysfunction and further contributes to cognitive decline, which has been suggested as a possible mechanism for CI concerning atherosclerosis.^{45,46}

In addition, this study reported that RI was significantly associated with the memory index score of MoCA in PD individuals, concurring with prior studies that found higher RI was associated with steeper decline in intelligence.⁴⁴ Most research has reported that PD individuals commonly exhibited fronto-striatal deficits with executive dysfunctions being the most prominent manifestation,⁴⁷ while 40% of PD individuals presented cognitive impairments in memory, language and visuospatial abilities.⁴⁸ In this study, we failed to find an association between cerebral hemodynamic parameters and executive dysfunction in PD individuals. One possible explanation for this might be the limited sample size available. Moreover, executive functions and visuospatial abilities were assessed together with MoCA scale, which may impact statistical results. Furthermore, the mechanisms that probably underlie the deficits in memory and executive functions in PD may differ.

Moreover, our study indicated that age, age at onset, education, LED, UPDRS-III, H&Y stage, maximum EDV, average EDV and minimum RI were independently associated with cognitive impairment in PD. Previous studies showed that mild cognitive impairment in PD was associated with older age, lower education, longer disease duration, higher LED and more severe motor symptoms,⁴⁹ which is in line with our results. However, for the first time, our study showed that cerebral hemodynamic parameters were associated with cognitive decline in PD and further constructed a concise and precise model combining the clinical and hemodynamic parameters for discriminating or predicting of cognitive impairment in PD, which might be a potentially practical tool for detection of cognitive decline in PD.

To our knowledge, this is the first study investigating the association between cerebrovascular characteristics indicated by transcranial ultrasound and CI in PD. This study has confirmed the hypothesis that vascular factors are associated with cognition in order to explain the difference in PD phenotypes, which is in accordance with previous studies.¹⁷ In addition, we provided an effective tool that is helpful for the discrimination of CI in PD.

However, our study has some limitations. First, the major drawback of our study is the lack of longitudinal data, which may provide evidence for a potentially causal relationship between cerebral hemodynamics and CI. Secondly, the sample size is relatively small. Further studies with larger sample sizes in different populations are warranted.

Conclusion

In our study, cerebrovascular functions were significantly associated with cognitive performance in PD individuals, especially with memory performance. The established model was effective in identifying CI in PD individuals, which may be a potentially useful tool to screen cognitive decline in PD individuals at an early stage of the disease. Our observations collectively suggest that subsequent studies should include vascular parameters to balance the effect of vascular factors. Further longitudinal studies with larger sample sizes in different populations are warranted.

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Disclosure

None of the authors have any conflicts of interest to report in this work.

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