Differential Changes in Arteriolar Cerebral Blood Volume between Parkinson's Disease Patients with Normal and Impaired Cognition and Mild Cognitive Impairment (MCI) Patients without Movement Disorder – An Exploratory Study

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Abbreviations: Parkinson's disease (PD), mild cognitive impairment (MCI), arteriolar cerebral blood volume (CBVa), PD dementia (PDD), cerebral blood flow (CBF), presupplementary motor area (preSMA), inflow-based vascular-space-occupancy (iVASO), gray matter (GM), time of repetition (TR), time of inversion (TI), statistical parametric mapping (SPM), signal-to-noise ratio (SNR), magnetic resonance imaging (MRI), Unified Parkinson's Disease Rating Scale (UPRDS)

ABSTRACT

Cognitive impairment amongst Parkinson's disease (PD) patients is highly prevalent and associated with an increased risk of dementia. There is growing evidence that altered cerebrovascular functions contribute to cognitive impairment. Few studies have compared cerebrovascular changes in PD patients with normal and impaired cognition and those with mild-cognitive-impairment (MCI) without movement disorder. Here, we investigated arteriolar-cerebral-blood-volume (CBVa), an index reflecting the homeostasis of the most actively regulated segment in the microvasculature, using advanced MRI in various brain regions in PD and MCI patients and matched controls. Our goal is to find brain regions with altered CBVa that are specific to PD with normal and impaired cognition, and MCI-without-movement-disorder, respectively. In PD patients with normal cognition (n=10), CBVa was significantly decreased in the substantia nigra, caudate and putamen when compared to controls. In PD patients with impaired cognition (n=6), CBVa showed a decreasing trend in the substantia nigra, caudate and putamen, but was significantly increased in the presupplementary motor area and intracalcarine gyrus compared to controls. In MCI-patients-without-movement-disorder (n=18), CBVa was significantly increased in the caudate, putamen, hippocampus and lingual gyrus compared to controls. These findings provide important information for efforts towards developing biomarkers for the evaluation of potential risk of PD dementia (PDD) in PD patients. The current study is limited in sample size and therefore is exploratory in nature. The data from this pilot study will serve as the basis for power analysis for subsequent studies to further investigate and validate the current findings.

INTRODUCTION

Parkinson's disease (PD) is defined by its characteristic motor symptoms of bradykinesia, rigidity, and tremors. However, non-motor symptoms such as cognitive impairment are frequently reported in PD, with more than one-third of patients showing signs of impairment in at least one cognitive domain at the time of diagnosis with PD (1). Gaining a better understanding of the mechanistic underpinnings of cognitive impairment is important, as cognitive impairment is associated with accelerated functional decline and neuropsychiatric symptoms including anxiety and depression, and the risk of progression to dementia is over four times greater in PD patients with cognitive impairment than in PD patients with normal cognition (2, 3). Despite significant efforts, currently there is no robust measure to predict which patients with PD are at the greatest risk of developing PD dementia (PDD).

Cognitive impairment in PD is likely due to the presence of pathologic alpha-synuclein in the cortex, although in ~30% of individuals, there is additional amyloid and tau pathology (4–6). There is also growing evidence that cerebrovascular disease is an

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important contributor to cognitive impairment. Cerebrovascular abnormalities including altered cerebral blood flow (CBF), cerebral blood volume (CBV), and blood–brain barrier permeability (7–10) have been linked with pathophysiology in various dementias (11, 12). Following those reports(13), we previously used advanced neuroimaging methods to show increased volumes of small pial arteries and arterioles (arteriolar cerebral blood volume, CBVa) in several brain regions such as the orbitofrontal cortex and the hippocampus in elderly adults with mild cognitive impairment (MCI) compared with the volumes of those in age-matched elderly controls. Cerebral vascular risk factors have also been associated with PDD. Within PDD, there is growing recognition regarding the importance of vascular pathology. Among individuals in the Parkinson's Progression Markers Initiative cohort, we found that the rate of change in measures of global cognition was greater among those with white matter hyperintensities on magnetic resonance imaging (MRI) (14). Altered CBF, CBV, and microvasculature have also been shown in patients with PD (15–23). However, to date, few studies have examined and compared cerebrovascular changes in PD patients with normal cognition, PD patients with impaired cognition, and MCI due to Alzheimer's disease.

PD-related cognitive impairment and AD-related cognitive impairment manifest differently (24), with the former being a subcortical dementia and the latter a cortical dementia (25–28). The type and regional distribution of pathology differ between PD and AD. The pathognomonic changes in PD include loss of pigmented dopaminergic cells and presence of Lewy bodies in the substantia nigra (29, 30). Dopamine loss changes the relationship within the basal ganglia pathways and subsequently changes the signaling between the basal ganglia and the cortex, leading to motor and some executive dysfunctions observed in individuals with PD (31). Indeed, multiple studies have shown small blood vessel damage in patients with PD, mainly in the substantia nigra, caudate, and putamen (15–23). The presupplementary motor area (preSMA) receives significant inputs from the basal ganglia and, in individuals with PD, significant atrophy (32), metabolic changes (33), and hypoactivation (34) have been observed in their preSMA. These are considered to be markers of changes in motor planning and not cognitive change per se. Although hypoactivation and atrophy in the entorhinal cortex, hippocampus, parahippocampus, and posterior cingulate gyrus have been identified in individuals with AD (26–28, 35) and in those with PD-related cognitive changes (36–38), other brain regions including the intracalcarine gyrus (39), thalamus (40), and lingual gyrus (41) appear to subserve PD-related cognitive impairment than AD-related amnestic MCI. Still other areas such as the nucleus accumbens (26–28, 42, 43) are affected primarily in AD-type dementia than in PD-related cognitive impairment. Different patterns of neuronal loss were reported in the nucleus basalis of Meynert in AD, PD, and PDD (44).

In this study, we used the inflow-based vascular-space-occupancy (iVASO) MRI approach (45–50) to determine potential arteriolar abnormalities (CBVa) in the brain in a cohort of patients with PD and matched controls and in a cohort of MCI patients without movement disorders and matched controls. Pial arteries and arterioles are the most actively regulated blood vessels (51–55) and are affected by aging before venous vessels (56). Therefore, the measurement of changes in CBVa may provide a more sensitive marker than measurement of changes in total CBV and CBF, which include both arteriolar and venous vessels. Hua et al. (13) have previously reported on the MCI without movement disorder cohort and their data has been reanalyzed here with a different approach (see Methods). Based on the literature discussed previously, CBVa in preselected brain regions was calculated and compared in patients and matched controls in each cohort, with the goal of finding brain regions with altered CBVa that are specific to PD with normal cognition, PD with impaired cognition, and MCI without movement disorder.

METHODS

Study Participants

In total, 2 cohorts of participants were recruited for this study. The first cohort includes 10 PD patients with normal cognition, 6 PD patients with impaired cognition, and 7 healthy controls matched in age, sex, and education level. All patients with PD had a clinically established or clinically probable PD diagnosis according to the criteria described in the study by Postuma et al. (57). The Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (58, 59) was used as a key part to evaluate clinical symptoms. All participants were recruited through the Johns Hopkins Parkinson's Disease and Movement Disorders Center. This study has been approved by the Johns Hopkins Institutional Review Boards. Demographic data for this PD cohort are summarized in Table 1.

The second cohort consists of 18 MCI patients without movement disorder and 22 age-, sex-, and education-matched cognitively normal controls. This second cohort was recruited at the University of Zurich, Switzerland. The current study uses recently published MRI and clinical data of this cohort (13). The published MRI data was reanalyzed using a different method in the current study (see Data Analysis). As reported earlier, the study procedures were in accordance with guidelines issued by the local ethics committee (Kantonale Ethikkommission Zürich), as well as with the Declaration of Helsinki (60). Demographic data for this MCI without movement disorder cohort are summarized in Table 2 [data indicated in Table 2 has been published recently in (13)].

In both cohorts, each participant gave written informed consent for their participation. Each participant completed an MRI session on a 7T human MRI system and received a cognitive assessment (see Cognitive Assessment). None of the participants had other neurologic disorders or met *Diagnostic and Statistical Manual-5* criteria for psychiatric disorders.

Cognitive Assessment

All participants completed a cognitive assessment. All cognitive tests were administered and scored according to standardized procedures. The cognitive battery for the PD cohort consists of the following tests:

(1) The Logical Memory Subset of the Wechsler Memory Scale (WMS–III) (62)

Table 1. Demographic Data and Clinical and Cognitive Assessment of the Parkinson's Disease (PD) Cohorts

				P[a]			
	Controls (Con)	PD Cognitive Normal (PDcn)	PD Cognitive Impaired (PDci)	Overall	PDcn vs Con	PDci vs Con	PDci vs PDcn
Demographics							
N	7	10	6	N/A	N/A	N/A	N/A
Sex (female)	4	5	3	.95	.77	.80	1
Age (years)	59.86 ± 6.09[b]	64.90 ± 7.85	66.33 ± 10.37	.32	.16	.22	.78
Education (years)	15.71 ± 2.69	17.20 ± 1.40	16.50 ± 3.21	.46	.22	.65	.63
Disease Duration (years)	N/A	2.80 ± 1.34	3.36 ± 1.41	N/A	N/A	N/A	.45
Unified Parkinson's Disease Rating Scale							
Motor	N/A	25.11 ± 8.09	27.02 ± 6.33	N/A	N/A	N/A	.55
Neuropsychological Assessment							
Logical Memory Subset of the Wechsler Memory Scale	26.75 ± 6.80	27.30 ± 4.19	19.00 ± 5.57	.02	.80	.05	.02
Logical Memory Subset of the Wechsler Memory Scale Recall	25.00 ± 5.29	25.20 ± 4.47	11.60 ± 7.06	.001	.95	.01	.009
Controlled Oral Word Association Test	88.50 ± 16.20	97.30 ± 12.92	70.00 ± 15.76	.007	.108	.04	.01
HVLT-R Learning Trials	22.00 ± 6.32	23.90 ± 5.00	14.80 ± 4.32	.02	.62	.05	.005
HVLT-R Recall	6.75 ± 2.63	7.40 ± 3.66	3.60 ± 2.88	.14	.72	.13	.05
60-Item Boston Naming Test	51.67 ± 3.51	52.30 ± 1.34	53.80 ± 6.22	.06	.08	.06	.08
Longest Digit Span Forward	6.75 ± 9.00	6.70 ± 1.83	7.00 ± 2.00	.95	.95	.81	.79
Longest Digit Span Backward	5.00 ± 7.00	5.70 ± 1.34	4.60 ± 1.34	.25	.13	.54	.17

Please see Methods on details regarding the test applied.
[a] *P* values were derived with the ANOVA, chi-square test, or *t* test, as appropriate.
[b] mean ± standard deviation.

(2) Controlled Oral Word Association Test (COWAT) (62)
(3) Hopkins Verbal Learning Test–Revised (HVLT-R) (62)
(4) The 60-item Boston Naming Test–2nd Edition (BNT-60) (62)
(5) Digit Span Forward and Backward (63).

Individuals were classified as either PD with normal cognition or PD with impaired cognition according to the Level 1 classification outlined by Litvan et al. (64). In particular, individuals with impairment on at least 2 tests were stratified to the PD with impaired cognition group.

In the MCI without movement disorder cohort, the following cognitive tests were performed:

(1) The Mini-Mental State Exam (MMSE)
(2) The Revised Boston Naming Test (BNT-15) (65)
(3) Digit Span Backward (63)
(4) Trail Making Test (TMT) (66)
(5) Verbal Learning and Memory Test (VLMT) (67).

Participants were categorized as cognitively normal or cognitively impaired according to established criteria (61).

MRI

Participants in both cohorts underwent a 7T MRI scan (Philips MRI scanner; Philips Healthcare, Best, The Netherlands). The hardware and software on the 7T MRI systems at both sites were identical. A 32-channel phased-array head coil (Nova Medical, Wilmington, MA) was used for radiofrequency reception and a head-only quadrature coil for transmittal. High-resolution anatomical images were acquired with a 3D Magnetization Prepared RApid Gradient Echo (MPRAGE) sequence (voxel = 0.75 mm isotropic) (68, 69). A 3D iVASO MRI scan covering the entire brain (13, 70, 71) was performed to measure regional gray matter (GM) CBVa using the following parameters: time of repetition (TR)/time of inversion (TI) = 10 000/1383, 5000/1093, 3800/884, 3100/714, 2500/533, and 2000/356 millisecond; voxel = $3.5 \times 3.5 \times 5$ mm^3, slices = 20; and parallel imaging acceleration (SENSE) = 2×2. A reference scan (TR = 20 seconds, other parameters identical) was obtained so that the scaling factor M0 in iVASO images can be determined to calculate absolute CBVa values.

Data Analysis

The statistical parametric mapping (SPM) software package (Version 8, Wellcome Trust Centre for Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/) and other in-house code programmed in Matlab (MathWorks, Natick, MA) were used for image analyses. Motion correction in iVASO images, coregistration between anatomical and iVASO images, and normalization to the Montreal Neurological Institute space were performed using SPM. Regional GM CBVa maps in the whole brain were calculated from the iVASO signals after

Table 2. Demographic Data and Clinical and Cognitive Assessment of the Age-Related MCI Patients Without Movement Disorder

	Controls	Age-Related MCI Patients Without Movement Disorder	P[a]
Demographics			
N	22	18	N/A
Sex (female)	8	6	1
Age (year)	72 ± 5[b]	75 ± 7	.08
Education (year)	13.64 ± 2.56	15.06 ± 3.28	.13
Number of APOE4 Alleles	7	9	N/A
Neuropsychological Assessment			
Mini-Mental State Exam	29.45 ± 0.86	28.44 ± 1.42	.01
15-Item Boston Naming Test	14.41 ± 0.73	14.17 ± 1.25	.47
Digit Span Backward	6.27 ± 1.39	5.94 ± 1.76	.52
Verbal Learning and Memory	11.05 ± 2.57	5.39 ± 2.93	<0.001
Trail Making B/A	2.98 ± 1.37	2.75 ± 1.40	.62

Please see Methods on details regarding the test applied; Data indicated in Table 2 have been published recently in (13).
[a]*P* values from 2-sample *t* tests between the 2 groups, or from chi-square test for categorical variables.
[b]mean ± standard deviation.

surround subtraction (72) based on the iVASO equations [73]. GM, white matter, and cerebrospinal fluid maps generated from the anatomical images using the SPM segmentation algorithm were applied to correct for the partial volume effects of white matter and cerebrospinal fluid on the iVASO difference signal in GM (74). A signal-to-noise ratio (SNR) threshold of one standard deviation below the mean SNR was applied to exclude low SNR voxels from further analysis (73).

The IBASPM116 atlas (75–79) (PickAtlas software, Wake Forest University, NC) was used to identify the preselected anatomical regions based on the literature reviewed in the Introduction, from which average CBVa values were calculated. Group differences in GM CBVa in each region were examined using analysis of covariance with age, sex, education, regional GM volume from anatomical scans, and motion parameters estimated from the motion correction routine in SPM as covariates in the analysis. Effect size was estimated with Cohen's *d*. All statistical tests were corrected for multiple comparisons by controlling the false discovery rate (adjusted $P < .05$) (80). Note that data from all patients and their corresponding control participants were acquired at the same site and no statistical comparison between the data acquired from different sites was performed in this study.

Note that the current study adopted a region of interest–based analysis strategy to test our hypotheses in preselected brain regions based on literature. CBVa in each brain region identified on magnetic resonance images using the IBASPM116 atlas was averaged and compared. This result is different from that of our previous study on the MCI without movement disorder cohort (13), in which CBVa was compared across the brain on a voxel basis and significant clusters of altered CBVa were identified. CBVa in each cluster within each brain region (which may not cover the entire region) was averaged and compared.

RESULTS

Demographic data for the PD cohorts are summarized in Table 1. Age, sex, and education levels were matched among PD patients with normal or impaired cognition and controls ($P > .1$). Disease duration and UPDRS motor score were matched among PD patients with normal or impaired cognition ($P = .45, .55$). Significant deficits were observed in PD patients with impaired cognition compared with the other 2 groups in the following tests: Logical Memory Subset of the Wechsler Memory Scale ($P = .02$), Controlled Oral Word Association Test ($P = .007$), and HVLT-R ($P = .02$); and trending significant in BNT-60 ($P = .06$).

Demographic data for the MCI without movement disorder cohort are summarized in Table 2. Individuals with MCI and controls in this cohort had matched age, sex, and education levels ($P > .1$). Patients with MCI showed significantly lower scores compared with controls on the Verbal Learning And Memory Test ($P < .001$) and Mini-Mental State Exam ($P = .01$).

The main findings in CBVa changes are summarized in Tables 3–5, and in Figure 1. The CBVa values in controls in all brain regions investigated were in the normal range of CBVa reported for healthy human subjects in the literature (81).

In PD patients with normal cognition (n = 10), CBVa was significantly decreased in the substantia nigra ($P = .04$), caudate ($P = .04$), and putamen ($P = .01$) compared with controls (n = 7), but comparable with controls in all the other regions investigated.

In PD patients with impaired cognition (n = 6), CBVa showed a trend toward decrease in the substantia nigra ($P = .06$), caudate ($P = .09$), and putamen ($P = .06$) compared with controls (n = 7). CBVa was significantly increased in the preSMA ($P = .01$) and intracalcarine gyrus ($P = .03$) compared with controls, and it also showed a trend toward increase in the hippocampus ($P = .07$), entorhinal cortex ($P = .09$), and parahippocampus ($P = .07$).

Table 3. Altered Gray Matter CBVa in PD Patients Compared With Controls—CBVa Values in Each Brain Region

Regions	Control (n = 7)		PD Cognitive Normal (n = 10)		PD Cognitive Impaired (n = 6)	
	Mean	SD	Mean	SD	Mean	SD
Substantia Nigra	0.90	0.15	0.63	0.22	0.63	0.31
Caudate	0.90	0.05	0.76	0.26	0.71	0.26
Putamen	0.90	0.09	0.63	0.20	0.63	0.32
Nucleus Accumbens	0.89	0.06	0.85	0.19	0.92	0.07
Posterior Cingulate Cortex	0.93	0.04	0.87	0.20	0.96	0.07
Hippocampus	0.91	0.08	0.90	0.13	1.01	0.12
Entorhinal Cortex	1.00	0.06	1.01	0.05	1.33	0.46
Parahippocampus	0.99	0.10	1.01	0.07	1.35	0.46
Presupplementary Motor Area	1.10	0.08	1.06	0.12	1.34	0.13
Thalamus	0.99	0.09	0.97	0.04	1.09	0.15
Intracalcarine Gyrus	1.08	0.09	1.14	0.45	1.50	0.37
Lingual Gyrus	1.04	0.03	1.04	0.16	1.20	0.24
Nucleus Basalis of Meynert	1.00	0.03	1.02	0.07	1.03	0.09
Cerebellum	1.03	0.01	1.01	0.08	1.04	0.07

In MCI patients without movement disorder (n = 18), CBVa was significantly increased in the caudate ($P = .04$), putamen ($P = .05$), hippocampus ($P = .02$), and lingual gyrus ($P = .05$) compared with controls (n = 22). CBVa showed a trend toward increase in the nucleus accumbens ($P = .08$), posterior cingulate cortex ($P = .06$), entorhinal cortex ($P = .06$), and parahippocampus ($P = .06$).

In all patients with PD and MCI, the CBVa values in the cerebellum were not significantly different from those in controls in the respective cohorts.

Table 4. Altered Gray Matter CBVa in PD Patients Compared With Controls—Statistical Results

Regions	PD Cognitive Normal vs Control					PD Cognitive Impaired vs Control					PD Cognitive Impaired vs PD Cognitive Normal				
	Relative Change (%)[a]	Effect Size[b]	*P*	*t*	df[c]	Relative Change (%)	Effect Size	*P*	*t*	df	Relative Change (%)	Effect Size	*P*	*t*	df
Substantia Nigra	−29.56%	−1.31	.04	−4.32	12	−29.63%	−1.01	.06	−3.04	11	−0.11%	0.01	.99	−0.01	11
Caudate	−14.86%	−0.57	.04	−2.90	15	−20.30%	−0.84	.09	−2.86	10	−6.39%	−0.19	.55	−0.65	12
Putamen	−29.78%	−1.45	.01	−5.96	14	−29.63%	−1.00	.06	−3.29	11	0.21%	0.01	.99	0.02	11
Nucleus Accumbens	−4.04%	−0.21	.38	−0.96	15	3.75%	0.50	.31	1.28	10	8.12%	0.44	.10	1.94	14
Posterior Cingulate Cortex	−6.38%	−0.32	.17	−1.60	15	3.34%	0.48	.27	1.37	11	10.38%	0.54	.06	2.38	14
Hippocampus	−0.99%	−0.08	.80	−0.28	13	11.97%	1.01	.07	2.86	11	13.10%	0.94	.03	3.31	12
Entorhinal Cortex	1.24%	0.23	.65	0.57	11	32.67%	0.88	.09	2.99	10	31.04%	1.14	.10	2.92	10
Parahippocampus	1.96%	0.24	.68	0.53	11	35.36%	0.93	.07	3.10	10	32.75%	1.19	.09	3.06	10
Presupplementary Motor Area	−3.45%	−0.33	.34	−1.18	12	22.37%	2.14	.01	6.21	11	26.75%	2.28	.01	7.73	12
Thalamus	−1.58%	−0.28	.69	−0.51	11	10.48%	0.79	.11	2.27	11	12.25%	1.25	.07	3.35	10
Intracalcarine Gyrus	5.67%	0.15	.48	0.76	15	38.86%	1.36	.03	4.51	10	31.40%	0.85	.03	3.11	13
Lingual Gyrus	0.05%	0.00	.99	0.02	15	15.38%	0.80	.11	2.73	10	15.33%	0.82	.09	2.51	11
Nucleus Basalis of Meynert	1.60%	0.25	.36	−1.33	14	3.33%	0.46	.24	0.81	10	1.71%	0.23	.51	0.97	13
Cerebellum	−1.70%	−0.24	.27	−1.26	14	1.37%	0.26	.47	0.88	10	3.13%	0.41	.19	1.51	13

[a] Relative change was defined as 100 × (mean CBVa in patients − mean CBVa in controls)/(mean CBVa in controls) %.
[b] Effect size was estimated with Cohen's d = (mean CBVa in patients − mean CBVa in controls)/s, where s is the pooled standard deviation of the 2 groups.
[c] Degree of freedom.

Table 5. Altered Gray Matter CBVa in Age-Related MCI Patients Without Movement Disorder Compared With Matching Controls

Regions	MCI (n = 18)		Control (n = 22)						
	Mean	SD	Mean	SD	Relative Change (%)[a]	Effect Size[b]	*P*	*t*	df[c]
Substantia Nigra	1.15	0.83	1.09	0.88	5.50%	0.07	.59	0.55	31
Caudate	2.31	1.65	1.17	1.31	97.44%	0.77	.04	3.22	35
Putamen	2.15	1.38	1.29	1.01	66.67%	0.72	.05	3.15	35
Nucleus Accumbens	1.52	1.00	1.02	0.99	49.02%	0.50	.08	3.01	32
Posterior Cingulate Cortex	1.55	0.78	1.11	0.82	39.64%	0.55	.06	3.06	32
Hippocampus	1.77	0.93	1.07	0.65	65.42%	0.89	.02	3.33	34
Entorhinal Cortex	1.89	0.78	1.08	0.52	75.00%	1.25	.06	3.05	32
Parahippocampus	1.81	0.53	1.05	0.70	72.38%	1.21	.06	3.05	32
Presupplementary Motor Area	1.76	0.47	1.32	0.52	33.33%	0.88	.12	1.97	36
Thalamus	1.63	0.71	1.17	0.66	39.32%	0.67	.15	1.90	36
Intracalcarine Gyrus	1.82	0.68	1.50	0.77	21.33%	0.44	.13	1.95	36
Lingual Gyrus	1.85	0.88	1.45	0.69	27.59%	0.51	.05	3.12	35
Nucleus Basalis of Meynert	1.21	0.98	1.17	1.00	3.42%	0.04	.60	0.57	35
Cerebellum	1.29	1.01	1.19	0.88	8.40%	0.11	.50	0.69	35

[a] Relative change was defined as 100 × (mean CBVa in patients − mean CBVa in controls)/(mean CBVa in controls) %.
[b] Effect size was estimated with Cohen's d = (mean CBVa in patients − mean CBVa in controls)/s, where s is the pooled standard deviation of the 2 groups.
[c] Degree of freedom.

DISCUSSION

In this study, microvascular abnormalities as reflected by volume changes in small pial arteries and arterioles (CBVa) were investigated using iVASO MRI in PD patients, MCI patients without movement disorder, and matched controls. As pial arteries and arterioles are the primary regulators of regional perfusion in brain tissues (82–84), CBVa is considered as an indicator of the homeostasis of microvasculature that may provide additional information regarding the underlying neurophysiological changes than behavioral measures and conventional structural MRI. The same MRI scans and analyses were performed in 2 separate cohorts of PD patients and MCI patients without movement disorder and corresponding control groups recruited at 2 sites. This allowed us to better match the controls in each cohort, as the age and many other factors can differ substantially among PD patients and MCI patients without movement disorder. The MRI scans were acquired on a 7T human MRI system with identical hardware and software at both sites. Only data acquired on the same MRI system were compared to minimize the confounding effects from the potential differences between the 2 sites.

Patients with PD who enrolled for this study had an average disease duration of ~3 years and an average UPDRS score of 20–30, which is generally considered to be early stage (but not prodromal) PD (85). The degree of cognitive decline in PD patients with impaired cognition group was mild, as reflected by their performance on the cognitive assessments, and was comparable to that in the MCI patients without movement disorder group as reported in our previous study (13).

The main finding in this study is that PD patients showed significant CBVa *decreases* in the substantia nigra, caudate, and putamen compared with controls, whereas MCI patients without movement disorder and PD patients with impaired cognition showed significant CBVa *increases* in several brain regions closely related to cognition, compared with controls. We interpret the decreased CBVa as an indicator for microvascular damage, especially in the substantia nigra in PD patients, as evidenced in several studies in the literature (15–23). In contrast, similar to our previous studies in MCI patients without movement disorder (13) and Huntington's Disease patients (86) in which the same MRI methods were used, one possible explanation for the elevated CBVa observed in several brain regions may be a *compensatory* mechanism in the earlier stages of the diseases, in which the number of blood vessels increases to normalize the restricted blood flow owing to the reduction of diameter in individual vessels. The exact mechanism is unclear and warrants further investigation that integrates MRI and other imaging and histological techniques.

The substantia nigra is one of the first brain regions that accumulates Lewy bodies in postmortem pathological studies in PD. In our data, CBVa decreased in the substantia nigra in both PD patients with normal cognition and PD patients with impaired cognition. CBVa in the substantia nigra in MCI patients without movement disorder did not show significant changes compared with controls. The dorsal striatum, which consists of the caudate and the putamen, is another region that is known to be affected early in PD. Interestingly, our data showed decreased CBVa in

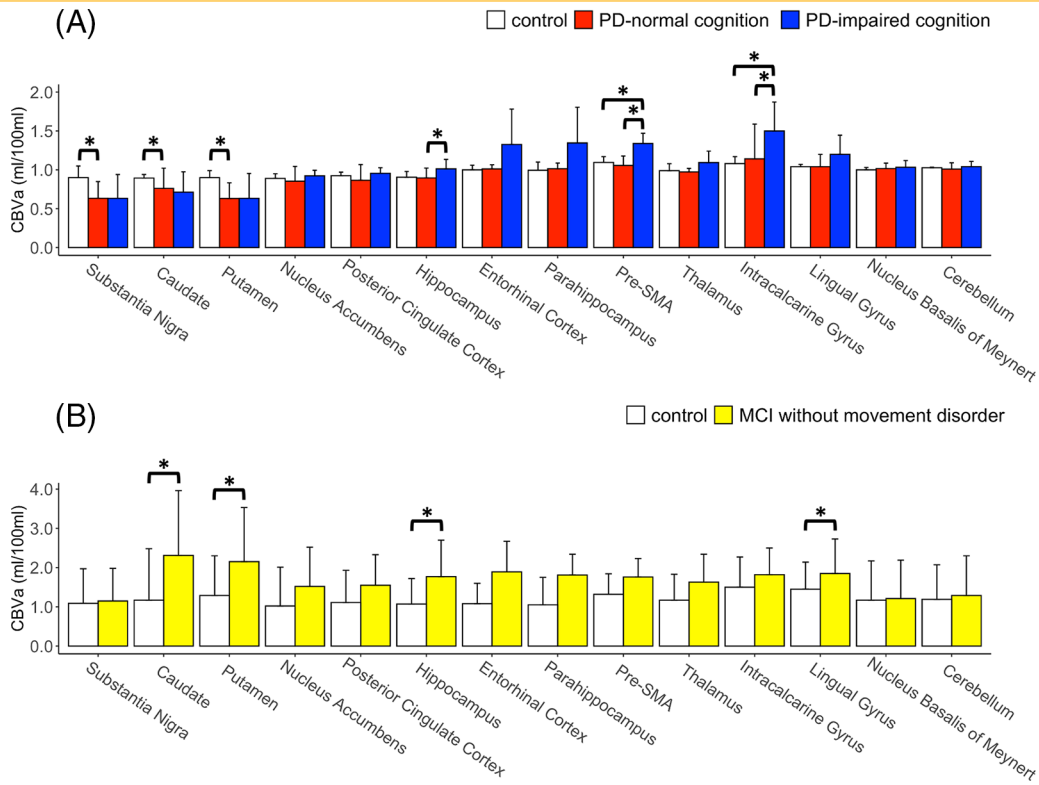

Figure 1. Comparisons of arteriolar cerebral blood volume (CBVa) values in chosen brain regions between Parkinson's Disease patients with normal cognition, PD patients with impaired cognition (A), and mild cognitive impairment (MCI) patients without movement disorder with matching controls (B). $*P < .05$.

the caudate and putamen in PD patients but increased CBVa in these regions in MCI patients without movement disorder compared with their respective controls.

In this exploratory study, our data seem to suggest that CBVa increase in the preSMA and intracalcarine gyrus, and possibly the hippocampus, entorhinal cortex, and parahippocampus, may be differentiating between PD patients with normal cognition and patients with impaired cognition. The hippocampus, entorhinal cortex, and parahippocampus are closely related to overall cognition and to episodic memory and are known to be affected in dementia (87–91). Our data showed relatively large effect sizes (close to 1) in CBVa increase in these three regions in both PD patients with impaired cognition and MCI patients without movement disorder compared with matching controls. In PD patients with normal cognition, CBVa values in these regions did not show significant changes. The preSMA and intracalcarine gyrus are two regions that are considered to be primarily affected in PDD but not in AD-MCI. In our data, PD patients with impaired cognition showed significantly increased CBVa in these two regions compared with controls, with the largest effect sizes among all regions investigated. No significant changes in CBVa in PD patients with normal cognition and MCI patients without movement disorder were detected in these two regions. In contrast, the opposite CBVa changes in the caudate and putamen, along with CBVa changes in the substantia nigra, nucleus accumbens in the ventral striatum, and the posterior cingulate cortex, seem to suggest that measuring CBVa in these regions may be key in differentiating between PD patients with impaired cognition and MCI patients without movement disorder. In addition, the lingual gyrus is another region that showed increased CBVa only in the MCI patients without movement disorder cohort. To the best of our knowledge, there are very few studies currently on the potential differential neurovascular changes in different brain regions among PD, PD-MCI, and AD-MCI. The preliminary findings in this study require further investigation and validation in subsequent studies.

The cerebellum is known to be largely spared in the early stages of both PD and AD-MCI. In our data, all PD and MCI patients showed comparable CBVa values in the cerebellum as in controls in respective cohorts. Besides, the CBVa values in all regions in the control subjects were in the normal range of CBVa in human subjects reported in the literature (81). These results provide validation for the CBVa values measured in this study.

No comparison between the MCI patients without movement disorder and PD cohorts were conducted in the analysis described in Results, as the data were acquired on the same type of MRI system but at two different sites. Nevertheless, the CBVa values in the MCI without movement disorder cohort seemed to be slightly greater overall than those in the PD cohort. As CBVa values tend to increase with age (81), one possible explanation is the ~10-year age difference between the patients in MCI and PD cohorts.

There are several limitations in this exploratory study. First, although significant effects were detected in our data, the sample size is small, especially for the PD cohort. Subsequent studies will continue to recruit PD patients with normal and impaired cognition and matched controls at the Johns Hopkins site to validate the current findings. Second, the cross-sectional design is also a fundamental limitation. Future studies with longitudinal measures at different stages of the disease are required to evaluate whether regional CBVa changes can be a predictor for the risk of developing PDD in PD patients. Using the smallest effect size (~0.5) for significant between-group CBVa differences detected in this study, we were able to conduct a power analysis that determined we would need ~30 participants per group in subsequent studies to achieve a power of 0.8 with alpha = 0.05.

In summary, CBVa abnormalities in different brain regions were detected in PD patients with normal cognition, in PD patients with impaired cognition, and in MCI patients without movement disorder compared with matched controls by use of iVASO MRI. Our data implies that CBVa changes in several key brain regions may be specific to each condition and thus may provide clues to differentiate one condition from the others. These findings provide further details regarding microvascular abnormalities in different brain regions in PD patients and in MCI patients without movement disorder who have not been reported in existing literature. This may help advance our understanding of the pathophysiology of PDD and may aid the development of imaging biomarkers in PDD. The data from this study will serve as the basis for power analysis for subsequent studies to further investigate and validate the current findings.

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