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White Matter Hyperintensities Related to Parkinson's Disease Executive Function

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Abstract: Background: People with Parkinson's disease (PD) can develop multidomain cognitive impairments; however, it is unclear whether different pathologies underlie domain-specific cognitive dysfunction.
Objectives: We investigated the contribution of vascular copathology severity and location, as measured by MRI white matter hyperintensities (WMHs), to domain-specific cognitive impairment in PD.
Methods: We studied 85 PD (66.6 ± 9.2 years) and 18 control (65.9 ± 6.6) participants. Using the Fazekas scale for rating the severity of WMH, we subdivided PD into 14 $PD^{-}WMH^{+}$ and 71 $PD^{-}WMH^{-}$. Participants underwent global, executive, visuospatial, episodic memory, and language testing. We performed nonparametric permutation testing to create WMH probability maps based on PD-WMH group and cognitive test performance.
Results: The $PD^{-}WMH^{+}$ group showed worse global and executive cognitive performance than the $PD^{-}WMH^{-}$ group. On individual tests, the $PD^{-}WMH^{+}$ group showed worse Montreal Cognitive Assessment (MoCA), Stroop, Symbol Digit Modalities Test (SDMT), and Digit Span scores. WMH probability maps showed that in the $PD^{-}WMH^{+}$ group, worse Stroop was associated with lesions centered around the corticospinal tract (CST), forceps major, inferior-fronto-occipital fasciculus, and superior longitudinal fasciculus; worse SDMT with lesions around the CST, forceps major, and posterior corona radiata; worse Digit Span with lesions around the posterior corona radiata; and worse MoCA with lesions around the CST.
Conclusions: We found that WMH severity was associated with PD executive dysfunction, including worse attention, working memory, and processing speed. Disruption of key white matter tracts in proximity to vascular lesions could contribute to these specific cognitive impairments. Early treatment of vascular disease might mitigate some executive dysfunction in a subset of patients with PD.

Parkinson's disease (PD) is the second-most common neurodegenerative disorder and affects 2-3% of adults aged >65 years. Alongside the cardinal motor symptoms, many nonmotor symptoms contribute to reduced health-related quality of life.[1] Cognitive impairment and dementia are among the most devastating nonmotor symptoms, with deficits occurring in multiple cognitive domains, including executive function/attention, visuospatial ability, language, and memory.[2]

With increasing age, there is also an increased risk for incidental cerebral white matter hyperintensities (WMHs) to be found on routine MRI scans. As one form of small vessel disease, these WMHs are speculated to represent areas of incomplete infarcts,[3,4] tend to progress with time,[5] and are associated with motor[6] and cognitive dysfunction in older, healthy adults.[7] Specifically, WMHs are primarily associated with decline in executive/attention abilities, but there are also reports of WMH-associated global cognitive impairment as well as deficits in motor control and visuoconstructional abilities.[8,9]

At autopsy, PD patients often show multiple copathologies in addition to Lewy bodies, with Alzheimer's and vascular copathology being the most common.[10] Lewy-body pathology with and without Alzheimer's copathology are strongly linked to

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PD-associated cognitive impairments.[11,12] However, it is less clear whether vascular copathology contributes to PD-associated cognitive impairments.[13,14] Some studies in PD patients who showed WMHs on MRI are associated with deficits in executive function, attention, memory, and visuospatial abilities,[15,16] whereas others did not find an association.[17] Furthermore, it is unclear whether the location of the WMH is related to domain-specific cognitive impairments.

We studied whether incidental WMHs observed on routine MRI scans could be associated with cognitive impairments in patients with PD. We hypothesized that the severity and location of WMH would contribute to domain-specific cognitive dysfunction in PD. To test this hypothesis, we first studied the impact of WMH severity on cognitive performance in PD. Second, we determined the detrimental effect of WMH location by calculating the lesion probability map as a function of WMH severity and cognitive test performance.

Participants and Methods

Participants

We recruited 121 participants from the Stanford Movement Disorders Clinic and the surrounding community as previously described.[18–20] PD was diagnosed using the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.[21] Healthy controls (HCs) were neurologically normal on exam and within 1.5 standard deviations (SDs) of normative values on comprehensive cognitive testing. The Stanford Institutional Review Board approved this study, and all study participants provided their informed written consent.

An experienced researcher, who was blinded to participant information, rated cerebral WMH using the Fazekas scale for deep and periventricular WMH.[22] We excluded 2 participants because of WMH in the basal ganglia, 7 because of lacunar infarcts, and 8 because microbleeds were suspected on T_1 and fluid-attenuated inversion recovery (FLAIR) scans. PD participants were subcategorized into a WMH-positive group (PD^-WMH^+) if they had deep WMH grades 2 or 3, or periventricular WMH grade 3, and a WMH-negative group (PD^-WMH^-) if they had deep WMH grades 0 or 1, or periventricular WMH grades 0, 1, or 2.[4] One HC was WMH^+ according to these criteria.

Cognitive Testing

All participants underwent comprehensive cognitive testing while on their regularly prescribed dopaminergic medications, as previously published.[18] We assessed global cognitive function using the Montreal Cognitive Assessment (MoCA) and domain-specific cognitive function in four domains. For executive function, including attention and working memory, we used the Wechsler Memory Scale-III Digit Span (Digit Span),[23] Symbol Digit Modalities Test (SDMT),[24] Controlled Oral Word Association Test-letters F-A-S (FAS),[25] Trail Making Test part B (TMT-B),[26] and Stroop Color and Word Test (Stroop).[27] For visuospatial ability, we used the Hooper Visual Organization Test[28] and the Benton Judgement of Line Orientation.[29] For episodic memory, we used the California Verbal Learning Test[30] and the Brief Visuospatial Memory Test-Revised.[31] For language, we used the Boston Naming Test[32] and Semantic Fluency Test.[25] We used standardized age- and education-matched normative values to determine whether a participant had cognitive impairment, which was defined by scores >1.5 SDs below normative values on at least two tests, regardless of domain.[33] We then determined whether cognitively impaired participants had domain-specific impairment, if at least one test within the domain had a score > 1.5 SDs below the normative values.[33] Dementia was defined as the Clinical Dementia Rating Scale ≥0.5 and impairment in activities of daily living attributed to cognition, as determined by the neurologist who was blinded to WMH ratings.[34]

Three PD participants did not perform the Stroop because of being colorblind, and 1 PD participant did not perform the TMT-B because of fatigue; these 4 participants were excluded from executive domain-level categorization and test-level analysis.

MRI Data Acquisition

Participants were scanned on a 3 Tesla (T) General Electric SIGNA scanner (GE Healthcare, General Electric Company, Waukesha, WI) using an eight-channel radiofrequency receive head coil contained within a quadrature transmit coil (Nova Medical, Inc., Wilmington, MA). We performed structural MRI (FLAIR and T_1) sequences, similar to those performed during routine MRI. Specifically, we performed two-dimensional FLAIR with axial slices covering the whole brain (repetition time [TR] = 8,000.0 ms, echo time [TE] = 120.0 ms, field of view [FOV] = 220 × 220 mm^2, matrix size of 512 × 512, and spatial resolution of 0.43 × 0.43 × 5.00 mm^3) and three-dimensional inversion recovery spoiled gradient echo T_1-weighted MRI with 158 axial slices (TR = 6.0 ms, TE = 2.0 ms, FOV = 220 × 220 mm^2, matrix size of 256 × 256, flip angle = 5 degrees, and spatial resolution of 0.86 × 0.86 × 1.00 mm^3).

WMH Mask and Volume Assessments

We extracted WMH volumes using the FMRIB Software Library (FSL; v5.0; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). First, we used the Brain Intensity AbNormality Classification Algorithm (BIANCA) to perform automatic WMH segmentation by applying a k-nearest neighbor algorithm.[35] As training data, we used WMH masks, manually segmented by a single researcher, from 15 FLAIR scans and FLAIR- and T_1-weighted MRI for intensity feature extraction. To make the training data more local, we set the spatial weighting value to 2 and defined the subject-specific training data to use all lesion points available and an equal number of nonlesion points while excluding voxels close to the lesion's edge. We binarized the resulting WMH masks for further processing, and a single researcher applied

manual corrections to masks with false positives (labeled incorrectly as WMH) and/or false negatives (missing WMH segmentation). Second, we registered the WMH masks from FLAIR-native space to the T_1-weighted Montreal Neurological Institute (MNI-152) 1-mm standard-space MRI template using FLIRT and FNIRT.[36] We linearly registered each participant's FLAIR scan and lesion masks to the same participant's T_1 image using FLIRT with 6 degrees of freedom (DOF). We linearly registered T_1 images to MNI space with 12 DOF affine registration and subsequently refined with nonlinear registration using FNIRT. We used the resulting transformation matrices and warp fields to register the lesion masks to MNI space. To preserve binary values, we set the threshold for the resulting masks at 0.5 and binarized. In order to account for small variations caused by registration from native to MNI space,[36] we then subsampled the resulting masks to a voxel size of $2 \times 2 \times 2$ mm^3 and rebinarized with a threshold of 0.5. Third, we extracted total WMH volumes in MNI-152 (2-mm) standard space (Table 1).

Lesion Distribution and Lesion Probability Maps

Lesion Distribution Map

We generated a lesion distribution map showing lesion locations in the PD group by merging all standard-space binary lesion masks.

Lesion Probability Maps

We performed nonparametric permutation testing using FSL randomise[37] to create lesion probability maps, which identified the probability of lesion location, as predicted by worse cognitive test performance and the two PD subgroups (PD^-WMH^+ vs. PD^-WMH^-). We here tested for an interaction effect of worse cognitive performance on lesion location in the PD^-WMH^+ versus PD^-WMH^- groups. For all analyses, we concatenated standard-space lesion masks into a four-dimensional data matrix, then applied an MNI-152 (2-mm) standard-space brain mask to mask out non-brain voxels. In addition to modeling in information on the two PD-WMH groups, the raw cognitive scores were first demeaned within the total group and then split into explanatory variables, based on the two PD-WMH groups. Because age can influence both cognitive test scores and WMH lesion load, we used raw cognitive test scores and adjusted the general linear model for age, education, and lesion load (total WMH volume in standard space) as covariates of no interest to the model, which we demeaned within the total group. We used permutation testing, which is robust to unequal group variances, with 5,000 permutations randomly generated by reshuffling the labels of the design matrix to build up a null distribution to test against (for each voxel). To avoid overfitting, we performed four permutation tests using a different general linear model (GLM) for each covariate of interest (i.e., cognitive score). We thresholded the results using threshold-free cluster enhancement,[38] outputting only voxels with familywise error (FWE)-corrected P values <0.05. We identified white matter tracts overlapping with significant lesion clusters using the Johns Hopkins University (JHU) White-Matter Tractography Atlas and JHU ICBM-DTI-81 White-Matter Labels atlas in MNI space, as part of the FSLeyes graphical user interface.

Statistical Analyses

We performed all statistical analyses using IBM SPSS Statistics software (version 25.0; SPSS Statistical Package for Social Science, IBM Corp; https://www.ibm.com). For all analyses, we used two-tailed P values and defined $P \leq 0.05$ as significant. We assessed between-group differences using chi-square tests for categorical variables, Mann-Whitney U tests for non-normally distributed variables (two groups), univariate one-way analyses of variance (ANOVAs) for normally distributed variables (three groups), and Kruskal-Wallis tests for non-normally distributed variables (three groups), with post-hoc Bonferroni or Mann-Whitney U tests for multiple-comparison correction, where appropriate.

For the lesion probability map analyses, we used GLMs with the lesion probability at each voxel as the dependent variable, PD-WMH group and raw cognitive test score as the predictor variables, and age, education, and lesion load as covariates of no interest. In this analysis, we used the raw cognitive test score and adjusted for age in the model, rather than using age-matched normative values, given that age can influence both cognitive test scores and WMH lesion load.

Results

Cohort Characteristics

Comparing all participants with and without WMH, there was no age difference between 85 PD and 19 HC participants ($P = 0.972$), and WMHs were just as frequent in PD as they were in HCs ($P = 0.731$). See Table 1 for detailed between-group analyses after excluding the 1 HC^-WMH^+ participant. Within the PD group, PD^-WMH^+ participants were older ($P = 0.001$) and had worse International Parkinson and Movement Disorder Society UPDRS (MDS-UPDRS) Part III Off ($P = 0.022$) compared to the PD^-WMH^- group.

PD Cognitive Impairment Related to WMH Severity and Location

The number of PD participants with and without cognitive impairment did not differ between WMH groups (Table 2). However, the PD^-WMH^+ group showed worse performance on the MoCA than the PD^-WMH^- group ($P = 0.020$).

Within the cognitive domains, more PD^-WMH^+ participants showed executive impairment (Table 1) compared to the PD^-WMH^- group, which maintained a trend relationship after Bonferroni's correction for multiple comparisons ($P = 0.05/4 = 0.013$). We then determined between-group differences on individual executive tests using standardized age- and education-matched

TABLE 1 *HC and PD group characteristics*

Characteristic	$HC^{-}WMH^{-}$	$PD^{-}WMH^{-}$	$PD^{-}WMH^{+}$	*P* Value	Post Hoc
No.	18	71	14		
Demographics					
Age, years	65.9 ± 6.6 [57–78]	65.1 ± 8.5 [42–83]	74.4 ± 9.0 [55–85]	0.001[1]	[7,8]
Female[#]	10 (55.6)	31 (43.7)	4 (28.6)	0.312[2]	
Education	17.4 ± 1.7 [15–20]	16.7 ± 2.4 [12–20]	16.4 ± 2.8 [12–20]	0.601[3]	
Disease duration	–	5.3 ± 4.3 [0–22]	5.8 ± 3.9 [0–15]	0.426[4]	
Clinical features					
LEDD	–	586.4 ± 349.4 [0–1,560]	645.7 ± 416.7 [0–1,450]	0.717[4]	
MDS-UPDRS-I	–	11.7 ± 6.2 [2–29]	13.5 ± 5.1 [4–23]	0.182[4]	
MDS-UPDRS-II	–	11.8 ± 7.1 [1–35]	16.2 ± 7.2 [7–27]	0.047[4]	
MDS-UPDRS-III On	–	17.4 ± 9.7 [4–48]	23.6 ± 12.4 [5–50]	0.073[4]	
PIGD On	–	2.2 ± 2.5 [0–13]	3.9 ± 3.6 [0–14]	0.036[4]	
Tremor On	–	3.4 ± 3.4 [0–14]	4.8 ± 3.1 [1–9]	0.070[4]	
Bradykinesia-Rigidity On	–	10.3 ± 6.1 [0–28]	12.7 ± 8.1 [2–27]	0.381[4]	
H & Y On	–	1.9 ± 0.7 [1–4]	2.2 ± 0.6 [1–3]	0.080[4]	
MDS-UPDRS-III Off	–	31.4 ± 10.9 [6–59]	39.2 ± 11.4 [19–59]	0.022[5]	
PIGD Off	–	3.0 ± 2.7 [0–15]	5.2 ± 4.0 [0–14]	0.020[4]	
Tremor Off	–	6.9 ± 5.3 [0–20]	8.9 ± 4.5 [3–15]	0.127[4]	
Bradykinesia-Rigidity Off	–	17.8 ± 7.0 [5–37]	20.9 ± 8.1 [9–32]	0.148[5]	
H & Y Off	–	2.1 ± 0.7 [1–5]	2.4 ± 0.5 [2–3]	0.020[4]	
MDS-UPDRS-IV	–	3.9 ± 3.5 [0–15]	5.5 ± 3.3 [0–11]	0.123[4]	
Vascular risk factors					
Arterial hypertension[#]	6 (35.3)	22 (31.0)	5 (38.5)	0.842[2]	
Diabetes mellitus[#]	1 (5.9)	0 (0.0)	1 (7.7)	0.084[2]	
Smoking[#]	2 (25.0)	18 (31.6)	3 (25.0)	0.858[2]	
Hypercholesterolemia[#]	7 (41.2)	21 (29.6)	7 (53.8)	0.198[2]	
Body mass index(kg/m^3)	26.7 ± 4.9 [19–36]	25.9 ± 5.2 [18–46]	24.5 ± 5.5 [19–41]	0.262[3]	
Total WMH volumes					
Native space (cm^3)	1.86 ± 2.16 [0.05–8.95]	2.11 ± 1.62 [0.14–8.93]	19.55 ± 16.90 [0.67–56.93]	<0.001[3]	[7,8]
Standard space (cm^3)	7.06 ± 6.81 [0.21–24.18]	8.10 ± 5.51 [1.02–29.71]	48.41 ± 33.72 [8.42–134.80]	< 0.001[3]	[7,8]
Total brain volume					
Native space (cm^3)	1,071.85 ± 130.23 [837.99–1,275.95]	1,088.59 ± 112.11 [890.21–1,499.78]	1,083.64 ± 141.81 [889.33–1,376.23]	0.868[1]	
Standard space (cm^3)	1,357.10 ± 85.77 [1,205.94–1,510.70]	1,384.61 ± 86.65 [1,201.86–1,604.67]	1,327.31 ± 111.97 [1,162.45–1,601.17]	0.075[1]	

Table shows group comparisons after excluding the 1 $HC^{-}WMH^{+}$ participant, leaving a final cohort of 18 $HC^{-}WMH^{-}$ participants.
All values shown as mean ± SD [range], except when designated with a pound sign ("#") for number (percent within total group).
[1] One-way ANOVA, across all three groups.
[2] Chi-square, across all three groups.
[3] Kruskal-Wallis test, across all three groups.
[4] Mann-Whitney U test, between the two PD groups.
[5] Student's *t* test, between the two PD groups.
Post-hoc test (Bonferroni for all one-way ANOVAs, Mann-Whitney U test for all Kruskal-Wallis tests) significant for:
[6] $HC\text{-}WMH^{-}$ vs. $PD\text{-}WMH^{-}$.
[7] $HC\text{-}WMH^{-}$ vs. $PD\text{-}WMH^{+}$.
[8] $PD\text{-}WMH^{-}$ vs. $PD\text{-}WMH^{+}$.
LEDD, levodopa equivalent daily dose.

TABLE 2 *Cognitive function in the HC and PD groups*

	$HC^{-}WMH^{-}$	$PD^{-}WMH^{-}$	$PD^{-}WMH^{+}$	*P* Value	Post Hoc
No.	18	71	14		
All cognitively impaired#	0 (0.0)	33 (46.5)	10 (71.4)	< 0.001[1]	[3,4]
Dementia#	0 (0.0)	7 (9.9)	5 (35.7)	0.005[1]	[4,5]
Impaired cognitive domains					
Executive impairment#	0 (0.0)	28 (39.4)	10 (76.9)	<0.001[1]	[3,4,5]
Visuospatial impairment#	0 (0.0)	7 (9.9)	4 (28.6)	0.032[1]	[4]
Episodic memory impairment#	0 (0.0)	28 (39.4)	9 (64.3)	<0.001[1]	[3,4]
Language impairment#	0 (0.0)	10 (14.1)	4 (28.6)	0.063[1]	[4]
Cognitive tests					
MoCA	27.8 ± 1.7 [24–30]	25.4 ± 4.6 [24–29]	22.8 ± 4.4 [19–26]	0.002[2]	[3,4,5]
Digit Span*	11.3 ± 2.1 [7–16]	11.4 ± 3.5 [9–14]	9.1 ± 2.2 [8–10]	0.025[2]	[4,5]
SDMT*	53.9 ± 8.4 [46–80]	46.2 ± 14.8 [41–53]	37.6 ± 15.3 [26–49]	0.001[2]	[3,4,5]
Stroop*	45.6 ± 6.4 [34–56]	45.1 ± 8.1 [40–50]	39.7 ± 5.9 [35–44]	0.046[2]	[4,5]
TMT-B*	54.6 ± 4.4 [47–62]	45.4 ± 16.2 [40–56]	37.0 ± 17.0 [25–56]	0.010[2]	[3,4]
FAS*	52.1 ± 9.5 [30–70]	50.0 ± 13.9 [40–62]	46.1 ± 12.9 [36–56]	0.391[2]	

Table shows group comparisons after excluding the 1 $HC^{-}WMH^{+}$ participant, leaving a final cohort of 18 $HC^{-}WMH^{-}$ participants. Digit Span is the combined score, SDMT is the oral score, and Stroop is the interference score.
All values shown as mean ± SD [range], except when designated with a pound sign ("#") for number (percent within total group). For those designated with an asterisk ("*"), we used standardized age- and education-matched normative values.
[1] Chi-square, across all three groups.
[2] Kruskal-Wallis, across all three groups.
Significant post-hoc tests (Mann-Whitney U for Kruskal-Wallis tests):
[3] $HC^{-}WMH^{-}$ versus $PD^{-}WMH^{-}$.
[4] $HC^{-}WMH^{-}$ versus $PD^{-}WMH^{+}$.
[5] $PD^{-}WMH^{+}$ versus $PD^{-}WMH^{-}$.

normative values (Table 2). The $PD^{-}WMH^{+}$ group showed worse performance on Digit Span ($P = 0.014$), SDMT ($P = 0.015$), and Stroop ($P = 0.026$), compared to the $PD^{-}WMH^{-}$ group.

As seen in the lesion distribution map (Fig. 1), the majority (94%) of PD participants showed lesions around the frontal horns of the lateral ventricles and almost half (47%) showed lesions

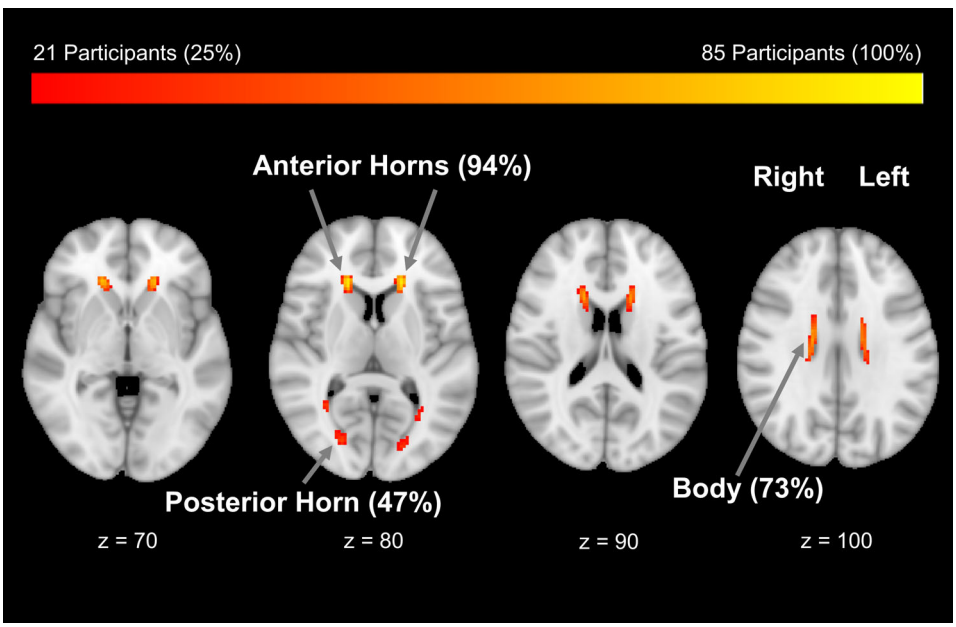

FIG. 1. Topography of WMH in PD participants overlaid onto standard-space brain mask. The majority showed WMH around the anterior horns of the lateral ventricles, with a maximum of 81 PD participants showing a lesion in a single voxel location.

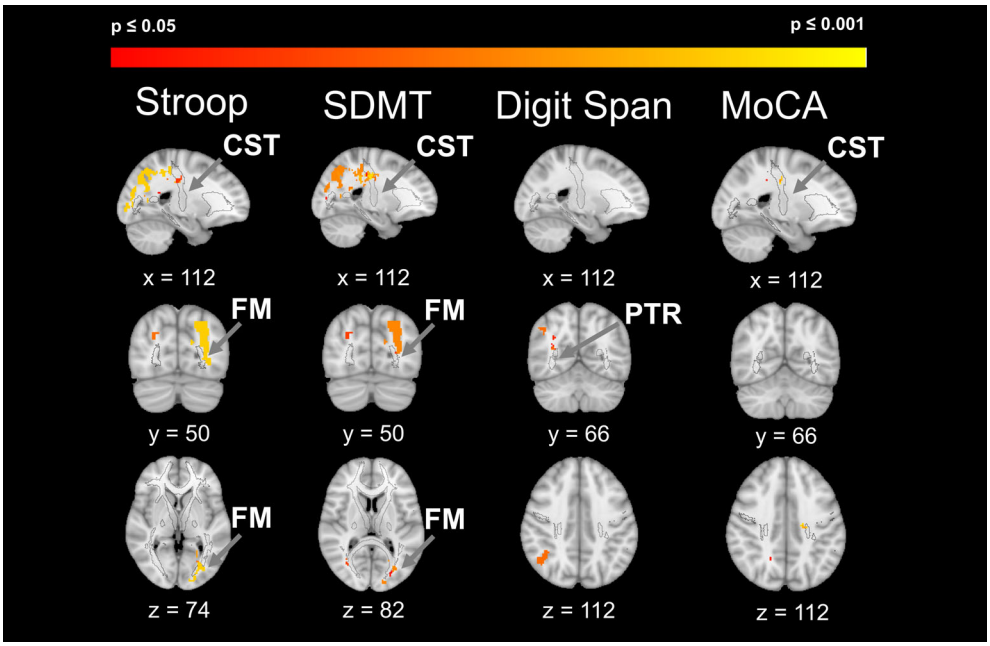

FIG. 2. Lesion locations associated with worse cognitive test performance in the $PD^{-}WMH^{+}$ versus the $PD^{-}WMH^{-}$ group. Major fiber tracts are shown in black outlines. Clusters shown, FWE-corrected $P = 0.05$ to 0.001. PTR, posterior thalamic radiation.

around the posterior horns. This resembles the pattern in our HC group (data not shown) and is similar to studies in healthy older adults.[39]

As seen in the lesion probability map, for worse Stroop performance in the $PD^{-}WMH^{+}$ compared to the $PD^{-}WMH^{-}$ group, we found significant lesion clusters ($P < 0.05$, FWE-corrected) in the left corticospinal tract (CST), forceps major (FM), inferior fronto-occipital fasciculus, and superior longitudinal fasciculus. For worse SDMT performance, we found significant lesion clusters in the left CST, left FM, right posterior corona radiata, and left corpus callosum. For worse Digit Span performance, we found significant lesion clusters in the right posterior thalamic radiation and left corpus callosum. Finally, for worse MoCA performance, we found a significant lesion cluster in the left CST (Fig. 2; Table 3).

TABLE 3 *Fiber tracts associated with WMH lesion cluster*

Contrast and Fiber Tract(s)	Hemisphere	Voxels	MAX (Z)	X (Voxel)	Y (Voxel)	Z (Voxel)
Stroop						
CST, forceps major, inferior fronto-occipital fasciculus, superior longitudinal fasciculus	L	1,704	0.99	116	54	88
*Forceps major	R	794	0.98	70	72	122
SDMT						
CST, Forceps major	L	1,594	0.99	112	104	106
*Posterior corona radiata	R	1117	0.99	72	70	114
Posterior corona radiata	R	21	0.95	68	96	106
Splenium of corpus callosum	L	16	0.99	102	130	96
–	–	14	0.96	106	108	120
Digit Span						
*Posterior corona radiata	R	153	0.98	50	64	106
Body of corpus callosum	L	11	0.97	102	130	96
Posterior thalamic radiation	R	11	0.96	58	68	102
MoCA						
CST	L	13	0.99	112	104	106

Key(s): Voxels, number of voxel within cluster; MAX (Z), value of maximum z-statistic; X/Y/Z (voxel), location of MAX (Z) voxel in MNI-152 standard-space coordinates (voxel).
Stroop, SDMT, Digit Span, and MoCA: lesion probability map results for the contrasts worse cognitive performance in $PD^{-}WMH^{+}$ versus worse cognitive performance in $PD^{-}WMH^{-}$. Major fiber tracts passing through or (*) near the significant WMH lesion cluster.
Only clusters with ·10 voxels are reported.

Discussion

In this study, we showed an association between cerebral WMH and domain-specific cognitive dysfunction in people with PD. We found that in PD patients, more severe WMHs of presumed vascular origin were associated with executive dysfunction, attention, and working memory. Finally, we identified several white matter tracts in PD patients with more severe WMHs, where lesions were associated with poorer cognitive performance. Our findings suggest that the severity and location of incidental WMH lesions observed on routine MRI might contribute to cognitive heterogeneity found in PD.

Vascular Brain Injury Could Contribute to the Heterogeneity of Cognitive Impairments in PD

PD patients commonly exhibit comorbidity beyond Lewy-body pathology at autopsy.[40,41] Whereas Alzheimer's copathology is most common,[13,14] comorbid small-vessel vascular brain injury is also frequent. One large retrospective study of 617 autopsy-proven PD cases showed that almost 45% of patients had comorbid vascular brain injury,[42] but their specific impact on early disease symptoms is still unclear. Studies investigating WMH on MRI, as a proxy for vascular brain injury, have sought to resolve this question.[14]

We studied the relationship between vascular injury and cognitive dysfunction in PD by comparing participants with and without WMH using MRI. Earlier studies in PD reported an association between WMH and performance on the Mini-Mental State Examination.[43] We found that PD participants with more severe WMH showed greater impairment on the MoCA, which is more commonly used clinically because of its greater sensitivity[44] in detecting early PD cognitive impairments.[18,45]

We then examined the relationship between WMH and domain-specific cognitive impairments given that earlier studies show conflicting results.[46] For example, two studies found WMH associated with executive function/attention and memory in PD,[15,47] but others did not find this association.[48,49] One of these studies limited the analysis to cholinergic white matter tracts,[50] as has been used in the study of WMH in Alzheimer's disease patients. Our findings suggest that white matter tracts, in addition to the cholinergic system, should be studied with regard to executive dysfunctions in PD. Another used lower-MRI-field-strength images,[48,49] which could account for the negative results. We used high-field MRI (3T) and found that more PD with WMH showed executive impairment, compared to those without WMH.

We then found more impaired executive function (Stroop), processing speed (SDMT),[51] and attention/working memory (Digit Span)[52] in PD patients with more severe WMH. This is consistent with studies in healthy adults showing that WMHs are associated with worse executive function and information processing speed.[53] Interestingly, processing speed also is abnormal in other neurological disorders, primarily affecting the white matter tracts, such as multiple sclerosis.[54]

WMH Locations Are Associated With the Specific Subtypes of PD Cognitive Impairment

For our lesion probability map analyses, we further studied the relationship between WMH severity and specific tests of executive function. We used lesion probability mapping to show that severe WMH in proximity to specific white matter tracts might explain some of the executive function deficits. We found most lesions centered around the CST, FM, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and posterior corona radiata. Previous studies in people with PD have reported an association between executive function and anterior white matter tracts,[55] which was independent of WMH load. In our study, we grouped people with PD based on WMH severity to study the mechanistic effects of severe vascular lesions on PD cognition (and with regard to presumed crossing fiber tracts). Similar to the Melzer et al. study, we here also added lesion load as a covariate of no interest to our model.

For the Stroop and SMDT, we found that the largest lesion cluster overlapped with regions of the left CST and FM. This is of interest, given that Zheng et al.[56] used diffusion tensor imaging (DTI) to measure white matter integrity in relation to domain-specific cognitive function in PD and found that the left CST was associated with attention. Bohnen and Albin[14] speculated that periventricular WMH results in damage of both periventricular ascending thalamocortical and descending CST fibers, which would lead to impaired gait and postural control in participants with PD and WMH. Indeed, the CST travels from the cerebral cortex to the spinal cord and is typically associated with motor and sensory function. Studies have shown lower CST integrity to be associated with worse perceptual speed in persons with older age,[57] but also higher neurite density in the CST to be associated with faster nondecision time in reaction time tasks, implying a more efficient network for voluntary actions.[58] In persons with relapsing-remitting multiple sclerosis, Riccitelli et al. determined that lesions in the CST and FM are associated with poor SDMT performance.[59] Studies in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy have shown that damage of the left CST is associated with poor processing speed.[60–62] Whereas CST lesions have mostly been attributed to motor slowing on the written form of the SDMT, our study used the orally administered SDMT, thus minimizing the motor component of the test and highlighting the association with cognitive slowing.

Our lesion probability map findings are of particular interest with respect to the FM and posterior thalamic radiation. The FM white matter fiber bundle is one of the tracts that connects to the cingulate gyrus and posterior cingulate cortex, which are affected early in patients with Alzheimer's disease. The FM has been shown to be disrupted in early Alzheimer's disease patients

with amnestic mild cognitive impairment, compared to persons with subjective cognitive decline[63] and persons with subjective cognitive decline compared to HCs.[64] The fiber pathways of the posterior thalamic radiation connect the thalamus with the parietal and occipital lobes and typically are associated with motor and sensory information transmission. However, greater microstructural integrity in the posterior thalamic radiation has been associated with better executive functioning performance in older adults.[65]

We also found that the SDMT and Digit Span associated lesion clusters in the bilateral corona radiata. WMHs in the posterior corona radiata have shown to accelerate the brain aging process in otherwise healthy elderly with WMHs.[66] Studies using DTI have suggested that damage to these tracts is associated with executive function and/or attention capacity in participants with PD.[56]

Our goal was to study WMH specifically associated with cognitive impairments in patients with PD. In addition to the between-group differences in cognition, we incidentally found that PD participants with WMH showed worse gait and balance compared to PD without WMH, as noted on the MDS-UPDRS postural instability and gait disturbance (PIGD) subscale both On and Off dopaminergic medications. By contrast, we did not identify increased bradykinesia, rigidity, or tremor in PD with WMH. Numerous studies have found similar results, and a recent comprehensive review of the contributions of WMH to motor and gait symptoms in PD had similar conclusions[67]; namely, that WMH severity was significantly related to freezing of gait, but that the relations to bradykinesia and rigidity were inconsistent, and there was no association between WMH severity and tremor.

Methodological Considerations and Limitations

Our study has several methodological considerations. First, because the $PD^{-}WMH^{+}$ group had a relatively small sample size with only 14 subjects, the conclusions from the present work may not be generalizable to the greater PD patient population and should be validated. Second, our HC group only included 1 participant defined as WMH^{+}. We thus could not compare $HC^{-}WMH^{+}$ to $PD^{-}WMH^{+}$, which would have allowed us to determine whether the impact of WMH on cognition in PD is different from the impact on cognition in general aging. Third, our two PD-WMH groups were not matched for age. To account for this, we used standardized age- and education-matched normative values in the behavioral analyses and raw scores with age and education as covariates in the lesion probability map analyses. Fourth, our lesion probability map analyses tested for interaction effects between the PD-WMH groups and cognitive test performance. This means that our significant clusters refer to a difference in the slope of the cognitive data between the PD-WMH groups that varies as a function of cognitive performance.

In this study, we used WMH as a proxy for vascular brain injury. However, we did not find any differences between the $PD\text{-}WMH^{+/-}$ groups in current and past vascular risk factors. A possible explanation for this could be our chosen grouping, where irregular periventricular WMH in the $PD^{-}WMH^{+}$ group might reflect increased periventricular water content or an intense venous network in this region rather than arteriosclerotic or periarteriorlar tissue damage.[4] Another explanation could be that nonarteriosclerotic factors, such as orthostatic dysregulation[18,43] and watershed/border-zone infarcts, contribute to the development of WMH on MRI in PD.

Previous studies showed mixed results when considering PD cognitive impairment based on WMH and cognitive category, such as mild cognitive impairments.[48,68,69] We did find a between-group difference in the number of participants with dementia, but this result should be interpreted with caution given the very low number of demented patients per WMH group. Furthermore, we determined groups based on WMH severity type, rather than cognitive function,[69] and included punctate WMH in the $PD^{-}WMH^{-}$ group. Studies on healthy elderly adults suggest that later-stage early confluent WMHs are associated with vascular pathology and cognitive disturbances, whereas punctate WMHs are not.[7] Thus, in the lesion probability analysis, we grouped the PD participants by WMH^{+} and WMH^{-} with the aim of testing for specific location effects based on underlying pathology and associated cognitive effects. It is reassuring that despite these differences in approach, similar conclusions can be made. Namely, executive dysfunction in PD is related to the severity of WMH on MRI.

Finally, some studies have suggested that the incidental WMH observed on FLAIR could represent later-stage, as opposed to early, vascular lesions. Longitudinal studies using DTI techniques, such as neurite orientation dispersion and density imaging,[70] might be more sensitive for earlier-stage vascular lesions. Therefore, longitudinal studies should consider a mixture of techniques to determine the relationship between visibly apparent WMH and the onset of PD executive impairments.

In conclusion, our study used lesion probability mapping to determine the relationship between domain-specific PD cognitive impairments and WMH severity and location. Understanding whether vascular brain injury or other mechanisms, such as orthostatic hypotension or neuroinflammation, lead to the development of WMH in PD patients will be critical in guiding patient management given that early treatment targeting such mechanisms could mitigate some executive dysfunction in a subgroup of PD patients at risk.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution,

C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

P.L.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
C.M.: 1C, 2A, 2B, 2C, 3A, 3B
M.S.: 1C, 2B, 2C, 3A, 3B
T.F.L.: 1B, 1C, 3B
L.T.: 1C, 2A, 2C, 3B
B.C.: 1C, 2A, 2C, 3B
K.L.P.: 1A, 1B, 1C, 2A, 2C, 3A, 3B

Disclosures

Ethical Compliance Statement: This study was approved by the Stanford Institutional Review Board, and all study participants provided their informed written consent that was obtained in person. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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