White matter hyperintensity burden predicts cognitive but not motor decline in Parkinson's disease. Results from the ONDRI

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Running title: WMH burden predicted cognitive decline in PD.

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Abstract

Background: The pathophysiology of Parkinson's disease (PD) negatively affects brain network connectivity, and in the presence of brain white matter hyperintensities (WMH) cognitive and motor impairments seem to be aggravated. However, the role of WMH in predicting accelerating symptom worsening remains controversial.

Objective: To investigate whether location and segmental brain WMH burden at baseline predicts cognitive and motor declines in PD after 2 years.

Methods: 98 older adults followed longitudinally from Ontario Neurodegenerative Diseases Research Initiative (ONDRI) with PD of 3-8 years in duration were included. Percentages of WMH volumes at baseline were calculated by location (deep and periventricular) and by brain regions (frontal, temporal, parietal, occipital lobes, and basal ganglia+thalamus). Cognitive and motor changes were assessed from baseline to 2-year follow-up. Specifically, global cognition, attention, executive function, memory, visuospatial abilities, and language were assessed as were motor symptoms evaluated using MDS-UPDRS Part III, spatial-temporal gait variables, Freezing of Gait questionnaire and Activities-Specific Balance Confidence Scale.

Results: Regression analysis adjusted for potential confounders showed that total and periventricular WMH at baseline predicted decline in global cognition ($p<0.05$). Also, total WMH burden predicted the decline of executive function ($p<0.05$). Occipital WMH volumes also predicted decline in global cognition, visuomotor-attention and visuospatial-memory declines ($p<0.05$). WMH volumes at baseline did not predict motor decline.

Conclusion: WMH burden at baseline predicted only cognitive decline in PD. The motor decline observed after 2-years in these participants with early to mid-stage PD is probably related to the primary neurodegenerative process more than comorbid WM pathology.

Keywords: MDS-UPDRS-III; deep white matter hyperintensities; periventricular white matter hyperintensities, brain regions; balance confidence

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, worldwide. The pathological hallmark of PD involves accumulation of aggregated α-synuclein protein, identified as Lewy bodies and Lewy neurites, and associated neurodegeneration in the dopaminergic substantia nigra compacta as well as several other central and peripheral nervous system regions [1,2]. These structural brain changes explain the presence of motor and non-motor symptoms. Clinical symptom heterogeneity is extremely common in patients with PD, and this may be related to pathological spreading of the multisystem neurodegeneration to different brain regions and its severity in each individual.

Symptom heterogeneity among patients with PD may also be associated with copathologies including the presence of white matter hyperintensities (WMH). WMH are strongly linked with cerebral small vessel disease that can be quantified through Magnetic Resonance Imaging (MRI) [3,4]. White matter has an important role in establishing connectivity through brain neural networks that modulate motor and cognitive performance [5]. Therefore, presence of white matter lesions has been associated with worsened cognitive and motor performance in PD [3,6,7,8,9]. This association has been explained by the fact that WMH may disrupt many neurotransmission pathways, thus worsening the connectivity between subcortical-cortical tracts [10].

Although the combination of PD and WMH burden may aggravate typical cognitive and motor impairments in patients with PD, longitudinal studies investigating WMH burden as a predictor of cognitive and motor performance declines over time in PD have presented contradictory results [11,12,13,14,15], which may be explained by differences related to methodological approaches used for WMH quantification, small sample sizes and PD sample characteristics (i.e., drug-naïve patients or not; differences in disease duration and

motor and cognitive severity) included in the studies. Additionally, there is scarce and conflicting literature on whether the location of WMH (i.e., deep or periventricular) and regional brain WMH burden predicts symptoms decline, specifically regarding motor features.

The current study aimed to investigate whether the location and the segmental brain WMH burden at baseline predict cognitive and motor declines in early to mid-stage PD within 2-years of follow-up. Based on previous cross-sectional and longitudinal studies that have shown an association between WMH burden and impaired performance in non-motor and motor symptoms due to disrupting neuronal networks [3], also based on that some cognitive domain performances are related to specific brain regions and others are dependent on multiple brain regions [16,17], and considering that motor performance requires the interaction of cortical and subcortical brain areas, we hypothesized that white matter burden, specifically the total and periventricular WMH volumes, at baseline would predict different aspects of cognitive (i.e., attention, memory, executive function, language, and visuospatial abilities) and motor (i.e., motor symptoms and global functional motor performance) declines, in PD after 2 years of follow-up. We also hypothesized that increased WMH volumes from different brain regions at baseline would predict cognitive and motor declines during the follow-up.

Method

This was a longitudinal multi-site study using a convenience sample of 98 participants with 2 years of complete follow-up, between 56 - 85 years of age, with idiopathic Parkinson's disease from the Ontario Neurodegenerative Disease Research Initiative (ONDRI) cohort (https://ondri.ca/). Data representing clinical, cognition, motor, and neuroimaging accessed in the ONDRI PD cohort adhered to rigorous standards for data collection, data processing, and curation [18]. All research procedures were approved previously by multiple Human

Research Ethics Committees since ONDRI is a multi-site research. All participants provided written informed consent.

Inclusion criteria for the Parkinson's disease cohort were idiopathic Parkinson's disease based on the United Kingdom Parkinson's Disease Society Brain Bank (UKBB), including acceptable and sustained response to the dopaminergic drug therapy, time since diagnosis of PD of 3-8 years, Hoehn & Yahr (H&Y) stage 1 to 3, years of education greater than or equal to 8, Montreal Cognitive Assessment (MoCA) score ≥18/30, ability to walk with or without assistive aids [19]. The ineligibility criteria were a neurological disease other than PD (i.e., another cause of parkinsonism), unstable health condition, decompensated diabetes mellitus, history of alcohol or drug abuse, untreated major depression within 90 days of the screening visit [19,20].

Clinical assessments

Clinical assessments included gathering data on socio-demographic (age, sex, years of education), clinical history (disease duration, levodopa equivalent daily dose - LEDD, vascular risk factors, weight, height), disease stage using H&Y scale and disease severity using the MDS-UPDRS – Part III (the revised version of the Unified Parkinson's Disease Rating Scale). Clinical vascular risk factors for small-vessel disease included obtaining the presence of 5 factors: obesity, diabetes mellitus, hyperlipidemia, smoking, and high blood pressure [21]. The individual's vascular risk index (VRI) was obtained by the sum of each positive vascular risk [19]. All procedures were performed in the "on" phase of PD medications.

Motor assessment (gait, FOG and balance confidence)

Gait was assessed while participants walked a 6-meter path at their usual pace, using accelerometers (Gulf Coast Inc., Shimmer Inc) attached bilaterally to hips and ankles. Participants started walking one meter before the path and finished one meter after the end

of the path [20]. The variables gait speed (m/s), step number, and cadence (steps per minute) were obtained.

Freezing of Gait Questionnaire (FOG-Q) was used to assess the participant's severity of freezing. The FOG-Q score ranges from 0 to 24 points with a higher score indicating worse FOG [22].

The Activities-Specific Balance Confidence Scale (ABC Scale), a 16-item daily tasks questionnaire, was administered to evaluate the individuals' self-reported balance confidence [23]. Items are rated from 0% (no confidence) to 100% (complete confidence). The scale has been used to evaluate the risk of falling [24].

Cognitive assessment

Cognitive evaluation included a global cognitive performance using the Montreal Cognitive Assessment Test (MoCA), and two tests for each of the five specific cognitive domain tests as follows: attention/working memory (Trail Making Test part A and digit span forward), executive function (Trail Making Test part B and digit span backwards), memory (Brief Visuospatial Memory – Delayed Recall and Rey Auditory Verbal Learning Test – long delay), visuospatial abilities (Judgment of Line Orientation and Brief Visuospatial Memory Test-Revised – copy), and language (Boston Naming Test and category fluency – naming animals) as previously reported [20,25]. Besides MoCA total score, we also calculated MoCA index score for memory, executive function, visuospatial, language, attention, and orientation [26,27].

White matter hyperintensity volume

Multi-site 3T-MRI systems were used to acquire images in all participants using a previously published standardized, comprehensive neuroimaging protocol (i.e., Canadian Dementia Imaging Protocol) [28] and processing pipeline [29]. The WMH volumes were

generated using a multi-feature (T1, PD/T2, FLAIR) segmentation approach and manually quality controlled for potential false positives/negatives. Each lesion type was further subdivided into a region-based class (periventricular or deep) based on their 3-dimensional location by an automated algorithm as previously reported [29]. Percentages of WMH volumes per location (deep and periventricular) then were calculated in each *brain region* (frontal, temporal, parietal, occipital lobes, and basal ganglia+thalamus). The percentage of WMH volumes was used to correct for differences in head-size. The percentage of total WMH in each brain region was calculated using the total volume across all aforementioned *brain regions*.

Before image processing for volumetric extraction, all MRI scans were evaluated by a neuroradiologist (S.S.) for clinical incidental findings, and by a medical biophysicist (R.B.) and team (C.S., C.B., M.H., M.O.) to ensure high imaging quality. These assessors were blinded to the participants' clinical information.

Statistical Analysis

Measures of central tendency (i.e., means, standard deviation, and frequency) were calculated for sample characterization. Cognitive and motor performances were evaluated at baseline (T0) and after 2 years (T2) and the change in performance was calculated, by subtracting the values (Δ= T2 – T0). Differences between motor and cognitive symptoms and WMH volumes at baseline and after 2-years were analysed using two-way repeated-measures Analysis of variance (ANOVA). Partial eta-squared (ηp^2) for the between-within repeated-measures ANOVA was used to estimate effect size.

Due to the non-normal distribution, WMH volumes were transformed following the two-step method proposed by Templeton (2011)[30]. After data were transformed, Kolmogorov-Smirnov confirmed the normality of the distribution.

Multiple linear regression analysis was performed to investigate associations between WMH volumes at baseline (independent variables) and changes in cognitive and motor function (MDS-UPDRS-III, FOGQ, gait, balance confidence) performance (dependent variables).

Regression analyses were adjusted for age, sex, years of education, disease duration, LEDD, VRI, and H&Y. False discovery rate (FDR) post hocs were applied to correct p-values in each adjusted linear regression model [31]. After FDR, the alpha level for statistical significance was set at $p \leq .05$. Data analysis was carried out using the IBM SPSS 25.0 software (SPSS Inc.).

Results

From the total of 140 participants enrolled in the ONDRI-PD cohort, 42 were excluded. Therefore, 98 participants with PD were included. The main drop out reasons in the entire ONDRI PD cohort (n=140) were: withdrew consent (n=10), disease progression (n=12), adverse effect (n=1), non-informed reason (n=9), and death (n=4). Also, 6 participants were excluded because they did not complete all assessments used as dependent or independent variables in the analysis. Participants were predominantly men (80.6%; mean age 67 years), H&Y stage 2, completed 15 years of education, and had 4.6 years of disease duration. Table 1 summarizes participants' characteristics at baseline.

Table 1

WMH, cognitive, and motor changes after 2-years

The adjusted two-way repeated-measures ANOVA showed a significant main effect of time for total WMH [$F(1.00, 90.00)=27.12$; $p < 0.001$, $\eta p^2 =0.232$], and periventricular WMH [$F(1.00, 90.00)=27.51$; $p < 0.001$, $\eta p^2 =0.234$] (Table 2) with a significant increase in the total WMH volume and in the periventricular WMH volume after two years.

Related to brain regions, adjusted two-way repeated-measures ANOVA showed a significant main effect of time for total frontal WMH [$F(1.00, 90.00)=18.60$; $p < 0.001$, $\eta p^2 =0.171$]; periventricular frontal WMH [$F(1.00, 90.00)=20.33$; $p < 0.001$, $\eta p^2 =0.184$]; total parietal WMH [$F(1.00, 90.00)=22.05$; $p < 0.001$, $\eta p^2 =0.197$]; periventricular parietal WMH [$F(1.00, 97.00)=21.69$; $p < 0.001$, $\eta p^2 =0.194$]; total temporal WMH [$F(1.00, 90.00)=8.21$; $p= 0.005$, $\eta p^2 =0.084$]; periventricular temporal WMH [$F(1.00, 90.00)=8.35$; $p= 0.005$, $\eta p^2 =0.085$]; total occipital WMH [$F(1.00, 90.00)=10.01$; $p= 0.002$, $\eta p^2 =0.100$] and periventricular occipital WMH [$F(1.00, 90.00)=7.49$; $p= 0.007$, $\eta p^2 =0.077$] (Table 2). Overall, WMH volumes increased in the aforementioned brain regions during the follow-up period.

Related to cognitive symptoms, adjusted two-way repeated-measures ANOVA showed a significant main effect of time for attention/working memory [$F(1.00, 89.00)=6.45$; $p=0.01$, $\eta p^2=0.068$); executive function [$F(1.00, 90.00)=43.74$; $p=0.05$, $\eta p^2 =0.04$] and language [$F(1.00, 87.00)=8.92$; $p= 0.004$, $\eta p^2 =0.093$]. Participants on average had statistically significantly worse performance on the TMT Parts A and B, and the Boston Naming test at follow-up compared to baseline as shown in Table 2. Related to the MoCA index score, participants had a performance decline for memory index (MoCA-MIS) [$F(1.00, 89.00)=6.42$; $p=0.01$, $\eta p^2=0.067$) and visuospatial index (MoCA-VIS) [$F(1.00, 89.00)=4.37$; $p=0.04$, $\eta p^2=0.047$) within 2 years of follow-up.

Related to motor symptoms, adjusted two-way repeated-measures ANOVA showed a significant main effect of time only for MDS-UPDRS-III [$F(1.00, 97.00)=4.78$; $p=0.03$, $\eta p^2 =0.047$] (Table 2). MDS-UPDRS-III was on average higher at follow-up compared with baseline.

Table 2

Association between WMH and cognition overtime

A multiple linear regression adjusted for potential confounders showed that transformed percentage of total and periventricular WMH volumes at baseline predicted the decline of global cognition after 2-years in participants with PD (p-value < 0.05). Also, transformed percentage of total WMH volume predicted the decline of executive function after p-value FDR corrections (p-value < 0.05). On the other hand, multiple regression analysis showed that WMH volumes at baseline did not predict motor declines (Table 3).

Table 3

Regarding brain regions, our results showed an association between transformed percentage of total WMH in the occipital lobe at baseline and the decline in global cognition, attention/working memory, and memory after p-value FDR corrections. No associations were observed with motor symptom changes after a 2-years follow-up (Table 4).

Table 4

Discussion

In the current study, we investigated whether the WMH burden at baseline predicted cognitive and motor decline over a 2-year follow-up period in participants with PD who were classified at baseline as having mild to moderate disease severity based on MDS-UPDRS-III and with an early to mid-stage of PD based on H&Y Scale. Besides the total WMH volumes, we investigated whether WMH location (i.e. deep and periventricular) and brain regions (frontal, parietal, temporal, occipital, and basal ganglia+thalamus) differently predict the symptom decline in PD. We confirmed our hypotheses that total and periventricular WMH burden at baseline predicted the global cognitive decline, independent of age, sex, years of education, LEDD, disease duration, VRI, and disease stage. Also, total WMH burden predicted the decline of executive

function. Regarding brain regions, WMH volumes in the occipital lobe at baseline also predicted the decline of global cognition. Our hypothesis confirmed associations between WMH regions and cognitive domains, but only for occipital WMH burden and attention/working memory, and visuospatial memory. Our hypothesis related to motor symptoms was not confirmed, since the WMH volume at baseline did not significantly predict motor decline after 2 years. Cognitive impairment observed in PD has been associated with frontal-striatal circuit dysfunction and cholinergic pathways disruption [32]. In our cohort study, neuropsychological assessments showed that attention/working memory, executive function, and language were the cognitive domains that declined within a 2-year follow-up.

In the presence of white matter burden, cognitive impairment seems to be aggravated in PD due to the disruption of many neurotransmission pathways that affect the connectivity between subcortical-cortical tracts [10,33]. This aligns with our results that also showed that total WMH volume at baseline predicts the decline in global cognition in PD, independent of potential confounding variables (i.e. age, sex, years of education, disease duration, LEDD, VRI, and H&Y). Specifically, Dadar et al (2018, n=365)[12] found that MoCA decline is associated with a high WMH burden at baseline in PD. Other longitudinal studies showed that the white matter burden predicts the progression to mild cognitive impairment (MCI) and dementia in PD which also is characterized by a significant reduction in global cognitive performance [15,34,35]. In contrast, other longitudinal studies have not observed an association between WMH and cognitive decline [13,14]. Discrepancies between previous studies and ours may be explained on the basis of sample size differences[13] or the patients' characteristics (i.e., drug-naïve patients)[14].

Our results also are in agreement with those found by de Shipper et al (2019, n=163)[36] and Mak et al (2015, n=90)[37] who observed in their cross-sectional studies in PD

that WMH volumes were larger in periventricular compared to deep brain location. Also, our results showed that deep and periventricular WMH volumes predicted worsening of global cognition, however, after FDR adjusted p-value, only periventricular WMH burden predicted cognitive decline, which is aligned with previous studies that showed periventricular WMHs are more associated with cognitive impairment than are deep WMH [37,38,39]. On the other hand, Rane et al (2020, n=41)[40] observed that deep WMH burden is more associated with worsened global, executive function, and language performance than periventricular WMH in PD. Possible explanations for such discrepancies include small sample sizes, different population characteristics, unbalanced numbers of men and women (more women than men), few confounding variables used in the statistical adjustments, and the lack of p-value corrections. These issues should be further investigated in future studies.

Fang et al (2021, n=19)[9], in a cross-sectional study, observed that total and periventricular WMH, and WMH in frontal, pre-frontal, and parietal regions were associated with MoCA scores in PD. Our results showed that the percentage of WMH volume at baseline in the occipital lobe is associated with the change in MoCA (i.e., larger WMH volume at baseline is associated with the decline in MoCA performance). Considering our results, WMH burden is more associated with global cognition decline than specific cognitive domains, which was suggested previously by Mak et al (2015)[37] in their cross-sectional study.

A possible explanation for the WMH burden total and periventricular to specifically predict global cognition and executive function (set-shifting) declines, is the fact that MoCA total score includes several different cognitive domains (memory, attention/working memory, executive function, language, and visuospatial) in its total score; while white matter lesions may disrupt brain connectivity consequently slowing down processing speed [41] used for executive functions. Therefore, the WMH burden may

be a marker of global cognitive performance and executive function decline, despite limited longitudinal associations with all cognitive domains. We cannot discard, however, that a longer longitudinal design would significantly predict decline in other cognitive domains, which is supported by the fact that before FDR p-value corrections WMH burden predicted some other cognitive domain declines. Therefore, a longer follow up and/or a larger sample would have increased the power of the associations consequently making association statistically significant with more cognitive domains. Noteworthy, we also found a very specific association between larger WMH burden in the occipital lobe at baseline and decline in visuospatial function overtime. This suggests that WMH in visual regions should be taken as an important limitation factor since vision is a sensory feedback highly used by PD patients to compensate for their sensorimotor impairments)[42] including balance and gait difficulties and activities of daily living[43] relying on visual function including driving, cocking, negotiating obstacles, etc…. Clinical applicability of these findings should be put into perspective for targeted rehabilitation strategies when assessing the burden and location of WMH.Similar to our findings, in a 4-year longitudinal study Scamarcia et al (2022, n=154)[15] observed that the increase in WMH volumes was associated with worse global cognition in PD. Our study, however, was able to demonstrate that WMH can predict global cognitive decline in a much shorter period of time (2-years follow-up) which can function as an efficient guide for longitudinal designs of future interventional studies.

Similar to Scamarcia et al (2022)[15], we also observed an association between WMH volumes at baseline and language decline. However, after FDR corrections, the associations between WMH location (i.e., total and deep WMH) and regional brain segmentation (i.e. frontal, parietal, temporal) and language were not maintained. Communication impairment is a common manifestation in patients with PD and it is influenced by both motor (i.e. speech and muscle control) and cognitive dysfunctions [44]. A

larger sample could have increased the statistical power of the study making p-values lower, and therefore resistant to FDR corrections or a longer follow-up as conducted by Scamarcia et al (2022)[15], i.e., 4 years, would be necessary. Additionally, the brain segmentation used in our study might not have been sensitive to identify the language decline within 2 years of disease progression.

Although the multiple regression analysis revealed associations between total and periventricular WMH and WMH in frontal, parietal and temporal lobes at baseline and executive function decline, after p-value FDR corrections, the significant values were no longer observed, except for the total WMH. After p-value FDR corrections, only occipital WMH burden maintained the prediction of attention/working memory, and memory declines after 2 years. Occipital cortex is involved with visuospatial function and shape recognition[45], which may explain the association observed between WMH lesions and worse performance of BVMT delayed recall test and Trail Making test part A after 2 years of follow-up. This is the first time a study showing an association between larger WMH burden in the occipital cortex and decline in cognitive tests requiring strong visuospatial capabilities in idiopathic PD.

In cross-sectional studies, white matter burden has been associated with greater motor impairments in PD [7,8,9,46,47]. WMHs have been proposed to impair the neuronal networks involved in motor activities[48]. Although de Shipper et al (2019)[36] in a cross-sectional study found that periventricular WMH volumes were associated with gait impairment and postural instability using MDS-UPDRS-III, we did not find associations between WMH volumes and change in gait variables and ABC scale score motors after 2-years of follow-up.

Regarding longitudinal studies, Pozorski et al (2019)[13], in an 18-month follow-up, showed an association between the increase of WMH accumulation and worsened UPDRS

motor score in PD, without association with cognitive decline (sample size=29). Dadar et al (2020)[33], in 36 months of follow-up, observed that WMH was associated with an increase of cognitive and motor deficits (UPDRS-III and gait impairment) in PD (sample size=39 at 36 months). However, our results did not show any association between WMH at baseline and motor decline after 2 years. Aligned with our results, Song et al (2013, n=56)[49] followed participants with early stage of PD (H&Y stage 1) for 2 years and did not observe an association between WMH scores and motor decline. Also, this association remained non-significant in a longer follow-up of 4 years conducted by Scamarcia et al (2022)[15].

Also contrary to our results, Chung et al (2019, n=268)[50], in a retrospective longitudinal study, observed that patients with PD and moderate-severe WMH evaluated using visual rating scale scores had worse motor deficits and had a higher risk of developing FOG over time. Our study, however, shows that WMH at baseline did not predict worsened FOG after 2-years of follow-up. Our failure to show a clear relationship between WMH and motor decline in early to mid-stage PD suggests that the change in motor performance over 2 years in this patient population may depend more heavily on the underlying neurodegenerative process than the presence of vascular copathology or because motor symptoms in the participants with PD from the ONDRI cohort have remained more stable.

Our study has several strengths including the use of a 3.0 T MRI system to evaluate WMH, and the evaluation of WMH location (i.e., periventricular and deep) and brain regions involvement (frontal, parietal, temporal, occipital, and basal ganglia + thalamus), as well as total brain WMH volumes. Additionally, potential confounding factors were included in our statistical model as covariates, such as the sum of risk factors for brain vascular lesions to prevent comorbidity bias in our results. One study limitation was the short follow-up which prevents us from verifying the ability of WMH burden to predict changes over the entirety of patients' disease progression. Additionally, the lack of more

refined brain segmentation may have prevented us to observe significant associations between WMH burden with language or other cognitive functions. Therefore, further studies should include more participants and a more refined brain segmentation of the temporal lobe into anterior/posterior, and/or superior, middle, and inferior temporal gyrus if aiming to further investigate the interplay between PD and white matter burden with respect to language.

Conclusions

High white matter burden at baseline predicts the global cognitive decline in participants with PD after 2-years of follow-up. Increased WMH volume in occipital lobe specifically predicts attention/working memory and visuospatial memory declines. WMH burden can be used as an index of cognitive prognosis in PD. Further studies are still needed to understand the effect of reducing WMH burden, through risk factor management, as a potential strategy to slow down the cognitive decline in Parkinson's disease

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Author's roles:

Daniela Cristina Carvalho de Abreu, Frederico Pieruccini-Faria and Manuel Montero-Odasso contributed to the study concept, analysis, writing, editing the final version of the manuscript. Anthony E. Lang, Connie Marras, Paula McLaughlin, Robert Bartha, Sean Symons, Mario Masellis, Sandra E. Black, William McIlroy, Manuel Montero-Odasso contributed to the conceptualization of the ONDRI platforms in the study, clinical assessments, physical resources, writing (review and editing), supervision, and funding acquisition.

Paula McLaughlin, Donna Kwan, Alicia Peltsch, Joseph B. Orange, Brian Levine, Angela C. Roberts, Angela K. Troyer contributed to assessments and curation of neuropsychology data.

Julia Fraser, Benjamin Cornish, Karen Van Ooteghem, Yanina Sarquis-Adamson, Alanna Black, Frederico Pieruccini-Faria contributed to the data curation of gait data and physical assessments.

Joel Ramirez, Christopher Scott, Melissa Holmes, David P. Breen, Miracle Ozzoude, Sabrina Adamo, Stephen R. Arnott, David Grimes, Thomas Steeves, Nuwan Nanayakkara, Seyyed Mohammad Hassan Haddad, Courtney Berezuk, Mojdeh Zamyadi, Athena Theyers contributed to the analysis of magnetic resonance data and assessments.

Malcolm Binns, Stephen Strother, Stephen R. Arnott, Derek Beaton, Wendy Lou, Sujeevini Sujanthan, Kelly Sunderland and Mandar Jog contributed to general data curation. Brian Tan contributed to data curation of clinical data.

All authors read and approved the final manuscript.

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Table 1. Participant's characteristics (mean ± standard deviation and frequencies).

Baseline characteristics	**PD (N=98)**
Age (years)	67.55±5.60
Sex (men, %)	79 (80.6%)
Years of education	15.66±2.65
Height (m)	1.73±0.09
Weight (kg)	82.33±15.82
Body mass index (kg/m^2)	27.29±4.82
Disease duration (years)	4.64±1.59

Table 2. Baseline and 2-years follow-up of white matter hyperintensity (WMH) volumes, cognitive and motor variables (mean ± SD).

PD (N=98)	Baseline	2-years follow-up	p-value
White Matter Hyperintensities			
total WMH mm^3	4901.34±6411.61	6832.33±7934.57	<0.001*
total periventricular WMH mm^3	4419.43±5938.79	6189.85±7491.98	<0.001*
total deep WMH mm^3	481.91±682.43	642.48±831.67	0.56
Regional brain White Matter Hyperintensities			
Total WMH - Frontal mm^3	1944.76±2703.41	2455.07±3151.97	<0.001*
Periventricular WMH - Frontal mm^3	1725.97±2460.11	2178.03±2888.33	<0.001*
Deep WMH – Frontal mm^3	218.79±438.35	277.04±505.973	0.35
Total WMH – Parietal mm^3	1607.95±2789.72	2284.91±3661.35	<0.001*
Periventricular WMH – Parietal mm^3	1393.47±2677.66	2083.44±3565.75	<0.001*
Deep WMH – Parietal mm^3	214.48±372.65	201.47±311.21	0.21
Total WMH – Temporal mm^3	595.51±792.45	878.15±891.01	0.005*
Periventricular WMH - Temporal mm^3	548.98±764.89	822.09±870.12	0.005*
Deep WMH – Temporal mm^3	46.53±89.58	56.06±84.27	0.52
Total WMH – Occipital mm^3	711.00±965.02	1047.24±1241.19	0.002*
Periventricular WMH - Occipital mm^3	662.45±980.59	958.67±1270.16	0.007*
Deep WMH – Occipital mm^3	48.55±93.53	88.57±205.98	0.88
Total WMH - Basal ganglia mm^3	165.62±216.76	166.94±249.58	0.97
Periventricular WMH - Basal ganglia mm^3	145.00±195.96	147.61±233.88	0.21
Deep WMH – Basal ganglia mm^3	20.62±51.07	19.33±36.52	0.14
Cognitive function			
MoCA (0-30)	26.33±2.43	25.60±3.02	0.06
MoCA-MIS (0-15)	12.10±3.15	11.76±2.99	0.01*
MoCA-EIS (0-13)	11.69±1.42	11.49±1.49	0.56
MoCA-VIS (0-7)	6.33±0.86	6.04±1.05	0.04*
MoCA-LIS (0-6)	5.32±0.88	5.24±0.93	0.53
MoCA-AIS (0-18)	16.86±1.47	16.61±1.47	0.18
MoCA-OIS (0-6)	5.88±0.33	5.79±0.54	0.67
TMT A (sec)	44.10±17.44	49.55±27.04	0.01*
Digit-span forward (0-16), Mean±SD	10.58±2.25	10.53±2.19	0.46
TMT B (sec)	111.07± 62.51	125.95±75.14	0.05*
Digit span backward (0-14), Mean±SD	7.14±2.10	6.99±2.19	0.96
BVMT-delayed recall, Percent retained (0-100%)	89.28±13.05	86.94±21.35	0.12
RAVLT long-delay (0-15), Mean±SD	7.42 ±3.50	7.24±3.71	0.32
Judgment of Line Orientation (0-30)	25.54±4.55	24.88±4.62	0.14
BVMT-R copy (0-12)	11.49±0.84	10.67±1.48	0.83
Boston Naming Test (0-100%)	93.86±7.98	89.02±10.66	0.004*
Category fluency – naming animals	19.27±5.95	19.06±6.5	0.47
Motor function			
MDS-UPDRS – Part III (0-132)	21.86±10.73	24.17±13.64	0.03*
FOGQ (0-24)	2.87±3.67	3.49±3.62	0.40
Gait speed (m/s)	1.02±0.24	1.08±0.27	0.19
Cadence (step/min)	104.68±22.22	106.75±7.96	0.58
Step number	11.55±2.28	10.71±2.57	0.16
ABC scale (0-100%)	87.06±14.88	80.72±19.41	0.49

PD= Parkinson's disease, WMH = white matter hyperintensity, MoCA = Montreal Cognitive Assessment; MoCA-MIS= MoCA-Memory Index score; MoCA-EIS = MoCA-Executive Index score; MoCA-VIS = MoCA-

Visuospatial Index score; MoCA-LIS = MoCA-Language Index score; MoCA-AIS = MoCA-Attention Index score; MoCA-OIS = MoCA-Orientation Index score; TMT A = Trail Making test part A, TMT B = Trail Making test part B, BVMT- delayed recall = Brief Visuospatial Memory – delayed recall, RAVLT = Rey Auditory Verbal Learning Test-long delay; BVMT-R copy = Brief Visuospatial Memory Test-Revised – copy; MDS-UPDRS – III= revision version of the Unified Parkinson's Disease Rating Scale - motor part, FOGQ = Freezing of Gait Questionnaire, ABC scale = Activities-Specific Balance Confidence Scale; SD= standard deviation *$p < 0.05$ in the comparison between baseline and 2-year follow-up according to two-way repeated-measures ANOVA, adjusted for age, years of education, sex, disease duration, levodopa equivalent daily dose, Hoehn & Yahr, and vascular risk index.

Table 3. Association between the percentage of total, deep and periventricular WMH volumes at baseline and changes (Δ) in cognition and motor symptoms after 2-years in PD.

Independent variable	**Dependent variable**			**FDR adjusted P-values**
Predictors	**Variables**			
		Multiple regression	**Beta, eta², 95% CI, p-value**	
% total WMH	Cognition	Δ global cognition (MoCA)	-2.62, 0.12, -4.01 - -1.15, **0.001**	**0.01**
		Δ attention and working memory (TMT A)	12.15, 0.17, -1.22 – 25.52, 0.07	0.20
		Δ attention and working memory (Digit-span forward)	-0.09, <0.001, -1.01 – 0.83, 0.85	0.93
		Δ executive function (TMT B)	34.48, 0.07, 8.85 – 60.13, **0.009**	**0.05**
		Δ executive function (Digit span backward)	-0.497, 0.01, -1.54 – 0.55, 0.35	0.64
		Δ memory (BVMT-delayed recall)	-3.72, 0.003; -17.00 – 9.57, 0.58	0.71
		Δ memory (RAVLT long-delay)	-0.45, 0.004, -1.97 – 1.07, 0.56	0.77
		Δ language (Boston)	-4.93, 0.04, -9.66 - -0.19, **0.04**	0.15
		Δ language (category fluence)	-1.81, 0.02, -4.59 – 0.98, 0.20	0.44
		Δ visuospatial abilities (JLO)	0.12, <0.001, -2.25 – 2.49, 0.92	0.92
		Δ visuospatial abilities (BVMT-R copy)	-0.43, 0.01, -1.34 – 0.47, 0.35	0.55
	Motor function	**Motor symptoms**	**Beta, eta², 95% CI, p-value**	**--**
		Δ MDS-UPDRS-III	4.29, 0.03, -0.99 – 9.58, 0.11	0.66
		Δ FOGQ	-0.33, 0.001, -2.43 – 1.75, 0.75	0.75
		Global motor performance	**Beta, eta², 95% CI, p-value**	--
		Δ gait speed	-0.10, 0.03, -0.24 – 0.04, 0.15	0.45
		Δ step number	0.83, 0.02, -0.56 – 2.23, 0.24	0.36
		Δ cadence	2.30, 0.001, -11.55 – 16.16, 0.74	0.88
		Δ ABC scale	-5.34, 0.02, -13.60 – 2.92, 0.20	0.40
% deep WMH	Cognition	Δ global cognition (MoCA)	-11.17, 0.05, -21.72 - -1.70, **0.02**	0.22
		Δattention and working memory (TMT A)	15.12, 0.001, -72.08 – 102.32, 0.73	1
		Δ attention and working memory (Digit-span forward)	1.004, 0.001, -4.89 – 6.89, 0.74	0.90
		Δ executive function (TMT B)	133.73, 0.03, -34.21 – 301.66, 0.12	0.33
		Δ executive function (Digit span backward)	-2.49, 0.006, -9.19 – 4.19, 0.46	0.84
		Δ memory (BVMT-delayed recall)	1.19, <0.001, -85.34 – 87.72, 0.98	0.98
		Δ memory (RAVLT long-delay)	-11.79, 0.06, -21.39 - -2.18, **0.02**	0.11
		Δ language (Boston)	-33.77, 0.05, -63.97 - -3.56, **0.03**	0.10
		Δ language (category fluence)	-7.77, 0.008, -25.71 – 10.16, 0.39	0.85
		Δ visuospatial abilities (JLO)	-2.58, 0.001, -17.4 – 12.26, 0.73	1
		Δ visuospatial abilities (BVMT-R copy)	-0.14, <0.001, -5.91 – 5.64, 0.96	1
	Motor function	**Motor symptoms**	**Beta, eta², 95% CI, p-value**	--
		Δ MDS-UPDRS-III	22.53, 0.02, -12.17 – 57.23, 0.20	0.60
		Δ FOGQ	2.45, 0.002, -10.90 – 15.82, 0.72	0.86
		Global motor performance	**Beta, eta², 95% CI, p-value**	--
		Δ gait speed	-0.74, 0.03, -1.61 – 0.13, 0.09	0.54
		Δ step number	3.68, 0.009, -5.32 – 12.69, 0.42	0.63
		Δ cadence	-13.35, 0.001, -103.49 – 76.79, 0.77	0.77

		Δ ABC scale	-23.36, 0.009, -75.70 – 28.98, 0.37	0.74
% periventricular WMH	Cognition	Δ global cognition (MoCA)	-2.89, 0.12, -4.51 - -1.29, **0.001**	**0.01**
		Δattention and working memory (TMT A)	14.20, 0.04, -0.45 - 28.85, 0.06	0.22
		Δ attention and working memory (Digit-span forward)	-0.11, 0.001, -1.13 – 0.91, 0.83	0.91
		Δ executive function (TMT B)	33.93, 0.06, 6.23 – 61.62, **0.02**	0.11
		Δ executive function (Digit span backward)	-0.56, 0.01, -1.71 – 0.59, 0.33	0.52
		Δ memory (BVMT-delayed recall)	-2.30, 0.001, -16.93 – 12.32, 0.75	1
		Δ memory (RAVLT long-delay)	-0.23, 0.001, -1.91 – 1.45, 0.78	0.95
		Δ language (Boston)	-4.40, 0.03, -9.64 – 0.84, 0.09	0.24
		Δ language (category fluence)	-1.78, 0.01, -4.86 – 1.29, 0.25	0.45
		Δ visuospatial abilities (JLO)	-0.05, <0.001, -2.65 – 2.56, 0.97	0.97
		Δ visuospatial abilities (BVMT-R copy)	-0.61, 0.02, -1.61 – 0.38, 0.22	0.48
	Motor function	**Motor symptoms**	**Beta, eta^2, 95% CI, p-value**	**--**
		Δ MDS-UPDRS-III	5.09, 0.03, -0.73 – 10.91, 0.08	0.48
		Δ FOGQ	-0.30, 0.001, -2.61 – 2.00, 0.79	0.79
		Global motor performance	**Beta, eta^2, 95% CI, p-value**	--
		Δ gait speed	-0.11, 0.02, -0.26 – 0.04, 0.15	0.45
		Δ step number	1.04, 0.02, -0.50 – 2.58, 0.18	0.36
		Δ cadence	3.84, 0.003, -11.50 – 19.18, 0.62	0.74
		Δ ABC scale	-6.12, 0.02, -15.23 – 2.98, 0.18	0.27

% total WMH = percentage of total white matter hyperintensity; % deep WMH = percentage of deep white matter hyperintensity; % periventricular WMH = percentage of periventricular white matter hyperintensity, MoCA = Montreal Cognitive Assessment ; TMT A = Trail Making test part A, TMT B = Trail Making test part B, BVMT- delayed recall = Brief Visuospatial Memory – delayed recall, RAVLT = Rey Auditory Verbal Learning Test-long delay; JLO= Judgment of Line Orientation; BVMT-R copy = Brief Visuospatial Memory Test-Revised – copy; MDS-UPDRS – III= revision version of the Unified Parkinson's Disease Rating Scale - motor part, FOGQ = Freezing of Gait Questionnaire, ABC scale = Activities-Specific Balance Confidence Scale, FDR= false discovery rate. Statistical model adjusted for age, sex, years of education, disease duration, levodopa equivalent daily dose, Hoehn & Yahr, and vascular risk index. Significant associations at p<.05 in bold.

Table 4. Association between brain regional WMH volumes at baseline and changes (Δ) in cognition and motor symptoms after 2-years of follow-up in PD.

Independent variable **Predictors**	**Dependent variable**			**FDR adjusted P-values**
Brain region WMH	**Variables**			
% Frontal WMH	Cognition	**Multiple regression**	**Beta, eta², 95% CI, p-value**	
		Δ global cognition (MoCA)	-1.69, 0.07, -2.90 - -0.47, **0.007**	0.07
		Δattention and working memory (TMT A)	9.75, 0.03, -1.15 – 20.65, 0.08	0.22
		Δ attention and working memory (Digit-span forward)	-0.15, 0.002, -0.88 – 0.57, 0.67	0.73
		Δ executive function (TMT B)	23.19, 0.05, 2.71 – 43.67, **0.03**	0.16
		Δ executive function (Digit span backward)	-0.43, 0.01, -1.25 – 0.39, 0.30	0.47
		Δ memory (BVMT-delayed recall)	-4.83, 0.08, -15.85 – 6.19, 0.38	0.52
		Δ memory (RAVLT long-delay)	-0.67, 0.01, -1.88 – 0.54, 0.27	0.59
		Δ language (Boston)	-4.01, 0.05, -7.82 - -0.20, **0.04**	0.14
		Δ language (category fluence)	-1.18, 0.01, -3.39 – 1.02, 0.28	0.51
		Δ visuospatial abilities (JLO)	0.13, <0.001, -1.76 – 2.03, 0.89	0.89
		Δ visuospatial abilities (BVMT-R copy)	-0.28, 0.007, -1.00 – 0.43, 0.43	0.52
	Motor function	**Motor symptoms**	**Beta, eta², 95% CI, p-value**	**--**
		Δ MDS-UPDRS-III	4.34, 0.04, 0.11 – 8.58, **0.04**	0.24
		Δ FOGQ	-0.25, 0.001, -1.90 – 1.39, 0.76	0.76
		Global motor performance	**p-value; Beta; eta²**	--
		Δ gait speed	-0.09, 0.03, -0.22 – 0.02, 0.11	0.33
		Δ step number	0.67, 0.02, -0.45 – 1.79, 0.23	0.46
		Δ cadence	4.41, 0.008, -6.70 – 15.53, 0.43	0.51
		Δ ABC scale	-3.99, 0.02; -10.58 – 2.58, 0.23	0.34
% Parietal WMH	Cognition	**Multiple regression**	**Beta, eta², 95% CI, p-value**	**--**
		Δ global cognition (MoCA)	-1.37, 0.07, -2.37 - -0.37, **0.008**	0.08
		Δattention and working memory (TMT A)	6.05, 0.02, -2.97 – 15.06, 0.18	0.33
		Δ attention and working memory (Digit-span forward)	-0.004, <0.001, -0.61 – 0.59, 0.98	0.98
		Δ executive function (TMT B)	16.71, 0.04, -0.25 – 33.68, **0.05**	0.18
		Δ executive function (Digit span backward)	-0.20, 0.004, -0.89 - 0.48, 0.55	0.75
		Δ memory (BVMT-delayed recall)	-2.11, 0.002, -10.94 – 6.72, 0.64	0.70
		Δ memory (RAVLT long-delay)	-0.45, 0.009, -1.44 – 0.54, 0.37	0.58
		Δ language (Boston)	-3.48, 0.05, -6.60 - -0.37, **0.03**	0.16
		Δ language (category fluence)	-1.69, 0.04, -3.51 – 0.12, 0.06	0.16
		Δ visuospatial abilities (JLO)	0.46, 0.004, -1.09 – 2.01, 0.56	0.68
		Δ visuospatial abilities (BVMT-R copy)	-0.49, 0.03, -1.08 – 0.09, 0.10	0.22
	Motor function	**Motor symptoms**	**Beta, eta², 95% CI, p-value**	**--**
		Δ MDS-UPDRS-III	1.81, 0.01, -1.67 – 5.31, 0.30	0.60
		Δ FOGQ	-0.43, 0.004, -1.79 – 0.94, 0.53	0.63
		Global motor performance	**Beta, eta², 95% CI, p-value**	--
		Δ gait speed	-0.05, 0.02, -0.14 – 0.03, 0.24	0.72
		Δ step number	0.59, 0.02, -0.33 – 1.52, 0.21	1
		Δ cadence	-0.03, <0.001, -9.22 – 9.15, 0.99	0.99

		Δ ABC scale	-2.80, 0.01, -8.18 – 2.58, 0.30	0.45
% Temporal WMH	Cognition	**Multiple regression**	**Beta, eta², 95% CI, p-value**	--
		Δ global cognition (MoCA)	-2.90, 0.05, -5.43 - -0.37, **0.02**	0.22
		Δattention and working memory (TMT A)	7.68, 0.005, -15.05 – 30.41, 0.50	0.55
		Δ attention and working memory (Digit-span forward)	0.60, 0.007, -0.90 – 2.11, 0.43	0.52
		Δ executive function (TMT B)	46.17, 0.05, 3.83 – 88.52, **0.03**	0.16
		Δ executive function (Digit span backward)	-1.35, 0.03, -3.04 – 0.35, 0.12	0.26
		Δ memory (BVMT-delayed recall)	-10.94, 0.01, -32.79 – 10.92, 0.32	0.44
		Δ memory (RAVLT long-delay)	-1.51, 0.02, -3.99 – 0.97, 0.23	0.42
		Δ language (Boston)	-8.18, 0.04, -15.88 - -0.49, **0.04**	0.14
		Δ language (category fluence)	-4.15, 0.04, -8.69 – 0.38, 0.07	0.19
		Δ visuospatial abilities (JLO)	1.23, 0.004, -2.62 – 5.09, 0.53	0.53
		Δ visuospatial abilities (BVMT-R copy)	-0.81, 0.01, -2.29– 0.67, 0.28	0.44
	Motor function	**Motor symptoms**	**Beta, eta², 95% CI, p-value**	--
		Δ MDS-UPDRS-III	9.20, 0.05, 0.61 – 17.79, **0.04**	0.24
		Δ FOGQ	-1.53, 0.009, -4.95 – 1.89, 0.37	0.55
		Global motor performance	**Beta, eta², 95% CI, p-value**	--
		Δ gait speed	-0.11, 0.01, -0.35 – 0.12, 0.33	0.66
		Δ step number	1.61, 0.02, -0.71 – 3.95, 0.17	0.51
		Δ cadence	9.83, 0.01, -13.04 – 32.70, 0.39	0.46
		Δ ABC scale	-2.57, 0.002, -16.01 – 10.86, 0.70	0.70
% Occipital WMH	Cognition	**Multiple regression**	**Beta, eta², 95% CI, p-value**	--
		Δ global cognition (MoCA)	-1.41, 0.09, -2.33 - -0.49, **0.003**	**0.03**
		Δattention and working memory (TMT A)	9.96, 0.06, 2.11 – 17.82, **0.01**	**0.04**
		Δ attention and working memory (Digit-span forward)	-0.28, 0.01, -0.84 – 0.27, 0.31	0.34
		Δ executive function (TMT B)	11.14, 0.02, -4.89 – 27.17, 0.17	0.26
		Δ executive function (Digit span backward)	-0.46, 0.02, -1.09 – 0.17, 0.15	0.27
		Δ memory (BVMT-delayed recall)	-11.23, 0.08, -19.18 - -3.29, **0.006**	**0.03**
		Δ memory (RAVLT long-delay)	-0.47, 0.01, -1.41 – 0.46, 0.31	0.37
		Δ language (Boston)	-2.36, 0.03, -5.23 – 0.51, 0.10	0.22
		Δ language (category fluence)	-1.47, 0.03, -3.16 – 0.21, 0.08	0.22
		Δ visuospatial abilities (JLO)	-0.42, 0.004, -1.84 – 1.00, 0.56	0.56
		Δ visuospatial abilities (BVMT-R copy)	0.29, 0.01, -0.26 – 0.84, 0.30	0.41
	Motor function	**Motor symptoms**	**Beta, eta², 95% CI, p-value**	--
		Δ MDS-UPDRS-III	1.89, 0.01, -1.41 – 5.20, 0.26	0.78
		Δ FOGQ	0.10, <0.001, -1.16 – 1.38, 0.87	1
		Global motor performance	**Beta, eta², 95% CI, p-value**	--
		Δ gait speed	-0.06, 0.02, -0.15 – 0.03, 0.16	0.96
		Δ step number	0.52, 0.02, -0.39 – 1.44, 0.26	0.52
		Δ cadence	-0.73, <0.001, -9.82 – 8.36, 0.87	0.87
		Δ ABC scale	0.83, 0.001, -4.19 – 5.85, 0.74	1
% Basal Ganglia + Thalamus	Cognition	**Multiple regression**	**Beta, eta², 95% CI, p-value**	--
		Δ global cognition (MoCA)	-0.62, 0.006, -2.25 – 1.02, 0.45	0.99
		Δattention and working memory (TMT A)	0.44, <0.001, -13.34 – 14.23, 0.95	0.95
		Δ attention and working memory (Digit-span forward)	0.23, 0.003, -0.72 – 1.19, 0.62	0.97
		Δ executive function (TMT B)	11.97, 0.08, -15.29 – 39.22, 0.38	1

		Δ executive function (Digit span backward)	0.25, 0.002, -0.83 – 1.35, 0.64	0.88
		Δ memory (BVMT-delayed recall)	4.38, 0.004, -10.03 – 18.79, 0.55	1
		Δ memory (RAVLT long-delay)	1.49, 0.04, -0.08 – 3.08, 0.06	0.33
		Δ language (Boston)	3.49, 0.02, -1.42 – 8.42, 0.16	0.58
		Δ language (category fluence)	-0.36, 0.001, -3.28 – 2.56, 0.81	0.99
		Δ visuospatial abilities (JLO)	-0.14, <0.001, -2.56 – 2.28, 0.90	0.99
		Δ visuospatial abilities (BVMT-R copy)	-1.35, 0.08, -2.27 - -0.42, **0.005**	0.06
	Motor function	**Motor symptoms**	**Beta, eta^2, 95% CI, p-value**	**--**
		Δ MDS-UPDRS-III	-1.13, 0.002, -6.83 – 4.57, 0.68	1
		Δ FOGQ	-0.20, <0.001, -2.38 – 1.97, 0.85	1
		Global motor performance	**Beta, eta^2, 95% CI, p-value**	--
		Δ gait speed	0.11, 0.02, -0.04 – 0.25, 0.16	0.32
		Δ step number	-1.30, 0.04, -2.84 – 0.23, 0.09	0.54
		Δ cadence	0.31, <0.001, -15.09 – 15.71, 0.96	0.96
		Δ ABC scale	-7.13, 0.03, -15.92 – 1.66, 0.11	0.33

% total WMH = percentage of total white matter hyperintensity, MoCA = Montreal Cognitive Assessment, TMT A = Trail Making test part A, TMT B = Trail Making test part B, BVMT- delayed recall = Brief Visuospatial Memory – delayed recall, RAVLT = Rey Auditory Verbal Learning Test-long delay, JLO= Judgment of Line Orientation; BVMT-R copy = Brief Visuospatial Memory Test-Revised – copy; MDS-UPDRS – III= revision version of the Unified Parkinson's Disease Rating Scale - motor part, FOGQ = Freezing of Gait Questionnaire, ABC scale = Activities-Specific Balance Confidence Scale, FDR= false discovery rate. Statistical model adjusted for age, sex, years of education, disease duration, levodopa equivalent daily dose, Hoehn & Yahr, and vascular risk index. Significant associations at $p<.05$ in bold.