Associations of White Matter Lesion Patterns with Clinical Features of Parkinson's Disease Through Multi-Site MRI Analysis

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Background and Aims

Accumulating evidence suggests **neurovascular dysfunction** may be implicated **in Parkinson's disease** (PD)[1,2]. **White matter lesions** (WML) are an accepted neuroimaging marker of small vessel disease[3].

Findings on WML in PD remain conflicted[4,5], likely due to the heterogeneity of the disease and methodological approaches. We performed an initial **large-data analysis** of **WML patterns** and associations with **clinical features** in a multi-site cohort from the **ENIGMA-PD** (Enhancing Neuroimaging Genetics through Meta Analysis) consortium.

Methods

T1 and **FLAIR** images for all subjects were input into our previously developed **ENIGMA-PD-WML pipeline** (https://github.com/UCL-ARC/Enigma-PD-WML) which performs automated WML segmentation using the UNet-pgs algorithm[6]. **Binary WML maps** in MNI space were generated for group analyses.

Regional analyses were performed using the Bullseye[7] tool and **voxel-wise analyses** were performed using NiiStat[8] in MATLAB.

Associations were assessed between WML and **Hoehn and Yahr** (H&Y) stage, **MDS-UPDRS Part III** scores, **MoCA** scores and **subtype** in PD patients and MoCA scores in healthy controls (HC) using FDR correction at a significance level of $p<0.05$. WML in white matter tracts were located using the NatBrainLab atlas[9].

Table 1: Demographic features of all subjects in analyses, stratified by cohort. Values given as means, standard deviations in parentheses, range in square brackets.

		Buffalo	*Graz*	*NW England*	*PPMI-1*	*PPMI-2*	*UCSF*	*Total*
N	*PD*	28	109	49	196	NA	23	405
	HC	21	NA	34	90	93	16	254
Age	*PD*	60.8 (7.59) [42 - 74]	60.9 (10.90) [30 - 82]	69.0 (7.73) [52 - 89]	61.7 (10.09) [34 - 85]	NA	63.7 (7.46) [40 - 75]	63.2 (8.75) [30 – 89]
	HC	56.9 (10.25) [31 - 76]	NA	66.3 (7.21) [52 - 81]	61.0 (11.54) [31 – 83]	64.5 (11.78) [30 - 85]	66.0 (6.35) [46 - 72]	63.0 (9.43) [30 – 85]
Male/Female %	*PD*	64.3/35.7	71.6/28.4	75.5/24.5	66.3/33.7	NA	60.9/39.1	67.7/32.3
	HC	33.3/66.7	NA	47.1/52.9	65.6/34.4	48.4/51.6	68.8/31.2	52.6/47.4
*H&Y Stage**		1.8 (0.75)	1.9 (0.47)	2.6 (0.94)	1.6 (0.52)	NA	NA	2.0 (0.67)
*Illness Duration**		7.0 (5.37)	4.4 (4.52)	7.2 (4.45)	NA	NA	NA	6.2 (4.78)
*LEDD**		NA	251 (298)	600 (342)	NA	NA	NA	426 (320)
*MDS-UPDRS Part III**		25.4 (10.29)	28.8 (11.98)	38.0 (11.57)	20.8 (8.71)	NA	26.8 (11.50)	28.0 (10.81)
MoCA	*PD*	25.1 (3.98)	26.0 (3.14)	24.8 (3.78)	26.8 (2.26)	NA	27.2 (2.04)	26.0 (3.04)
	HC	27.5 (2.32)	NA	28.0 (2.34)	28.3 (1.11)	27.3 (2.11)	27.7 (1.63)	27.8 (1.90)
Vascular Risk Score	*PD*	0.4 (1.07)	1.5 (1.18)	1.7 (1.67)	1.2 (1.18)	NA	NA	1.2 (1.28)
	HC	1.2 (2.01)	NA	2.0 (1.73)	1.1 (1.04)	0.9 (1.23)	NA	1.6 (1.50)

Buffalo: Buffalo Neuroimaging Analysis Center New York USA; **Graz**: Medical University of Graz Austria; **HC**: Healthy Controls; **H&Y**: Hoehn and Yahr Scale; **LEDD**: Levodopa Equivalent Daily Dose; **MDS-UPDRS**: Movement Disorder Society Unified Parkinson's Disease Rating Scale; **MoCA**: Montreal Cognitive Assessment; **NW England**: University of Manchester UK; **PD**: Parkinson's Disease; **PPMI**: Parkinson's Progression Markers Initiative; **UCSF**: University of California San Francisco USA. **PPMI-1** collated by Amsterdam UMC, **PPMI-2** collated by UCL. Asterisk represents clinical features only collected in PD patients.

Results

Six sites contributed clinical and neuroimaging data: 405 PD (mean age=63.2 ± 8.8 years, 32% female) and 254 controls (mean age=63.0 ± 9.4 years, 47% female) [**Table 1**].

No significant differences in overall WML burden were found between PD (n=405) and HC (n=254) (volume $t(657)=1.65$, $p=0.099$; frequency $t(657)=1.95$, $p=0.052$).

The Bullseye plots of WML spatial distribution are shown in **Figure 1**.

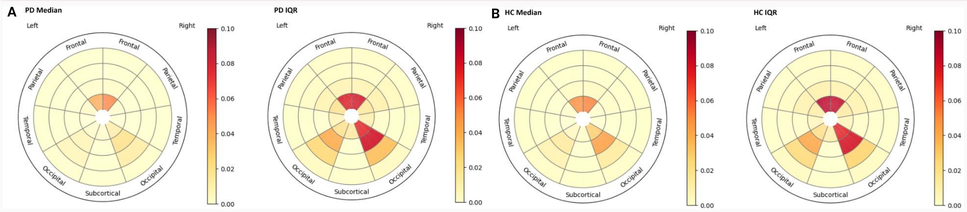

Figure 1: Bullseye plots showing the spatial distribution of WML in PD (n=405) and HC (n=254) subjects. Panel A shows the median and interquartile range WML frequency per region for PD. Panel B shows the same for HC. WML frequency is defined as the volume of WML in that region divided by the total volume of the region. Red regions represent greater frequency; yellow regions represent lower frequency. The layer closest to the centre of the plot represents the most periventricular layer; the outer layers represents the layer which meets the cortex.

Frontal layer 1 (F1) and occipital layers 1, 2 and 3 (O1, O2, O3) were picked as regions of interest following Bullseye analysis [**Figure 2**].

In PD, significant associations were found between F1 and H&Y stage ($p=0.048$ [0.00 to 0.02]), MDS-UPDRS Part III (0.022 [0.01 to 0.11] and subtype ($p = 0.003$ [0.19 to 0.89]); O1 and MoCA ($p=0.035$ [-0.03 to 0.00]); and O3 and H&Y stage ($p=0.035$ [0.00 to 0.05]) when age, sex and vascular risk were included in the model as confounders [**Table 2**].

No significant association with MoCA was found in HC.

Table 2: Statistical associations of WML frequency in frontal layer 1 and occipital layers 1, 2 and 3 with H&Y stage, MDS-UPDRS Part III, MoCA and subtype in PD subjects. Age, sex and vascular risk were included in the model. Presented as p-values with 95% confidence intervals in brackets.

	H&Y Stage (n=375)	*MDS-UPDRS Part III (n=378)*	*MoCA (n=380)*	*Subtype (n=317)*
Frontal Layer 1	**0.048** (0.00 to 0.02)	**0.022** (0.01 to 0.11)	0.663 (-0.01 to 0.01)	**0.003** (0.19 to 0.89)
Occipital Layer 1	0.305 (-0.01 to 0.03)	0.763 (-0.05 to 0.06)	**0.035** (-0.03 to 0.00)	0.057 (-0.00 to 0.02)
Occipital Layer 2	0.994 (-0.02 to 0.02)	0.698 (-0.07 to 0.04)	0.122 (-0.00 to 0.02)	0.452 (-0.02 to 0.01)
Occipital Layer 3	**0.035** (0.00 to 0.05)	0.445 (-0.07 to 0.16)	0.660 (-0.03 to 0.02)	0.231 (-0.05 to 0.01)

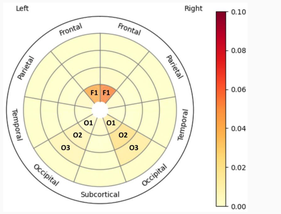

Figure 2: Bullseye plots showing the four regions of interest used to assess association between WML and clinical features in Table 2.

In voxel-wise analyses, WML were associated with higher H&Y stage (n=375, z-score 3.13 to 6.76) [**Figure 3, Table 3**], worse MDS-UPDRS Part III scores (n=398, z-score 3.70 to 6.39) [**Figure 4, Table 4**] and worse MoCA scores (n=403, z-score -3.05 to -6.02) [**Figure 5, Table 5**].

No significant associations were found with subtype in PD or MoCA in HC.

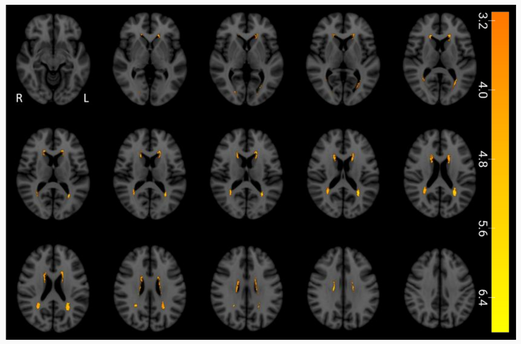

Figure 3: Voxels showing significant association between WML and H&Y stage for PD subjects (n=375). Q-value of 0.05, WML present in a minimum of 20 subjects. Significant z-scores ranging from 3.13 to 6.76.

Table 3: Clusters showing a significant association between WML and H&Y stage in PD (n=375). Q-value of 0.05, WML present in a minimum of 20 subjects. The tract containing each cluster peak is shown in bold.

White Matter Tracts	*Cluster size (mm^3)*	*Peak MNI coordinates (mm)*	*Peak z-score*
L Internal Capsule L Corpus Callosum, L Corticospinal , L Optic Radiation, L Cortico-ponto-cerebellar, L Inferior Longitudinal Fasciculus, L Inferior Occipito-frontal Fasciculus	1276	-27x53x18	6.76
R Internal Capsule R Arcuate Posterior Segment, R Corpus Callosum, R Inferior Occipito-frontal Fasciculus, R Cingulum	864	23x-49x29	6.06
R Corpus Callosum	1439	18x-16x31	6.05
L Corpus Callosum L Inferior Occipito-frontal Fasciculus, L Uncinate	1647	-18x25x11	5.85
R Corpus Callosum R Inferior Occipito-frontal Fasciculus	91	22x-81x3	4.73
L Corpus Callosum	34	-20x82x3	4.19

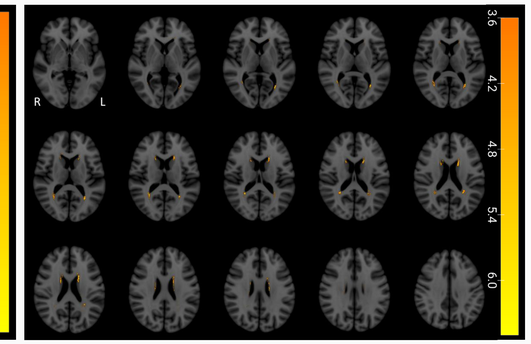

Figure 4: Voxels showing significant association between WML and MDS-UPDRS Part III scores for PD subjects (n=398). Q-value of 0.05, WML present in a minimum of 20 subjects. Significant z-scores ranging from 3.70 to 6.39.

Table 4: Clusters showing a significant association between WML and MDS-UPDRS Part III scores in PD (n=398). Q-value of 0.05, WML present in a minimum of 20 subjects. The tract containing each cluster peak is shown in bold.

White Matter Tracts	*Cluster size (mm^3)*	*Peak MNI coordinates (mm)*	*Peak z-score*
L Corpus Callosum	484	-18x-15x27	6.39
L Optic Radiation L Corpus Callosum, L Internal Capsule, L Inferior Longitudinal Fasciculus, L Cortico-ponto-cerebellar, L Corticospinal, L Inferior Occipito-frontal Fasciculus	396	-30x-62x7	5.72
R Internal Capsule R Corpus Callosum, R Arcuate Posterior Segment, R Inferior Occipito-frontal Fasciculus, R Inferior Longitudinal Fasciculus	383	30x-52x13	5.44
R Corpus Callosum	244	18x-8x23	5.38
R Corpus Callosum	41	13x12x20	5.12

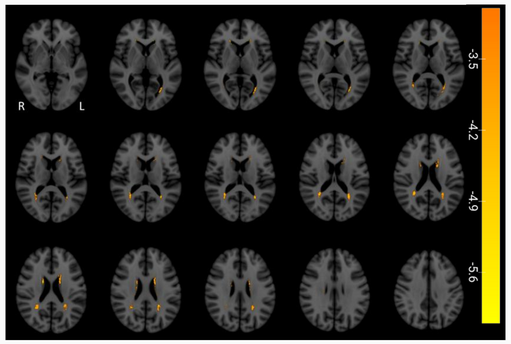

Figure 5: Voxels showing significant association between WML and MoCA score for PD subjects (n=403). Q-value of 0.05, WML present in a minimum of 20 subjects. Significant z-scores ranging from -3.05 to -6.02.

Table 5: Clusters showing a significant association between WML and MoCA score in PD (n=403). Q-value of 0.05, WML present in a minimum of 20 subjects. The tract containing each cluster peak is shown in bold.

White Matter Tracts	*Cluster size (mm^3)*	*Peak MNI coordinates (mm)*	*Peak z-score*
L Inferior Longitudinal Fasciculus L Corpus Callosum, L Internal Capsule, L Optic Radiation, L Corticospinal, L Cortico-ponto-cerebellar, L Inferior Occipito-frontal fasciculus	987	-29x-67x5	-6.02
R Corpus Callosum	230	17x0x22	-5.96
L Corpus Callosum	40	-14x29x4	-5.29
L Corpus Callosum L Inferior Occipito-frontal fasciculus	612	-17x9x23	-5.27
R Internal Capsule R Corpus Callosum, R Arcuate Posterior Segment, R Inferior Occipito-frontal fasciculus	712	29x-49x19	-5.13
R Corpus Callosum R Inferior Occipito-frontal fasciculus, R Uncinate	70	20x30x4	-5.05
R Corpus Callosum	35	16x27x13	-4.82

Conclusions

WML in important white matter tracts are associated with motor and cognitive symptoms and disease stage in PD, suggesting WML could serve as potential biomarkers of vascular pathophysiology of PD.

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References:
1. Paul G, Elabi OF. Microvascular Changes in Parkinson's Disease – Focus on the Neurovascular Unit. Frontiers in Aging Neuroscience. 2022;14.
2. Lau K et al. Blood–brain barrier alterations and their impact on Parkinson's disease pathogenesis and therapy. Translational Neurodegeneration. 2024;13(1).
3. Wardlaw JM et al. What are White Matter Hyperintensities Made of? Journal of the American Heart Association. 2015;4(6).
4. Butt A et al. White matter hyperintensities in patients with Parkinson's disease: A systematic review and meta-analysis. Journal of the Neurological Sciences. 2021;426:117481.
5. Carvalho de Abreu DC et al. Is white matter hyperintensity burden associated with cognitive and motor impairment in patients with Parkinson's disease? A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews. 2024;161:105677.
6. Park G et al. White matter hyperintensities segmentation using the ensemble U-Net with multi-scale highlighting foregrounds. NuroImage. 2021;237:118140.
7. Sudre CH et al. Bullseye's representation of cerebral white matter hyperintensities. Journal of Neuroradiology. 2017;45(2):114–122.
8. NeuroImaging Tools and Resources Collaboratory. NITRC: NiiStat: Tool/Resource Info. Nitrc.org.
9. Catani M, Thiebaut M. Atlas of Human Brain Connections. Oxford University Press; 2012.

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