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Microstructural changes of normal-appearing white matter in Vascular Parkinsonism

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ABSTRACT

Objective: Several evidences demonstrated the role of white matter (WM) lesions in the pathogenesis of Vascular Parkinsonism (VP), a clinical entity characterized by parkinsonism, postural instability, marked gait difficulty and poor response to levodopa. However, the involvement of normal appearing white matter (NAWM) in VP still remains unknown. This study aimed to investigate the microstructural integrity of NAWM in VP compared to Parkinson's disease (PD) and controls using neuroimaging approach.

Methods: Magnetic resonance imaging data were acquired from 50 participants (15 VP, 20 PD and 15 controls). Diffusion tensor imaging (DTI) and Tract-based spatial statistics (TBSS) were performed to assess microstructural NAWM changes. In order to evaluate the relationship between specific fiber tract involvement and clinical picture, diffusion alterations were correlated with clinical features.

Results: Compared to PD patients and controls, significantly reduced fractional anisotropy (FA) and increased mean diffusivity (MD) and radial diffusivity (RD) in NAWM of corpus callosum, internal and external capsule, and corona radiata were present in VP. By contrast, DTI metrics were normal in NAWM-PD and controls. A significant correlation was found between FA and MD of anterior third of corpus callosum and clinical variables (postural instability, freezing-of-gait and symmetry of parkinsonism).

Conclusions: This study improves the knowledge on WM pathology in VP, as our results demonstrate that NAWM damage occurs in VP, but not in PD nor in controls. NAWM damage might relate to clinical picture and suggest that non-clearly-visible WM alterations may contribute to the physiopathology of this vascular disease.

1. Introduction

Vascular parkinsonism (VP) is a heterogeneous parkinsonian syndrome which may include in its clinical picture different subtypes. In accordance with recent expert working group's international criteria [1] there are three different clinical subtypes of VP: i) the acute/sub acute post-stroke VP (acute onset and asymmetric parkinsonism); ii) the insidious VP (more frequent presents with a combination of symptoms

including lower body progressive parkinsonism with poor levodopa responsiveness, postural instability and gait difficulties, rigidity, cognitive impairment and pyramidal and cerebellar signs and incontinence); iii) mixed VP or overlapping syndrome with Parkinson's disease (PD). Actually, the diagnosis of VP is based on the convergence of clinical parkinsonism (associated to other clinical symptoms) with clinical and imaging findings consistent with cerebrovascular disease [1].

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Indeed, it is well documented that cerebral small vessel disease (SVD) including white matter lesions (WML) and lacunar infarcts plays a crucial role in the pathogenesis of VP [2–4].

The neuroimaging spectrum of VP is characterized by lesions visually appreciable on conventional Magnetic Resonance Imaging (MRI) scans, including extensive WML, multiple cerebral infarctions in basal ganglia or a combination of both [3]. Moreover, several studies demonstrated that in VP patients the WM damage is crucial for both the development of specific clinical features and severity of the disease [2,3]. In a clinic-based study [2], it has been reported that patients with VP showed gait difficulty and postural instability rather than tremor as compared to those with PD. A diffusion tensor imaging (DTI) study [3] demonstrated that disruption of WM microstructural organization was related to severity of the disease in VP patients.

The visually appreciable WML, however, tend to develop gradually in the brain, thus representing only the tip of the iceberg of WM pathology [5]. Thus, an increasing scientific interest has recently focused on early changes in normal appearing WM (NAWM) as these abnormalities may precede by several years the appearance of visually appreciable WML [4,5]. A robust method for investigating the NAWM tissue microstructure is the Tract-based spatial statistics (TBSS) analysis. It allows to regionally analyze DTI metrics across the whole-brain WM without any a priori hypotheses [6]. TBSS provides more reliable alignment of the WM tracts with the advantage of mitigating the problems of obtaining optimal anatomical correspondence across subjects than conventional DTI voxel-based methods [6]. TBSS has also been used in the investigation of SVD both in elderly subjects [7] and in young with cerebral genetic form of arteriopathy with leukoencephalopathy [8].

To date, no study previously investigated NAWM tissue in patients with VP. We hypothesized that the NAWM involvement might be different across groups of patients. In particular, VP patients characterized by visually appreciable extensive WML on MRI scan could also have tissue damage in NAWM. Thus, in the current study, using a neuroimaging approach we investigated the microstructural integrity of NAWM tissue in patients with VP compared to those with PD and controls. Furthermore, we tested the hypothesis that NAWM involvement in specific tracts may be related to the clinical features of our patients.

2. Materials and methods

2.1. Participants

Fifty subjects (15 patients with VP, 20 patients with PD and 15 age- and sex-matched controls) were included in this study. All VP patients fulfilled established clinical criteria for VP [9] and all PD patients those for Parkinson's Disease [10]. All patients underwent a complete neurological examination. Presence of cardiovascular risk factors such as hypertension, smoking, hyperlipidemia, family history of stroke was reordered in participants. Neurological examinations were performed using Unified Parkinson's Disease Rating Scale motor score (UPDRS-ME) [11], Hoen &Yahr (H&Y) rating scale and FOG-Questionnaire (FOG-Q) [12]. Response to acute levodopa administration was evaluated in all patients. Patients were classified as responsive if the motor improvement was equal or higher than 30%. In all patients, cognitive functions were evaluated using Mini Mental State examination (MMSE) [13]. Controls were defined as a no history of neurological or severe general medical diseases, no vascular lesions on MRI scan and a UPDRS-ME = 0. All participants gave written informed consent, which was approved by the Ethical Committee of the University "Magna Graecia" of Catanzaro, according to the Helsinki Declaration.

2.2. MRI protocol

Participants underwent MRI on a 3T GE system (GE Healthcare,

Rahway, NJ). The protocol included whole-brain, 3D FSPGR T1-weighted images (TI/TE/TR = 650/3.7/9.2 ms; flip angle = 12°; number of slices 184; no slice gap; voxel size $1 \times 1 \times 1 \text{ mm}^3$), DTI (TE/TR = 83.9/9750 ms; b = 0,1000; diffusion weighting along 27 non-collinear gradient directions; matrix size 128×128 ; 80 axial slices; number of b0 images = 4; NEX = 2; voxel size $2 \times 2 \times 2 \text{ mm}^3$) and conventional T2-weighted and FLAIR images WML due to vascular pathology were manually delineated on FLAIR images by an expert radiologist, in order to obtain a map of WML distribution in the brain of VP patients. Presence of WML was scored on axial T2-weighted MR images using the Fazekas scale and total score was calculated adding individual periventricular and deep WML scales together [14]. Details on the generation of DTI maps of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) are in [Supplementary Material](#) [15]. Subsequently, TBSS was performed on FA/MD/AD/RD of normal-appearing tissue (i.e., we subtracted from each image all those voxels that had been labelled as WML in the group lesion map).

3. Statistical analysis

Sex distribution was compared using the χ^2 test. Differences in age at examination and UPDRS-ME, were assessed using Student's t-test. The Mann-Whitney U test was used to assess differences in age at onset, disease duration, UPDRS, Hoehn-Yahr, FOG-Q and MMSE scores. Distributions of vascular risk factors, categorical clinical features and response to Levodopa were compared using Fisher's exact test. All tests were two-tailed, with significance level $p = 0.05$ after Bonferroni correction for multiple comparisons. To test for localized differences across the groups, voxel-wise statistics was performed for each point on the common skeleton, for all DTI metrics. A permutation-based approach [16] that accounts for "family-wise errors" was used to control for multiple comparisons. Specifically, permutation-based inference on cluster size ($t > 1$, $P < 0.05$) was used to test whether FA/MD/RD/AD were different in VP compared to PD and controls. We built a general linear model in which age and gender were treated as nuisance variables and the pairwise t-tests for the comparisons PD > HC; PD < HC; VP > HC; VP < HC; PD > HC; PD < HC were performed and subsequently corrected across contrasts. Spearman's correlation was used to test for relationships between clinical variables and NAWM imaging characteristics. We identified the corpus callosum as region of interest for this analysis, because this bundle might bring indirect insight into the different cortical regions connected through its fibers. Briefly, normal-appearing corpus callosum was manually segmented by an expert on the midsagittal plane of T1-weighted images. To accurately and automatically extract the bundle thickness profile we used an approach that allowed us to obtain a smooth centerline along the corpus callosum divided into 50 equidistant nodes (from the splenium to the genu) [17–19]. At each node, the distance of the line orthogonal to the superior and inferior boundaries of the corpus callosum represented its thickness. We then extracted the values of MD and FA from the same 50 nodes by overlaying the thickness profile onto the T1-coregistered DTI maps. At each node, we computed the MD/FA value as a weighted 2D Gaussian average with radius 2 mm. Spearman's correlation was tested between each of the clinical variables and, in turn, each of the three imaging features from the entire corpus callosum (i.e., thickness, FA, MD). Correlation significance level was set at $p = 0.05$ after correcting for multiple comparisons according to the false discovery rate method [20].

4. Results

Demographic and clinical characteristics of participants are summarized in [Table 1](#). Patients groups were not statistically different regarding onset, disease duration and severity of disease ([Table 1](#)). VP had higher prevalence of cardiovascular risk factors and significant

Table 1
Demographic and clinical features of patients and controls.

Variables	VP (n = 15)	PD (n = 20)	Controls (n = 15)	P -value
Age (y)	75.5 ± 6.4	69.6 ± 4.2	72.9 ± 6.1	0.15 ^a
Men (n,%)	9(60)	14(70)	11(73)	0.7 ^b
Age at onset (y)	71.2 ± 7.8	63.3 ± 3.7	–	0.06 ^c
Disease duration (y)	4.2 ± 2.7	4.9 ± 3.9	–	0.54 ^d
Vascular risk factors n (%)				
Family history of	6(40)	3(15)	0(0)	0.09 ^b
Stroke				
Hypertension	12(80)	7(35)	5(33)	0.01 ^b
Smoking	10(67)	8(40)	3(20)	0.03 ^b
Dyslipidemia	8(53)	5(25)	2(13)	0.05 ^b
Clinical features n (%)				
Tremor	4(27)	15(75)	0(0)	0.005 ^b
Bradykinesia	14(93)	20(100)	0(0)	< 0.001 ^b
Rigidity	14(93)	20(100)	0(0)	< 0.001 ^b
Lower body-	8(53)	0(0)	0(0)	–
Involvement				
Symmetric-	12(80)	0(0)	0(0)	–
Parkinsonism				
Freezing of gait	11(73)	0(0)	0(0)	–
Pyramidal signs	6(40)	0(0)	0(0)	–
Postural Instability	9(60)	0(0)	0(0)	–
UPDRS-ME score	25.3 ± 5.7	21.7 ± 3.9	–	0.6 ^c
H-Y score	2.3 ± 0.5	2.00 ± 0.3	–	0.29 ^d
FOG-Q	10.8 ± 10.2	0(0)	–	< 0.001 ^d
Response to Levodopa n (%)	9(60)	20(100)	–	0.04 ^b
Neuropsychological Evaluation				
MMSE	25.0 ± 3.9	26.6 ± 2.6	–	0.161 ^d

VP: Vascular Parkinsonism; PD: Parkinson's disease; Controls: control subjects.
^a ANOVA test.

^b Fisher's exact test, followed by pairwise proportion test with Bonferroni correction.

^c Unpaired t-test.

^d Mann-Whitney U test.

difference in FOG-Q score and symmetry of parkinsonism, compared to PD (Table 1). On conventional MRI, status cribriform of basal ganglia was present in VP, but not in PD and controls. The mean Fazekas total score in VP, PD and controls was 4.47 ± 1.64 (maximum 6), 0.4 ± 0.49 (maximum 1) and 0 respectively. Supplementary Fig. 1 shows WML manual segmentation results in VP, which was used as exclusion mask to focus TBSS on NAWM. Fig. 1 shows widespread regions of significant changes in NAWM of VP compared to PD ($p < 0.001$, corrected). Supplementary Fig. 2 shows results for the contrast VP vs controls. FA was significantly reduced and MD and RD were significantly increased in corpus callosum, in internal and external capsules, and in other major white matter tracts (i.e., corona radiata). AD was also significantly increased, but in more narrow regions, corresponding to corona radiata and internal capsule. Supplementary Fig. 3 further shows that significant TBSS findings in NAWM were adjacent but not overlapping to the WML map (FA results are shown for example). For details on the size, location and statistics value of the regions of significant difference, please see Supplementary Tables 1–4. Correlation analyses revealed significant relationships between clinical variables and neuroimaging characteristics of the anterior third of the corpus callosum (Fig. 2). In particular, we found that presence of postural instability in all patients correlated negatively with thickness ($\rho = -0.64$, p -value = 0.05) and FA ($\rho = -0.65$, p -value = 0.04), and positively with MD ($\rho = 0.57$, p -value = 0.05). FOG-Q scores correlated negatively with thickness ($\rho = -0.68$, p -value = 0.04) and FA ($\rho = 0.70$, p -value = 0.03), and positively with MD ($\rho = 0.66$, p -value = 0.04). Presence of symmetry of parkinsonism correlated negatively with callosal thickness ($\rho = -0.66$, p -value = 0.03) and FA ($\rho = -0.69$, p -value = 0.03), and positively with MD ($\rho = 0.68$, p -value = 0.04). Fig. 3 shows different levels of

association between clinical and imaging variables in anterior versus posterior corpus callosum.

5. Discussion

To the best of our knowledge, this is the first study investigating microstructural integrity of NAWM tissue in patients with VP compared to those with PD and healthy controls. In particular, we found that VP patients had significantly lower regional FA and significantly higher regional MD and RD in NAWM of corpus callosum, internal and external capsule, compared to PD and controls. The combination of alterations in FA, MD and RD, but to a very less extent in AD, seems consistent with the occurrence of myelin damage and secondary degeneration. Furthermore, NAWM tissue damage of the anterior third of corpus callosum correlated with typical symptoms of VP, such as postural instability, FOG and symmetry of parkinsonism, whereas no significant correlation existed with the posterior corpus callosum.

Changes in NAWM have been well described in the general elder population. This is not surprising, considered that age is strongly associated with WML appearance on MRI scan. Evidence suggests that, in healthy elderly, WML may represent the ultimate end of WM pathology, resulting from a continuous process of degeneration over time. Indeed, in a longitudinal study [21].investigating the time course of WM degeneration in elderly subjects with and without cognitive impairment, authors suggested that DTI and FLAIR might provide crucial information for describing the conversion from NAWM into WML. A subsequent longitudinal study [4] also confirmed that, in the general population, NAWM subtle changes detected by DTI might precede the development of WML by several years. Furthermore, severity of NAWM tissue damage has been found strongly related to WML volume and location [5].

Regional microstructural changes in NAWM were also reported in patients with early-stage MS, and it is thought to contribute to clinical severity. In MS, changes in NAWM have also been confirmed histopathologically, and are thought to underlie microglial activation, axonal pathology and myelin reduction [22]. All these findings support the hypothesis that changes in NAWM may precede the development of WML by several years and may be involved in the clinical picture of the disease. Thus, investigating NAWM before it converts into visually appreciable WML on MRI may provide important clinical implications in the study of VP.

FA and MD are quantitative DTI-derived metrics, which describe magnitude and directionality of water molecules diffusion in the brain [23] and sensitively reflect the integrity of axonal microstructure. Indeed, usually FA decreases and MD increases in regions of WM degeneration, thus reflecting histopathological processes such as gliosis, demyelination and axonal loss. These indices are commonly used to elucidate the microstructural tissue integrity in the brain, and we can speculate that VP patients with reduced NAWM-FA and increased NAWM-diffusivities might already have damaged WM fibers, although not visually detectable on MRI. Differently from VP, NAWM diffusion parameters were normal in all PD and controls. This finding is not surprising because both PD patients and controls did not show pathological WML on MRI scan.

Interestingly, in our study VP patients had significantly higher prevalence of postural instability and symmetry of parkinsonism and FOG-questionnaire scores than PD patients. Of note, although DTI indices were significantly altered in the whole corpus callosum in VP compared to PD, the correlation with clinical symptoms was restricted to the anterior third of this structure, while the posterior part seemed to be not related to these features. According to Witelson's classification [24], anterior third of corpus callosum includes fibers connecting bilaterally prefrontal, premotor, and supplementary motor cortical areas, which play a crucial role in the control of gait patterns. Our results are in agreement with a previous study [25] reporting strong association between the loss of microstructural integrity of NAWM in the anterior corpus callosum and gait disorders in individuals with cerebral small

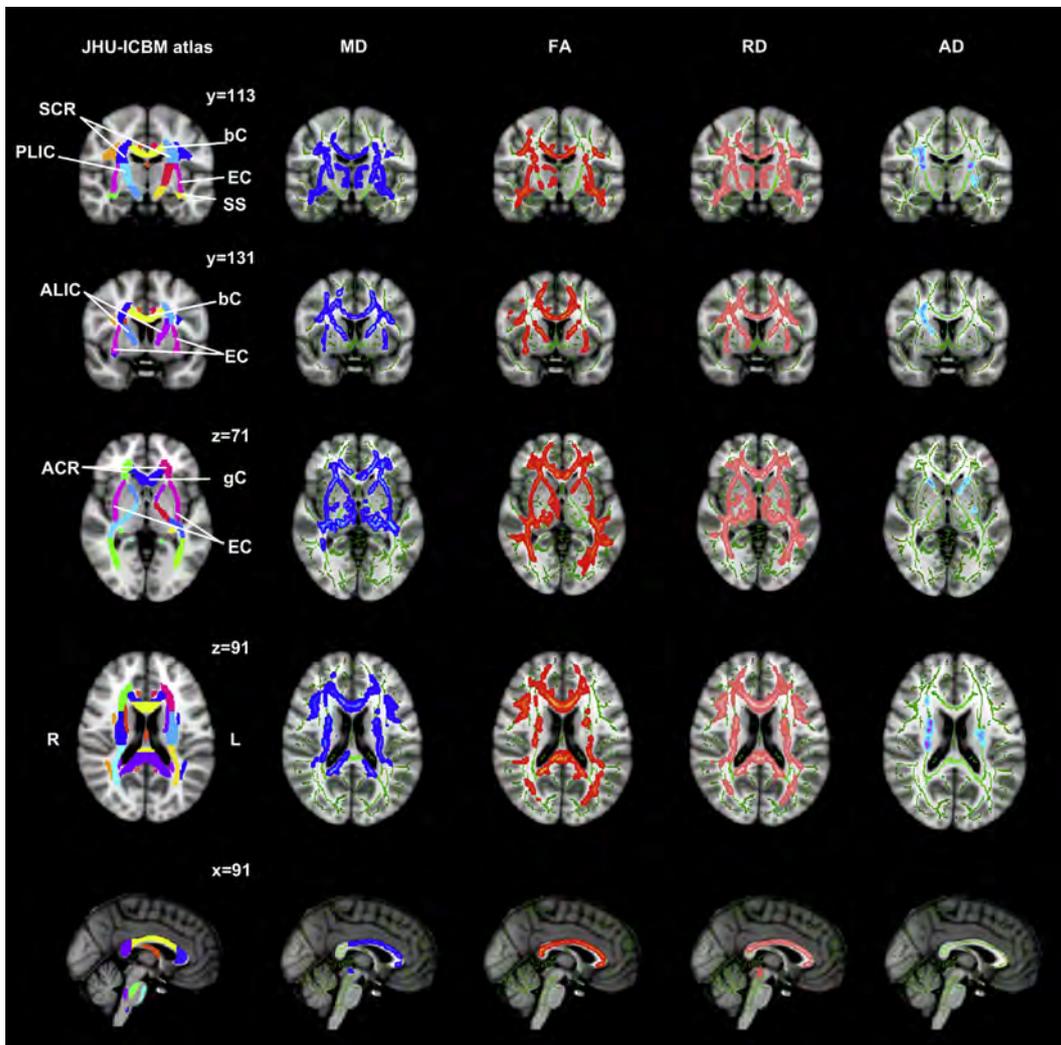


Fig. 1. Group-wise TBSS results. TBSS on NAWM: left-side column shows, as reference, the JHU-ICBM atlas of principal white matter tracts. The other columns show the changes in VP compared to PD: significant MD increases, significant FA decreases, significant RD and AD increases. *Abbreviations:* MD: mean diffusivity; FA: fractional anisotropy; RD: radial diffusivity; AD: axial diffusivity; ACR: anterior corona radiata; SCR: superior corona radiata; ALIC: anterior limb of external capsule; PLIC: posterior limb of external capsule; bCC: body of corpus callosum; gCC: genu of corpus callosum; EC: external capsule; SS: sagittal stratum.

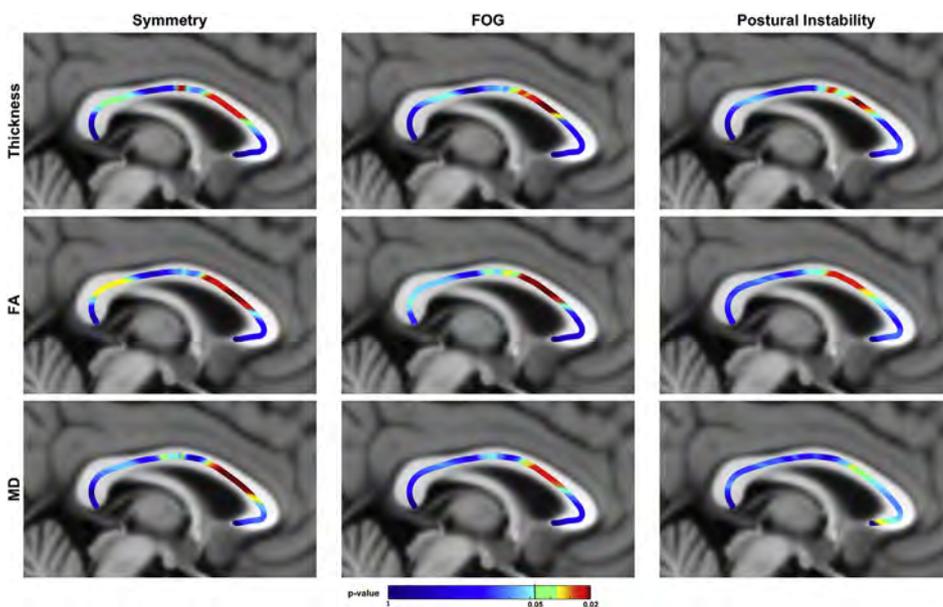


Fig. 2. Correlation between clinical and imaging variables. Significance of Spearman's correlation between clinical variables (symmetry of parkinsonism, FOG-score, postural instability) and the neuroimaging metrics measured along the callosal profile; on the color map, green corresponds to the significance threshold $p = 0.05$, corrected for multiple comparisons with false discovery rate approach. *Abbreviations:* FOG = Freezing-Of-Gait; FA = Fractional Anisotropy; MD = Mean Diffusivity.

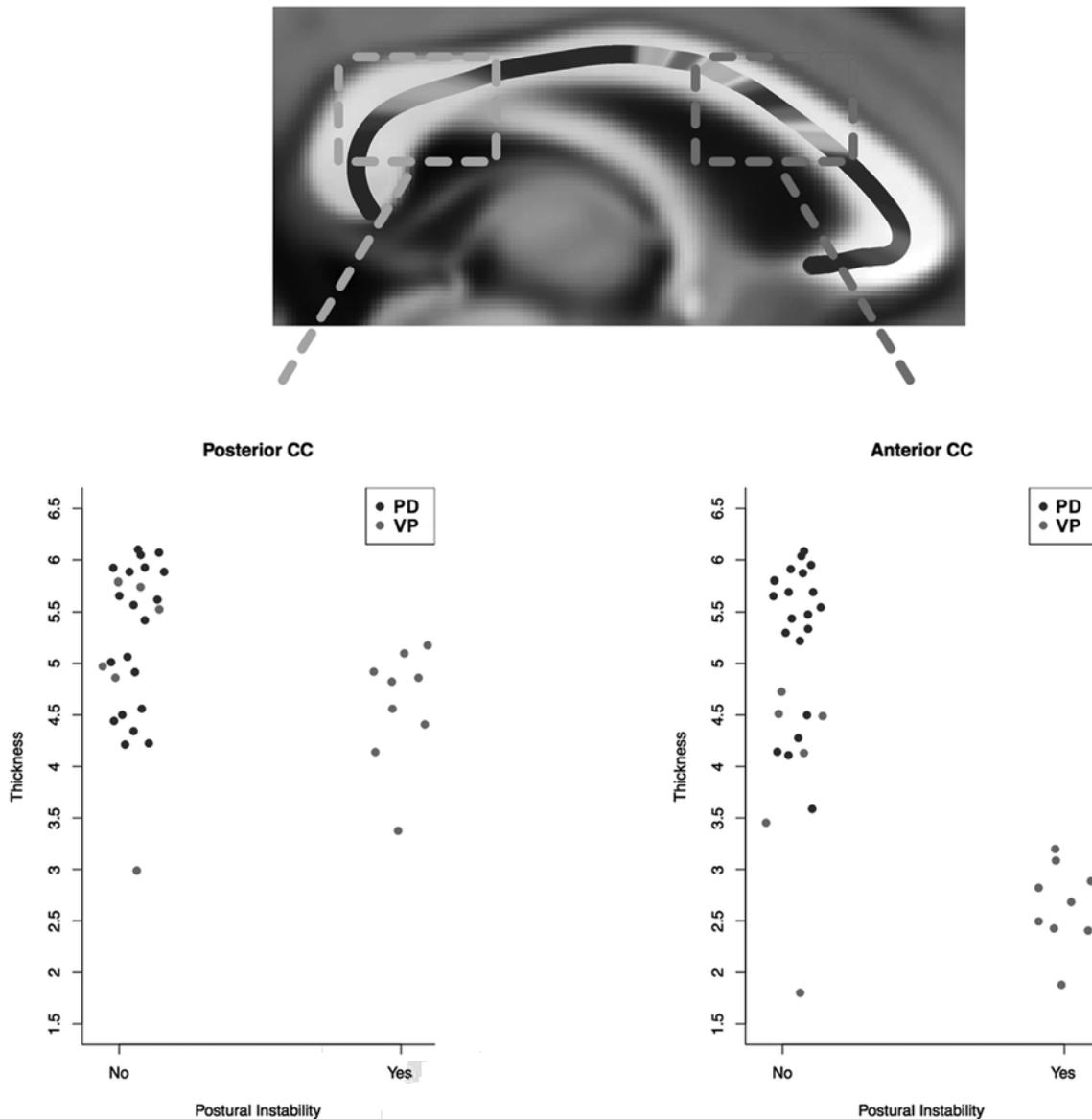


Fig. 3. Correlations in anterior vs posterior corpus callosum. Descriptive results of the different degrees of association in anterior versus posterior corpus callosum between callosal thickness and postural instability. Abbreviations: PD: Parkinson's disease; VP: Vascular Parkinsonism.

vessel disease without dementia and parkinsonism. Authors concluded that disruption of WM integrity, predominantly in NAWM of the genu of corpus callosum, was involved in the pathogenesis of gait disorders in elderly subjects [25].

Of note, we found significant correlation between NAWM-FA and NAWM-MD of the anterior third of corpus callosum and the presence of symmetry of parkinsonism in VP patients. This is not surprising because the commissural fibers connecting bilaterally the motor cortex are situated in this callosal subregion [26]. Thus, we can speculate that abnormalities in this compartment might cause functional alterations in the cortico-striatal loops underlying development of parkinsonism. DTI abnormalities along the transcallosal motor tract in the corpus callosum have been reported by other authors [27] differentiating patients with postural instability and gait disorder parkinsonism from those with PD. These authors suggested that callosal impairment rather than abnormalities in the basal ganglia could explain why certain parkinsonism patients developed postural instability and gait problems more than others [27]. Our findings are in agreement with this study, because we found significant correlation between DTI indices in the anterior third of corpus callosum and the presence of postural instability. Supporting

a non-dopaminergic origin of postural instability and gait disorders, these features are often observed in patients that are poor responsive to dopaminergic treatment [28] as is the case of our VP patients. Taken together, our findings suggest that loss of microstructural integrity in NAWM of the anterior corpus callosum may play a crucial role in the development of the typical clinical symptoms of VP.

A few studies [3,29] investigated WM microstructure using DTI analysis in patients with VP with visually appreciable WML on MRI scans. Some authors reported that, in VP patients, the disruption of frontal WM was associated with the severity of disease, and that frontal lobe disconnection was crucial for the core features of VP, such as gait disorder [3]. Our study differs from the latter study [3] in several ways. First, we investigated NAWM integrity in patients with VP compared to PD and controls, whereas these authors evaluated global WM and grey matter in VP patients compared to controls. Second, we used TBSS for investigating NAWM microstructural tissue damage, whereas the latter authors performed a whole-brain voxel-wise analysis of DTI parameters. TBSS is restricted to voxels of the WM skeleton, which can be accurately matched across subjects; conversely, whole-brain voxel-wise DTI analysis requires very accurate spatial correspondence between the

images, which is not always guaranteed by registration techniques, thus limiting results reliability. Overall, compared to whole-brain voxel-based approaches to DTI analysis, TBSS has the advantage of mitigating the problems of obtaining optimal anatomical correspondence across subjects. Third, we also investigated PD patients demonstrating that this group without WML did not have NAWM tissue damage, supporting the hypothesis that NAWM abnormalities in VP patients may be due to vascular pathology.

There are also evidences [30] of wide alteration of WM microstructure in patients with PD. Indeed, DTI-metrics changes have been reported in bilateral crus anterior capsulae interna, bilateral capsula externa, right anterior corona radiata, body and bilateral corpus callosum of PD patients even at the early stages of the disease. Further evidence [31] has also demonstrated widespread alterations of WM microstructure and GM atrophy in PD patients without cognitive impairment, using VBM analysis and performing TBSS on the side where the symptoms were observed at first. In our study, we did not use the WBM analysis because we were focused only on NAWM alterations and performed TBSS analysis not considering the clinical affected side. Moreover, we investigated the NAWM in PD without alterations in brain WM.

There were some limitations to the study. First, the sample size of our cohort is small, which causes the results from correlation analysis to be of descriptive nature. It is estimated that about 3–6% of all cases of parkinsonism have a vascular cause [32] and VP remains an entity difficult to diagnose especially in early phase of disease. A sample including more VP patients is needed to confirm the nature of DTI abnormalities found in NAWM tissue. Second, in absence of histopathological data, it is not possible to know whether our patients with VP had microscopic small vessel disease in the brain, suggestive of a vascular origin of their parkinsonism, or whether they had a parkinsonism of degenerative origin with coexistent WML and NAWM tissue abnormalities. Third, we considered early-mild stage PD clinically characterized by poor motor axial symptoms and can not exclude that NAWM differences found between VP and PD may also reflect the different disease severity.

In conclusion, our study demonstrates *in vivo* that NAWM tissue was damaged in VP patients, whereas it seemed to be preserved in patients with PD and controls. Our study opens a new horizon on the involvement of whole WM pathology (lesional and normal) in the pathogenesis of VP. Longitudinal studies investigating the conversion of NAWM damage into visually appreciable WML are needed in order to monitor the progression of VP. Moreover, DTI metrics of damaged NAWM in the anterior third of corpus callosum correlated with freezing of gait and postural instability. This association with cardinal signs of VP suggests that NAWM damage may be involved in the development of vascular clinical features.

Conflict of interest

None of the authors has financial conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2019.02.046>.

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