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ABSTRACT

BACKGROUND AND PURPOSE: Postural instability gait disorder is a motor subtype of Parkinson disease associated with predominant gait dysfunction. We investigated the periventricular white matter comprising longitudinal, thalamic, and callosal fibers using diffusion tensor MR Imaging and examined clinical correlates in a cohort of patients with Parkinson disease and postural instability gait disorder and healthy controls.

MATERIALS AND METHODS: All subjects underwent the Tinetti Gait and Balance Assessment and brain MR imaging. The DTI indices (fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity) from ROIs dropped over the superior and inferior longitudinal fasciculi, inferior fronto-occipital fasciculus, anterior thalamic radiation, anterior and posterior limbs of the internal capsule, and the genu and body of corpus callosum were evaluated.

RESULTS: Our findings showed that the superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, anterior thalamic radiation, genu of the corpus callosum, and body of the corpus callosum are more affected in postural instability gait disorder than in those with Parkinson disease or healthy controls, with more group differences among the longitudinal fibers. Only the callosal fibers differentiated the postural instability gait disorder and Parkinson disease groups. DTI measures in the superior longitudinal fasciculus, frontostriatal fibers (anterior thalamic radiation, anterior limb of the internal capsule), and genu of the corpus callosum fibers correlated with clinical gait severity.

CONCLUSIONS: Findings from this case-control cohort lend further evidence to the role of extranigral pathology and, specifically, the periventricular fibers in the pathophysiology of postural instability gait disorder.

ABBREVIATIONS: AD = axial diffusivity; ALIC = anterior limb of the internal capsule; ATR = anterior thalamic radiation; BCC = body of the corpus callosum; FA = fractional anisotropy; GCC = genu of the corpus callosum; HC = healthy controls; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; MD = mean diffusivity; PIGD = postural instability gait disorder; PD = Parkinson disease; PLIC = posterior limb of the internal capsule; RD = radial diffusivity; SLF = superior longitudinal fasciculus

The 4 hallmark symptoms of Parkinson disease (PD) are shaking tremor, stiffness, bradykinesia, and difficulty with balance and coordination.[1] Postural instability gait disorder (PIGD) is a

motor subtype of PD associated with predominant gait dysfunction. These patients often progress rapidly and are at higher risk for nonmotor deficits such as dementia and cognitive impairment.[2] Conventional medical interventions for PD are less effective in patients with PIGD, with gait and balance deficits more resistant to levodopa therapy on disease progression,[3] thus prompting the need to further explore the pathophysiology underlying the PIGD subtype to evaluate more targeted therapies.

Diffusion tensor imaging is a noninvasive MR imaging tool widely used to evaluate microstructural changes in brain white matter in vivo.[4] The principle behind DTI is its ability to differentiate the magnitude and directionality of the diffusion of water in neural tissue because water diffuses irregularly and is fastest along the major axis parallel to the neural fibers. An analysis of the DTI indices, namely fractional anisotropy (FA), mean

(MD), radial (RD), and axial diffusivity (AD), across patient groups may provide insight into the histopathologic process[5] underlying PIGD.

Traditionally, studies in PD are focused on pathophysiologic changes in the nigrostriatal and extrapyramidal pathways. There is increasing evidence of the role of cortical and subcortical structures in postural control and the freezing of gait.[6-9] Recent age-related imaging studies also showed that periventricular white matter lesions play a role in balance impairment, mobility, and cognitive deficits in otherwise healthy elderly individuals, further emphasizing the importance of the integrity of afferent and efferent subcortical-cortical projections.[10]

The aim of this study was to investigate whether periventricular white matter longitudinal, thalamic, and callosal fibers are differentially affected in patients with PIGD parkinsonism, compared with patients with typical tremor-dominant PD and healthy, neurologically intact controls (HC) using an ROI approach to brain DTI MR imaging analysis. We hypothesized that microstructural changes in these periventricular white matter fibers on DTI are correlated with motor dysfunction in PD, and especially in PIGD.

MATERIALS AND METHODS
Study Subjects
The study was undertaken with the written informed consent of each subject and the approval of the SingHealth Centralised Institutional Review Board. All protocols were approved by the SingHealth ethics committee.[11] Twenty-one patients with PD and 19 with PIGD were recruited at a tertiary referral center, where they were diagnosed by a movement disorders neurologist on the basis of established clinical criteria[12,13] from the United Kingdom PD Brain Bank (https://www.parkinsons.org.uk/research/parkinsons-uk-brain-bank) and Deprenyl and Tocopherol Antioxidative Therapy Of Parkinsonism Trial (DATATOP, https://jamanetwork.com/journals/jamaneurology/fullarticle/589418). Exclusion criteria included patients who were wheelchair-bound from severe disability, showed evidence of cognitive dysfunction (based on the Mini- Mental State Examination score), had features of Parkinson-plus syndrome or normal pressure hydrocephalus, or had a history of head injury, encephalitis, stroke, exposure to neuroleptic drugs, and MR imaging contraindications. Patients with evidence of cognitive dysfunction (based on the Mini-Mental State Examination score) were also excluded. Twenty HC who were age- and sex-matched to the patient cohort were also recruited during the same period. All 60 subjects were evaluated with the Tinetti Gait and Balance score (https://fallpreventiontaskforce.org/wp-content/uploads/2014/10/Tinettitool.pdf) as an indicator of his or her mobility and fall risk.[14]

MR Imaging
The MR imaging brain scans were acquired on a 3T scanner (Magnetom Trio; Siemens, Erlangen, Germany) using a 12-channel phased array head coil. To minimize head motion during the scan, we secured the subjects' heads with securing straps.

The DTI scan was a spin-echo echo-planar imaging sequence (TR = 8200 ms, TE = 86 ms, diffusion sensitization in 30 non-collinear directions, in-plane resolution = 1.875×1.875 mm, FOV = 240×240 mm, matrix = 128×128, 64 contiguous 2-mm-thick slices, b-value = 800 s/mm^2, integrated parallel acquisition technique factor = 2, B$_0$ averages = 2). Images from the structural FLAIR and T1- and T2-weighted scans were screened to exclude pathology in the ROIs.

Image Analysis
An ROI approach was adopted for DTI MR imaging analysis, using the commercially available Leonardo workstation, Version VE50A (Siemens, Erlangen, Germany) for image postprocessing. Two independent raters blinded to subject status drew 30-mm^3 ROIs over various brain regions on the basis of neuroanatomic knowledge. The DTI indices of FA, MD, AD, and RD were recorded and averaged for paired fibers.

Circular ROIs (Figure) were placed within the periventricular white matter fibers comprising the superior (SLF) and inferior longitudinal fasciculi (ILF), inferior fronto-occipital fasciculus (IFOF), anterior thalamic radiation (ATR), anterior (ALIC) and posterior limbs of internal capsule, and genu (GCC) and body of the corpus callosum on representative sections at −2 mm (IFOF), 0 mm (ILF), +4 mm (ATR, ALIC), +6 mm (posterior limb of the internal capsule), +12 mm (GCC), +26 mm (body of the corpus callosum), and +28 mm (SLF) from the section containing the anterior and posterior commissures. Precaution was taken to avoid focal lesions or infarcts and immediate periventricular margins, so as to reduce spurious partial volume averaging artifacts on the DTI measurements by reviewing the structural images and color FA, diffusion trace, MD map, and B$_0$ images side by side during ROI placement.

Statistical Analysis
Statistical analysis was performed by using R 3.4.2 (www.r-project.org). Interrater and intrarater reliability for the DTI indices of FA, MD, AD, and RD were assessed using the intraclass correlation coefficient. The Kruskal-Wallis test was used to find group differences in the DTI indices of the periventricular white matter fibers, and a univariable logistic regression was performed to evaluate the ability of the DTI indices of each periventricular ROI to differentiate between PD and PIGD, PD and HC, and PIGD and HC, after adjusting for age and sex. Last, a multivariable linear regression was performed to evaluate the relationship between the DTI indices of each ROI and the Tinetti score (Total, Balance, and Gait) for the patients with PD and PIGD. The 2-sided significance was set at .05.

RESULTS
A total of 60 subjects (19 with PIGD, 21 with PD, 20 HC) were enrolled in this study, and their clinical data are summarized in Table 1. The mean Tinetti scores in PIGD and PD were significantly lower than those for HC ($P < .01$), and PIGD had the lowest score among the 3 subject groups. The interrater and intrarater reliability for the DTI indices (On-line Table 1) had a minimum score of 0.7, with most being >0.8.

On-line Table 2 details the DTI indices of each periventricular ROI in the 3 subject groups. Results of the Kruskal-Wallis test and logistic regression are addressed in Tables 2 and On-line Table 3, respectively. In general, both PD and PIGD groups had lower median
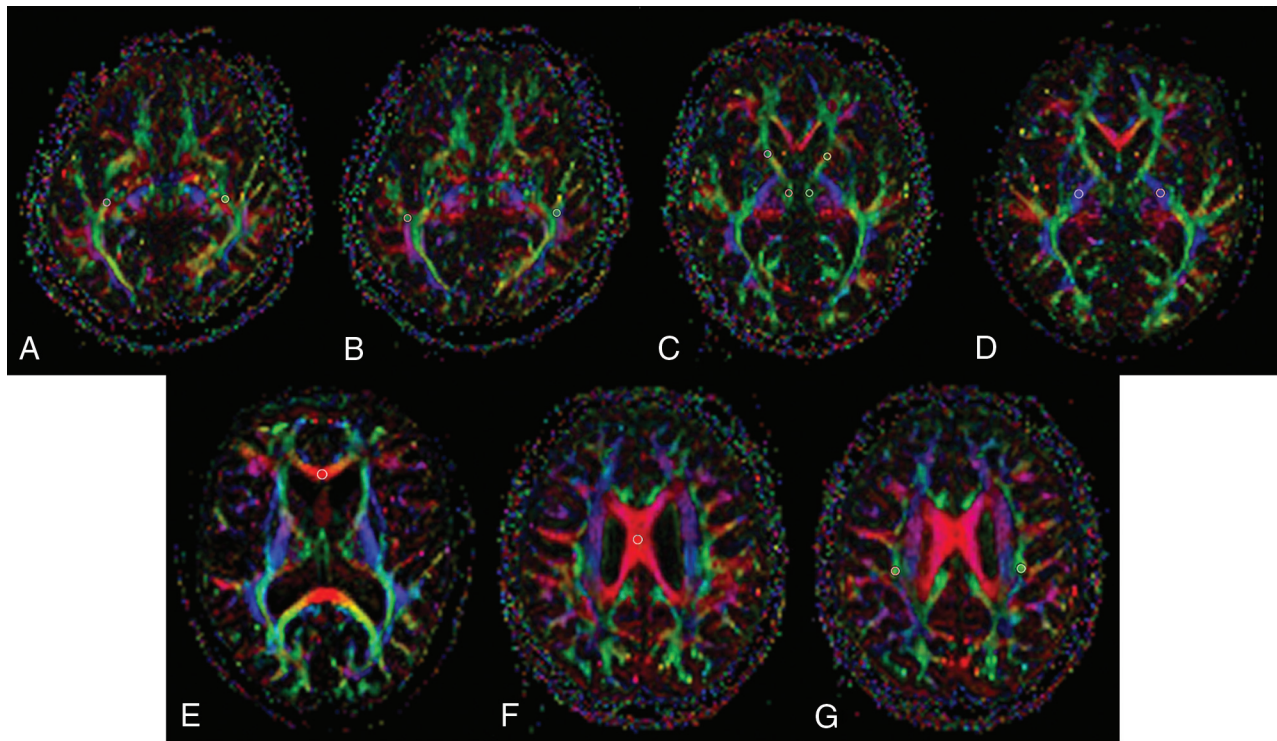
FIGURE. Axial DTI FA color maps depicting placement of *circular ROIs* in the inferior fronto-occipital fasciculus (*A*), ILF (*B*), anterior thalamic radiation (paramedian ROIs), and anterior limb of the internal capsule (anterolateral ROIs) (*C*), posterior limb of the internal capsule (*D*), genu (*E*) and body of the corpus callosum (*F*), and superior longitudinal fasciculus (*G*).

Table 1: Clinical features of study subjects

				P Values		
Groups	**PIGD**	**PD**	**HC**	**PIGD vs HC**	**PD vs HC**	**PIGD vs PD**
No.	19	21	20			
Sex (male/female)	15:4	17:4	16:4	1.00	1.00	1.00
Mean age (yr)	73.7 ± 6.7	72.0 ± 4.8	71.5 ± 4.9	0.24	0.742	0.36
Tinetti score (median) (IQR)						
Balance	9 (7.5–11)	12 (11–13)	15 (15–16)	<.001	<.001	0.03
Gait	7 (4.5–8.5)	9 (8–10)	12 (11–12)	<.001	<.001	0.01
Total	16 (12–19)	22 (20–23)	27 (26–27.3)	<.001	<.001	0.02

Note:—IQR indicates interquartile range.

Table 2: Results of Kruskal-Wallis test showing group differences in DTI indices among periventricular white matter ROIs[a]

	PIGD vs HC				PD vs HC				PIGD vs PD			
Group Comparisons	**FA**	**MD**	**AD**	**RD**	**FA**	**MD**	**AD**	**RD**	**FA**	**MD**	**AD**	**RD**
WM fiber DTI indices												
SLF		+	+								+	
P value		0.04[b]	0.03[b]								0.04[b]	
Longitudinal												
ILF	−	+		+		+						
P value	0.01[b]	0.001[b]		0.004[b]		0.009[b]						
IFOF	−	+		+	−	+		+				
P value	0.001[b]	0.003[b]		0.008[b]	0.01[b]	0.001[b]		0.04[b]				
Thalamic												
ATR	−											
P value	0.04[b]											
Callosal												
BCC			+								+	
P value			0.02[b]								0.003[b]	
GCC										+	+	
P value										0.01[b]	0.03	

Note:—+ indicates higher group value; −, lower group value.
[a] Empty cells indicate no significant differences.
[b] Significant.

FA and higher median diffusivity (MD, AD, RD) values compared with HC across the periventricular ROIs. The periventricular longitudinal ROIs showed the most DTI differences between disease and HC groups, with all 3 showing differences in at least 2 DTI indices between the PIGD and HC groups. Among the thalamic ROIs, only the ATR differentiated between PIGD and HC groups. Both the ALIC and PLIC did not show any difference for any DTI index between groups. Only callosal ROIs differentiated PIGD and PD disease groups.

Results from the multivariable linear regression are shown in Online Table 4. Some DTI indices from the SLF and ALIC ROIs correlated with both Gait and Balance scores, but those from the GCC fibers correlated only with Gait and Total Tinetti scores. As expected, the Tinetti scores correlated negatively with the diffusivity indices and positively with FA, respectively.

DISCUSSION
Using an ROI approach in our case-control DTI study, we showed that periventricular longitudinal, thalamic, and callosal fibers are differentially affected in PIGD, PD, and HC, with generally reduced FA and increased diffusivity indices, lending further support to their use as biomarkers[4,5] for identification of gait deficits and quantifying performance. The need for additional biomarkers for gait performance for identification of PIGD is shown by Herman et al,[15] with their findings that gait metrics alone seem to be a poor indicator of the PIGD subtype. Periventricular white matter,[10] in particular, has been shown to play an important role in gait, and additional effort is needed to understand it.

Longitudinal fibers provide the link between orbital, motor, and premotor areas and other areas of the brain,[16,17] and deficits could affect visuospatial processing in gait.[8,9] Our study has shown that the IFOF and ILF show statistically significant differences between PD (regardless of subtype) and HC. However, the SLF showed differences between PIGD and HCs, but not PD and HCs. The changes in SLF are more severe in the PIGD subtype, which are supported by other studies showing SLF involvement in gait, and in congruence with SLF having connections to the supplementary motor area (part of cerebral cortex that is involved in the control of movement).[8,9]

Thalamic fibers have been shown to be implicated in functional studies of the basal ganglia-thalamo-cortical loop, which affects movement and perception.[6,18] The fibers involved in the loop (ATR) in our study also showed differences between PIGD and HC in DTI indices and a statistically significant correlation with Tinetti scores. Although most studies show disruptions to the basal ganglia functional connectivity,[19] few studies have interrogated the differences in their connecting fibers within PD and PIGD. Additionally, the ATR showed good ability to predict Tinetti Balance, but not Tinetti Gait scores. This suggests that the ATR has a more prominent role in balance, but not gait.

The corpus callosum was the only structure in this study that differentiated the PIGD and PD subtypes. It also showed a significant linear regression to Tinetti Gait and Total scores. This finding concurs with those in other studies showing that damage to the corpus callosum results in freezing of gait,[20] supporting the worse Gait scores in patients with PIGD.[11] However, because a

relationship between ageing and gait in the corpus callosum has also been reported,[21] control for age as a potential confounder is important when using it as a biomarker.

Our study supports other findings of compromised functionality in the frontostriatal circuitry reported in gait dysfunction.[22-24] Most studies have found that the prefrontal cortex functions are impaired in attention, dual task, set-shifting, and visuospatial activities in freezing of gait,[6,9,25,26] suggesting underlying changes in various white matter fibers. Our results showed a shift in diffusivity and FA in the periventricular fibers, possibly related to the change in functional performance. DTI indices of white matter fibers may serve as a more direct and clinically accessible measure of white matter integrity rather than functional re-organization. Indeed, our DTI findings of heavier extranigral white matter burden in the PIGD group may aid in understanding the differential gait responsiveness of patients with PIGD to deep brain stimulation compared with patients with PD [27] and may potentially play a role in patient selection.

In this study, we were interested in periventricular white matter fibers that could be directly differentiated on the color FA maps on the basis of our knowledge of neuroanatomy and orientation of these fibers. Hence, we used a simple, manual ROI approach with clearly defined brain slices and radiologic landmarks, on readily available, commercial imaging workstations, and yielded good inter- and intrarater reproducibility. An automated approach, such as tract-based spatial statistics would allow faster and more readily reproducible global brain analysis, albeit with attendant image coregistration challenges,[28] between a 3D high-resolution T1-weighted structural scan and the DTI scan due to inherent geometric distortions. In addition, this would require computing expertise and was outside the scope of our study.

Although we have shown structural abnormality in these white matter fibers, future studies could integrate whole-brain analyses in diffusion tensor imaging and clinical cognitive testing to further granulate motor and cognitive associations among the fibers. Furthermore, the integration of whole brain analysis and clinical cognitive testing can be elucidated along with advancements in MR imaging techniques such as myelin water imaging.

CONCLUSIONS
Our DTI findings in PIGD implicate reduced white matter integrity in the periventricular fibers of the GCC, ALIC, ATR, and SLF, suggesting that poor gait performance may be the result of impaired structural integration in the subcortical motor neural systems. These findings provide insights into the underlying pathophysiology of PIGD and may have potential impact on future treatment strategies.

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