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Original Article

Quantitative Susceptibility Mapping Changes Relate to Gait Issues in Parkinson's Disease

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ABSTRACT: ***Background:*** Quantitative susceptibility mapping (QSM) demonstrates elevated iron content in Parkinson's disease (PD) patients within the basal ganglia, though it has infrequently been studied in relation to gait difficulties including freezing of gait (FOG). Our purpose was to relate QSM of basal ganglia and extra-basal ganglia structures with qualitative and quantitative gait measures in PD. ***Methods:*** This case–control study included PD and cognitively unimpaired (CU) participants from the Comprehensive Assessment of Neurodegeneration and Dementia study. Whole brain QSM was acquired at 3T. Region of interests (ROIs) were drawn blinded manually in the caudate nucleus, putamen, globus pallidus, pulvinar nucleus of the thalamus, red nucleus, substantia nigra, and dentate nucleus. Susceptibilities of ROIs were compared between PD and CU. Items from the FOG questionnaire and quantitative gait measures from PD participants were compared to susceptibilities. ***Results:*** Twenty-nine participants with PD and 27 CU participants were included. There was no difference in susceptibility values in any ROI when comparing CU versus PD ($p > 0.05$ for all). PD participants with gait impairment ($n = 23$) had significantly higher susceptibility in the putamen ($p = 0.008$), red nucleus ($p = 0.01$), and caudate nucleus ($p = 0.03$) compared to those without gait impairment ($n = 6$). PD participants with FOG ($n = 12$) had significantly higher susceptibility in the globus pallidus ($p = 0.03$) compared to those without FOG ($n = 17$). Among quantitative gait measures, only stride time variability was significantly different between those with and without FOG ($p = 0.04$). ***Conclusion:*** Susceptibilities in basal ganglia and extra-basal ganglia structures are related to qualitative measures of gait impairment and FOG in PD.

RÉSUMÉ : Des changements observés à la cartographie quantitative de la susceptibilité, liés à des troubles de la démarche dans la maladie de Parkinson ***Contexte :*** La cartographie quantitative de la susceptibilité (CQS) permet de visualiser une teneur élevée en fer dans les noyaux basaux (appelés *noyaux gris centraux*) chez les patients atteints de la maladie de Parkinson (MP), mais peu d'études ont porté sur la quantité de ce corps en relation avec les troubles de la démarche, y compris le blocage brutal à l'initiation de la marche (expression réduite à *blocage initial*). L'étude avait donc pour but d'établir une relation entre les structures des noyaux basaux et des noyaux extrabasaux, observées à la CQS, et des mesures qualitatives et quantitatives de la démarche dans la MP. ***Méthode :*** Il s'agit d'une étude cas/témoins menée chez des sujets atteints de la MP ou de troubles cognitifs (TC), ayant participé à l'étude *Comprehensive Assessment of Neurodegeneration and Dementia*. Une CQS de tout le cerveau a été effectuée avec un appareil 3 T. Les images des régions d'intérêt, tirées au sort manuellement et à l'insu, ont été prises dans le noyau caudé, le putamen, le pallidum, le pulvinar du thalamus, le noyau rouge, la substance noire et le noyau dentelé. Les valeurs de la susceptibilité des régions d'intérêt ont été comparées entre les sujets atteints de la MP et ceux atteints de TC. Une comparaison a aussi été établie entre les éléments tirés du questionnaire sur le blocage initial ainsi que les mesures quantitatives de la démarche enregistrées chez les participants atteints de la MP, et les valeurs de la susceptibilité. ***Résultats :*** Ont participé à l'étude 29 sujets atteints de la MP et 27 sujets atteints de TC. Aucun écart des valeurs de la susceptibilité, relatives à quelque région d'intérêt que ce soit, n'a été relevé dans les comparaisons entre les TC et la MP ($p > 0{,}05$: tous). Les sujets atteints de la MP, présentant des troubles de la démarche ($n = 23$) avaient une susceptibilité significativement accrue dans le putamen ($p = 0{,}008$), le noyau rouge ($p = 0{,}01$) et le noyau caudé ($p = 0{,}03$) comparativement à ceux exempts de troubles de la démarche ($n = 6$). Par ailleurs, les sujets atteints de la MP, présentant un blocage initial ($n = 12$) avaient une susceptibilité significativement accrue dans le pallidum ($p = 0{,}03$) comparativement à ceux exempts de blocage initial ($n = 17$). Quant aux mesures quantitatives de la démarche, seules les variations du temps d'enjambée différaient grandement entre ceux qui étaient atteints de blocage initial et ceux qui en étaient exempts ($p = 0{,}04$). ***Conclusion :*** La susceptibilité des structures des noyaux basaux et des noyaux extrabasaux est liée aux mesures qualitatives des troubles de la démarche et du blocage initial dans la MP.

Keywords: Parkinson's disease; Magnetic resonance imaging; Basal ganglia; Geriatrics

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Introduction

Gait issues in Parkinson's disease (PD) are widespread and diverse in nature. These include decreased gait speed and step length, increased gait variability, and freezing of gait (FOG).[1] FOG manifests as hesitation when initiating walking, trying to turn, or navigating tight spaces.[2,3] Gait impairment in PD portends a poor prognosis[4] and increases risk of falls and cognitive impairment.[5]

Susceptibility-based MRI methods including susceptibility weighted imaging (SWI), relaxometry (R_2, R_2*), and quantitative susceptibility mapping (QSM) have shown elevated iron content in the brains of PD patients in the subcortical structures.[6,7] However, there is a paucity of literature relating iron detected with susceptibility-based MRI methods with gait in PD.

Studies that have used susceptibility-based MRI methods in relation to gait have compared estimates of iron content in deep gray matter structures to measures of gait impairment (namely FOG) and PD with postural instability-gait disorder (PIGD). Two studies demonstrated increased R_2* in the substantia nigra pars compacta in PD patients with FOG relative to PD patients without FOG.[8,9] Another study using SWI found significantly decreased signal intensity in the putamen and globus pallidus in PIGD patients compared to non-PIGD PD patients, with signal intensities of the putamen being positively correlated with the Tinetti balance score.[10] Increased susceptibility has also been seen in PIGD versus healthy controls in the substantia nigra pars reticulata and pars compacta using QSM.[11] In addition, SWI has been used to quantify the number of cerebral microbleeds in PD patients, where those with PIGD had significantly more cerebral microbleeds than other subtypes of PD.[12] More studies are needed to determine the validity of QSM as an imaging tool to predict PD gait impairment, and more aspects of gait need to be compared to QSM outside of looking solely at FOG.

The objectives of this study were to compare QSM in various brain region of interests (ROIs) in PD patients without dementia versus cognitively unimpaired (CU) participants and to ascertain if there was a relationship between iron content in specific ROIs and both qualitative and quantitative measures of gait which has not been investigated by other studies to date. We hypothesized that basal ganglia structures would show altered iron signal in relation to gait impairment. Specifically, we hypothesized that gait would be related to basal ganglia structures with direct dopamine projections (i.e., caudate and putamen), while FOG would be related to the final common basal ganglia output (i.e., globus pallidus).

Materials and Methods

Participants

Participants were included from the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND).[13] COMPASS-ND is a Canadian national study investigating those with dementia or other cognitive concerns that is observational in nature.[13] This sub-study of COMPASS-ND (Pro00061456) was approved by the University of Alberta Research Ethics Board (Pro00099707). All participants provided written informed consent for the study. CU participants were from the COMPASS-ND study and CBBRAIN, a neuroimaging study of healthy controls.[14] For the CBRAIN study, participants underwent cognitive screening using the National Institutes of Health Toolbox Cognitive Battery[15] which encompasses testing for verbal recall, working memory, processing speed, and episodic memory where participants needed to score within two standard deviations of the mean; participants also could not have a self-reported history of brain injury, neurologic or psychiatric conditions.[16] Inclusion and exclusion criteria for the PD participants were the same as for COMPASS-ND in general (outlined below, also see[13,17] for additional information). Consecutive patients with PD or PD with mild cognitive impairment (MCI) at the University of Alberta were included. Participants with PD (with or without MCI but without dementia; $n = 29$, referred to as the PD group) and age-matched CU ($n = 27$) were included. PD participants were not selected per se but, rather, were subjects that were willing to undergo additional neuroimaging at the University of Alberta that included QSM. This included patients who were on treatment and not on treatment. Patients who had undergone deep brain stimulation prior to study initiation were not included.

Functional impairment on the basis of cognition was necessary for the diagnosis of dementia. A Montreal Cognitive Assessment (MoCA) score <25 in a participant who otherwise met criteria for PD (based on the MDS criteria for MD)[18] defined PD-MCI, consistent with published criteria.[19] PD participants could be taking PD medications: levodopa equivalent daily dose was calculated.[20] Exclusion criteria have been published and included significant known chronic brain disease, developmental disorders, malignant tumors, current alcohol or drug abuse, lack of a study partner, insufficient proficiency in English or French, total MoCA score of less than 13, inability to comprehend test instructions, and incapable of walking more than 10 m independently.[13,17]

Participant Assessments

Patient assessments include the Movement Disorders Society United Parkinson's Disease Rating Scale (MDS-UPDRS). Items from Part II (patient's view of motor aspects of experiences of daily living) and Part III of the MDS-UPDRS (motor examination completed by the clinician) addressing gait difficulties and FOG were used.[21] The items included were 2.12 (difficulties with walking and balance), 2.13 (freezing), 3.10 (general gait impairment), and 3.11 (FOG specifically). Hoehn and Yahr scores provide an estimation of overall impairment in an individual with PD.[22]

Image Acquisition

Whole brain QSM images were acquired on a 3T (Siemens Prisma) scanner using a 20-channel head coil. Acquisition parameters were as follows: axial multi-gradient echo sequence with seven echoes (first echo at 3.82 ms and subsequent echoes spaced at 5.49 ms), TR = 45.0 ms, flip angle = 17°, 80 slices, 2.0 mm slice thickness for a total coverage of 160 mm, 240 × 218 mm FOV, voxel dimensions 0.9 mm × 0.9 mm × 2.0 mm = 1.62 mm^3 without interpolation, parallel imaging (generalized autocalibrating partially parallel acquisitions (GRAPPA) with an acceleration factor of 2), and a scan time of 5.65 minutes. Whole brain sagittal T1-weighted images were acquired using 3D magnetization-prepared rapid gradient echo (MPRAGE) with the following parameters: 192 slices, 1.0 mm slice thickness; 256 mm FOV; image matrix 256 × 256; voxel size of 1.0 mm × 1.0 mm × 1.0 mm = 1.0 mm^3 with no subsequent interpolation; TR = 2300 ms; TE = 2.98 ms; TI = 900 ms; flip angle 9°; parallel imaging (GRAPPA with acceleration factor of 2); scan time of 5.35 minutes.

Processing of Susceptibility Maps

After saving raw phase images, QSM was reconstructed using a series of steps including phase unwrapping, background field

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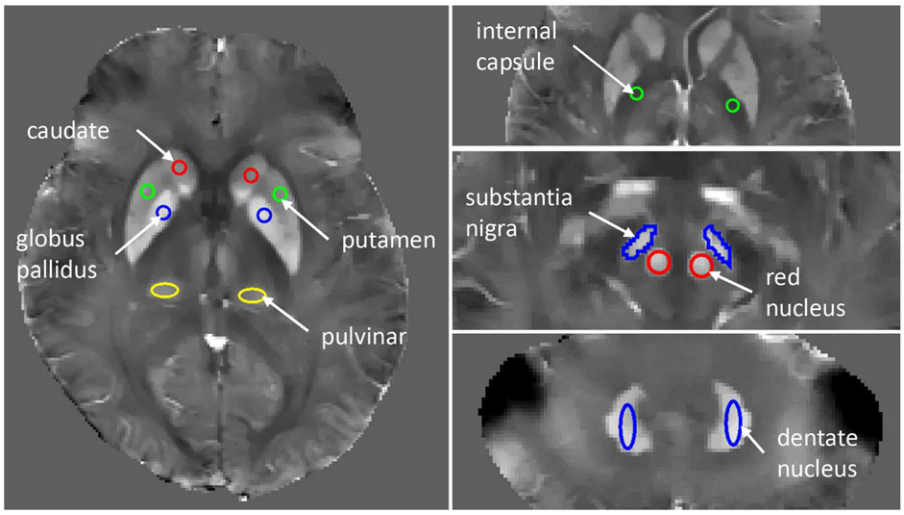

Figure 1: Sample quantitative susceptibility map outlining the regions of interest selected for analysis.

removal, and then susceptibility inversion.[23] Briefly, brain tissue was extracted using brain extraction tool[24] on the magnitude image of the first echo; coil-combined phase was unwrapped using phase region expanding labeler for unwrapping discrete estimates (PRELUDE),[25] background field was removed with the regularization enabled sophisticated harmonic artifact reduction on phase data (RESHARP) method,[26] and dipole inversion via total variation.[27]

ROI Analysis

ROIs investigated in our study included the caudate nucleus, globus pallidus, putamen, pulvinar nucleus of the thalamus, substantia nigra, red nucleus, and dentate nucleus. These were selected based on previous studies that have looked at and shown susceptibility changes in PD patients.[11,28]

Using ImageJ (https://imagej.nih.gov/ij/, 1997–2021), ROIs were drawn manually on the susceptibility maps by a single rater (NN) who was blinded to participant group using three separate axial slices. The slice with the largest cross section of the globus pallidus that also enabled visualization of each of the caudate nucleus, putamen, and pulvinar nucleus of the thalamus was selected as the first slice for looking at the aforementioned ROIs. ROIs were drawn bilaterally on the most central part of each area of interest (caudate nucleus, putamen, globus pallidus, pulvinar nucleus of the thalamus) with attention being given to avoid encompassing the edges of a given ROI to avoid inclusion of noise in the susceptibility measurement as much as possible. ROIs were placed bilaterally on a more caudal single slice in axial orientation (second slice) that best delineated the substantia nigra and red nucleus. ROIs for the dentate nucleus were placed bilaterally on an even more caudal single slice (third slice) that delineated this structure best.

The posterior limb of the internal capsule was examined as a reference region for which the ROI was drawn bilaterally on the same slice as the one that was used to outline the caudate, putamen, globus pallidus, and pulvinar nucleus of the thalamus (Figure 1). For each ROI tracing aside from the substantia nigra which was drawn individually for each subject, the size of each individual ROI was kept consistent across all subjects to enable for more consistent susceptibility measurements. Tracing was repeated on data from 10 randomly selected participants after an interval of 1 week to determine intra-rater reliability.

Volumetric Analysis

To determine the presence or absence of atrophy of structures included as ROIs, volumetric analysis was undertaken using T1-weighted images. Automated segmentation of subcortical brain regions and ventricles was performed using the "recon-all" pipeline in FreeSurfer (v6.0).[29] Processing was done on the Canadian Brain Imaging Research Platform,[30] a web-based software for distributed computing for neuroimaging research. Volumes of the caudate, putamen, globus pallidus, thalamus, and intracranial volume were estimated. The left and right volumes were summed and reported as a % of intracranial volume (summed volume/intracranial volume × 100%).

Clinical Gait Assessment

The original FOG questionnaire (FOGQ) developed by Giladi and colleagues was used.[31] This is a self-reported questionnaire with items addressing different aspects of gait which include the following: need for assistance during the individual's worst state of gait; if gait difficulties are affecting activities of daily living; if feet feel glued to the floor while walking or turning (freezing); the duration of the freezing episode; the duration of the typical start hesitation (freezing at time of gait initiation); and the duration of turning hesitation (freezing when turning).[31]

The PD group was classified into two different ways with respect to gait. First, participants were categorized as gait impaired if FOGQ total score ≥ 1 ($n = 23$) or not have gait impairment ($n = 6$). Second, participants were divided into those with FOG (FOG+, $n = 12$) and those without (FOG−, $n = 17$) where the FOG+ group consisted of the participants who scored ≥1 on items 3–6 inclusive. This approach was chosen as other studies have used only item 3 from the FOGQ[8,32]; however, items 4–6 also encompass other pertinent measures of freezing (i.e., duration of freezing episode, start hesitation, turning hesitation) which would help reflect the degree of FOG.

Quantitative Gait Assessment

Quantitative gait measures were determined as previously described in the ON state (on medication).[17,33] In brief, participants were instructed to walk on a 6 m electronic walkway (Zeno®-Protokinetics™) at their self-selected pace, starting 1 m from the

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Table 1: Demographics of 29 PD participants. All values reported as mean ± standard deviation or count (%)

				Gait status			FOG status		
	Min	Max	All PD participants	Impaired	Not impaired	*p*-value	FOG+	FOG−	*p*-value
N			29	23	6		12	17	
Age (years)	50	78	66.8 ± 6.1	66.4 ± 6.5	68.2 ± 4.7	0.5	66.3 ± 7.7	67.1 ± 5.0	0.7
Female			9 (31)	8 (35)	1 (17)	<0.001	4 (33)	5 (29)	<0.001
Number with MCI			8 (28)	5 (22)	3 (50)	<0.001	3 (25)	5 (29)	<0.001
Education (years)	9	20	15.3 ± 3.1	15.3 ± 3.0	15.2 ± 3.6	0.9	15.4 ± 3.2	15.2 ± 3.1	0.9
MoCA (0–30)	18	30	26.3 ± 3.4	26.6 ± 3.1	25.5 ± 4.4	0.5	26.2 ± 3.8	26.5 ± 3.2	0.8
LEDD (mg)	0	1400	718.4 ± 331.8	726.5 ± 332.2	687.5 ± 359.8	0.8	795.8 ± 256.3	663.8 ± 374.0	0.3
MDS-UPDRS II									
2.12 ≥ 1			27/28 (96)	21 (91)	6 (100)	1	11 (92)	17 (100)	0.4
2.13 ≥ 1			24/28 (86)	18 (78)	6 (100)	0.6	9 (75)	15 (88)	0.6
MDS-UPDRS-III									
Total	7	46	21.7 ± 9.8	22.9 ± 10.7	17.7 ± 3.9	0.3	27.9 ± 12.0	18.1 ± 6.0	0.009
3.10 ≥ 1			6/29 (21)	6 (26)	0 (0)	0.3	5 (42)	1 (6)	0.06
3.11 ≥ 1			1/29 (3)	1 (4)	0 (0)	1.0	1 (8)	0 (0)	0.4
Hoehn and Yahr score									
Total	1	3	2.1 ± 0.5	2.1 ± 0.5	2.2 ± 0.4	0.7	2.2 ± 0.6	2.1 ± 0.4	0.6
Score = I			2	2	0	0.7	1	1	0.6
Score = II			22	17	5		8	14	
Score = III			5	4	1		3	2	
FOGQ total score	0	15	3.9 ± 4.4	4.9 ± 4.4	0	0.01	8.0 ± 4.0	1 ± 1	<0.001

PD = Parkinson's disease; MoCA = Montreal Cognitive Assessment; LEDD = levodopa equivalent daily dose; UPDRS = United Parkinson's Disease Rating Scale; FOGQ = freezing of gait questionnaire.

walkway and ending 1 m beyond the walkway to minimize recording of accelerations and decelerations. Three trials were performed, and gait parameters were derived using Zeno®- Protokinetics™ software (stride velocity, cadence, stride length, step time, stride time variability, and double support time).

Statistical Analyses

GraphPad Prism (version 9.0.2; GraphPad Software, LLC) was used for statistical analyses. To compare groups with respect to participant demographics, all continuous variables were compared using two-sided *t*-tests and all categorical variables were compared using Fisher's exact test, with the exception of Hoehn Yahr score distribution between the groups, which was compared with Chi-squared test.

Intra-class correlation coefficient was used for 10 participants who had repeat ROI tracing (test, re-test, blinded to participant group in all instances, conducted by NN) to determine intra-rater reliability. To compare QSM values for each ROI between the left and right sides in CU and PD, unpaired *t*-tests were used. As there was no significant difference between left and right sides for any ROIs in CU and PD ($p > 0.05$), the average of left and right-side values was used for the remainder of analysis.

To test for whether the data followed a normal distribution or not, the D'Agostino and Pearson test was used. To compare QSM values for each ROI between CU and PD, unpaired *t*-tests were used for data that was normally distributed; in cases where data were not normally distributed, the Mann–Whitney nonparametric test was used instead. Pearson correlation coefficient was used to look for correlation between age and QSM values for each ROI in CU and PD; to look for correlation between sex and QSM values for each ROI in CU and PD; and to look for correlation between UPDRS-III total score and QSM values for each ROI in PD. In cases where data were not normally distributed, the Spearman correlation nonparametric test was used instead.

Unpaired *t*-tests were used to compare QSM values for each ROI between gait impaired and non-gait impaired PD participants. Unpaired *t*-tests were used to compare each of the quantitative gait measures between gait impaired and non-gait impaired PD participants. As above, in cases where data were not normally distributed, the Mann–Whitney nonparametric test was used instead. Unpaired *t*-tests were used to compare ROI volumes between gait impaired and non-gait impaired, and FOG+ versus FOG−. A *p*-value of ≤0.05 (two-tailed) was deemed statistically significant.

Results

Description of Participant Population

Participants in the CU group and PD group were age matched but not sex matched. The CU group had 12 males and 15 females, while the PD group had 20 males and 9 females. The average age of CU

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Table 2: Susceptibility values (ppm) in CIE ($n = 27$) and PD ($n = 29$)

	CU Mean ± SD	PD Mean ± SD	*p*-value	*p*-value with background correction
Caudate	0.039 ± 0.017	0.039 ± 0.019	0.82	0.80
Putamen	0.047 ± 0.019	0.055 ± 0.033	0.56	0.50
Globus pallidus	0.127 ± 0.031	0.132 ± 0.043	0.86	0.75
Pulvinar thalamus	0.038 ± 0.017	0.045 ± 0.016	0.08	0.15
Posterior limb of internal capsule	−0.055 ± 0.014	−0.056 ± 0.014	0.89	N/A
Red nucleus	0.100 ± 0.028	0.099 ± 0.036	0.88	0.95
Substantia nigra	0.088 ± 0.024	0.092 ± 0.042	0.64	0.62
Dentate nucleus	0.124 ± 0.041	0.125 ± 0.045	0.88	0.82

CU = cognitively unimpaired; PD=Parkinson's disease.

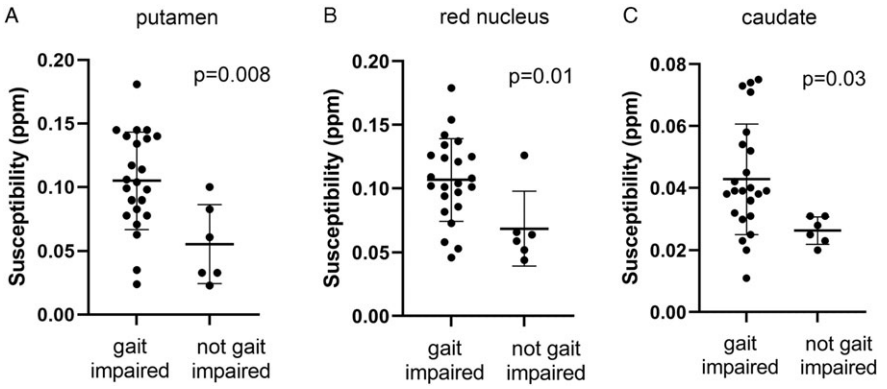

Figure 2: Susceptibility values in those Parkinson's disease patients with gait impairment compared to those without gait impairment in the (a) putamen, (b) red nucleus, and (c) caudate nucleus.

participants was 64.4 ± 6.2 years (mean ± standard deviation). Demographics of the PD participants are shown (Table 1). No patients were on cholinergic medications.

Reliability of the Analysis Method

Intra-class correlation coefficients were >0.90 ($p < 0.001$) except for the right globus pallidus which was 0.70 ($p = 0.04$). No differences were found between right and left sides for each ROI studied in CU or PD ($p > 0.05$) and so were combined for subsequent analyses.

Relationship between Susceptibility and Sex, Age, MoCA in CIE and PD participants

The mean susceptibility of ROIs in relation to sex in CU and PD showed a significant difference for the globus pallidus in CU ($r = 0.39$, $p = 0.05$, Spearman correlation), but otherwise no significant differences were seen for any other ROIs in CU or PD ($p > 0.05$ for all). In CU, there was a significant correlation between age and susceptibility in caudate nucleus ($r = -0.45$, $p = 0.02$, Pearson correlation coefficient) and dentate nucleus ($r = -0.53$, $p = 0.01$, Pearson correlation coefficient). In PD participants, there was no correlation between age and susceptibility in any of the ROIs ($p > 0.05$ for all). With respect to cognitive function, there was only a significant negative correlation between susceptibility of the dentate nucleus and MoCA scores in PD ($r = -0.47$, $p = 0.01$) but not for the rest of the ROIs, even with a MoCA score of <25 as a cut-off (all $p > 0.05$). As there few significant differences with no real consistent pattern when comparing susceptibility for the ROIs and sex, age, or cognitive status, these variables were not analyzed as co-variates for subsequent analyses.

Comparison of Susceptibilities of ROIs Between CU and PD

Susceptibility for each ROI in the 27 CU participants and the 29 PD participants is shown (Table 2). There was no significant difference between CU and PD for any ROI (all $p > 0.05$). Re-analyzing the data using the posterior limb of the internal capsule as a reference region did not change the significance for any ROI (all $p > 0.05$).

Relationship Between Susceptibilities and Qualitative Measures of Gait Impairment in PD

Comparing PD participants with gait impairment ($n = 23$) versus those without gait impairment ($n = 6$), there was a significant difference in susceptibility for the putamen ($p = 0.008$, Mann–Whitney test; Figure 2a), red nucleus ($p = 0.01$, unpaired *t*-test; Figure 2b), and caudate nucleus ($p = 0.03$, unpaired *t*-test; Figure 2c) but not for the pulvinar, posterior limb of the internal capsule, substantia nigra, or dentate nucleus (all $p > 0.05$; Table 3). When separating FOG+ ($n = 12$) versus FOG− ($n = 17$), there was a significant difference in susceptibility for the globus pallidus only ($p = 0.03$, Mann–Whitney test) but not for the other ROIs (all $p > 0.05$; Table 3).

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Table 3: Susceptibility values (ppm) in gait-impaired ($n = 23$), non-gait-impaired ($n = 6$), FOG+ ($n = 12$), and FOG− ($n = 17$) PD participants

	Gait-impaired Mean ± SD	Non-gait-impaired Mean ± SD	*p*-value
Caudate	0.043 ± 0.018	0.0266 ± 0.004	0.03
Putamen	0.105 ± 0.038	0.056 ± 0.031	0.008
Globus pallidus	0.137 ± 0.043	0.114 ± 0.018	0.21
Pulvinar thalamus	0.047 ± 0.014	0.036 ± 0.012	0.12
Posterior limb of internal capsule	−0.058 ± 0.013	−0.049 ± 0.010	0.15
Red nucleus	0.107 ± 0.032	0.069 ± 0.029	0.01
Substantia nigra	0.097 ± 0.042	0.065 ± 0.030	0.17
Dentate nucleus	0.129 ± 0.043	0.107 ± 0.033	0.29
	FOG + Mean ± SD	**FOG- Mean ± SD**	***p*-value**
Caudate	0.038 ± 0.014	0.040 ± 0.019	0.81
Putamen	0.052 ± 0.022	0.058 ± 0.038	0.63
Globus pallidus	0.151 ± 0.051	0.119 ± 0.024	0.03
Pulvinar thalamus	0.046 ± 0.012	0.045 ± 0.016	0.78
Posterior limb of internal capsule	−0.053 ± 0.012	−0.058 ± 0.014	0.31
Red nucleus	0.100 ± 0.024	0.098 ± 0.042	0.90
Substantia nigra	0.098 ± 0.044	0.087 ± 0.041	0.52
Dentate nucleus	0.129 ± 0.042	0.123 ± 0.043	0.73

FOG = freezing of gait.

Relationship Between Susceptibilities and Quantitative Measures of Gait Impairment in PD

There was no significant difference between gait-impaired versus not-gait-impaired PD participants in any quantitative gait measures (all $p > 0.05$, Supplemental Table 1). For FOG+ versus FOG−, there was a significant difference between groups only for stride time variability ($p = 0.04$, Supplemental Table 1).

Relationship Between Volumes of ROIs and Gait Impairment or FOG in PD

Volumes did not differ for any ROIs measured (caudate, putamen, globus pallidus, thalamus) between gait impaired versus not-gait impaired (all $p > 0.05$) or FOG+ versus FOG− (all $p > 0.05$) in PD participants.

Discussion

In this study, PD participants with gait impairment had increased susceptibility in basal ganglia (caudate, putamen) and extra-basal ganglia structures (red nucleus) compared to PD participants without gait impairment. For FOG specifically, susceptibility was increased in FOG+ PD participants in the globus pallidus versus FOG− PD participants. This suggests that gait impairment in general can lead to susceptibility changes across multiple structures, whereas FOG has a more focused localization in the globus pallidus, aligning with our hypothesis.

Aside from stride time variability in FOG+ versus FOG−, there was no between-group difference in any other quantitative gait measures. A recent study showed that microstructural changes in the thalamus and caudate detected with DTI correlated with quantitative gait parameters in PD patients, with different correlations in the ON (on medication) versus OFF state (off medication).[34]

The most likely substrate for the susceptibility changes seen is iron, though calcium and altered myelination could also contribute. Though we only used QSM, a meta-analysis looking at the different types of susceptibility MRI for iron deposition in PD found that QSM was the most reproducible of the susceptibility MRI methods.[35] Furthermore, the differences in susceptibility were not due to atrophy of these structures leading to more concentrated iron, as volumes of the ROIs studied were not significantly different between groups. The susceptibility obtained with QSM for the ROIs studied was similar to what has been measured by others.[27,36] Presuming that the susceptibility changes are primarily due to iron, the question that follows is what does the increase in iron deposition indicate? Some proposed mechanisms include buildup of iron in dopaminergic neurons with subsequent production of reactive oxygen species, altered iron trafficking, and increased expression of α-synuclein which can lead to both increased levels and redistribution of iron in neurons.[37,38]

Degeneration in dopamine rich structures would be postulated to lead to impaired response to dopamine treatment. Gait disorders are particularly implicated. The association between increased susceptibility in the caudate and putamen is consistent with this hypothesis. In contrast, the globus pallidus is the main outflow from the basal ganglia. Recent studies have showed that diffusion changes in the globus pallidus are associated with FOG.[39,40]

Within the landscape of susceptibility MRI studies in PD investigating the relationship between susceptibility and gait, our study aligns with another study demonstrating susceptibility changes in the putamen and globus pallidus.[10] Our study complements these susceptibility and diffusion MRI studies by showing that susceptibility changes in the globus pallidus are also implicated in FOG. Others have shown changes in the substantia nigra[8,9,11] which we did not see, perhaps due to differences in methodologic details and patient selection.

One strength of this study was that the method used for evaluating the ROIs was simple and demonstrated good intra-rater reliability and thus can be replicated by others rather than relying on automatic segmentation that may lead to variable results depending on the assumptions inherent to the software used. The use of a broader definition of gait impaired, encompassing use of specific items from the FOGQ rather than just using item 3 as others have,[8,32] was also a strength as we were able to identify ROIs with significant differences that would have otherwise been missed. As such, this is the first study to our knowledge that demonstrates distinct elevated iron content in the basal ganglia and extra-basal ganglia structures that relate to gait impairment and FOG in PD.

The simplicity of our method was a strength but could conversely be viewed as a weakness as we did not encompass the entire ROI. Nonetheless, our values were similar to those reported by others, suggesting that this method could be used reliably.[27,36] Another weakness was using single time points for gait and MRI, while patients were in the ON state. Hence, we were only examining features not responsive to medications. Furthermore, how the relationships between susceptibility values in these ROIs and gait evolve over time is unknown. Future studies would be enhanced with longitudinal imaging and multimodal imaging to see how susceptibility changes over time and to help clarify the relationship between different markers of neuronal damage and plasticity, respectively. Lastly, our study had imbalances in sex

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distribution with CU not being matched for sex. Consecutive PD patients and CU participants were used for analyses and balanced as well as possible given the available sample.

Conclusions

Susceptibility in basal ganglia and extra-basal ganglia structures is differentially related to gait impairment and FOG in PD patients. This warrants further investigation to ascertain the link between altered susceptibility suggestive of iron deposition and gait impairment.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2022.316.

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Conflict of Interest. None to declare.

Statement of Authorship. All authors participated in study conception and design, and interpretation of results. All the co-authors contributed to the project implementation and data collection. The first author analyzed data and drafted the first version of manuscript. The last author supervised the whole process. All authors revised and approved the manuscript before submission and take responsibility for contents of the article.

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