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Initial diagnostic workup of parkinsonism: Dopamine transporter positron emission tomography versus susceptibility map-weighted imaging at 3T

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ABSTRACT

Background and Purpose: Evaluation of dorsal nigral hyperintensity on MRI can help detect nigrostriatal degeneration. We aimed to compare the diagnostic performance between susceptibility map-weighted imaging (SMWI) and N-3-fluoropropyl-2-β-carbomethoxy-3-β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography (PET) as an initial diagnostic tool of parkinsonism.

Materials and methods: This local ethics committee-approved retrospective study enrolled 223 patients with parkinsonism and 15 healthy subjects (mean age, 69.7 years; 135 females) who underwent both SMWI at 3T and ^{18}F-FP-CIT PET. The diagnostic performances of the two tests for nigrostriatal degeneration were compared by evaluating whether the 90% confidence interval (CI) of the difference between the two tests was within the equivalence margin by using the DTComPair package of R. The concordance rate was tested by Cohen's kappa.

Results: The diagnostic sensitivities of SMWI and ^{18}F-FP-CIT PET were 94.5% and 100% per SN and 100% and 100% per participant, respectively; their specificities were 95.3% and 86.7% per SN and 94.4% and 84.0% per participant, respectively. While the diagnostic sensitivity was comparable between the two tests for each SN and participant, the lower 90% CI of the differences in the specificity were −0.086 per SN and −0.104 per participant, indicating a higher diagnostic specificity of SMWI than that of ^{18}F-FP-CIT PET. When excluding 20 participants with basal ganglia lesions, the two tests exhibited similar diagnostic performance and had excellent agreement (k = 0.899 per SN; k = 0.945 per participant).

Conclusion: For patients with parkinsonism, SMWI and ^{18}F-FP-CIT PET exhibit similar diagnostic performance.

1. Introduction

The current diagnostic criteria for idiopathic Parkinson's disease (IPD) describe that the diagnosis of IPD is made in the absence of absolute exclusion criteria, the presence of supportive criteria, and the presence or absence of red flags (the supportive criteria and red flags are counterbalanced) [1]. These diagnostic criteria adopted two imaging studies: dopamine transporter (DAT) imaging and metaiodobenzylguanidine (MIBG) scintigraphy. Normal DAT activity is one of the exclusion criteria, and cardiac sympathetic denervation that is determined by an MIBG scan is one of the supportive criteria [2].

It has recently been suggested that dorsal nigral hyperintensity (DNH) or nigrosome 1 on susceptibility-weighted imaging (SWI) at 3T or 7T may serve as a new imaging biomarker for IPD [3–12]. A recent meta-analysis showed that overall sensitivity and specificity for IPD versus the control at 3T were 94.6% and 94.4%, respectively [13]. It should therefore be tested if the DNH or nigrosome 1 on SWI can reflect the presynaptic dopaminergic function to help differentiate IPD patients from those with a normal DAT activity. Additionally, it is also necessary to test this imaging sign in patients who present with parkinsonism for use in daily clinical practice. A recent retrospective study using SWI showed a sensitivity of 88.8%, a specificity of 83.6%, and a concordance

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Abbreviations

SWI	susceptibility-weighted imaging
SMWI	susceptibility map-weighted imaging
QSM	quantitative susceptibility mapping

rate of 86.2% between SWI and DAT imaging in patients with IPD, multiple system atrophy (MSA), and progressive supranuclear palsy (PSP), disease controls, and healthy subjects [10]. Compared to the results of a recent meta-analysis [13], their diagnostic performance is lower, which may be attributable to their relatively lower spatial-resolution ($0.63 \times 0.63 \times 2\,mm^3$) SWI. Given the current technical limitations of 3T clinical scanners in terms of spatial resolution and contrast- and signal-to-noise ratios (CNR and SNR), it is necessary to obtain an optimized SWI to assess this small, but important region. Given the size of the nigrosome 1 region, it should also be precisely localized with high spatial-resolution imaging [14]. By using high spatial-resolution quantitative susceptibility mapping (QSM), a study recently proposed a method (susceptibility map-weighted imaging, SMWI) for improving both the CNR and SNR [15]. We hypothesized that this imaging can help improve diagnostic performance along with a higher concordance with DAT imaging in subjects who present with parkinsonism. The aims of this study were to compare the diagnostic performance between SMWI and N-3-fluoropropyl-2-β-carbomethoxy-3-β-(4-iodophenyl)nortropane (^{18}F-FP-CIT) positron emission tomography (PET) in subjects with parkinsonism and to assess the concordance rate between the two tests per participant and per basal ganglia-substantia nigra (SN).

2. Materials and Methods

All participants provided written informed consent, and this retrospective study was approved by the Institutional Review Board of Gil Medical Center.

2.1. Participants

Between November 2014 and October 2016, a total of 325 patients were evaluated for parkinsonism by a single movement specialist (Y.H.S. with 12 years of experience), with an additional follow-up evaluation. All patients underwent a head MRI with a 3T scanner as an initial diagnostic workup. Of the 315 patients, 92 patients were excluded from this study for the following reasons: no ^{18}F-FP-CIT PET due to a fear of radiation exposure or socioeconomic reasons (n = 78), an interval longer than one year between the MRI and ^{18}F-FP-CIT PET (n = 10), and an indeterminate diagnosis (n = 4). We included 15 healthy subjects who underwent both MRI and ^{18}F-FP-CIT PET. As a result, a total of 238 participants were enrolled in this study (Fig. 1). The demographic and clinical characteristics of the study population are summarized in Table 1. According to the clinical diagnosis, the patients were divided into groups with or without nigrostriatal degeneration (loss of the dopaminergic neurons in the SN, which are projected to the ipsilateral putamen and caudate nucleus) [16]: IPD, MSA, and PSP versus other diseases (for details on the clinical diagnoses, see Appendix E1). The mean interval between the MRI and ^{18}F-FP-CIT PET was 13.8 days (standard deviation, 44.1 days; range, 0–319 days).

2.2. MR image acquisition

All participants underwent MR imaging using a 3T scanner with a 32-channel coil (MAGNETOM Skyra; Siemens Healthineers, Forchheim, Germany). Whole-brain sagittal three-dimensional magnetization-prepared rapid acquisition of gradient echo (MP-RAGE) imaging was initially obtained with the following parameters: repetition time (TR), 1800 ms; echo time (TE), 3 ms; inversion time, 920 ms; matrix 256 × 256; a field of

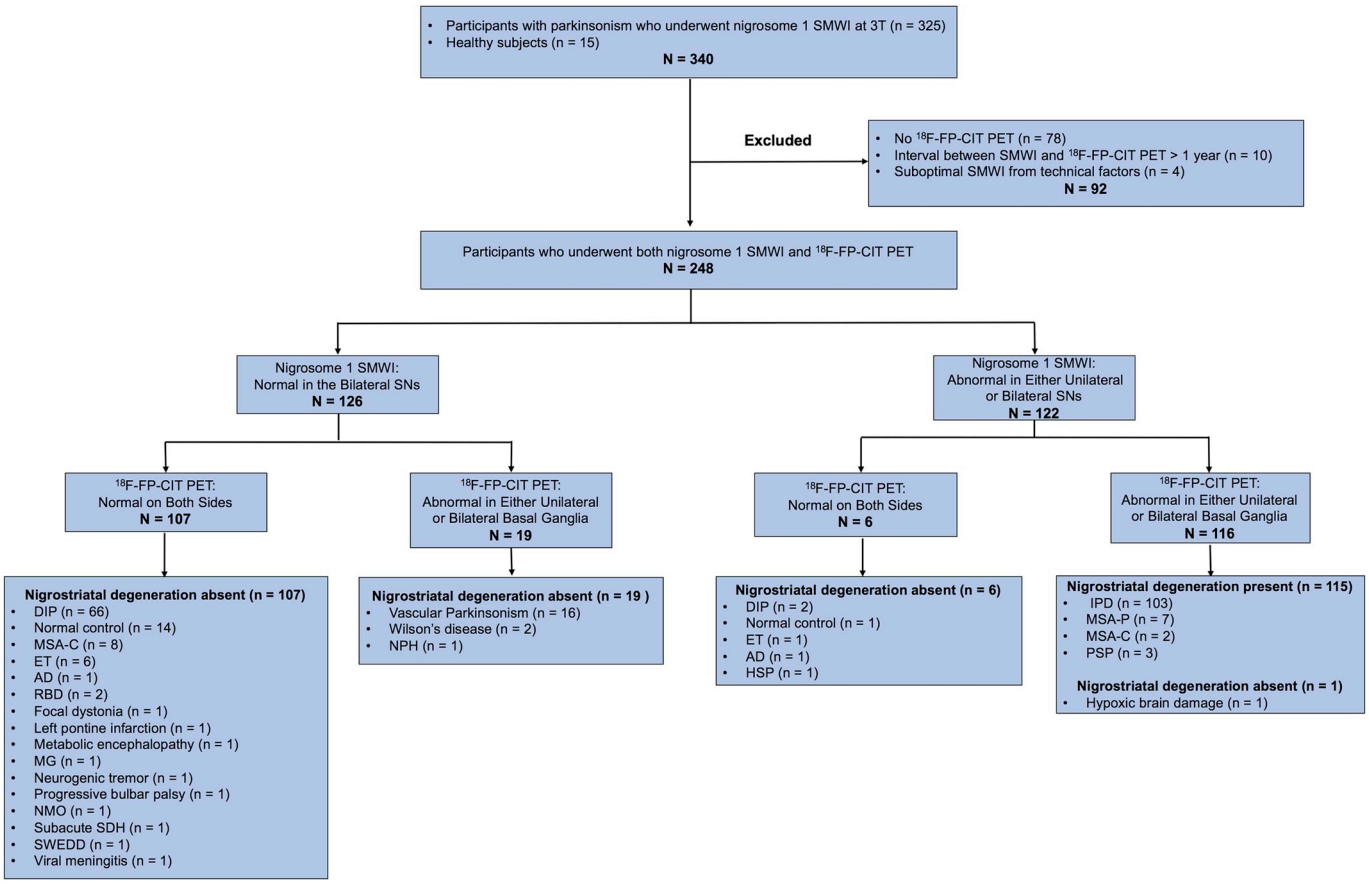

Fig. 1. Cohort flowchart.

Table 1
Demographics and clinical characteristics in the study population.

Disease Category	Clinical Diagnosis	Number	Age	Sex (M:F)	Onset duration	H&Y stage
Nigrostriatal degenerative diseases	IPD	103	71 (65–76)	54:49	12 (5–24)	2 (2–2.5)
	MSA	7	64 (60–78)	3:4	12 (9.5–16.5)	3 (2.4–4)
	PSP	3	75	2:1	4	2
Non-nigrostriatal degenerative diseases	DIP	68	70 (65–75)	24:44	5 (2–12)	2 (2–3)
	RBD	2	54.5	1:1		–
	ET	7	72 (45–75)	2:5		–
	AD	2	72	1:1		–
	VP	16	76.5 (71.3–80)	8:8		–
	Wilson's disease	2	34	1:1		–
	SWEDD	1	67	M		–
	Subacute SDH	1	71	M		–
	Hydrocephalus	1	77	M		–
	Left pontine infarction	1	67	F		–
	Hypoxic brain damage	1	53	M		–
	NMO	1	31	M		–
	Focal dystonia	1	56	F		–
	MG	1	76	F		–
	HSP	1	70	F		–
	Metabolic encephalopathy	1	74	M		–
	Neurogenic tremor	1	75	M		–
	Progressive bulbar palsy	1	81	F		–
	Viral meningitis	1	81	F		–
Normal Control		15	69 (64–71)	7:8		
Total		238	71 (65–76)	103:135		

Note.—Data are median with interquartile ranges in parentheses. H&Y, Hoehn and Yahr; IPD, idiopathic Parkinson disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; DIP, drug-Induced Parkinsonism; RBD, rapid eye movement (REM) sleep behavior disorder; ET, essential tremor; AD, Alzheimer disease; VP, vascular Parkinsonism; SWEDD, scans without evidence of dopaminergic deficits; SDH, subdural hemorrhage; NMO, neuromyelitis optica; MG, myasthenia gravis; HSP, hereditary spastic paraplegia; –, not applicable.

view (FOV), 250 × 250; an acceleration factor, two; and acquisition time, 3:36 min. Oblique coronal three-dimensional multi-echo combination imaging (MEDIC), which generates a combined image from multi-echo gradient-recalled echo images, was obtained parallel to the plane from the posterior commissure and the top of the pons, which was localized with sagittal MP-RAGE imaging [17]. The scan parameters for the MEDIC were as follows: TR, 88 ms; minimum TE, 11.1 ms; maximum TE, 66.9 ms; six echoes; echo spacing, 11.1 ms; flip angle, 10°; echo train length, 6; thickness, 1 mm; number of sections, 28; matrix, 384 × 384; FOV, 192 × 192; acceleration factor, two; and acquisition time, 7 min and 19 s. The k-space data of the MEDIC images were processed to reconstruct SMWI (for details, see Appendix E1 [online])

2.3. Visual rating of DNH on SMWI

A neuroradiologist (E.Y.K. with 13 years of experience) and a

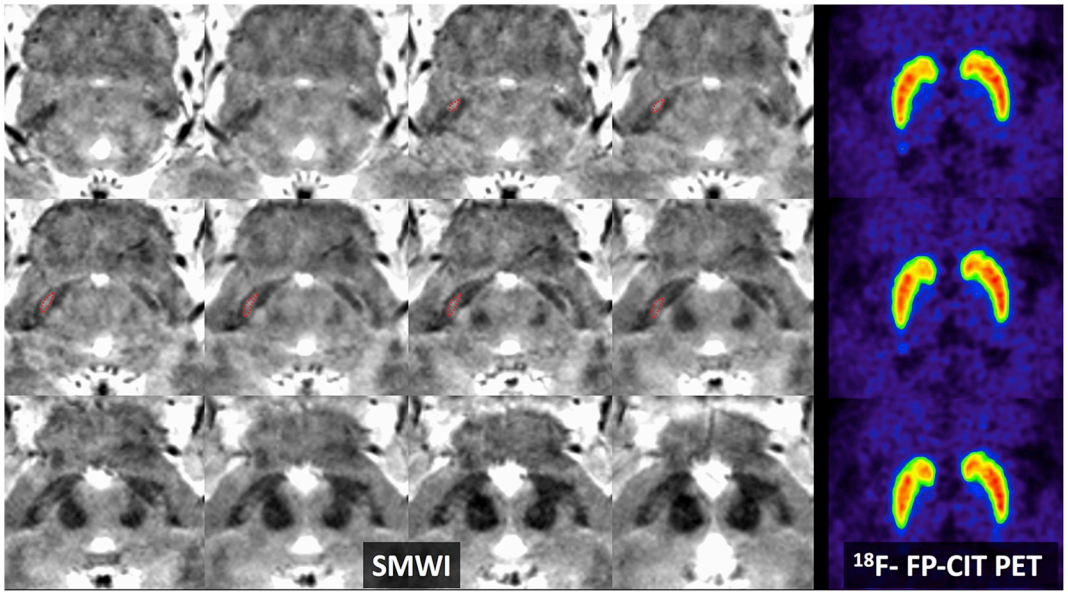

Fig. 2. The normal DNH region on the SMWI and normal ^{18}F-FP-CIT PET in a 63-year-old healthy female. The hyperintense regions in the hypointense substantia nigra below the level of the inferior border of the red nucleus are considered the DNH region on the SMWI in this study, which are indicated by the dotted red line. The uptake is normal and symmetric in the bilateral basal ganglia on the ^{18}F-FP-CIT PET.

neurologist (Y.H.S. with 12 years of experience) independently reviewed anonymized images without any clinical information using OsiriX Lite (version 8.0.2, Pixmeo Co., Switzerland). SMWI were classified into three grades: 'normal' (iso- or hyperintensity in the central portion of the presumed DNH) (for details, see Appendix E1 and Fig. 2), 'possibly abnormal' (hypointensity in less than 50% of the presumed DNH) (in the left SN, Fig. 3), and 'definitely abnormal' (hypointensity in equal to or greater than 50% of the presumed DNH) (in the right SN, Fig. 3). Each side was rated separately. To simplify the statistical analysis, we combined the 'possibly abnormal' and 'definitely abnormal' in the individual SN and reclassified them into 'abnormal'. The participants were re-classified as abnormal if any abnormality was determined on either side of the DNH; subjects were classified as normal only when the bilateral regions of the DNH were determined as normal. Any discrepancy between the two readers was resolved by consensus.

2.4. Acquisition and visual rating of the ^{18}F-FP-CIT PET

All participants underwent ^{18}F- FP-CIT PET imaging of the brain 120 min after injection of 5 mCi (185 MBq) with a PET/CT scanner (Biograph-6; Siemens, Erlangen, Germany). Visual analysis of ^{18}F-FP-CIT binding to the caudate nucleus and the putamen was performed by two nuclear medicine specialists (K.H.H. and H.L. with 16 and 4 years of experience, respectively) without clinical information (for details, see Appendix E1 [online]).

2.5. Statistical analyses

Inter-rater agreement was assessed using Cohen's kappa. For the presence or absence of abnormality, the agreement between each DNH region on SMWI and the ipsilateral basal ganglia on the ^{18}F-FP-CIT PET was tested using Cohen's kappa. The diagnostic performances of SMWI and ^{18}F-FP-CIT PET per participant were compared with the final clinical diagnoses and the expected nigrostriatal degeneration for each disease entity as the reference standard (for details, see Appendix E1 [online]). For per SN analysis, we used the findings on the ^{18}F-FP-CIT PET as the reference standard to test the diagnostic performances for each side of the basal ganglia – SN in the group with nigrostriatal degeneration. In the group without nigrostriatal degeneration, they were considered to have normal SNs on both sides regardless of the findings on ^{18}F-FP-CIT PET. Patients with a structural abnormality in the basal ganglia may show false positive findings on ^{18}F-FP-CIT PET, but they have normal presynaptic dopaminergic function and are therefore expected to exhibit a normal DNH on SMWI. Accordingly, statistical analyses were separately conducted for all participants and for participants without any structural abnormalities in the basal ganglia. To compare the diagnostic accuracy between SMWI and ^{18}F-FP-CIT PET, the differences in the sensitivity and specificity for each test were calculated. When the 90% confidence interval (CI) of the difference between the two diagnostic tests was within the equivalence margin (−0.1–0.1) for both sensitivity and specificity, it was considered that they were comparable. Statistical analyses were conducted with SPSS (version 18, Chicago, IL) and the "DTComPair" package of R for Windows, version 3.3.3.

3. Results

3.1. Interrater reliability

For the 238 total participants (472 SN), the two reviewers showed a discrepancy for interpreting the DNH on SMWI in 7 patients (2.9%) and in 13 SNs (2.7%), showing excellent agreement (k = 0.941 [95% CI, 0.919–0.963] per participant; k = 0.945 [95% CI, 0.930–0.960] per SN). The interrater agreement between the two reviewers on the visual rating of the ^{18}F-FP-CIT PET was excellent (k = 0.919 [95% CI, 0.903–0.935] per participant; k = 0.904 [95% CI, 0.871–0.937] per basal ganglia).

3.2. Imaging findings in the respective diagnostic groups

All IPD patients showed a decreased uptake in either the unilateral (n = 6) or bilateral basal ganglia (n = 97) on ^{18}F-FP-CIT PET. All patients with MSA-P (n = 7) and PSP (n = 3) showed a decreased uptake on both sides on ^{18}F-FP-CIT PET. Because of presence of structural abnormalities in the basal ganglia, patients with VP (n = 16), Wilson's disease (n = 2), normal pressure hydrocephalus (n = 1), and hypoxic

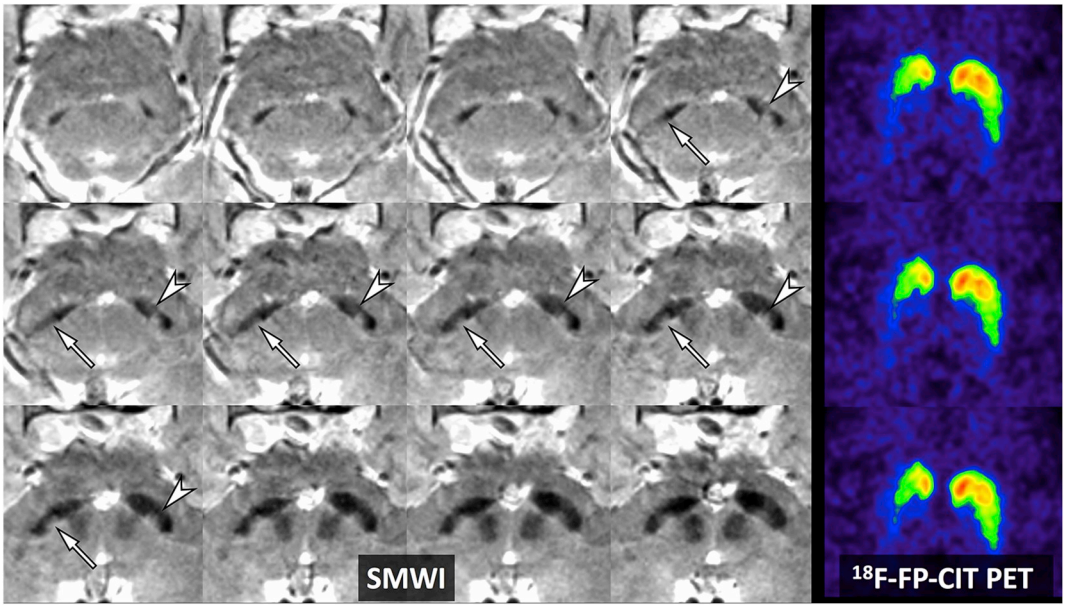

Fig. 3. Abnormal DNH on the SMWI in a 56-year-old female patient with idiopathic Parkinson's disease. The left DNH region loses its normal hyperintensity less than 50% (arrowheads), and is considered "possibly abnormal", whereas the right DNH region shows an abnormal hypointensity greater than 50% of its normal portion in the substantia nigra with a decrease in volume (arrows). The uptake is much more decreased in the right basal ganglia than in the left on the ^{18}F-FP-CIT PET, which is well correlated with the findings on the SMWI.

brain damage (n = 1) showed a decreased uptake in either the unilateral or bilateral basal ganglia on ^{18}F-FP-CIT PET (Table 2). The other patients and all healthy subjects had a normal ^{18}F-FP-CIT PET.

All 103 patients with IPD showed abnormal DNH in either the unilateral (n = 10) or bilateral SN (n = 101) on SMWI. All 113 patients with neurodegenerative parkinsonism including MSA-P and PSP had abnormal SMWI, whereas 6 of 133 patients with non-neurodegenerative parkinsonism had abnormal SMWI. One of 15 healthy subjects was interpreted as abnormal on SMWI in our study (for details, see Table E1 [online]).

3.3. Concordance of SMWI findings and PET findings

After consensus reviews of SMWI and ^{18}F-FP-CIT PET, the agreements between the imaging findings of SMWI and ^{18}F-FP-CIT PET were substantial (k = 0.790 [95% CI, 0.712–0.868] per participant; k = 0.774 [95% CI, 0.718–0.831] per SN) for all participants, and excellent (k = 0.945 [95% CI, 0.901–0.988] per participant; k = 0.899 [95% CI, 0.858–0.940] per SN) for the participants without any structural abnormalities in the basal ganglia (for details, see Table E2-3 [online]).

3.4. Diagnostic performance of SMWI for nigrostriatal degeneration in all participants

Diagnostic sensitivity and specificity of SMWI for nigrostriatal degeneration were 94.5% and 95.3% per SN and 100% and 94.4% per participant, respectively. Therefore, diagnostic accuracy of SMWI for nigrostriatal degeneration were 95.0% per SN and 97.2% per participant respectively. After consensus agreement, false positive interpretations were found in 12 SNs from 8 participants (Table E1 [online]) (Fig. 4A) and false negative interpretations in 12 SNs (unilateral SN of the IPD [n = 10] and MSA-P [n = 2] patients) for SMWI (i.e., no false negative interpretation per participant) (Table E4 [online]) (Fig. 4B), whereas false positive interpretations were found in 34 basal ganglia with structural abnormalities in 20 patients (Fig. 5) without any false negative interpretations on the ^{18}F-FP-CIT PET (Table 2). Five of the 7 patients with MSA-P and all three patients with PSP showed an abnormality in the bilateral DNH regions on SMWI, which were concordant with the findings on the ^{18}F-FP-CIT PET (Fig. E1 [online]).

3.5. Comparison of the diagnostic performance between SMWI and ^{18}F-FP-CIT PET

Table 3 summarizes the comparison of the diagnostic performance between SMWI and ^{18}F-FP-CIT PET for all participants. The 90% CIs of the differences in the diagnostic sensitivity per SN and per participant were within the equivalence margin between SMWI and ^{18}F-FP-CIT PET. However, the lower 90% CIs of the differences in the specificity were −0.086 per SN and −0.104 per participant, indicating a higher diagnostic specificity for SMWI compared to that of the ^{18}F-FP-CIT PET.

Twenty participants were determined to have false positive findings on the ^{18}F-FP-CIT PET (Table 2). Nineteen patients, excluding the patient with hypoxic brain damage, showed a normal DNH on SMWI. Because these 20 patients may influence the uptake on the ^{18}F-FP-CIT PET due to structural abnormalities in the basal ganglia, the other 218 participants were reanalyzed to compare the diagnostic performance of SMWI and ^{18}F-FP-CIT PET per participant and per SN. The 90% CIs of the differences in both the sensitivity and specificity were within the equivalence margin, indicating similar diagnostic performance between SMWI and ^{18}F-FP-CIT PET (Table 3).

4. Discussion

This study demonstrated that the interpretations of SMWI and ^{18}F-FP-CIT PET per SN and per participant are concordant in 88.7% and 89.5% in all participants and in 95.0% and 97.2% in participants without any structural abnormalities in the basal ganglia, respectively. The diagnostic performance was comparable between SMWI and ^{18}F-FP-CIT PET per SN and per participant when the participants with structural abnormalities in the basal ganglia were excluded. For all participants, however, the diagnostic performance of SMWI was superior to that of the ^{18}F-FP-CIT PET because the former had fewer false positive interpretations in patients with structural abnormalities in the basal ganglia. In addition, SMWI exhibited perfect sensitivity. Accordingly, the study results suggest that SMWI may serve as an alternative imaging tool to DAT imaging for screening subjects with normal presynaptic dopaminergic function. It may also be helpful to evaluate patients who have structural abnormalities in the basal ganglia.

Compared to the previous study that assessed the concordance between DAT imaging and DNH on SWI with a spatial resolution of

Table 2
Visual interpretations of the SMWI and ^{18}F-FP-CIT PET in the participants with any structural abnormalities in the basal ganglia.

Participant	Age	Sex	SMWI			^{18}F-FP-CIT PET			Final Diagnosis
			Right	Left	Per Patient	Right	Left	Per patient	
1	53	F	N	N	N	A	N	A	VP
2	64	F	N	N	N	A	A	A	VP
3	80	F	N	N	N	A	N	A	VP
4	72	M	N	N	N	A	A	A	VP
5	78	M	N	N	N	A	N	A	VP
6	71	F	N	N	N	A	A	A	VP
7	87	F	N	N	N	A	N	A	VP
8	79	M	N	N	N	A	N	A	VP
9	72	F	N	N	N	A	A	A	VP
10	72	M	N	N	N	A	A	A	VP
11	78	M	N	N	N	A	A	A	VP
12	65	M	N	N	N	A	A	A	VP
13	80	F	N	N	N	A	N	A	VP
14	82	F	N	N	N	A	A	A	VP
15	75	M	N	N	N	A	A	A	VP
16	81	M	N	N	N	A	A	A	VP
17	32	M	N	N	N	A	A	A	Wilson's disease
18	36	F	N	N	N	A	A	A	Wilson's disease
19	77	M	N	N	N	A	A	A	NPH
20	53	M	A	A	A	A	A	A	Hypoxic brain damage

Note.—F, female; M, male; A, abnormal; N, normal; VP, vascular parkinsonism; NPH, normal pressure hydrocephalus.

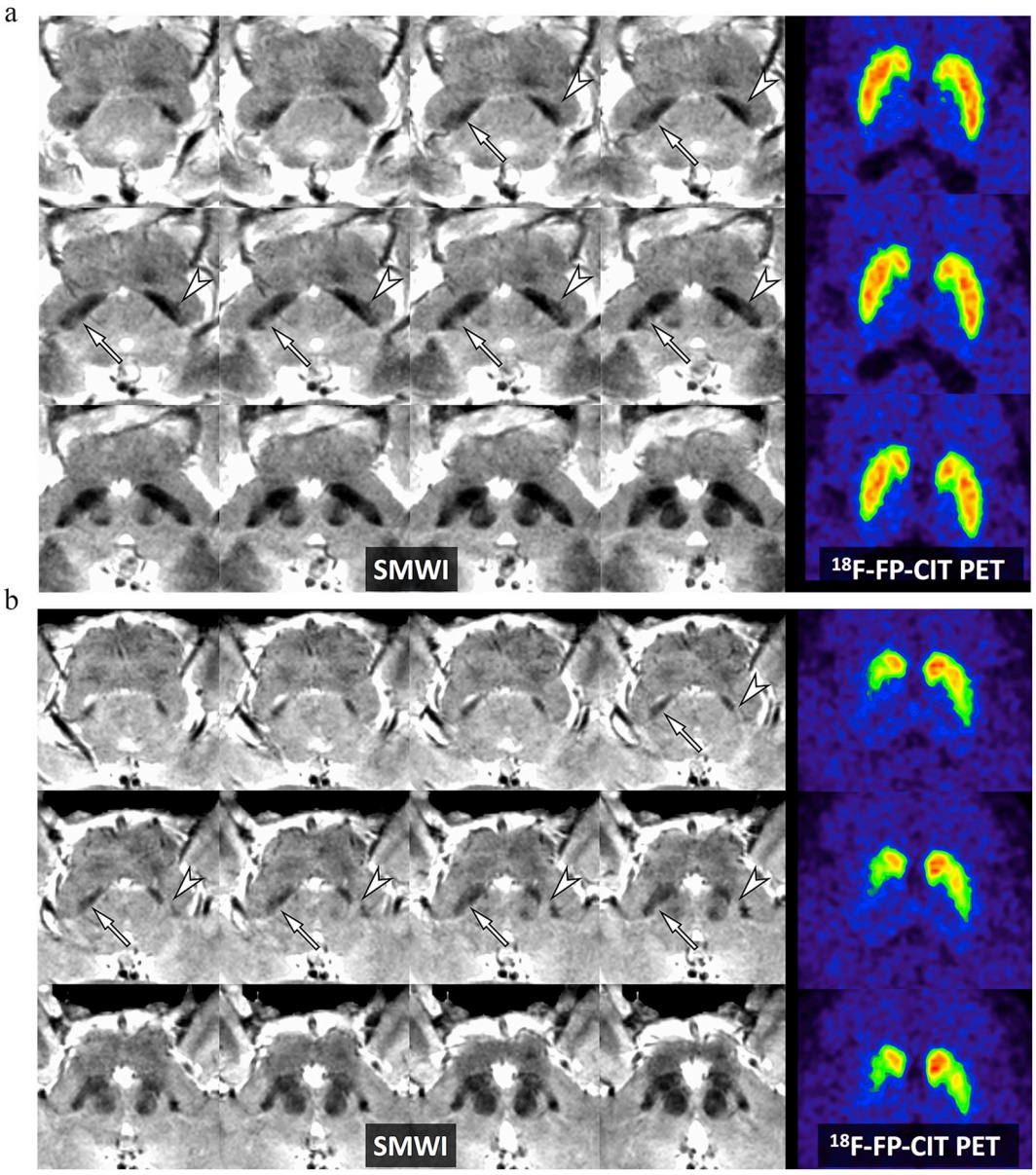

Fig. 4. False negative and false positive interpretations of the SMWI. A. The bilateral DNH regions are definitely abnormal on the SMWI (arrows on the right and arrowheads on the left). The uptakes in the bilateral basal ganglia are slightly decreased but considered within normal limit in this healthy 70-year-old male participant. As a result, the interpretations on the SMWI are false positive on both sides. B. The right DNH region (arrows) is definitely abnormal, whereas the left DNH is normal (arrowheads) on the SMWI in a 56-year-old female with idiopathic Parkinson's disease (Hoehn & Yahr stage 1). However, the ^{18}F-FP-CIT PET exhibits an abnormality in the bilateral basal ganglia with right more affected than left. Thus, the DNH SMWI results in a false negative interpretation in the left substantia nigra, but it still determines an abnormal presynaptic dopaminergic function per patient.

$0.63 \times 0.63 \times 2\,mm^3$ [10], this study had a higher diagnostic sensitivity and specificity along with a higher concordance rate. We surmise that such improved diagnostic performance may be attributable to adopting an SMWI that has an improved SNR and CNR while maintaining a spatial resolution of $0.5 \times 0.5 \times 1.0\,mm^3$. Although we had false negative interpretations for 12 SNs from 10 patients with IPD and two patients with MSA-P for SMWI, we were able to observe the abnormality in the contralateral DNH regions in all of them, which resulted in zero false negative interpretations per participant. These false negative interpretations per SN may be explained by the presence of a subtle abnormality in the less affected SN in early-stage IPD in which patients usually present with asymmetric symptoms and signs. In fact, most of these 10 patients with IPD were in the early stages (median Hoehn and Yahr stage, 1; stage 1 [n = 7], stage 2 [n = 2], and stage 2.5 [n = 1]). The other 2 patients with MSA-P had both parkinsonian and cerebellar features with the former being predominant (i.e., not pure MSA-P). Clinicians with expertise in movement disorders often have difficulty differentiating VP from IPD. They generally use DAT imaging to determine a normal presynaptic dopaminergic function. However, this strategy is only effective in a small portion of patients with VP (32.5%) [18] because many of them have a diffuse reduction of DAT with a pattern similar to that described in IPD [18,19]. For these reasons, VP was excluded from previous studies that compared SWI with DAT imaging [10]. Our study, however, assessed 16 patients with VP and found that these patients showed no abnormality in the DNH regions on SMWI whereas the ^{18}F-FP-CIT PET showed unilateral or bilateral abnormalities in the basal ganglia. The pathomechanism of VP is different from the disease entities with primary degeneration in the substantia nigra such as IPD, MSA-P, and PSP. Previous pathologic studies showed that a large number of patients with basal ganglia

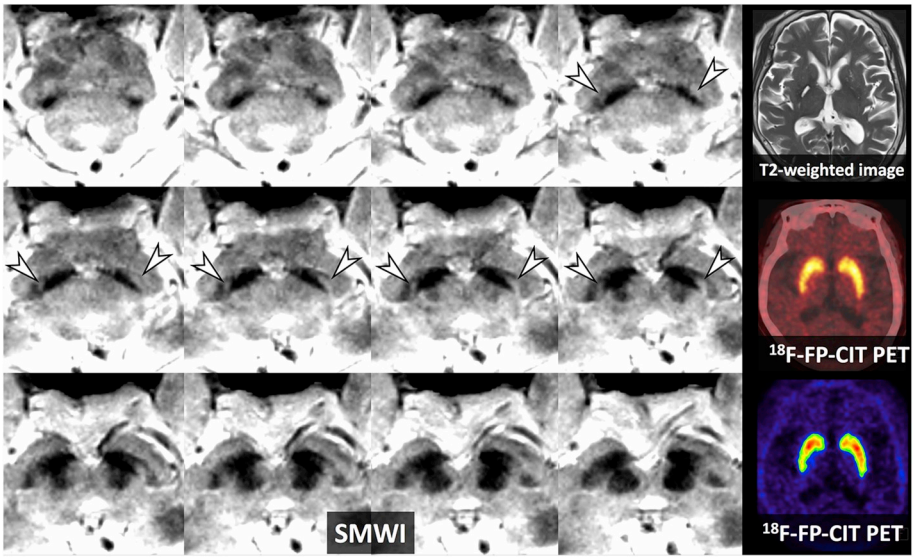

Fig. 5. Vascular Parkinsonism, An 80-year-old female patient presented with bilateral bradykinesia, rigidity on the left, and resting tremor (left greater than right). She also had visual hallucination and memory impairment (mini-mental state examination, 9). There is an old infarct in the right globus pallidus on the T2-weighted imaging. The ^{18}F-FP-CIT PET shows a decreased uptake in the right basal ganglia. With these imaging studies, the first impression was Parkinson's disease with dementia or dementia with Lewy body disease. However, the DNH regions (arrowheads) are normal on both sides on the SMWI, suggesting vascular parkinsonism with memory impairment.

Table 3
Comparison of the diagnostic performance between the SMWI and ^{18}F-FP-CIT PET.

All Participants (n = 238)						
		SMWI	^{18}F-FP-CIT PET	Difference	90% Lower CI	90% Upper CI
Per substantia nigra	Sensitivity	94.5 [91.5, 97.5]	100 [100, 100]	0.055	0.029	0.080
	Specificity	95.3 [92.7, 97.9]	86.7 [82.6, 90.9]	−0.086	−0.127	−0.045
Per participant	Sensitivity	100 [100, 100]	100 [100, 100]	0	0	0
	Specificity	94.4 [90.4, 98.4]	84.0 [77.6, 90.4]	−0.104	−0.168	−0.040
The Participants without Any Structural Abnormalities in the Basal Ganglia (n = 218)						
		SMWI	^{18}F-FP-CIT PET	Difference	90% Lower CI	90% Upper CI
Per substantia nigra	Sensitivity	94.4 [91.5, 97.5]	100 [100, 100]	0.055	0.029	0.080
	Specificity	95.4 [92.6, 98.2]	100 [100, 100]	0.046	0.023	0.070
Per participant	Sensitivity	100 [100, 100]	100 [100, 100]	0	0	0
	Specificity	93.4 [88.7, 98.1]	99.1 [97.2100]	0.057	0.020	0.094

Note.—Data in brackets are 95% confidence interval; CI, confidence interval.

infarction had cell loss in the ipsilateral SN, which is explained by retrograde or transneuronal degeneration [20,21]. We surmise that such secondary degeneration in the substantia nigra in VP leaves less damage in the DNH region compared to primary degenerative disorders, resulting in no definite signal alteration in the DNH region. However, this specific disease entity needs to be further investigated with more data to better understand the imaging findings of SMWI. Nevertheless, our results suggest that SMWI may be helpful for differentiating VP from IPD particularly when ^{18}F-FP-CIT PET is abnormal.

This study has several limitations. First, we retrospectively assessed SMWI and ^{18}F-FP-CIT PET although we had prospectively obtained them. Second, there may be incorrect diagnoses for each participant because we did not have pathological validation for all participants. However, we tried to adhere to the diagnostic criteria, and conducted clinical follow-ups for a period of over 6 months. We also designed this study to reflect real clinical practice where DAT imaging is indicated. Third, we used the findings on the ^{18}F-FP-CIT PET to test the diagnostic performance of SMWI per SN. This approach may lead to incorrect diagnoses per SN due to the lack of pathologic validation. Fourth, the range between MRI and ^{18}F-FP-CIT PET was up to 319 days. Nevertheless, the mean interval between the two studies was 13.8 days (standard deviation, 44.1 days). Finally, there may be a selection bias because we excluded 78 patients who did not undergo ^{18}F-FP-CIT PET. Nonetheless, the reasons that patients gave for not undergoing the DAT imaging rather stress the strength of SMWI because MRI is generally indicated for patients with parkinsonism. In fact, we obtained SMWI along with a conventional head MRI for participants with parkinsonism.

5. Conclusions

In summary, this study showed that SMWI and ^{18}F-FP-CIT PET are concordant with similar diagnostic performance for patients who present with parkinsonism, which can help clinicians predict presynaptic dopaminergic function.

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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.2018.12.019.

References

[1] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, J. Obeso, K. Marek, I. Litvan, A.E. Lang, G. Halliday, C.G. Goetz, T. Gasser, B. Dubois, P. Chan, B.R. Bloem, C.H. Adler, G. Deuschl, MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (12) (2015) 1591–1601.

[2] W. Poewe, K. Seppi, C.M. Tanner, G.M. Halliday, P. Brundin, J. Volkmann, A.E. Schrag, A.E. Lang, Parkinson disease, Nat. Rev. Dis. Primers 3 (2017) 17013.

[3] D.H. Kwon, J.M. Kim, S.H. Oh, H.J. Jeong, S.Y. Park, E.S. Oh, J.G. Chi, Y.B. Kim, B.S. Jeon, Z.H. Cho, Seven-Tesla magnetic resonance images of the substantia nigra in Parkinson disease, Ann. Neurol. 71 (2) (2012) 267–277.

[4] A.I. Blazejewska, S.T. Schwarz, A. Pitiot, M.C. Stephenson, J. Lowe, N. Bajaj, R.W. Bowtell, D.P. Auer, P.A. Gowland, Visualization of nigrosome 1 and its loss in PD: pathoanatomical correlation and in vivo 7 T MRI, Neurology 81 (6) (2013) 534–540.

[5] S.T. Schwarz, M. Afzal, P.S. Morgan, N. Bajaj, P.A. Gowland, D.P. Auer, The 'swallow tail' appearance of the healthy nigrosome - a new accurate test of Parkinson's disease: a case-control and retrospective cross-sectional MRI study at 3T, PLoS One 9 (4) (2014) e93814.

[6] M. Cosottini, D. Frosini, I. Pesaresi, M. Costagli, L. Biagi, R. Ceravolo, U. Bonuccelli, M. Tosetti, MR imaging of the substantia nigra at 7 T enables diagnosis of Parkinson disease, Radiology 271 (3) (2014) 831–838.

[7] M. Cosottini, D. Frosini, I. Pesaresi, G. Donatelli, P. Cecchi, M. Costagli, L. Biagi, R. Ceravolo, U. Bonuccelli, M. Tosetti, Comparison of 3T and 7T susceptibility-weighted angiography of the substantia nigra in diagnosing Parkinson disease, AJNR Am. J. Neuroradiol. 36 (3) (2015) 461–466.

[8] E. Reiter, C. Mueller, B. Pinter, F. Krismer, C. Scherfler, R. Esterhammer, C. Kremser, M. Schocke, G.K. Wenning, W. Poewe, K. Seppi, Dorsolateral nigral hyperintensity on 3.0T susceptibility-weighted imaging in neurodegenerative Parkinsonism, Mov. Disord. 30 (8) (2015) 1068–1076.

[9] Y. Noh, Y.H. Sung, J. Lee, E.Y. Kim, Nigrosome 1 detection at 3T MRI for the diagnosis of early-stage idiopathic Parkinson disease: assessment of diagnostic accuracy and agreement on imaging asymmetry and clinical laterality, AJNR Am. J. Neuroradiol. 36 (11) (2015) 2010–2016.

[10] Y.J. Bae, J.M. Kim, E. Kim, K.M. Lee, S.Y. Kang, H.S. Park, K.J. Kim, Y.E. Kim, E.S. Oh, J.Y. Yun, J.S. Kim, H.J. Jeong, B. Jeon, S.E. Kim, Loss of nigral hyperintensity on 3 tesla MRI of parkinsonism: comparison with (123) I-FP-CIT SPECT, Mov. Disord. 31 (5) (2016) 684–692.

[11] B. Heim, F. Krismer, R. De Marzi, K. Seppi, Magnetic resonance imaging for the diagnosis of Parkinson's disease, J. Neural. Transm. 124 (8) (2017) 915–964.

[12] S. Lehericy, D.E. Vaillancourt, K. Seppi, O. Monchi, I. Rektorova, A. Antonini, M.J. McKeown, M. Masellis, D. Berg, J.B. Rowe, S.J.G. Lewis, C.H. Williams-Gray, A. Tessitore, H.R. Siebner, P. International, G. Movement Disorder Society -Neuroimaging Study, The role of high-field magnetic resonance imaging in parkinsonian disorders: pushing the boundaries forward, Mov. Disord. 32 (4) (2017) 510–525.

[13] P. Mahlknecht, F. Krismer, W. Poewe, K. Seppi, Meta-analysis of dorsolateral nigral hyperintensity on magnetic resonance imaging as a marker for Parkinson's disease, Mov. Disord. 32 (4) (2017) 619–623.

[14] L.A. Massey, M.A. Miranda, O. Al-Helli, H.G. Parkes, J.S. Thornton, P.W. So, M.J. White, L. Mancini, C. Strand, J. Holton, A.J. Lees, T. Revesz, T.A. Yousry, 9.4 T MR microscopy of the substantia nigra with pathological validation in controls and disease, Neuroimage Clin. 13 (2017) 154–163.

[15] Y. Nam, S.M. Gho, D.H. Kim, E.Y. Kim, J. Lee, Imaging of nigrosome 1 in substantia nigra at 3T using multiecho susceptibility map-weighted imaging (SMWI), J. Magn. Reson. Imag. 46 (2) (2017) 528–536.

[16] W. Dauer, S. Przedborski, Parkinson's disease: mechanisms and models, Neuron 39 (6) (2003) 889–909.

[17] Y.H. Sung, Y. Noh, J. Lee, E.Y. Kim, Drug-induced parkinsonism versus idiopathic Parkinson disease: utility of nigrosome 1 with 3-T imaging, Radiology 279 (3) (2016) 849–858.

[18] S. Benitez-Rivero, V.A. Marin-Oyaga, D. Garcia-Solis, I. Huertas-Fernandez, F.J. Garcia-Gomez, S. Jesus, M.T. Caceres, F. Carrillo, A.M. Ortiz, M. Carballo, P. Mir, Clinical features and 123I-FP-CIT SPECT imaging in vascular parkinsonism and Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 84 (2) (2013) 122–129.

[19] M. Lorberboym, R. Djaldetti, E. Melamed, M. Sadeh, Y. Lampl, 123I-FP-CIT SPECT imaging of dopamine transporters in patients with cerebrovascular disease and clinical diagnosis of vascular parkinsonism, J. Nucl. Med. 45 (10) (2004) 1688–1693.

[20] L.S. Forno, Reaction of the substantia nigra to massive basal ganglia infarction, Acta Neuropathol. 62 (1–2) (1983) 96–102.

[21] J.C. Zijlmans, S.E. Daniel, A.J. Hughes, T. Revesz, A.J. Lees, Clinicopathological investigation of vascular parkinsonism, including clinical criteria for diagnosis, Mov. Disord. 19 (6) (2004) 630–640.