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Research article

Subtypes evaluation of motor dysfunction in Parkinson's disease using neuromelanin-sensitive magnetic resonance imaging

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HIGHLIGHTS

- Our results indicate a potential diagnostic value of NM-MRI to discriminate PD motor subtypes.
- The medial part of ipsilateral SNc shows the highest power to discriminate PD motor subtypes.
- NM-MRI provides new evidence for the neuropathology-based differences between the two subtypes.

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ABSTRACT

Parkinson's disease (PD) is characterized by the loss of neuromelanin (NM)-containing neurons in the substantia nigra pars compacta (SNc), and it is divided into two motor subtypes: the postural instability gait difficulty (PIGD) and the tremor dominant (TD) subtypes. With NM-sensitive Magnetic Resonance Imaging (NM-MRI), investigators have been able to accurately detect signal attenuation in SNc of PD; however, the difference of NM loss between PIGD and TD subtypes is still unclear. Thus, the aim of this study was to evaluate the differences in NM-MRI between PD motor subtypes. PD patients were classified into PIGD (n = 14) and TD groups (n = 9); 20 age and sex matched controls were recruited. We compared the signal intensity contrast ratios in medial and lateral regions of the SNc using NM-MRI in PIGD, TD, and controls, respectively. Remarkable signal attenuation was observed in the lateral part of SNc in PD when compared with the controls, and we were able to detect more severe signal attenuation in the medial part of SNc in PIGD patients in comparison with that in the TD group. Also, the medial part of SNc, ipsilateral to the most clinically affected side, showed the highest power to discriminate the PD motor subtypes (AUC, 81%; sensitivity, 71.4%; specificity, 77.8%). Our results indicated a potential diagnostic value of NM-MRI to discriminate the PD motor subtypes, providing new evidence for the neuropathology-based differences between the two subtypes.

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1. Introduction

Parkinson's disease (PD) is a heterogeneous neurodegenerative disorder, pathologically characterized by the loss of neuromelanin (NM)-containing neurons in the substantia nigra pars compacta (SNc) [2,15,31]. This heterogeneity is consistent with the existence of motor subtypes, empirically divided into tremor dominant (TD) and non-tremor dominant (NTD, either postural instability gait difficulty or akinetic-rigid) subtypes, and these subtypes are associated with different disease progression and neuropathological features [11,22]. Compared to the NTD subtype, TD patients exhibit a more favorable disease course, fewer non-motor symptoms and

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less cognitive decline [11,22,29]. Although the pathological changes observed in the TD patients differ from those observed in the NTD patients [12], the neural mechanism underlying these disparate presentations is still uncertain.

With NM-sensitive Magnetic Resonance Imaging (NM-MRI), a significant decrease in the signal intensity, area, and volume of the SNc in PD has been detected, with a high diagnostic sensitivity and specificity [1,4,13,21,24,27]. Hitherto, there is no report evaluating the differences between the PD motor subtypes by NM-MRI. The purpose of present study is to elucidate whether differences between PD patients with two different motor subtypes can be characterized by the underlying SN degeneration based on NM-MRI.

2. Patients and methods

2.1. Patients and control subjects

Patients with probable idiopathic PD were prospectively recruited in the Movement Disorder Clinic, Shandong Provincial Hospital Affiliated to Shandong University, having been assessed by a neurologist experienced in the movement disorders according to the UK PD Brain Bank criteria [9].

The Hoehn and Yahr (H-Y) stage and the motor part (part III) of the Unified Parkinson's disease rating scale (UPDRS) were used to assess the severity of illness during an "off" phase (at least 12 h off medicine).

We excluded patients with H-Y stage 4–5, Mini Mental State Examination score (MMSE) < 24/30, history of Deep Brain Stimulation, motor or neurological comorbidities affecting test performance, claustrophobia, medical or psychiatric conditions preventing the subject from undergoing an MRI examination.

PD patients were divided into postural instability gait difficulty (PIGD, can be seen as a counterpart of akinetic-rigid patients, n = 14), TD (n = 9) or indeterminate (n = 8) based on the method used by Jankovic et al. [11] as the average global tremor score (UPDRS items 16 and 20–21: right and left arm tremor by history; rest tremor of either face, lips, or chin, all 4 limbs; postural or action tremor of both arms by examination. Total score divided by 8)/the average global 'PIGD' score (UPDRS items 13–15, 29, 30: walking, freezing, and falls by history; postural instability and gait by examination. Total score/5). The TD subtype was defined as the ratios of 1.5 or more; whereas PIGD subtype as the ratios $\leq$ 1.0 and indeterminate subtype as the ratios between 1.0 and 1.5. In addition, patients with a zero in the average global 'PIGD' score were classified as TD; patients with a zero in the mean global tremor score were classified as PIGD. Subjects with an indeterminate subtype were excluded from further analysis. The control group consisted of 20 age and sex matched patients recruited from Neurology clinic, Shandong Provincial Hospital Affiliated to Shandong University, without neurological disorders or a family history of neurodegenerative disease, also having been assessed by a movement disorder specialist.

This study was approved by the Institutional Review Board of Shandong Provincial Hospital Affiliated to Shandong University. Written informed consent was obtained from all participants prior to the study.

2.2. Magnetic resonance imaging protocol

All images were acquired using a 3.0-T MRI scanner (Philips Achieva TX, Best, Netherlands) with 8-channel head coil. The NM-MRI pulse sequence was a T1-weighted turbo field echo (TFE) sequence similar to that previously described by Ogisu et al. [18] with repetition time, 13 ms; echo time, 2.2 ms; flip angle, 20°; echo train length, 2; number of excitations, 8; matrix size, 320 × 326; field of view, 220 × 220 mm^2; pixel size, 0.69 mm × 0.80 mm; number of slices, 40; slice thickness, 1.0 mm; gapless; MTC: angle, 600°; duration, 20 ms; frequency, 600 Hz. The total acquisition time was 5 min 21 s. These images were set perpendicular to the fourth ventricle floor (Fig. 1). The area coverage extended from the splenium of the corpus callosum to the inferior border of the pons.

Axial T1 and T2-weighted MRI, fluid attenuated inversion recovery MRI, and diffusion weighted images of the whole brain were also obtained in all subjects and evaluated by an experienced neuroradiologist to exclude coexisting central nervous system disorders such as ischemic stroke and other pathological imaging changes, which in other words, changes in the parkinsonian index and other atypical parkinsonian syndrome changes that would interfere with further analysis.

Table 1
Demographics for PIGD, TD, and control subjects.

	PIGD	TD	Controls	*P* Value
No. (female/male)	14(8/6)	9(6/3)	20(11/9)	0.847
Age, y(mean ± SD)	59.8 ± 8.4	58.8 ± 7.7	66 ± 9.9	0.123
Duration, y(mean ± SD)	3.3 ± 1.7	3.8 ± 3.4	–	0.582
H-Y stage	2.2 ± 0.3	2.1 ± 0.4	–	0.206
UPDRS(part III)	30.2 ± 7.7	32.1 ± 9.9	–	0.614

SD, standard deviation.

2.3. Data processing and statistical analyses

For quantitative evaluation of the signal intensity of the SNc on the NM-MRI, the regions of interest (ROIs) were measured on a liquid crystal display using round cursors at the following locations: bilateral SNc and the decussation of the superior cerebellar peduncle (SCP) at the section through the inferior edge of the inferior colliculus [21]. The high-signal area of the bilateral SNc was divided into lateral and medial parts. One of the authors (Tao Gong), who was blinded to subject information, performed manual measurements three times using round cursors of 10 mm^2 for the SNc and 20 mm^2 for the SCP, and the obtained signal intensity values were averaged.

Contrast ratio (CR) of the SNc was calculated using the following equations: $CR = (S_{SNc} - S_{SCP})/S_{SCP}$, wherein S_{SNc} stood for the averaged values of the signal intensity of the bilateral SNc (including lateral and medial parts), and the S_{SCP} represented that of the decussation of SCP.

Statistical analysis was performed to determine differences in the CR, age and, sex among PIGD, TD, and controls using ANOVA and Bonferroni tests. We used Student's *t*-test to compare the CR, disease duration, H-Y stage, and UPDRS between PIGD and TD. To determine the sensitivity and specificity of the NM-MRI for discriminating differences between PIGD and TD, receiver operating characteristic (ROC) analyses were performed; wherein the cut-off values were determined using the Youden index when the area under the ROC curve (AUC) was >0.7. The alpha level for all analyses was 0.05.

3. Results

Clinical characteristics of the 43 subjects were summarized in (Table 1). No significant differences were observed in sex and age among the three groups (P = 0.847, 0.123, respectively). Moreover, significant differences were also not observed between PIGD and TD patients in disease durations, H-Y stage, and UPDRS (part III) scores (P = 0.582, 0.206, 0.614, respectively). All the patients reported asymmetric onset of motor symptoms.

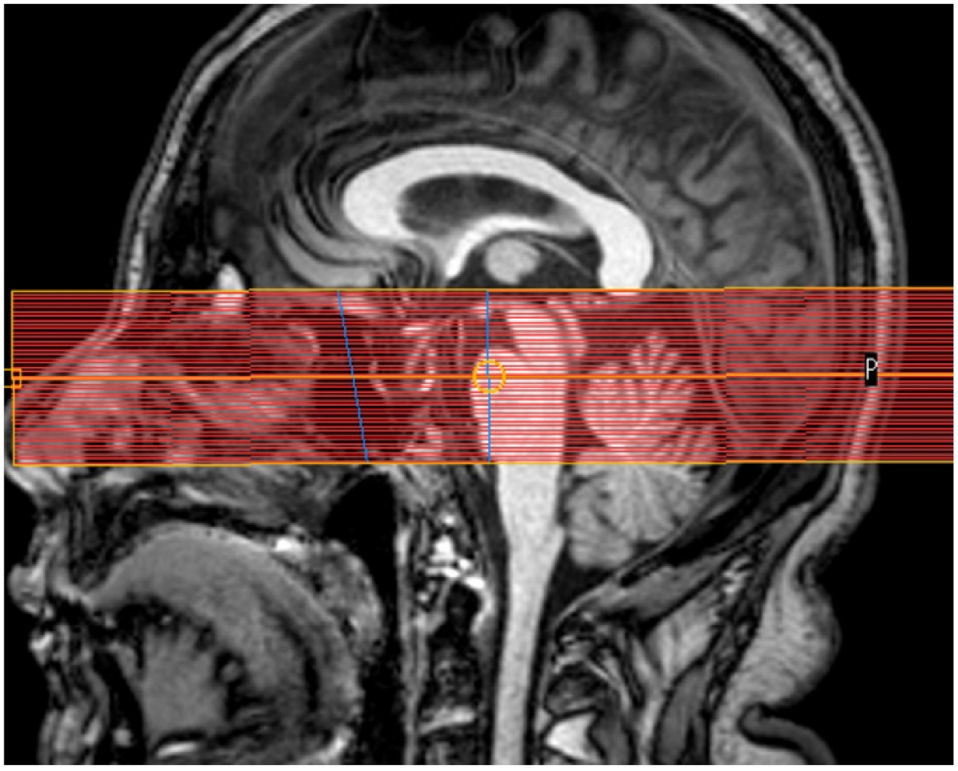

Fig. 1. The NM-MR and conventional MR axial Imaging of SN were set perpendicular to the fourth ventricle floor.

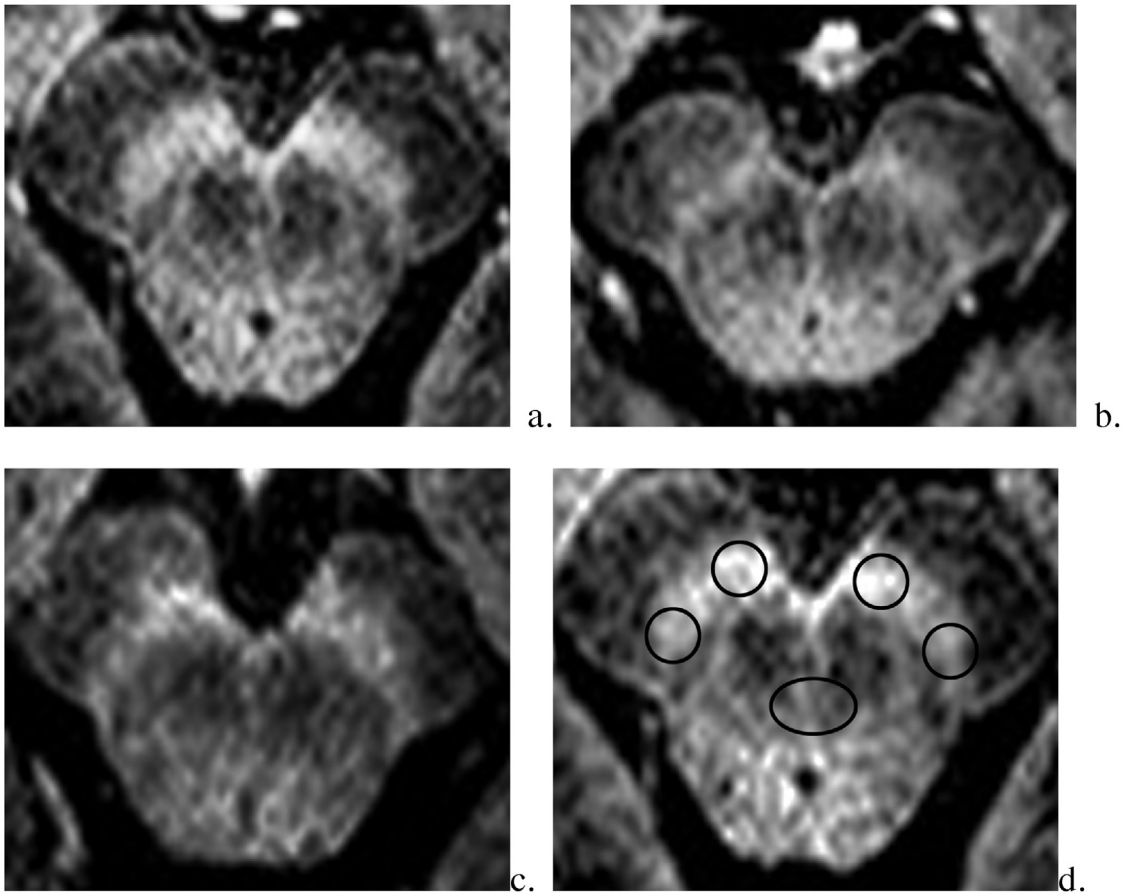

Fig. 2. NM-MR images of the SN of a healthy control (a), PIGD(b), TD(c). (d)the circular regions of interest for quantitative measurements were established in the lateral and medial parts of the SNc and the decussation of the superior cerebellar peduncle (SCP).

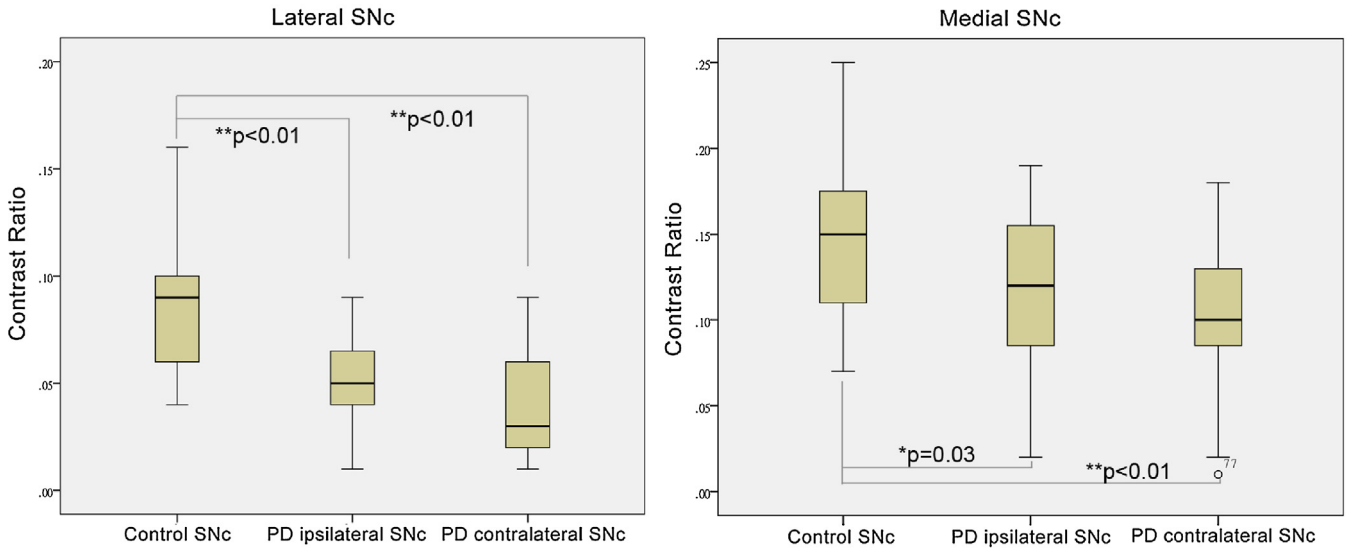

Fig. 3. Contrast Ratios of the lateral and medial SNc high-intensity region on NM-MRI in controls and patients with PD; * P < 0.05, ANOVA and Bonferroni tests.

Table 2
Subregional (Lateral and medial region) contrast ratios of SNc in controls and PD.

	Number	Mean ± SD	F value	P value[a]
Lateral SNc			23.67	0.00
Controls	40	0.09 ± 0.03		
PD Contralateral	23	0.04 ± 0.02		
PD Ipsilateral	23	0.05 ± 0.02		
Medial SNc			8.64	0.00
Controls	40	0.15 ± 0.05		
PD Contralateral	23	0.10 ± 0.04		
PD Ipsilateral	23	0.12 ± 0.05		

[a] Statistical analysis using ANOVA.

The image quality was set up to clearly identify the high-signal area in the SN region of all the subjects. Compared to the control group, the signal intensity of the SNc on NM-MRI was obviously reduced in PD, especially in the lateral parts (Fig. 2). Moreover, the measured CRs of both contralateral and ipsilateral SNc to the most clinically affected side were significantly reduced in the PD group when compared with the controls (Table 2; Fig. 3). However, the CRs of the SNc in PD only showed a trend for greater reduction in the SNc contralateral to the clinically predominantly affected side when compared with the ipsilateral part but not statistically significant (lateral: P = 0.71; medial: P = 0.75) (Fig. 3).

A more significant decline was observed in the CRs of the medial part of SNc high signal area of PIGD patients, compared to those of the TD, especially the ipsilateral SNc to the most clinically affected side, while the CRs of the lateral part showed no significant differences between the two subtypes (Table 3).

The area under the ROC curve (AUC) of the medial part of ipsilateral SNc and contralateral SNc for differentiating between PIGD and TD were 81% (95% CI: 60% to 94%, sensitivity 71.4%, specificity 77.8%) and 77% (95%CI: 55% to 92%, sensitivity 78.6%, specificity 66.7%), respectively. ROC analysis indicated that there were no significant differences between contralateral and ipsilateral SNc for differentiating between PIGD and TD (P = 0.72) (Fig. 4).

Table 3
Subregional (Lateral and medial region) contrast ratios of SNc in PIGD and TD.

	PIGD	TD	P value[a]
Lateral SNc(Mean ± SD)			
Contralateral	0.04 ± 0.02	0.04 ± 0.02	0.93
Ipsilateral	0.05 ± 0.02	0.06 ± 0.02	0.27
Medial SNc(Mean ± SD)			
Contralateral	0.09 ± 0.04	0.12 ± 0.03	0.04
Ipsilateral	0.10 ± 0.04	0.15 ± 0.05	0.02

[a] Statistical analysis using Student's *t*-test.

4. Discussion

In the current study, we successfully detected remarkable signal attenuation in the SNc of PD patients, especially in the lateral part, which were consistent with the previous NM-MRI studies in PD [1,4,13,18,21,23,24,26,27]. We were also able to detect significant differences of signal attenuation in the medial part of SNc in PIGD patients compared to the TDs, enabling the differentiation of PIGD from TD group with relatively high sensitivity and specificity.

In our study, the most significant signal attenuation was detected in the lateral part of the SNc in PD patients. This result was consistent with neuropathological findings showing that the neuronal loss in PD was more pronounced in the ventrolateral region of the SNc with relative preservation of the dorsal region [7,30]. Previous neuropathological and neuroimaging studies consistently showed that the losses of neurons were asymmetric during the course of PD [5,17], while in our study, the contralateral SNc to the most clinically affected side showed a trend for a greater degree of signal attenuation than the ipsilateral part, but did not reach statistical significance, which may be attributed to the limited number of recruited PD cases.

In the present study, we found more severe signal attenuation in the medial part of SNc in PIGD patients compared to the TDs, while the CRs of the lateral part showed no significant differences between the two subtypes. These results were consistent with previous neuropathological findings that showed more severe SN neuronal losses and faster progression of the PIGD patients than those of the TDs [3,19,25]. Previous neuropathological studies reported that the most severe cell loss occurred in the ventrolateral nigra of the PD subjects, whereas the medial nigra showed the greatest difference between the Benign tremulous PD and PD controls [28]. It has been reported that the PD presymptomatic neurodegenerative process lasts for 2–40 years [2,14]. Further studies with a higher sample size and more early patients will be required to further compare the differences of the lateral part of SNc between the two subtypes.

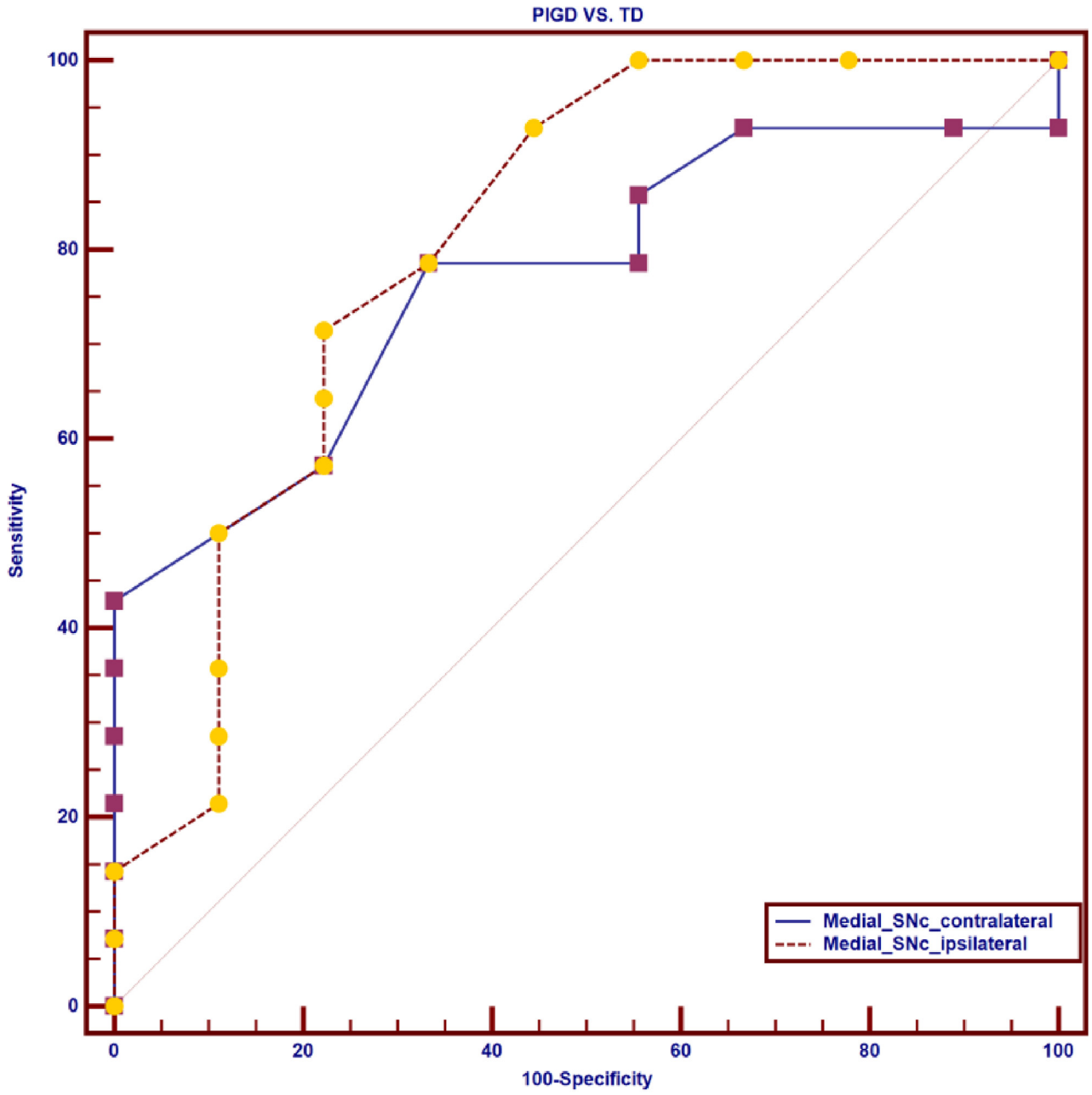

Fig. 4. ROC curve of the contrast ratios for differentiating between PIGD and TD. Area under the ROC curve (AUC) of Medial SNc (contralateral), Medial SNc (ipsilateral) were 77% (95% CI, 55% to 92%) and 81% (95% CI, 60% to 94%), respectively. The sensitivity and specificity of Medial SNc (contralateral) were 78.6% and 66.7%, and the cutoff value was 0.10; The sensitivity and specificity of Medial SNc (ipsilateral) were 71.4% and 77.8%, and the cutoff value was 0.12. Pairwise comparison of ROC curves showed no differences between contralateral and ipsilateral (P = 0.72).

The present NM-MRI study showed that the medial part of SNc, both ipsilateral (AUC 81%, sensitivity 71.4%, specificity 77.8%) and contralateral parts (AUC 77% sensitivity 78.6%, specificity 66.7%) to the most clinically affected side, had relatively high power to discriminate the PD motor subtypes, and there were no significant differences between both of them (P = 0.72). The obtained sensitivity and specificity are not so high for PD subtypes' discrimination which might be intrinsically related to different amounts of NM in the extracellular space in addition to the loss of NM-containing neurons [32,33] and the differences of iron [6,10] in the SN of the two subtypes. To the best of our knowledge, this is the first report evaluating the differences between the PD motor subtypes by NM-MRI. Previous studies have shown that NM-MRI can help to detect specific PD subgroups, such as patients with RBD [8], and distinguish PD from atypical parkinsonism [16,20,24].

There are several limitations in our study. Firstly, it was a cross-sectional study with small sample size, advocating selection bias and the PD diagnosis was only based on the clinical symptoms without confirmation by pathological examination. Besides, there was a significant difference in disease duration among the patients. A larger number of patients in a prospective study will specifically investigate the difference in SN NM-MRI changes in PD clinical subtypes.

Secondly, the inspection process was time-consuming, motion artifacts during image acquisition and partial volume effects were some of the difficulties in our patients, mainly in the TD subtypes, which were resolved by a temporary supply of medication.

However, the inconsideration of the influence of drugs was also one of the limitations of this study. Further improvement of this technique may lie in a prerequisite to improving the image contrast, and the influence of drugs should also be taken into account.

Thirdly, although our manual analysis is operator dependent, it is rapid and can be widely used without requiring post-processing software. Reproducibility of these measurements between assessors has not been fully evaluated. Larger studies are necessary in the future to address the issue for broad application.

5. Conclusions

Our study indicates a potential diagnostic value of NM-MRI for discriminating PD motor subtypes. This suggests that NM-MRI assessment may be a diagnostic tool in clinical practice and for future research, contributing to a better understanding of clinical and pathological heterogeneous characteristics of PD.

Conflicts of interest

The authors declare that they have no conflict of interest.

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