# Signal Alteration of Substantia Nigra on 3.0T Susceptibility-weighted Imaging in Parkinson's Disease and Vascular Parkinsonism*

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**Summary**: Recent researches have found that 7 Tesla SWI can detect the alteration of substantia nigra hyperintensity in Parkinson's disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP). The aim of this study was to investigate whether 3 Tesla SWI (3T SWI) can visualize anatomical alterations occurring in a hyperintense structure of the substantia nigra in PD and vascular parkinsonism (VP), and whether the evaluation of abnormal signal can be used as a factor in the differential diagnosis of PD and VP. Using 3 Tesla MRI, we evaluated 38 healthy subjects, 33 patients with PD and 34 patients with VP. Two blinded readers independently assessed the images. We found that the dorsolateral nigral hyperintensity was absent in 31 of 33 patients with PD and 15 of 34 patients with VP. The dorsolateral nigral hyperintensity was present in 19 of 34 patients with VP and 35 of 38 healthy controls. Group comparisons of absence of dorsolateral nigral hyperintensity revealed significant differences between the patients with PD and those with VP ($P<0.001$). The sensitivity of SWI for PD was 93.9% and the specificity was 92.1%. Visual assessment of dorsolateral nigral hyperintensity on high-field SWI scans may serve as a new simple diagnostic imaging marker for PD. And our study results indicate that 3T SWI can be used as a tool to identify PD and VP.
**Key words**: magnetic resonance imaging; susceptibility-weighted imaging; Parkinson's disease; vascular parkinsonism; substantia nigra

Parkinson's disease (PD) is the second largest neurodegenerative disorder in the nervous system. The incidence of PD is 2%–3% in people over 65 years old. The loss of dopaminergic neurons in the substantia nigra compact area was at least 50% when PD patients developed clinical symptoms. The loss of dopaminergic cells in PD first occurs in the substantia nigra compacta of the midbrain[1]. Damier named this structure nigrosomes, which are mainly composed of five subregions (nigrosome-1 to nigrosome-5)[2]. It suggests that the imaging changes of this structure may be a reliable tool for early diagnosis of PD. Using 7 Tesla susceptibility weighted imaging (7T SWI), some groups found a high-signal region in the substantia nigra of the control group that conformed to the nigrosome-1 structure, but the high-signal region was not found in patients with PD[3, 4]. In the study, they found a bright high-intensity signal region along the dorsolateral substantia nigra in the control subjects; whereas in patients with PD, the bilateral hyperintensity disappeared and the area was presented as a hypointense signal region. Simultaneously, some researchers reported that similar sensitive and specific findings could be obtained using 3T SWI[5, 6]. The alteration of nigral hyperintensity was well detected by 7T SWI in progressive supranuclear palsy, multiple system atrophy and PD[7]. On one hand, we carried out this research to explore the specificity and sensitivity of 3T SWI for the diagnosis of PD. On the other hand, to fully develop the role of 3T SWI in the diagnosis of PD, we believe that further studies are necessary to investigate whether the nigral hyperintensity on 3T SWI is present in patients with vascular parkinsonism (VP) and whether the evaluation of abnormal signal can be used as a factor in the differential diagnosis of PD and VP.

# 1 SUBJECTS AND METHODS

## 1.1 Subjects

For this study, we recruited healthy volunteers with no signs of neurodegenerative disease and patients with PD or VP from The First Affiliated Hospital of University of Science and Technology of China between September 2015 and May 2017. The inclusion criteria were as follows: Mini-Mental State Examination scores of 24; age between 20 and 90 years; and absence of any neurological diseases except for PD or VP. The exclusion criteria were the presence of one or more of the following items: aneurysm clip, cochlear implant, history of claustrophobia, pregnancy and any irremovable metallic object in the body. The clinical diagnosis of PD and VP was made according to the criteria[8, 9]. In order to reduce the misdiagnosis rate, we had followed up for at least 1 year for each patient. We recruited patients with early-stage PD in Hoehn and Yahr stage less than or equal to 2. This study was carried out in accordance with the recommendations of The Institutional Medical Ethics Committees and Review Boards with written informed consent from all subjects.

## 1.2 Magnetic Resonance Imaging (MRI)

MRI scanning was performed at 3T with a Sense Head Coil (Achieva and Ingenia; Philips, Best, Netherlands). In this study, SWI used VEN-BOLD-HR three-dimensional gradient echo sequence. MRIs in our study were conducted with conventional parameters instead of customized imaging sequences designed for the midbrain. The MRI protocol included axial SWI 3D sequences with a flip angle of 10, a slice thickness of 1.2 mm, a field of view of $220 \times 180$ mm$^2$, a voxel size of $1.0 \times 0.99 \times 0.6$ mm$^3$. For patients with tremors, MRI was performed when tremors were mild or absent. Two neuroradiologists, blinded to the clinical diagnoses, independently assessed the 3T MRI results and determined the presence or absence of the nigral hyperintense structure. All the Images were evaluated twice after one month to test inter- and intra-observer coherence.

## 1.3 Statistical Analysis

Data were compared using Chi-squared tests and One-way analysis of variance tests. Sensitivity, specificity, and accuracy were calculated. Inter- and intra-observer agreements were tested using Cohen $k$ statistics. $P$ values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (version 17.0; SPSS, USA).

# 2 RESULTS

## 2.1 Clinical Characteristics of the Subjects

Clinical findings are summarized in table 1. Between September 2015 and March 2017, 35 patients with PD, 36 patients with VP and 38 healthy subjects, a total of 109 subjects underwent 3T SWI at our hospital. Because of the severe motion artifacts, 2 patients with PD and 2 patients with VP were excluded from the assessment of nigra signal. Therefore, a total of 105 subjects were included in our study, 55 women and 50 men;  age range, 37–85 years; mean age, 66.0±10.9 years. There were no significant differences in the age distribution (65.8±10.1 *vs*. 69.8±8.8 years, *P*=0.25) and symptom duration (4.7±4.3 *vs*. 3.0±3.3 years, *P*=0.20) between the patients with PD and patients with VP. Sixteen patients with PD underwent 3T SWI at Hoehn and Yahr stages 1 or 2, and 17 patients at Hoehn and Yahr stages 3 or 4.

## 2.2 Performance of 3T SWI According to Clinical Diagnosis

The image assessment results were divided into three groups: "abnormal" (unilateral or bilateral disappearance of dorsolateral nigral hyperintensity) *versus* "normal" (dorsolateral nigral hyperintensity at both sides) *versus* "non diagnostic" (dorsolateral nigral hyperintensity at one side and poor quality of substantia nigra (SN) evaluation at the other side or poor quality of SN evaluation at both sides). We found that the appearance of nigral bright signal in SWI of healthy subjects varied based on the level of substantia nigra (fig. 1 A1–A3). Along the longitudinal axis, nigrosome-1 appeared as a bright signal region embedded in the medial aspect of hypointense SN like a pocket or swallow-tail. It was observed that the nigral hyperintensity continued to the caudal level of substantia nigra. This resulted in a three fold pattern composed of the bright oval regions and two external low signal regions. The overall appearance of the normal SN on SWI sequences was named as "swallow-tail-sign" or "nigrosome-1" and it was shown to be absent in some patients with VP and almost all patients with PD.

Both neuroradiologists found that bilateral nigral

**Table 1 Demographic and clinical characteristics of the final 105 subjects**

| Group (*n*) | Sex distribution (male/female) | Age at MRI (mean±SD, years) | Disease duration at MRI (mean±SD, years) |
|---|---|---|---|
| Parkinson's disease (33) | 16/17 | 65.8±10.1 | 4.7±4.3 |
| Vascular Parkinsonism (34) | 17/17 | 69.8±8.8 | 3.0±3.3 |
| Healthy Control (38) | 17/21 | 62.0±12.8 | – |
| *P* | 0.90 | 0.01 | 0.20 |

hyperintensity existed in 35 of 38 healthy subjects. On the contrary, the nigral hyperintensity was bilaterally lost in almost all patients with PD (fig 1 B1–B3). In abnormal group, there were 31 subjects with PD, 15 subjects with VP and 3 healthy controls (for 31 patients with PD, 7 in Hoehn and Yahr stage 1 [HY1]; 8 in HY2; 9 in HY3; 7 in HY4). The normal group included 2 subjects with PD, 19 subjects with VP and 35 healthy controls. The other subjects were in non-diagnostic group. The inter- and intra-observer coherence between the two raters were both excellent. Intra-observer coherence was 95.2% ($k$=0.89, $P$<0.001) for reader 1 and 96.1% ($k$=0.91, $P$<0.001) for reader 2. Interobserver coherence was 93.3% ($k$=0.87, $P$<0.001) for the first assessment and 98.1% ($k$=0.93, $P$<0.001) for the second assessment. Images of 19 out of 34 patients with VP were divided into normal group, however, not all nigral hyperintensity was intact in these 19 patients. At least one side of nigral hyperintensity was focal or partly present in 7 of the 19 patients (fig. 1 C1–C3). Punctate presence showed that nigral hyperintensity was a little lower than the normal or remained as the focal hyperintense spot. However, despite these changes in signal intensity, it was not difficult to assess the existence of nigral hyperintensity.

The sensitivity and specificity of 3T SWI were calculated on the basis of clinical diagnosis (table 2). For PD, the sensitivity and the specificity of SWI were 93.9% and 92.1%, respectively. Group comparisons of absence of dorsolateral nigral hyperintensity revealed significant differences between the patients with PD and patients with VP ($P$<0.001; Chi-squared tests), between the patients with PD and healthy controls as well ($P$<0.001; Chi-squared tests).

## 3 DISCUSSION

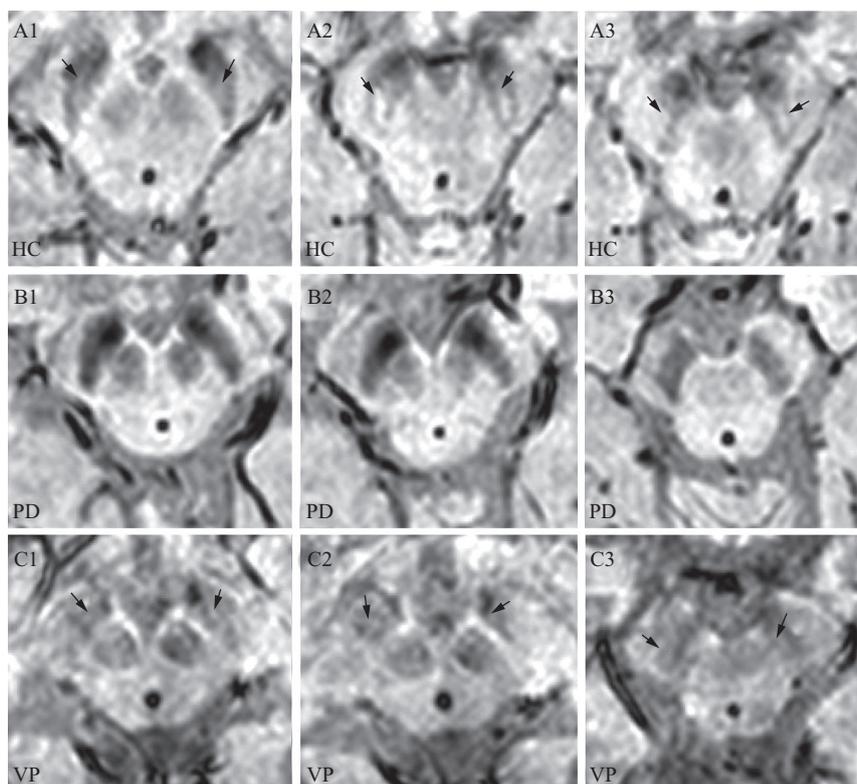In accordance with previous studies, normal



**Fig. 1** A1–A3: Representative 3T SWI images of a healthy subject (F/56), showing intact bilateral nigral hyperintensity in the substantia nigra of the midbrain (arrows). B1–B3: Images of a patient with PD (M/62), HY3, showing bilateral loss of nigral hyperintensity in the substantia nigra. C1–C3: Images of a patient with VP (F/55), showing that nigral hyperintensity was a little lower than the normal or remained as the focal hyperintense spot. HC: healthy control; PD: Parkinson's disease; VP: vascular parkinsonism; HY: Hoehn and Yahr stage

**Table 2 Performance of 3T SWI**

| Performance (%) | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|
| Rater 1, first reading | 93.9 | 92.1 | 88.6 | 94.4 | 91.5 |
| Rater 1, second reading | 90.9 | 94.7 | 90.9 | 92.1 | 91.5 |
| Rater 2, first reading | 90.9 | 92.1 | 88.2 | 91.9 | 90.1 |
| Rater 2, second reading | 90.9 | 94.7 | 90.9 | 92.1 | 91.5 |

PD: Parkinson's disease; PPV: positive predictive value; NPV: negative predictive value

nigral hyperintensity could be detected by 3T SWI and absence of the dorsolateral nigral hyperintensity on high field SWI scans distinguished patients with PD from healthy subjects with a discriminative power of greater than 90% in our study[5, 10]. Some studies reported the differential imaging diagnosis between PD and MSA-P was not sought[11, 12]. Our study focused on assessing dorsolateral nigral hyperintensity to differentiate PD from VP at 3T SWI. It showed that the dorsolateral nigral hyperintensity was absent in almost all patients with PD (31 in 33 patients), which is consistent with previous studies[5, 6]. We also found that most of VP patients showed bilateral presence of nigral hyperintensity on 3T SWI. The similar results were reported in the study of Bae et al[12].

The normal signal of the substantia nigra mainly consists of two components: a pocket-like indentation at the intermediate level and a contiguous focal hyperintensity in SN. In this study, bilateral nigral hyperintensity existed in 2 advanced-stage PD patients. So far, there is no reliable reasons for a small minority of patients with PD having high signal intensity in the substantia nigra. Some studies demonstrated that a few patients with PD presented bilateral reduction of 123I-FP-CIT binding, but intact bilateral nigral hyperintensity on 3T SWI[12].

Of the 34 patients with VP, we identified 15 patients who showed bilateral or unilateral absence of nigral hyperintensity on 3T SWI, and 19 patients who showed bilateral presence of nigral hyperintensity (7 showed that in at least one side there was indecisive or punctate presence, the others showed bilateral intact presence). Between the patients without nigral hyperintensity and those with nigral hyperintensity, symptom duration and age distribution were not significantly different. We should pay attention to the changes of nigral signal in patients with VP. In previous studies, the nigral hyperintensity has been named as a swallow-tail appearance or three-layered weave on 7T and 3T SWI[7, 10]. In this research, the signal of the substantia nigra was divided into three groups, the presence, non diagnostic or absence of nigral hyperintensity. In previous studies, a third class, that is intermediate class, is defined as "possible existence" or "possible abnormality" (nigrosome-1 hypointensity area <50% or nigral hyperintensity not entirely clear)[4, 5]. It is unknown whether indecisive presence was an intermediate stage between lack of nigral hyperintensity and intact nigral hyperintensity. Tracking the changes of nigral hyperintensity, such as changes of the volumetry and boundaries, in a larger patient population with VP and PD would be helpful in developing differential imaging tools between PD and VP. Some other factors may be the reasons for indecisive presence such as age, motion artifact, and spatial resolution of 3T MRI. First, we know that the

concentration of neuromelanin-iron complex increases with age in SN[13]. This may lead to nigral hyperintensity decreasing with age on SWI and make it difficult to identify the hyperintense signal. However, intact bilateral nigral hyperintensity was clearly detected in healthy elderly subjects, and there was no difference in the shape of nigral hyperintensity between younger subjects and elderly subjects. The age distribution was not significantly different between the patients with PD and those with VP. Second, compared with other MR techniques, SWI sequences are relatively sensitive to motion artifacts[14, 15]. Some studies found that motion artifacts reached 10% of the study participants[7, 14]. Third, regarding spatial resolutions, we conjectured that the high spatial resolutions ($0.55 \times 0.55 \times 0.7$ and $0.5 \times 0.5 \times 1.5$ mm$^3$) could scan the focal hyperintense spot better and might help to find the intermediate process from intact nigral hyperintensity to the absence of nigral hyperintensity.

So far, MRI has become a well-established method in routine clinical examination for patients with Parkinsonism[16, 17]. MRI can help identify symptomatic Parkinsonism caused by a variety of pathological factors, including vascular, metabolic, toxic, traumatic, tumor, or other structural lesions, as well as provide clues to differentiate PD from cortical basal degeneration, multiple system atrophy or progressive supranuclear palsy[16]. However, structural MRI is usually normal in the early stages of PD, and therefore can not provide positive and supportive information for clinical PD diagnosis[16]. Recent studies using advanced analytical techniques and multimodality imaging with high-field MRI have revealed multiple imaging abnormalities in PD, including evidence of changes in the microstructure of SN and basal ganglia[18, 19], increased iron deposition in substantia nigra[20, 21], and loss of neuromelanin[22]. In line with previous studies,[5] our results suggest that loss of dorsolateral nigral hyperintensity on high-field SWI scans might represent a new diagnostic marker for PD (early-stage PD as well). In addition, we found that SWI is useful in the differential diagnosis of PD and VP.

In this study, we had four subjects who were excluded from the analysis because of poor diagnostic quality. Poor image quality may be the result of motion artifacts caused by patients' motion symptoms, as SWI technology has higher sensitivity to movement artifacts. Artifacts from sphenoid sinus might be one of the possible reasons of poor diagnostic quality. In order to reduce the incidence of non-diagnostic images, it is necessary to carefully select the scanning parameters for clinical practice, such as optimal scan time for the prevention of movement artifacts. On one hand, MRI scans were performed when dyskinesia was mild or absent. On the other hand, in our series, we performed SWI sequences in the first part of the MRI protocol to

minimize motion artifacts.

Our study has several limitations. First, although clinical diagnoses were based on stringent criteria, in the absence of autopsy confirmation, misdiagnosis would happen even in the hands of experienced neurologists, and the misdiagnosis rate for the early stage of Parkinsonism syndromes was up to 25%.[16, 23]. Second, SWI was conducted using conventional parameters in this study, rather than using a customized midbrain imaging protocol. The customized midbrain imaging protocol may improve image quality and diagnostic performance of 3T SWI. Third, a simple MRI feature, that was, the absence of high intensity of the dorsolateral substantia nigra, might take the risk of rater subjectivity. The high reliability of our assessment of the loss of the nigral hyperintensity supports simple visual assessment in clinical settings.

In conclusion, almost all patients with PD presented the loss of nigral hyperintensity at 3T SWI. Our results suggested that the evaluation of abnormal signal can be used as a factor in the differential diagnosis of PD and VP.

**Conflict of Interest Statement**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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