Neuroscience Letters 638 (2017) 145–150

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

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

Yuanyuan Xiang[a,1], Tao Gong[b,1], Junwei Wu[c], Jifeng Li[a], Yan Chen[a], Yongxiang Wang[a], Shan Li[a], Lin Cong[a], Youting Lin[a], Yuxiang Han[a], Ling Yin[a], Guangbin Wang[b,**], Yifeng Du[a,*]

[a] Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, PR China
[b] Shandong Medical Imaging Research Institute Affiliated to Shandong University, Jinan, Shandong, PR China
[c] Department of Orthopaedics, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, PR China

## 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.

## ARTICLE INFO

*Article history:*
Received 21 June 2016
Received in revised form
16 November 2016
Accepted 15 December 2016
Available online 16 December 2016

*Keywords:*
Parkinson's disease
Motor subtypes
Neuromelanin
Substantia nigra
Magnetic resonance imaging

## 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.



## 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

* Corresponding author at: Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong University, No. 324 JingWu Road, 250021, Jinan, Shandong, PR China.
** Corresponding author at: Shandong Medical Imaging Research Institute Affiliated to Shandong University, No. 324 JingWu Road, 250021 Jinan, Shandong, PR China.
*E-mail addresses:* wgb7932596@hotmail.com (G. Wang), 13173015523@163.com (Y. Du).
[1] Authors Y.Y. Xiang and T. Gong contributed equally to the study.

http://dx.doi.org/10.1016/j.neulet.2016.12.036
0304-3940/

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.