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# Substantia nigra echogenicity correlated with clinical features of Parkinson's disease

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ABSTRACT

*Background:* Transcranial sonography can display structural alterations in the substantia nigra (SN) of patients with Parkinson's disease (PD), and is considered to be a potential useful tool for the diagnosis of PD. The aim of this study was to assess the correlation between SN echogenicity and clinical features in Chinese patients with PD.

*Methods:* A total of 420 subjects including 290 patients with PD and 130 controls were recruited from the neurological clinic or the community. Transcranial sonographic evaluations of the SN were performed in all subjects, and motor and non-motor symptoms were thoroughly assessed by a series of rating scales in PD patients.

*Results:* Two hundred and one patients were successfully assessed by transcranial sonography. SN hyperechogenicity was found to be associated with male sex ($p = 0.004$), higher scores on the Unified Parkinson's Disease Rating Scale (UPDRS) part II ($p = 0.001$) and autonomic symptoms scores ($p = 0.003$). Moreover, regression analysis revealed that UPDRS part II scores (odds ratio = 1.141, $p < 0.001$) and gender (odds ratio = 2.409, $p = 0.007$) could be the independent predictors for SN hyperechogenicity; in addition, among all items of UPDRS part II, speech, dressing, hygiene, and turning in bed and adjusting bed clothes significantly correlated with SN hyperechogenicity.

*Conclusions:* This is the first report suggesting the correlation between SN echogenicity and UPDRS part II, and we conclude that increased SN echogenicity might reflect more severe disease disability or poorer medical response.

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## 1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is associated with the progressive loss of dopaminergic neurons in the substantia nigra (SN). Transcranial sonography (TCS) is a convenient and noninvasive diagnostic technique that allows imaging of the brain parenchyma in two-dimensional black and white slices. TCS can display specific structural changes in the SN of PD patients, and hyperechogenicity in the anatomical area of the SN is believed to be a marker of PD [1,2]. Based on fluorodopa positron emission tomography (PET) studies, enlarged hyperechogenic size of the SN is considered to be associated with functional impairment of the nigrostriatal system [3]. Previous studies have suggested that SN hyperechogenicity (SN+) is associated with the disease severity, although the findings are conflicting [2,4–8]. To date, TCS data from Chinese patients with PD are limited [9,10]. Our study aimed to evaluate the correlation of the sonographic findings with the clinical features in Chinese PD patients including motor and non-motor characteristics.

## 2. Subjects and methods

### 2.1. Subjects

From March 2014 to May 2015, two hundred and ninety patients

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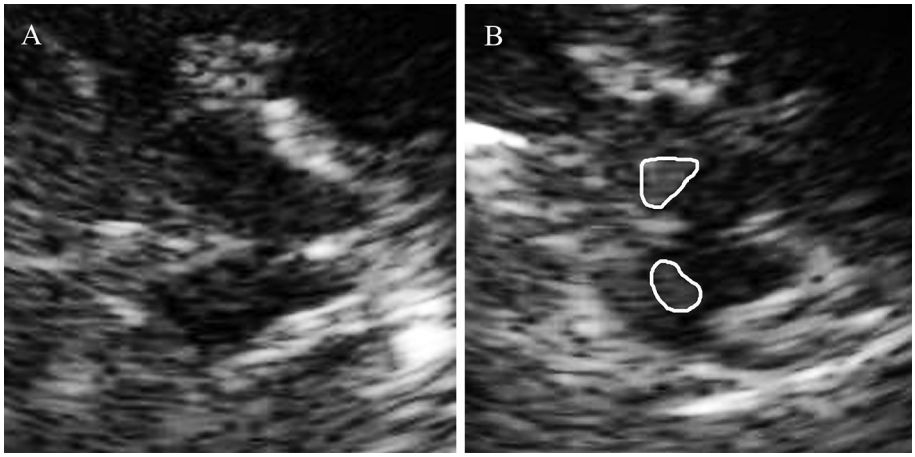


**Fig. 1.** Sonographic images of the mesencephalic brainstem in a healthy control (A) and a patient with Parkinson's disease (B). The butterfly shaped mesencephalic brainstem was surrounded by the hyperechogenic basal cisterns. The patient with Parkinson's disease exhibited hyperechogenic signals encircled by lines at both sides of SN, which were not seen in the control.

with PD meeting the criteria of the UK Parkinson's Disease Society Brain Bank were recruited from the movement disorders clinic at the Department of Neurology, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China. None of the PD patients demonstrated atypical features such as pyramidal signs, gaze palsy, or cerebellar ataxia, or had a history of stroke, neuroleptic intake or other identifiable possible causes of secondary parkinsonism. From March 2015 to July 2015, one hundred and thirty control subjects without CNS disorders were recruited by advertisement within the hospital's neurological clinic or from the Shanghai Wuliqiao community. All volunteers were assessed by movement disorder specialists and were excluded if there was a positive family history of PD or the possibility of mild parkinsonism. This study was approved by the Ethics Committee of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine. All participants were given written informed consent.

### 2.2. Midbrain transcranial sonography

The sonographic examinations were performed within 1 month after the clinical examinations (mean 10 days). An experienced sonographer (Yun-Yun Hu) who was blinded to the clinical findings of the subjects performed the examination. Through the acoustic bone window, the sonographer detected the echogenicity of the SN using a 2.5 MHz sonographic device (MyLab90, ESAOTE, Italy) with a depth of 16 cm and a dynamic range of 45 dB as described previously [9]. The SN was scanned through both temporal bone windows in the axial plane. Some subjects showed no identifiable or vague midbrain structures that were insufficient to be quantitatively assessed, and these were excluded from further assessment. After identifying the butterfly shaped hypoechogenic midbrain, which was surrounded by the hyperechogenic basal cistern, the clearest image of the hyperechogenic signals in the SN region was stored. Both sides of SN echogenic areas from stored images were then manually encircled and measured (Fig. 1). For inter-rater reliability analysis, all stored images were encircled and remeasured by another senior sonographer (Wei-Wei Zhan). To acquire a cutoff value for SN+, the larger SN echogenic areas ($SN_L$) were used in the receiver-operating characteristic (ROC) curve analysis.

### 2.3. Motor and non-motor symptoms assessment

To assess disease disability, the PD patients were examined using the Unified Parkinson's disease rating scale (UPDRS) part II and part III, and their Hoehn & Yahr Stage (H–Y stage) was graded while they were in the 'on' stage. Medication was also carefully documented and levodopa equivalent dose (LED) was calculated. To evaluate non-motor characteristics, a battery of scales was used. The Non-Motor Symptoms Questionnaire (NMSQuest), a 30-item self-completed questionnaire, was used to investigate the occurrence of non-motor symptoms. Odor discrimination was performed with the 16-item odor identification test from the extended version of sniffin' sticks (SS-16; Burghart Messtechnik, Wedel, Germany) as previously described, with a cut-off score for the SS-16 of 9.5 [9]. All the participants were evaluated with the rapid eye movement sleep behavior disorder screening questionnaire (RBDSQ). Autonomic dysfunction was assessed with a scale for outcomes in PD of autonomic symptoms (SCOPA-AUT), which was composed of 26 items. The Mini-Mental State Examination (MMSE) was used to evaluate cognitive function. The 17-item Hamilton Rating Scale for Depression (HAMD-17) was used to evaluate the severity of depressive symptoms.

### 2.4. Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 16.0 for Windows. An intra-class correlation coefficient (ICC) was used to determine inter-observer reliability of midbrain measurements. Reliability coefficients with 95% confidence intervals (CIs) were calculated for all subjects. The result of the ICC was 0.96 (0.89–0.98), indicating good inter-rater reliability. An optimal cutoff value to discriminate between PD patients and control subjects was obtained from ROC curve analyses, plotting sensitivity versus 1-specificity for every possible cutoff point. The cutoff was defined at the point where the sum of sensitivity and specificity was highest.

Continuous variables were given as means (±standard deviation, SD). Categorical variables were summarized by counts of patients and percentages. All variables were tested for normality (Kolmogorov–Smirnov). Two-sample t test, Mann–Whitney U test or Chi-square test was applied for the comparisons between the SN+ and SN− groups. To account for multiple testing, resulting nominal p values were adjusted according to the Bonferroni

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