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*Full Length Research Paper*

# Characterization of Substantia Nigra in Parkinson disease using MR Imaging

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**Visualizing with MR imaging and obtaining quantitative indices of degeneration of the substantia nigra in Parkinson disease has been extended- required goals. We investigated the possible character of length and width measurements at $T_2$ weighted images in differentiating Parkinson patients from controls, duration and age-related changes. Fifty controls and forty patients with Parkinson disease were imaged in $T_1$ , $T_2$ and FLAIR weighted sequence at 1.5 Tesla. The control group consisted of 37 (74%) males and 13 (26%) females, 30 to 86 years old (mean age, 49.04±11.51 years). The group with Parkinson's disease included 29 (72.5%) males and 11 (27.5%) females, 46 to 77 years old (mean age, 60.42±7.84years) with a mean duration of disease of 7.8±3.5 years (range, 2 to13 years). In axial $T_2$ weighted MR images of the midbrain, which included the mammillary body and red nucleus, the right and left substantia nigra width and length, were measured; compared with the controls and were correlated with patients ages and disease duration. Compared with that of controls, loss of substantia nigra was evident in patients. The visible nigral length and width were significantly smaller in patients compared with controls *P*=0.005 with hypointense character on $T_2$ weighted images. The duration of Parkinson disease has a significant impact in the nigral width reduction. $T_2$ weighted images may provide a convenient way to visualize nigral degeneration in Parkinson disease. New equations were established to predict the nigral width in the progression of Parkinson disease and age related changes in normal subjects.**

**Keywords:** Parkinson's disease, MRI, Substantia Nigra

## INTRODUCTION

Parkinson is a widespread disease, concerning degeneration of dopaminergic neurons in the substantia nigra. Incidence increases with age; therefore, this increase results in increasing troubles on health care scheme (Minati et al., 2007). From a neuroradiologic point of view, the most sensitive imaging techniques for the early diagnosis of Parkinson disease are positron-emission tomography (PET) and single- photon emission tomography (SPECT) (Ravina et al., 2005), but their unavailability and the cost of each imaging session is

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high (Ravina et al., 2005).

On the other hand, MR imaging is a simple, inexpensive technique that is widely available (Michael Hutchinson and Ulrich Raff, 2000). During recent years, variant techniques have been made to show nigral changes in Parkinson cases by using MR imaging, based on measurement of the $T_2$ and $T_2$* relaxation times (Ordidge et al., 1994; Gorell et al., 1995), nigral area on the basis of proton density weighted images (Oikawa et al., 2002); diffusion-weighted MR imaging (DWI) (Adachi et al., 1999), Inversion-recovery sequences characterizing the changes in the spin-lattice relaxation time ($T_1$) (Hutchinson and Raff, 1999).

Iron is deposited in the Substantia Nigra in normal aging, but, this may create difficulties in separating patients from normal subjects. Measurement of the width of the Substantia Nigra is important in the evaluation of Parkinson disease by using MR imaging (Moriwaka et al., 1992; Mauricio et al., 1990; Duguid et al., 1986), although thinning of this structure occurs in such cases and the nucleus width becomes only a few millimeters, it takes an irregular form as the disease developed. This makes the width difficult to characterize with accuracy.

In a study done previously; changes in $T_2$ weighted imaging findings did not correlate either with disease duration or with clinical complications (Antonini et al., 1993). Therefore, this study is considered as a trial to measure the length and width of Substantia Nigra and to correlate the findings with control subjects as well as duration of the diseases and age related changes using $T_2$ weighted MR imaging.

## MATERIALS AND METHODS

$T_1$ , $T_2$ and FLAIR-weighted MR studies of the substantia nigra were obtained for Parkinson's disease patients, and for control subjects who were examined at the Military hospital, Khartoum-Sudan during the period from July 2012 up to July 2014. The study protocol was approved by Research Ethical Committee -College of Medical Radiological Science-Sudan University of Science and Technology. The diagnosis of Parkinson's disease was based on clinical criteria, including the following neurologic signs: resting tremor, rigid muscles, bradykinesia, depression, disorder of postural reflex, gait disturbance, speech change. Patients with abnormal MR findings as abnormal high signal intensity on $T_2$ weighted images were excluded from the study. The control group consisted of 50 subjects 37 (74%) males and 13 (26%) females, 30 to 86 years old (mean age, 49.04±11.51 years) without neurologic insufficiency or abnormal findings on $T_1$ or $T_2$ weighted brain MR images. The group with Parkinson's disease included 40 patients, 29 (72.5%) were males and 11 (27.5%) were females, 46 to 77 years old (mean age, 60.42±7.84 years) with a mean duration of disease of 7.8±3.5 years (range, 2 to13 years).

The study was obtained Using a 1.5-T superconductive system (SIGNA HDE; GE medical systems, and Philips medical system 1.5 T. Coil: - HD 8 channels (neurovascular array). For $T_2$ weighted sequences; images were obtained using:-TR: 5200 ms TE: 90.2ms FOV: 25x22 cm slice thickness: 5.0 mm spacing: 1.0 mm. For $T_1$ weighted sequence; images were obtained using:-TR: 600ms TE: 20 ms FOV:-25x22cm, slice thickness: 5mm spacing: 1.0mm. For FLAIR TR: 9000ms TE: 80, TI: 1700–2500 ms and ETL: 16.

### Measurement of the Substantia Nigra

Axial images of the brain, which included the mammillary body and red nucleus, were obtained in all control subjects and patients. At this plane where the mid-brain appeared, the substantia nigra become visible as crescent in shape, so we measured the width of the substantia nigra axis and then the length at the same view , the measurements were taken in (mm).

### *Statistical Analysis*

The correlation between age and width of the right and left substantia nigra was tested in the control group using Excel programme, because the substantia nigra was expected to be reduced with age. Statistical tests were performed by using the Statistical Package for the Social Sciences, Version 16.0 (SPSS, Chicago, Illinois) Statistical comparisons of the width and length of the right and left substantia nigra between the control and Parkinson's disease groups, were based on results of an unpaired Student's *t*-test. *P*- values less than 0.005 were considered to indicate a significant difference. Also the correlation between age and width of the right and left substantia nigra was tested in the diseased group using Excel programme.

## RESULTS

The control group and Parkinson disease group were classified and arranged into classes, the control group ages: 27-36 were 7 (14%), 37-46 were 10 (20%), 47-56 were 23 (46%), 57-66 were 7 (14%) and ages >67 were 3 (6%). Parkinson disease age group: 37-46 were 1 (2.5%), 47-56 were 11 (27.5%), 57-66 were 20 (50%), >67 were 8 (20%).

**Table 1.** Mean and standard deviation (SD) Minimum and Maximum values of the Age, right and left Nigra length and width measured for the control group.

| | | age | RT NIGRA (Width) | RT NIGRA (Length) | LT NIGRA (Width) | LT NIGRA (Length) |
|---|---|---|---|---|---|---|
| N | Valid | 50 | 50 | 50 | 50 | 50 |
| Mean | | 49.04 | 3.88 | 11.65 | 3.51 | 11.44 |
| S. D | | 11.51 | .314 | .650 | .324 | .623 |
| Minimum | | 30.00 | 3.02 | 10.21 | 3.00 | 10.18 |
| Maximum | | 86.00 | 4.27 | 12.82 | 4.16 | 12.93 |

**Table 2.** mean and standard deviation (SD) Minimum and Maximum values of the Age , right and left Nigra length and width measured for the Parkinson disease group.

| | | age | RT NIGRA (Width) | RT NIGRA (Length) | LT NIGRA (Width) | LT NIGRA (Length) |
|---|---|---|---|---|---|---|
| N | Valid | 40 | 40 | 40 | 40 | 40 |
| Mean | | 60.42 | 3.31 | 10.37 | 2.9188 | 10.42 |
| S. D | | 7.844 | .394 | .228 | .31407 | .250 |
| Minimum | | 46.00 | 2.24 | 10.03 | 2.13 | 10.05 |
| Maximum | | 77.00 | 3.90 | 10.89 | 3.59 | 11.00 |

**Table 3.** mean and standard deviation (SD) values of the Age, the right and left Nigra length and width measured and classified according to gender for the control group

| Group Statistics [a] | | | | | |
|---|---|---|---|---|---|
| | Gender | N | Mean | Std. Deviation | Std. Error Mean |
| Age | Male | 37 | 49.1081 | 12.29224 | 2.02083 |
| | Female | 13 | 48.8462 | 9.37058 | 2.59893 |
| RT NIGRA | Male | 37 | 3.9073 | .31199 | .05129 |
| (Width) | Female | 13 | 3.8315 | .32738 | .09080 |
| RT NIGRA | Male | 37 | 11.5892 | .70298 | .11557 |
| (Length) | Female | 13 | 11.8562 | .43462 | .12054 |
| LT NIGRA | Male | 37 | 3.5568 | .33953 | .05582 |
| (Width) | Female | 13 | 3.3885 | .24627 | .06830 |
| LT NIGRA | Male | 37 | 11.3532 | .65702 | .10801 |
| (Length) | Female | 13 | 11.6969 | .44489 | .12339 |
| a. group = Control group | | | | | |

**Table 4.** Mean and standard deviation (SD) of the Age, the right and left Nigra length and width measured and classified according to gender for the Parkinson disease group

| Group Statistics[a] | | | | | |
|---|---|---|---|---|---|
| | Gender | N | Mean | S. D | Std. Error Mean |
| Age P=0.746 | Male | 29 | 60.1724 | 7.68147 | 1.42641 |
| | Female | 11 | 61.0909 | 8.60761 | 2.59529 |
| RT NIGRA (Width) P=0.730 | Male | 29 | 3.3245 | .36409 | .06761 |
| | Female | 11 | 3.2755 | .48308 | .14565 |
| RT NIGRA (Length) P=0.971 | Male | 29 | 10.3748 | .22775 | .04229 |
| | Female | 11 | 10.3718 | .24037 | .07247 |
| LT NIGRA (Width) P=0.663 | Male | 29 | 2.9052 | .34813 | .06465 |
| | Female | 11 | 2.9545 | .20830 | .06280 |
| LT NIGRA (Length) P=0.516 | Male | 29 | 10.4448 | .24247 | .04502 |
| | Female | 11 | 10.3864 | .27703 | .08353 |
| a. group = Parkinson disease group | | | | | |

Independent Samples Test[a] t-test for Equality of Means, significant when P value is less than 0.005

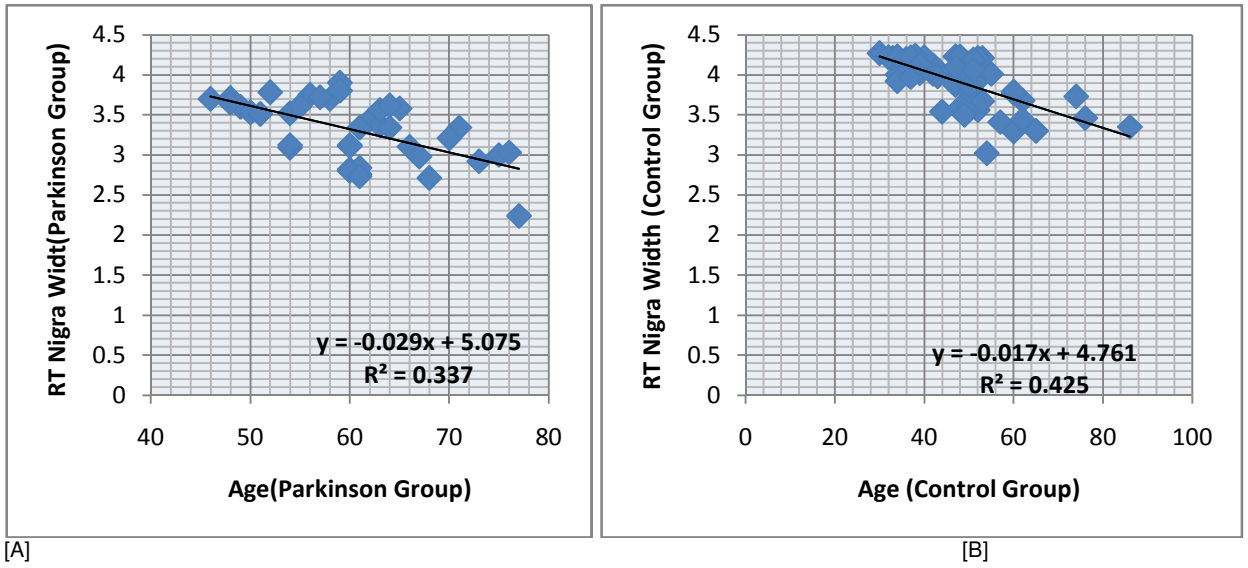
**Table 5.** Multiple comparisons between of the right and left Nigra length and width measured for the Control and Parkinson disease groups

| Multiple Comparisons | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Dependent Variable** | **Control** | **Parkinson** | **Mean Difference (Control - Parkinson)** | **Std. Error** | **Sig.** | **95% Confidence Interval** | |
| | | | | | | **Lower Bound** | **Upper Bound** |
| RT NIGRA (Width) | Control | Parkinson | 0.57660* | .0655 | .000* | .4471 | .7061 |
| RT NIGRA (Length) | Control | Parkinson | 1.28460* | .1006 | .000* | 1.0858 | 1.4834 |
| LT NIGRA (Width) | Control | Parkinson | 0.59425* | .0658 | .000* | .4642 | .7243 |
| LT NIGRA (Length) | Control | Parkinson | 1.01385* | .0986 | .000* | .8189 | 1.2088 |

*The differences are significant between the control Group and Diseased Group p=0.005

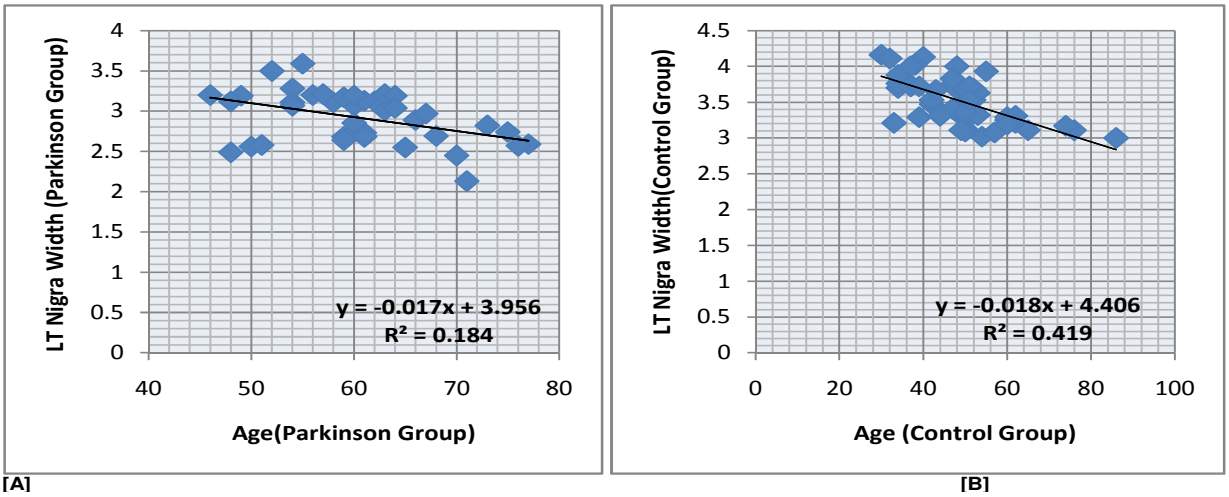
**Table 6.** Coefficient between of the right and left Nigra length and width measured for the Parkinson disease group with the disease Duration

| Coefficients [a] | | | | | |
|---|---|---|---|---|---|
| **Model** | **Un- standardized Coefficients** | | **Standardized Coefficients** | **t** | **Sig.** |
| | **B** | **Std. Error** | **Beta** | | |
| (Constant) | -6.102 | 43.997 | | -.139 | .891 |
| RT NIGRA (Width) | -5.812 | 1.846 | -.737 | -3.148 | .004* |
| RT NIGRA (Length) | -2.755 | 2.872 | -.546 | -.959 | .345 |
| LT NIGRA (Width) | 4.902 | 2.075 | .686 | 2.362 | .025* |
| LT NIGRA (Length) | 5.367 | 2.951 | .979 | 1.819 | .079 |
| a. Dependent Variable: Duration of Parkinson disease ,*Significant at p=0.005 | | | | | |




[A] [B]

**Figure 1.** [A] A scatter plot diagram shows a linear relationship between the Age ( Parkinson group) and the width of RT Nigra ,as the age increases the width decreases by 0.029/year starting from 5.075mm,$R^2$=0.337.The age has an effect of 58% on the RT Nigra width for the diseased group.[B] a linear relationship between the Age ( Control group) and the width of RT Nigra ,as the age increases the width decreases by 0.017/year starting from 4.761mm,$R^2$=0.425.The age has an effect of 65% on the RT Nigra width for normal population.




[A] [B]

**Figure 2.** [A] A scatter plot diagram shows a linear relationship between the Age ( Parkinson group) and the LT Nigra width, as the age increases the width decreases by 0.017/year starting from 3.956mm,$R^2$=0.184.The age has an effect of 43% on the LT Nigra width for the diseased group.[B] a linear relationship between the Age ( Control group) and the LT Nigra width, as the age increases the width decreases by 0.018/year starting from 4.406mm,$R^2$=0.419.The age has an effect of 65% on the LT Nigra width for the normal population.

## DISCUSSION

Characterization of the substantia nigra (SN) in Parkinson's disease (PD) by MR imaging procedures has been an advantageous practice. We obtained $T_1$ , $T_2$ and FLAIR (Fluid attenuation at inversion Recovery) techniques. We studied and observed $T_2$ signal changes of both the (SN) in the right and left side which affected the measurements done for the length and width; this was useful to support the diagnosis of PD; whereas controls did not show these features. Tables 1 and 2 showed the measurements taken for both control and disease groups. The gender was also taken into our consideration in the measurements. No significant differences were detected between the two genders and in control or diseased group. This was noticed in tables 3, and 4.

Table 5 presented the difference between the control group and the diseased group regarding the Nigral measurements. It significantly differs at p=0.000. Similar findings were studied by (Minati et al., 2007) who mentioned that the nigral area measured was significantly different between Parkinson patients and controls (Minati et al., 2007). The changes in intracellular compartment and in iron deposition were both being acknowledged factors for these differences. (Hutchinson et al., 2003; Vymazal et al., 1999)

In patients with Parkinson's disease, low signal intensity has been reported in the putamen, globus pallidus, and substantia nigra on $T_2$ weighted images, resulting from the accumulation of iron (Gorell et al., 1995). The causes of the measurement reduction and restoration of signal may be justified by the fact that in the dorsal lateral substantia nigra, a depletion of iron (due to increased cellular metabolic activity) or local cell death, result in an expansion of the extracellular space, as mentioned by (Rutledge et al., 1987).

When the SN is known to have high iron content and has been shown to be correlated with decreased signal intensity (associated with decreased $T_2$ relaxation times). (Drayer et al., 1986), the justification is that the SN contains neuromelanin (Braak and Braak, 1986; Yelnik et al., 1987) and iron can be stored in neuromelanin by the iron-storage protein ferritin (Zecca et al., 1994; Double et al., 2003). Iron alters the magnetic field uniformity in tissues and causes MR signal intensity within tissues to decrease (Rutledge et al., 1987; Tosk et al., 1992). Therefore the MR imaging_related signal intensity effects observed in the SN could be attributed to the paramagnetic neuromelanin or intracellular iron stores. In our study, we observed a characteristic signal-intensity difference in the SN, showing demarcation of this region with imaging using $T_2$ weighted sequences at 1.5T (Duguid et al., 1986).

The duration of the disease was also tested as one of the factors that may contribute in the nigra changes, table 6 showed that the substantia nigra width of the right and left sides were significantly reduced by the duration of disease. Measurements assessment prove that the substantia nigra degenerates from lateral to medial and in a rostral to caudal direction. There is also thinning, and the structure takes on a mottled appearance compared with the normal subjects, (Moriwaka et al., 1992). This is why the width of SN was reduced.

Some have reported that the clinical severity of Parkinson disease is strongly correlated with the width of the hyperintense band on $T_2$ weighted images (Pujol et al., 1992). The lack of thinning of the hyperintense band on $T_2$ weighted images in this study may be due to the mildness of the disease in the Parkinson disease

group. Another study mentioned that in patients with Parkinsonism of long duration, the striatonigral pathway could be damaged and the whole volume of the substantia nigra was reduced (Adachi et al., 1999).

The selected age classes were similar in both control and diseased group. It has been shown that the high frequencies of patients who were affected with Parkinson lie in the ages between 57-66 years old, with mean duration of disease of 7.8±3.5 years (range, 2 to13 years). Figures 1 and 2 showed the relations between the age and right and left nigral width in both normal and diseased groups. Magnetic resonance imaging showed that changes in nigra due to Parkinson could be predicted when it is associated with clinical neurological signs or changes according to advancing age. As it was mentioned previously, MR imaging benefits include the detection of presymptomatic and staging of disease especially in the inherited disorder which would allow the protection and early treatments of those determined to be at risk, and hence interventions in both presymptomatic and symptomatic patients (Brooks, 1998).

Prediction of the changes that may happen in the SN for the known age of Parkinson diseased patients can be described by the following equations:-

*RT Nigra Width= 5.075-0.029X patient's age*
*LT Nigra width=3.956- 0.017X patient's age*

In the normal group the changes of the nigral width regarding age can also be estimated for the known subjects' ages:-

*RT Nigra Width=4.761-0.017X subject's age*
*LT Nigra Width=4.406-0.018X subject's age*

## CONCLUSION

$T_2$ weighted imaging are acknowledged for depicting the change in the width and length of the substantia nigra in Parkinson disease patients. New equations were established to predict the changes in substantia nigra in normal subjects and patients with Parkinson disease.

### REFERENCE


Adachi M, Hosoya T, Haku T, et al (1999). Evaluation of the substantia nigra in patients with Parkinsonian syndrome accomplished using multishot diffusion weighted MR imaging. *AJNR Am. J. Neuroradiol*. 20:1500–1506

Antonini A, Leenders KL, Meier D, Oertel WH, Boesiger P, Anliker M (1993). T2 relaxation time in patients with Parkinson disease. *Neurol.* 43:697–700

Braak H, Braak E (1986). Nuclear configuration and neuronal types of the nucleus niger in the brain of the human adult. *Hum. Neurobiol*. 5:71–82

Brooks DJ (1998). The early diagnosis of Parkinson's disease. *Ann. Neurol*. 44(suppl 1):S10–S18

Double K, Gerlach M, Schu¨nemann V, et al (2003). Iron-binding characteristics fneuromelanin of the human substantia nigra. *Biochem. Pharmacol*. 66:489–494

Drayer B, Burger P, Darwin R, et al (1986). MRI of brain iron. *AJR Am. J. Roentgenol*. 147:103–110

Duguid JR, De La Paz R, DeGroot J (1986). Magnetic resonance imaging of the midbrain in Parkinson's disease. *Ann. Neurol*. 20:744–747

Gorell JM, Ordidge RJ, Brown GG, Deniau MS, Buderer NM, Helpern JA (1995). Increased iron-related MRI contrast in the substantia nigra in Parkinson's disease. Neurol. 45:1138– 1143

Hutchinson M, Raff U (1999). Parkinson's disease: a novel MRI method for determining structural changes in the substantia nigra. *J. Neurol. Neurosurg. Psychiatry*. 69:815–818

Hutchinson M, Raff U, Lebedev S (2003). MRI correlates of pathology in Parkinsonism: segmented inversion recovery ratio imaging (SIRRIM). *Neuroimage*. 20:1899–902

Mauricio JC, Coelho H, Sa J Martins A (1990). Importance of magnetic resonance in Parkinson disease: an analytic study of the pars compacta. *Acta Med. Port*. 3:85–88

Michael Hutchinson, Ulrich Raff (2000). Structural Changes of the Substantia Nigra in Parkinson's Disease as Revealed by MR Imaging *AJNR. Am. J. Neuroradiol*. 21:697–701.

Minati L, Grisoli M, Carella F, De Simone T, Bruzzone MG, Savoiardo M (2007). Imaging Degeneration of the Substantia Nigra in Parkinson Disease with Inversion-Recovery MR Imaging AJNR Am. J. Neuroradiol. 28:309 –313.

Moriwaka F, Tashiro K, Itoh K, Hamada T, Miyasaka K (1992). Magnetic resonance imaging in Parkinson's disease: the evaluation of the width of pars compacta on T2 weighted images (in Japanese). *Rinsho Shinkeigaku*. 32:8–12

Oikawa H, Sasaki M, Tamakawa Y, et al (2002). The substantia nigra in Parkinson disease: proton density-weighted spin-echo and fast short inversion time inversion- recovery MR findings. AJNR. Am. J. Neuroradiol. 23:1747–1756

Ordidge RJ, Gorell JM, Deniau JC, et al (1994). Assessment of relative brain iron concentrations using $T_2$ weighted and $T_2$ weighted MRI at 3 Tesla. *Magn. Reson. Med*. 32:335–341

Pujol J, Junque C, Vendrell P, Grau JM, Capudevila A (1992). Reduction of the substantia nigra width and motor decline in aging and Parkinson's disease. *Arch. Neurol.* 49:1119–1122

Ravina B, Eidelberg D, Ahlskog JE, et al (2005). The role of radiotracer imaging in Parkinson disease. *Neurol*. 64:208–215

Rutledge JN, Hilal SK, Silver AJ, Defendini R, Fahn S (1987). Study of movement disorders and brain iron by MR. AJNR Am. J. Neuroradiol. 8:397–411

Tosk J, Holshouser B, Aloia R, et al (1992). Effects of the interaction between ferric iron and L-dopa melanin on T1 and T2 relaxation times determined by magnetic resonance imaging. *Magn. Reson. Med*. 26:40–45

Vymazal J, Righini A, Brooks RA, et al (1999). T1 and T2 in the brain of healthy subjects, patients with Parkinson disease, and patients with multiple system atrophy:relation to iron content. *Radiol.* 211:489–495

Yelnik J, Franc¸ ois C, Percheron G, et al (1987). Golgi study of the primate substantia nigra. I. Quantitative morphology and typology of nigral neurons. *J. Comp. Neurol*. 265:455–472

Zecca L, Pietra R, Goj C, et al (1994). Iron and other metals in neuromelanin, substantia nigra, and putamen of human brain. *J. Neurochem*. 62:1097–1101