Determination of brain iron content in patients with Parkinson's disease using magnetic susceptibility imaging

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Abstract: Objective To compare the phase radians in several cerebral regions between patients with Parkinson's disease (PD) and control subjects, and to evaluate whether iron deposition quantified by susceptibility-weighted imaging (SWI) is related to the severity of motor symptoms of PD. **Methods** SWI consisted of both magnitude and phase images from a fully flow-compensated, 3-dimensional and gradient-echo (GRE) sequence. Magnitude and phase data were collected at GE HD 1.5T. The regions evaluated included frontal white matter, grey matter, cerebrospinal fluid, putamen, caudate nucleus (CN), substantia nigra pars compacta (SNc), substantia nigra pars reticulata (SNr), and red nucleus (RN). A total number of 42 patients (12 patients without cognitive dysfunction, and 30 with cognitive dysfunction from mild to moderate degrees) and 30 control subjects were employed in the present study. **Results** The phase radians of SNc, CN and RN in PD patients were lower than those in control subjects ($P < 0.05$). **Conclusion** The phase radians can be used to estimate the brain iron deposition in PD patients, which may be helpful in the diagnosis and longitudinal monitoring of PD.

Keywords: Parkinson's disease; phase radians; susceptibility-weighted imaging; iron deposition

1 Introduction

Parkinson's disease (PD) affects approximately 1% of the old population aged over 65 years. The clinical diagnosis of PD is based on the symptoms of the akinetic rigid syndrome (usually with an asymmetric onset), a resting tremor and a sustained response to levodopa^[1]. Definitive diagnosis of PD is confirmed by postmortem examination of the brain tissue of PD patients^[2], which has shown increased iron deposition in several cerebral regions in PD patients^[3,4].

The *in vivo* examination of iron in the brain tissue can be achieved using magnetic resonance imaging technique^[5,6].

PD is a neurodegenerative disorder that is characterized by loss of dopamine-producing neurons in the substantia nigra (SN). To date, the exact causes of SN neuronal loss in PD remain unclear. However, postmortem evidence of increased iron content in the SN of parkinsonian brain^[7] has suggested that the generation of reactive oxygen species, possibly facilitated by iron, may be responsible for cellular damage and the subsequent cell death. Others have suggested that iron levels increase with the progression of PD^[8]. Ascertaining the ongoing changes in the parkinsonian brain may be helpful in understanding disease pathogenesis^[9]. Nevertheless, the related *in vivo* techniques are limited. Iron accumulation^[10-13] in the brain occurs in PD, and measuring

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the amount of nonheme iron in the body may not only lead to a better understanding of the disease progression, but also help to predict the outcome in relation to patients' motor symptom.

Susceptibility-weighted imaging (SWI) technique is a novel imaging method that could maximize the sensitivity by combining a long-TE, high-resolution, fully velocity-compensated, and 3-dimensional (3D) gradient-echo scan with filtered phase information in each voxel to both enhance the contrast in magnitude images and add a susceptibility difference between different tissues. These characteristics enable SWI to have exquisite sensitivity to iron deposition.

Phase images offer contrasts in new facets, such as iron^[14] and calcium^[15], and help assess any other effect^[16] that depends on the difference in the susceptibility among the tissues. Different areas of the brain exhibit specific behaviors based on their chemical composition and susceptibility, both of which are intrinsic properties of the tissue. SWI is sensitive to the tissue through its phase^[5]. In the present study, the phase radians of frontal white matter (WM), grey matter (GM), cerebrospinal fluid (CSF), putamen (PUT), caudate nucleus (CN), substantia nigra pars compacta (SNc), substantia nigra pars reticulata (SNr), and red nucleus (RN) in both PD patients and control subjects were detected and presented. Other structures, such as the hippocampus, were not focused here, although they still have the potential for analysis. The purpose of this work is to compare the phase radians of these cerebral regions between PD patients and control subjects, and to evaluate whether iron deposition quantified by SWI technique is related to the motor dysfunction of PD patients.

2 Materials and methods

2.1 Patients A total number of 42 patients with PD, including 22 male and 20 female, at the mean age of (60±11) years (35-84 years old), and 30 control subjects, including 15 male and 15 female, at the mean age of (58±10) years (34-83 years old), were employed in the present study. Patients with PD were recruited from the movement disorder clinic, and they were diagnosed by 2 neurologists according to the core assessment program for intracerebral transplantations, based

on the observations of bradykinesia, tremor, rigidity, and the response to levodopa.

The PD patients were further subdivided into 2 groups, one included 12 patients without cognitive dysfunction, and the other included 30 patients with cognitive dysfunction from mild to moderate degrees.

2.2 Movement assessment Movement symptom severity for each side of the body was assessed using the motor examination of the United Parkinson's Disease Rating Scale (UPDRS) within one week after the overnight withdrawal of medication, during which magnetic resonance imaging (MRI) scan examination was also conducted.

2.3 Imaging protocols Although a variety of MRI sequences can be used for SWI, SWI is mainly based on the high resolution method. Conventional gradient-echo (GRE) images are extremely sensitive to the inhomogeneity of magnetic field since the signal is generated by the reversal of the readout gradient alone without an accompanying 180° phase reversal pulse. The radiofrequency excitation pulse is operator-selectable and is generally less than the 90° flip angle of the spin-echo (SE) pulse sequence. Here all the examinations were performed on a GE HD Excited 1.5 T scanner (GE Medical Systems, America) using a conventional circularly polarized 8 channel head coil. This SWI sequence was theoretically designed to be fully flow-compensated and tested in the case of linear flow to ensure that no phase effects from flow remained^[17].

The typical parameters of the SWI sequence were as follows: TR = 57 ms, TE = 40 ms, FA = 20°, FOV = 40, Nz = 32 slices, slice thickness (TH) = 2 mm, and matrix size (Ny×Nx) = 256×512. The images were zero filled in k-space to a 512×512 data matrix, and then Fourier transformed to create a 512×512 display matrix. A symmetric central Hanning low-pass k-space filter with a size of 64×64 was created and complex-divided into the original phase image. Practically, the background field inhomogeneity from the main magnet and the air/ tissue interfaces in the brain could be removed most efficiently with the 64×64 central filter.

2.4 Basic principles of SWI SWI is often superior and complementary to other methods in its susceptibility to iron deposition. Hemoglobin is a major blood oxygen carrier, and

is composed of 4 protein subunits. Each protein subunit contains a heme molecule that consists of an iron atom (Fe^{2+}) surrounded by a porphyrin ring. Then Fe^{2+} is bound to a porphyrin histidine nitrogen atom. When oxygen is dissociated from the iron atom, producing deoxyhemoglobin, a conformational change occurs to prevent the interaction between adjacent water molecules and the iron atom. The methemoglobin could be visualized the most easily by T1-weighted imaging method. In this state, there are few susceptibility effects. For most configurations, it will create local magnetic fields that vary spatially outside of its inner core, leading to signal dephasing. Irrespective of the diamagnetic or paramagnetic property of the sources, changes in the local magnetic field lead to spatial variations in phase outside the source, and therefore, to the dephasing of the signal and a reduction in $T2^*$ [18]. The amount of dephasing does not depend on whether the material is paramagnetic or diamagnetic, but on the field variations across a voxel.

Phase images could directly measure the magnetic field variations. The information in the phase image was gathered from the following equation: ϕ (phase) = $-\gamma \Delta B \cdot TE$, where γ represents the gyromagnetic ratio for protons (2.678×10^8 rad/s/T) and ΔB is the field difference between blood and the surrounding tissue. TE indicates the echo time. Since iron is a paramagnetic element, ΔB should be positive and the shift in phase will be negative. Within a given TE , the more iron in the tissue, the greater the phase will decrease. The field dependence can be expressed as follows: $\Delta B = c \cdot V \cdot \Delta \chi \cdot B_0$, where c is the concentration of iron, V is the volume of the voxel, and $\Delta \chi$ is the change in molar susceptibility between tissues where iron is present. Therefore, the phase contrast will depend on the iron content.

2.5 The regions of interest (ROIs) selection strategy ROIs selection was based on their different anatomical features. Besides, to avoid the signal heterogeneity-induced bias, the most homogeneous regions were employed. This strategy was adopted for all the selected tissues, including RN, PUT, SN, GM, WM, and CSF (Fig. 1). All the ROIs were 49 pixels.

For SN, one slice with a clear dividing line between the pars compacta (the darker region) and the pars reticulata (the brighter region) was used for analysis. The slice also con-

tained the superior colliculus, the RN and the mammillary bodies. SNc and SNr were then studied in the axial plane of the slice.

The phase values of the ROIs were determined and presented as mean $\pm$ SD. To minimize the partial volume effect, a number of potential errors were also considered[19]. The key to obtain consistent results is that the observer must correctly interpret the structures and draw the same ROIs within the structure. Since 3D images were used, choosing the same ROIs also implied choosing the correct slice.

Although it is not an issue of SWI data processing, the signal-related knowledge in WM, GM, and CSF is important for understanding the different phase values of each tissue relative to the zero phase value. As revealed by these phase-weighted data, CSF had a lower intensity than WM, and WM had a higher intensity than GM, allowing a reasonable separation of different tissue types. SWI original magnitude images were used to determine the signal intensity percentages of WM, GM and CSF, by weighting the percentages of the average signal of each tissue from the SWI magnitude images. The percentage signal contribution for GM, and the sum of WM and CSF were then calculated.

2.6 Statistical analysis Statistical analysis was performed using SPSS 10.0 software. $P < 0.05$ was considered as statistically significant. Group differences between PD and control groups were compared using independent sample student's t -test. Correlational analysis for the PD group was performed using the Pearson product moment technique for the analysis of phase radians and Spearman rank-order correlation coefficient for any analysis using the ordinal UPDRS data.

3 Results

3.1 The difference in phase radians of several cerebral regions between PD and control subjects The mean values of phase radians of GM, WM, CSF, CN, RN, SN, and other anatomical regions were shown in Table 1. SN could be subdivided into 2 parts: SNc and SNr. The phase in SNc was lower than that in SNr in PD groups, indicating a higher iron deposition in this area. Besides, the SNc exhibited severe atrophy, while the rest of the SN had normal phase values for

Fig. 1 A: a susceptibility-weighted image from a PD patient. Arrows indicated the ROIs corresponding to RN, SNc and SNr. B: a corrected phase image of the control group, where ROIs corresponded to CN and PUT. The brain structures, especially those with a high iron concentration, were surrounded by a light rim, which reflects the dipolar nature of the iron-induced paramagnetic susceptibility difference. C: a susceptibility-weighted image of the control group, where ROIs corresponded to PUT and CN. D: a T1-weighted image of the control group. The representative slice showed the areas where phase was measured in the front for GM, WM, and CSF.

iron and appeared to have fused with the RN. Moreover, no significant differences in the phase radians of GM, WM, CSF, PUT and SNr were found between control and PD patients ($P > 0.05$). However, there were significant differences in the phase radians of SNc, CN and RN between control subjects and PD patients ($P < 0.05$).

3.2 The differences in phase radians between PD patients with cognitive dysfunction and control subjects, and between PD patients with cognitive dysfunction and PD patients with-

out cognitive dysfunction The PD group was subdivided into 2 groups, one included 12 patients without cognitive dysfunction, and the other included 30 patients with cognitive dysfunction from mild to moderate degrees. Paired sample *t*-test analysis revealed significantly lower levels of phase radians in SNc, CN and RN in PD patients both with or without cognitive dysfunction than in control subjects ($P < 0.05$), while there was no significant difference between PD patients with cognitive dysfunction and controls in phase radi-

Table 1. The mean values of the phase radians in different cerebral regions (mean±SD)

	Phase Radians (ROI = 49)	Phase Radians (ROI = 49)
	PD	Control
WM	0.103±0.003	0.112±0.002
GM	0.0969±0.001	0.103±0.003
CSF	0.143±0.001	0.152±0.001
PUT	0.0617±0.002	0.0421±0.001
CN	-0.0254±0.002	0.00617±0.001*
RN	-0.0208±0.003	-0.0170±0.002*
SNC	-0.0733±0.001	-0.0134±0.001*
SNr	0.0188±0.002	0.0122±0.001

* $P < 0.05$ vs PD group.

ans in SNr ($P > 0.05$). However, no overall significant differences were detected between the 2 subgroups ($P > 0.1$).

3.3 Correlation between brain iron and motor symptom severity Due to the unilateral onset of Parkinson's disease, the most affected and the least affected sides were identified based on the symptom onset and the UPDRS motor assessment^[4] of the PD patients. The correlations between the motor symptom severity score of the affected sides in PD patients and the phase radians of ROIs in the corresponding contralateral brain hemisphere were analyzed. As shown in Fig. 2A, a positive correlation between UPDRS and SN phase radians in the most affected side in PD patients was observed ($P < 0.05$). However, there was no significant relationship

Table 2. Phase radians in SNC, CN and RN in PD patients and control subjects

	Control subjects (<i>n</i> = 30)	PD patients with cognitive dysfunction (<i>n</i> = 30)	PD patients without cognitive dysfunction (<i>n</i> = 12)
SNC	-0.0134±0.001	-0.0733±0.001*	-0.0752±0.002 [#]
SNr	0.0122±0.001	0.0188±0.002	0.0173±0.001 [#]
CN	0.00617±0.001	-0.0254±0.002*	-0.0261±0.001 [#]
RN	-0.0170±0.002	-0.0208±0.003*	-0.0199±0.002 [#]

* $P < 0.05$ vs control subjects; [#] $P > 0.1$ vs PD patients with cognitive dysfunction. **Fig. 2** Correlations between the SNC phase radians and UPDRS motor symptom score in (A) the most affected side, and (B) the least affected side of the body in patients with PD.

between the motor symptom severity score of the least affected side in PD patients and the contralateral SN phase radians ($P > 0.2$; Fig. 2B).

4 Discussion

The role of iron in PD, which was first proposed by Lhermitte *et al.* in 1924, has been substantiated by a number

of studies in recent years. Both Kosta *et al.*^[4] and Martin *et al.*^[20] have employed the same method of lateralizing the motor assessment scores and detected a higher iron level in the most affected side, and these findings suggest that the quantity of iron within the SN may be directly related to the motor symptom severity.

MRI can be used for *in vivo* estimation of iron levels in different brain regions based on the phase radians. If iron levels are sufficiently high, the phase radians will then be decreased, which is caused by the induced microscopic magnetic fields surrounding the iron deposits^[21].

4.1 Phases in GM, WM and CSF It is presumed that the image contrast between GM and WM is at least partially related to the increased iron content of GM. For example, the contrast difference in filtered phase images of iron-laden tissues is not visible on the corresponding T1 images. Using T2 method, quantifications of iron contents in SN, globus pallidus, PUT, and caudate have been done in PD patients, and the more precise quantification method may better indicate the disease onset or progression^[22]. Generally, we have found that the presence of iron in the brain enhances the SWI contrast among these tissues. Specifically, the iron in the tissue correlates directly with the phase in the SWI images^[5]. Since the phase is proportional to the local field, the difference in phase between CSF and GM, for example, should be proportional to the difference in susceptibility between the tissues. Based on this relationship, the phase difference is then correlated with the putative iron content in the brain^[15].

In the present study, values of phase radians in 3 different tissue types in the motor cortex, including WM, GM and CSF, were analyzed. For ROIs with 49 pixels, there was a significant difference in phase values among the 3 tissues. Besides, there was an overlap in the phase values between WM and CSF. CSF contains a negligible amount of MR-visible iron^[5], thus it was used as a reference since it is assumed that CSF does not contain iron. Although the iron content in CSF is assumed to be zero, its phase does not appear as zero. This is because the MR spectrometer chooses the central frequency from CSF with the greatest signal, which in this case comes from WM. The estimates of signal contribution validate this understanding. Therefore, for this more

limited volume, it is not surprising to find the zero point of the phase corresponding to the central frequency of the MR experiment.

4.2 Phase distribution in selected ROIs The phase was successfully mapped out in a variety of structures in the brain. As revealed by the resulting histograms, the phase distribution in each evaluated area was similar as the Gaussian-like distribution, making the calculation of standardized difference (SD) a reasonable way to estimate what lies inside and outside the normal phase variation for a broad class of individuals. These results make it possible to detect abnormal iron content in tissues by measuring the phase, and the iron content may be important in tissues and in many neurodegenerative diseases.

Phase difference between tissues is very common in that it does not depend on T1, T2, or even the phase of the radio frequency itself. This means that phase is a robust way to measure iron effects from system to system. The finding that the prevalence of increased SNc echogenicity is the same in all age groups^[23] leads to the hypothesis that SNc hyperechogenicity is a primary rather than a secondary phenomenon. This obvious heritability suggests the possible involvement of genes in brain iron metabolism in the development of some forms of PD. Although neurodegeneration inevitably develops in PD, there was no change in phase radians of SNc during disease progression. Here we demonstrate that SNc hyperechogenicity occurs in most PD patients and in people with subclinical impairment of the nigrostriatal system which is associated with increased iron level in SNc.

Impaired areas such as the SN in PD, associated with neuronal loss, are likely to contain increased content of tissue water, which potentially reduces the effect of iron. The most accurate quantification of brain iron is to measure the phase changes caused by local susceptibility (such as iron deposits) alone^[5]. Postmortem MR studies of brain iron in PD have revealed increased iron content in SN^[6]. Our results have also shown a significant increase in brain iron in SNc of PD patients than that of the control subjects.

In the present study, the high-field MRI was employed to examine the iron deposition in a group of 42 patients with

PD, to determine the relationship between cognitive dysfunction and brain iron within SNc. A higher level of iron, as estimated by phase radians, was detected in SNc in PD group, as compared to the healthy controls. Besides, the iron levels did not differ across the cross-section in SN. Moreover, the subgroup analysis indicates that PD subjects both with and without cognitive dysfunction exhibit increased phase radians in the SNc, PUT and RN, when compared to their age-matched controls (Table 2). This suggests that ferritin iron level increases in most of the subcortical structures in PD subjects with and without cognitive dysfunction, when compared to that in the controls. Indeed, according to the currently accepted functional neuroanatomy of SNc, there occurs increased activity of the GABAergic pathway in PD^[24]. The topographical localization of endogenous iron in the brain overlaps with the striato-pallido-nigral GABAergic pathways^[25].

Contrast to the findings in SN, previous studies of iron level in PUT in PD have come to different results. A study of brain iron in postmortem PD tissues using atom spectrophotometry showed a trend of iron increase in PD putamina^[26]. It should be noticed that the tissue used in that study came from unselected parts of PUT, that is, there was no control for a potential rostral/caudal gradient. The findings suggest that iron levels will vary according to the selected regions of PUT, and this may help explain some of the inconsistency in comparison between PD and control subjects^[27].

4.3 Correlation between brain iron and motor symptom severity The studies in PD patients showed increased SN phase radians bilaterally. However, a significant association between SN phase radians and UPDRS motor symptom severity was detected only in the most affected side in PD patients. This suggests that the level of brain iron within SN is related to the severity of PD motor symptoms in the side with the most prominent pathology.

The association between SN iron content and UPDRS symptom severity in PD is consistent with previous reports concerning the relation between motor disability and brain iron level^[28]. In a cross-sectional study, Martin *et al.*^[20] have found increased SN iron content in early PD that was correlated with UPDRS symptom severity on the most affected

side. The relationship between brain iron and motor symptom progression in PD is complex due to the differences in time course and symptoms among PD patients. The finding that higher SN iron levels are associated with greater motor symptom severity raises the possibility that early MR scan at the onset may be predictive for motor symptom progression. Neither Martin *et al.*^[20] nor the present study could provide direct information concerning PD progression. To make iron as a prognostic biomarker, MRI following diagnosis needs to be coupled longitudinally with a series of independent markers of disease progression and with MR brain iron imaging.

Further longitudinal investigations are required to determine whether assessment of SN iron level with MRI at an early clinical stage can predict the rate of progression of motor symptoms.

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磁敏感成像检测帕金森氏病脑铁沉积

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摘要: 目的 比较帕金森氏病(Parkinson's disease, PD)患者和健康对照者多个脑结构的相位偏移值(phase radians), 探讨相位偏移值的临床应用价值。方法 42名PD患者及30名年龄匹配的健康对照者均在1.5 T MR系统中进行头部检查。所有PD患者均存在轻度到中度认知功能缺损。采用磁敏感成像获得相位图, 测量双侧尾状核、壳核、黑质致密带、黑质网状带、红核、脑脊液、额叶白质及额叶灰质内所感兴趣区的相位偏移值。结果 与正常对照组相比, PD组黑质致密带的相位偏移值均数显著缩短($P < 0.05$)。此外, PD组双侧尾状核和红核的相位偏移值亦显著降低($P < 0.05$), 而黑质网状带的相位偏移值与对照组相比无统计学差异($P > 0.05$)。结论 通过对相位偏移值的测定可以估测PD患者脑内的铁沉积, 为PD的活体诊断及病情监测提供帮助。

关键词: 帕金森氏病; 相位偏移值; 磁敏感成像; 铁沉积