Brain iron deposition in Parkinson’s disease imaged using the PRIME magnetic resonance sequence

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Summary
Iron content of the basal ganglia was investigated in 25 patients with idiopathic Parkinson’s disease and 14 matched healthy control subjects using a partially refocused interleaved multiple echo sequence on a 1.5 Tesla MRI system. R2* (1/T2*) and R2'/H1 relaxation rates were higher in the substantia nigra of patients with Parkinson’s disease, which indicates that iron content is elevated in this region. R2’ was lower in the putamen, indicating reduced iron levels; reduction in this region was positively correlated with disease duration. Iron-related oxidative stress may contribute to the neurodegeneration of Parkinson’s disease, which may lead to alterations in the iron levels of the striatum. We describe a simple, non-invasive technique for measuring iron content.

Keywords: brain iron; idiopathic Parkinson’s disease; PRIME MRI sequence

Introduction
Iron promotes important metabolic processes in the brain (Wrigglesworth and Baum, 1988). However, it is also associated with the production of damaging free-radicals, which may lead to neurodegeneration via lipid peroxidation. Brain iron is stored in the protein ferritin (Hallgren and Sourander, 1958; Griffiths et al., 1999), which is present at a high concentration within some of the subcortical nuclei, specifically the globus pallidus, substantia nigra and red nucleus (Hallgren and Sourander, 1958; Hill and Switzer, 1984; Riederer et al., 1989). Additional iron accumulation, in the form of stable free radicals, has also been detected in the dopaminergic neurones of the substantia nigra in association with the pigment neuromelanin (Jellinger et al., 1992; Zecca et al., 1996; Shima et al., 1997).

The primary pathology of idiopathic Parkinson’s disease is degeneration of the substantia nigra pars compacta. This leads to a reduction in striatal dopamine, which results in the cardinal symptoms of bradykinesia, tremor and rigidity. Increased iron content is consistently reported post-mortem in the substantia nigra of patients with Parkinson’s disease (Dexter et al., 1987, 1991; Sofic et al., 1988; Riederer et al., 1989). This suggests that iron-related oxidative stress may be an important component of the neurodegenerative process in such patients (Sofic et al., 1988; Riederer et al., 1989; Griffiths and Crossman, 1993; Dexter et al., 1994; Loeffler et al., 1995; Griffiths et al., 1999).

It is possible to evaluate brain iron deposition in vivo using high-field strength spin-echo T2-weighted MRI (Drayer et al., 1986). T2 relaxation time is shortened in approximate proportion to regional iron content (Drayer et al., 1986; Bartzokis et al., 1993) and appears as signal hypointensity in T2-weighted MRI. Signal reduction is due to additional proton spin dephasing from iron-induced local field inhomogeneities. This additional dephasing is detected because radiofrequency refocusing cannot compensate for it. However, previous studies, which have used this methodology to examine iron deposition in patients with Parkinson’s disease, have been inconsistent with the findings compared with post-mortem investigations. This suggests that improved MRI techniques may be useful for assessing brain iron deposition with greater accuracy.

Our study was designed to address the inconsistency of the post-mortem and MRI studies reported in the literature.
by imaging iron deposition in the basal ganglia in patients with Parkinson’s disease and matched healthy control subjects, using a partially refocused interleaved multiple echo (PRIME) MRI sequence. This sequence yields both \(T_2^*\) and \(T_2\) information directly, from which \(T_2'\), a pure measure of local field inhomogeneity due to tissue iron content, can be obtained (Miskiel et al., 1997).

**Methods**

**Subjects**

In accordance with the declaration of Helsinki, all subjects gave informed consent to participate in the study, which was approved by the South Sheffield Research Ethics Committee. No subject had a history of head injury, stroke, or had any concurrent neurological condition other than idiopathic Parkinson’s disease. All subjects scored within the normal range on the neuropsychological tests detailed below.

**Patients**

Twenty-five patients diagnosed with Parkinson’s disease according to the Parkinson’s Disease Society Brain Research Centre clinical criteria (Daniel and Lees, 1993) were recruited from the Royal Hallamshire Hospital specialist movement disorders clinic. A consultant neurologist (R.A.G.) reviewed the clinical history of each patient and those with an atypical disease course were not included in the study. At disease onset they ranged in age from 24 to 62 years (mean 50.2 years, SD 9.5 years) and had a current disease duration which ranged from 3 to 21 years (mean 11.1 years, SD 4.5 years). All patients were taking levodopa; three patients had monotherapy, 21 had adjunct therapy with direct acting dopamine agonists, and one had adjunct therapy with a catechol-O-methyltransferase inhibitor.

**Healthy control subjects**

Fourteen healthy control subjects were recruited from the University of Sheffield, Section of Clinical Neurology volunteer database or were spouses of patients with Parkinson’s disease. They were selected to match the patient sample in gender and age.

**Neuropsychological assessment**

All subjects completed the following neuropsychological tests: (i) New Adult Reading Test (Nelson and O’Connell, 1978), a measure of pre-morbid IQ. (ii) Mini-Mental State Examination (Folstein et al., 1975), a measure of global cognitive performance with a validated cut-off score for the presence of clinical dementia. (iii) Wisconsin Card Sorting Test (Nelson, 1976), an assessment of executive function, which is often impaired in patients with Parkinson’s disease (Lees and Smith, 1983; Cools et al., 1984). (iv) Beck Depression Inventory (Beck et al., 1961), a measure of depression with a validated cut-off score for clinical relevance.

**Movement assessment**

The patients with Parkinson’s disease completed the following movement assessments when ‘on’ and ‘off’. The ‘on’ state was defined as ‘when you are at your best during the day’ and was determined by each individual patient. The ‘off’ assessment was completed first thing in the morning before any dopaminergic medication was taken. J.M.G. carried out all assessments, which were as follows: (i) Unified Parkinson’s Disease Rating Scale (Fahn et al., 1987). Both the motor, and activities of daily living sections of this instrument were completed. (ii) Alternate finger tapping. This is an assessment of bradykinesia. The subject was asked to alternately tap two keys on a keyboard as fast as possible. Two fingers of one hand were used, one finger allocated to each key, and the number of alternate taps was counted for a period of 30 s.

**Magnetic resonance imaging**

MRI was performed on a 1.5 Tesla system (Eclipse, Marconi Medical Systems, OH, USA) with 27 mT/m gradients and 72 mT/m/ms slew rate. All images were acquired with a cylindrical receive-only head coil with the patient packed using foam pads to reduce involuntary head movement. This was especially necessary in cases where patients with Parkinson’s disease had mild dyskinesia or tremor in this part of their body. All sequences were within FDA guidelines for radiofrequency-specific absorption rate and rate of field change \(dB/dt\), where \(B\) is magnetic flux density. Disposable ear protectors were used to reduce acoustic noise by \(\sim 30\) dBA.

A dual-echo, fast spin-echo sequence acquired 60 contiguous slices through the whole brain in the axial plane \([\text{TR (repetition time)} = 8040\, \text{ms}, \text{TE (echo time)} = 15\, \text{and} 75\, \text{ms}, \text{field-of-view (FOV)} = 230\, \text{mm}, \text{acquisition matrix} = 256 \times 256, \text{slice thickness} = 2.5\, \text{mm}]\).

The PRIME sequence comprised one spin-echo and five gradient-recalled echoes acquired for each 180° radiofrequency pulse. The two radiofrequency spin-echoes were refocused at echo times of 20 and 160 ms. The gradient echoes were refocused at 31, 42, 53, 64 and 75 ms for the first radiofrequency pulse and at 171, 182, 193, 204 and 215 ms for the second pulse. Each readout had a bandwidth of 20.83 kHz. The TR value was 3000 ms, acquisition matrix \(256 \times 256\), and a 230 mm FOV was used. Slice thickness was 2.5 mm and a total of 11 slices were acquired with no interslice gap. Images were acquired in the axial plane. Figure 1 illustrates the images associated with each of the first seven echoes of the PRIME sequence.

**Analysis**

**Qualitative analysis of MRI**

Using the dual-echo, fast spin-echo images, a neuroradiologist (N.H.) documented whether atrophy, beyond that expected
through normal ageing, was present in each of the four lobes of the brain. The structures of and related to the basal ganglia, including the caudate nucleus, the putamen, the globus pallidus, the substantia nigra and the thalamus, were also rated in the same manner for the right and left sides of the brain. This method of rating was used in preference to quantitative volumetric analysis because accurate volume estimates from the smallest structures, especially the substantia nigra, would have been very difficult to obtain; particularly in view of the motion artefact expected on the scans obtained from the patients.

**Quantitative analysis of MRI**

Quantitative analysis was performed using the software ANALYZE™ version 7.0 (Biodynamic Research Unit, Mayo Foundation, Rochester, Minn., USA) on a SPARC computer (Sun Microsystems Inc., Mountain View, Calif., USA). A region of interest (ROI) 5 × 5 pixels in size was placed within the head of the caudate nucleus, the putamen, the globus pallidus and, as a region of comparison, the frontal white matter. A rectangular 4 × 7 pixel ROI was placed within the substantia nigra. Figure 2 illustrates the typical positioning of each ROI, which were defined by a single rater (J.M.G.). The greyscale values of each ROI in the first seven echoes of the slice of interest were recorded. The relaxation rate $R_{2}^{*}$ ($1/T_{2}^{*}$) was calculated from the natural logarithmic fit to the greyscale values of the first six echoes from the first 180° radiofrequency pulse. $R_2$ ($1/T_2$) was calculated from a natural logarithmic fit of the intensities of the two spin-echoes and $R_{2}'$ ($1/T_2'$) was calculated using the formula: $R_2' = R_{2}^{*} - R_2$.

**Statistical analysis**

Patients with Parkinson’s disease were compared with healthy controls using a series of independent sample $t$-tests. Where appropriate, the Bonferroni correction for multiple comparisons was applied to the results. Correlational analysis was performed using the Pearson product-moment technique and, where appropriate, the Larzelere and Mulaik test for multiple comparisons was applied. The reproducibility of the results was examined using intraclass correlation, which considers variability within the rater over time, as well as between the individual subjects.

**Results**

**Qualitative analysis of MRI scans**

Of the 25 patients with Parkinson’s disease, two were discarded because of excessive movement artefact. A further
Table 1 Group characteristics (standard deviation) of the patients with Parkinson’s disease and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Parkinson’s disease patients n = 21</th>
<th>Healthy control subjects n = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.4 (7.3)</td>
<td>64.0 (6.6)</td>
</tr>
<tr>
<td>Gender</td>
<td>0.52 male</td>
<td>0.54 male</td>
</tr>
<tr>
<td>Pre-morbid IQ</td>
<td>111 (8.5)</td>
<td>115 (8.6)</td>
</tr>
<tr>
<td>Mini mental*</td>
<td>28.1 (2.0)</td>
<td>29.4 (1.0)</td>
</tr>
<tr>
<td>Wisconsin card sorting*</td>
<td>3.3 (2.5)</td>
<td>4.5 (1.7)</td>
</tr>
<tr>
<td>Beck depression*</td>
<td>11.7 (6.5)</td>
<td>5.5 (6.7)</td>
</tr>
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</table>

*P < 0.05.

two patients and one healthy control subject were also excluded because of unexpected ischaemic changes. Focal lesions were detected within structures of the basal ganglia in a number of subjects and we therefore excluded them from the analysis of that ROI only (see Table 2 for the number of subjects associated with each comparison).

Group characteristics
Table 1 illustrates that patients with Parkinson’s disease were matched to healthy controls with respect to gender, age and IQ. Patients were more cognitively impaired and depressed than controls (mini-mental: \( t = 2.56, P < 0.05 \); Beck depression inventory: \( t = 2.65, P = 0.012 \)) but neither score reached the cut-off value, indicating that the group differences were not of clinical relevance.

Quantitative analysis of PRIME data
Patients with Parkinson’s disease versus healthy control subjects
For each subject, and in each ROI, the \( R_2 \), \( R_2^* \) and \( R_2' \) values were averaged over the right and left sides of the brain. Mean values for the ROI were compared between the patient group and the healthy controls (Table 2). The \( R_2^* \) and \( R_2' \) relaxation rates were significantly higher in the substantia nigra of patients with Parkinson’s disease than in the matched healthy control subjects (\( R_2^*: t = 2.07, P = 0.047; R_2': t = 2.11, P = 0.043 \)). In contrast, the \( R_2' \) relaxation rate in the putamen was significantly lower in the patient sample (\( t = 2.07, P = 0.047 \)). A similar trend was also present in \( R_2' \) relaxation rate of the globus pallidus (\( t = 2.02, P = 0.052 \)).

Figure 3 suggests that \( R_2' \) in the putamen is related to the duration of Parkinson’s disease. Linear regression confirmed this association (\( r = 0.55, P = 0.01 \)), which was independent of age, duration of medication, severity of motor impairment and cognitive performance.

Correlation with severity of Parkinson’s disease
After correction for multiple comparisons, there was no correlation between \( R_2 \), \( R_2^* \) and \( R_2' \) relaxation rates from...
the side of the brain associated with onset of pathology or any measure of motor disability when ‘off’ (Table 3).

**Correlation with published post-mortem iron values**
The R$_2$' relaxation rate values from the nuclei of the basal ganglia were highly correlated with published post-mortem iron concentration values for both the healthy control subjects ($r = 0.99, P = 0.009$) (Hallgren and Sourander, 1958) and the Parkinson’s disease patients ($r = 0.96, P = 0.037$) (Griffiths et al., 1993).

**Intrarater reliability**
Each ROI was redefined by the same rater (J.M.G.) on 12 unselected scans to assess the reproducibility of the results. Table 4 shows the intraclass correlation in each ROI for the R$_2^*$ values. The mean intraclass correlation was 0.78, which is an acceptable level of reproducibility (Howell, 1997).

**Discussion**
Previous studies have examined iron deposition in the basal ganglia of patients with Parkinson’s disease using T$_2$-weighted MRI. In accordance with published post-mor tem findings, T$_2$ relaxation time is decreased in the substantia nigra compared with age-matched healthy control subjects (Antonini et al., 1993; Gorell et al., 1995; Ryvlin et al., 1995; Bartzokis et al., 1999; Vymazal et al., 1999), suggesting increased iron content in this region. However, T$_2$ relaxation time is also decreased in the putamen (Antonini et al., 1993; Chen et al., 1993; Ye et al., 1996; Bartzokis et al., 1999) and the globus pallidus (Ye et al., 1996; Bartzokis et al., 1999), regions that do not show alteration in iron content in autopsy investigations. Inaccuracy in the MRI studies may be responsible for these inconsistent findings.

Lewy body inclusions in the substantia nigra pars compacta at autopsy confirm the clinical diagnosis of Parkinson’s disease. When the Parkinson’s Disease Society criteria are used to identify patients with Parkinson’s disease (Daniel and Lees, 1993), there is an 18% false positive inclusion of conditions which clinically mimic Parkinson’s disease, such as multiple system atrophy and progressive supranuclear palsy (Hughes et al., 1992). Specifically, this may explain the finding of decreased T$_2$ relaxation time in the putamen in many previous Parkinson’s disease studies, since increased iron deposition has been reported in this region in patients with multiple system atrophy (Stern et al., 1989; Dexter et al., 1991; Schwarz et al., 1996; Martin et al., 1998; Vymazal et al., 1999).

In our investigation, we attempted to minimize sources of incidental errors by: (i) matching the patient and control samples for gender, age and IQ; (ii) excluding subjects with clinical depression or dementia; (iii) rigorously applying the Parkinson’s Disease Society criteria for idiopathic Parkinson’s disease (Daniel and Lees, 1993) in patient selection; (iv) a consultant neurologist (R.A.G.) reviewing the clinical history of each patient, leading to exclusion of those with atypical features; (v) a neuroradiologist (N.H.) reviewing the MRI scans, leading to elimination of any subjects with abnormally high levels of ischaemic changes, lesions within the basal ganglia or uninterpretable scans due to motion artefact.

Alteration of signal intensity in spin-echo T$_2$-weighted MRI sequences reflects global field inhomogeneities, which arise from the differing magnetic susceptibility of tissue interfaces, in addition to the local iron-induced field inhomogeneities of interest (Ordidge et al., 1994). When

![Fig. 3 R$_2$' relaxation rate in the putamen and disease duration in patients with Parkinson’s disease.](image-url)
using such sequences, a reduction in the T₂ relaxation rate may be observed in regions where iron content is not increased (Brooks et al., 1989). Bartzokis et al. attempted to overcome this limitation by employing a dual scanning technique at low- (0.5 T) and high- (1.5 T) field strength (Bartzokis et al., 1993). T₂ relaxation time is insensitive to iron content at low field strength, therefore the increase in relaxation rate between the two scans is an index of iron deposition. The disadvantage of this method is that interscan patient movement may obscure the results, especially in small regions of interest such as the substantia nigra. The approach taken by Ordidge et al. was to utilize a gradient-recalled echo MRI sequence rather than a standard spin-echo sequence (Ordidge et al., 1994). Gradient-echo images are governed by T₂* effects that reflect iron deposition more accurately because the radiofrequency pulse is not refocused. The sequence yields T₂* information and T₂ can be calculated from a mathematical model. The difference between these values reflects the changes due solely to iron-induced local field inhomogeneity. This parameter is called T₂*. Using this sequence in a 3T MRI system, Gorell et al. suggest that iron levels in the substantia nigra are elevated in direct proportion to the clinical severity of Parkinson’s disease (Gorell et al., 1995). No other structures in the basal ganglia were considered. Miszkiel et al. adapted the technique of Gorell et al. for use on a 1.5 T MRI system producing a partially refocused interleaved multiple echo sequence, yielding both T₂* and T₂ information directly, for the assessment of brain iron deposition (Gorell et al., 1995; Miszkiel et al., 1997).

It is known that iron is present in different concentrations in the specific nuclei of the basal ganglia (Hallgren and Sourander, 1958). The PRIME sequence yields R₂* values from healthy control subjects that are consistent with this ordering and which are highly correlated with published post-mortem iron concentrations. We can therefore be confident that the PRIME sequence produces a specific measure of brain iron deposition.

In accordance with previous post-mortem and MRI findings (Dexter et al., 1987; Sofic et al., 1988; Riederer et al., 1989; Antonini et al., 1993; Griffiths and Crossman, 1993; Gorell et al., 1995; Ryvlin et al., 1995; Bartzokis et al., 1999), our results show that iron deposition is increased in the substantia nigra of patients with Parkinson’s disease compared with matched healthy control subjects. The anatomical location of our ROI, as shown in Fig. 2C, favours the area of signal hypointensity lying ventral to the dark region of the red nucleus. This area has been defined as the substantia nigra.

### Table 3: The association of R₂, R₂* and R₂'/H₁₁₀₃₂ with the clinical severity of Parkinson’s disease

<table>
<thead>
<tr>
<th>ROI</th>
<th>Caudate</th>
<th>Putamen</th>
<th>Globus pallidus</th>
<th>Substantia nigra</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS motor</td>
<td>0.07</td>
<td>0.10</td>
<td>−0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>UPDRS daily activities</td>
<td>0.37</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>Alternate finger tapping</td>
<td>0.09</td>
<td>0.29</td>
<td>0.47</td>
<td>0.47</td>
</tr>
<tr>
<td>T₂</td>
<td>0.60</td>
<td>0.88</td>
<td>0.92</td>
<td>0.93</td>
</tr>
<tr>
<td>T₂*</td>
<td>0.60</td>
<td>0.88</td>
<td>0.92</td>
<td>0.93</td>
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### Table 4: Intraclass correlation of R₂* values

<table>
<thead>
<tr>
<th>ROI</th>
<th>Intraclass correlation</th>
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<tbody>
<tr>
<td>Caudate</td>
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<tr>
<td>Globus pallidus</td>
<td>0.92</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>0.93</td>
</tr>
<tr>
<td>Frontal white matter</td>
<td>0.58</td>
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pars reticulata by some authors, with the region of signal hyperintensity between this and the red nucleus labelled the substantia nigra pars compacta (Duguid et al., 1986; Ryvlin et al., 1995; Bartzokis et al., 1999). The two regions of the substantia nigra have been examined separately with MRI in previous studies but the findings are conflicting. Ryvlin et al. show increased T2 relaxation time solely in the pars compacta for patients with Parkinson’s disease (Ryvlin et al., 1995). However, Bartzokis et al. describe greater field-dependent R2 increase in both the pars compacta and pars reticulata of early-onset patients, but reduced field-dependent R2 increase in the pars reticulata of late-onset patients (Bartzokis et al., 1999). The anatomical boundaries separating these regions are poorly defined on MRI scans taken from patients with Parkinson’s disease, as the area of signal hyperintensity narrows with continued neurodegeneration (Duguid et al., 1986; Stern et al., 1989). This effect is illustrated in Fig. 4 and may account for the divergent findings cited above. It is generally agreed that the location of our substantia nigra ROI reflects the most valid comparison region between patients and healthy control subjects when using MRI (Antonini et al., 1993; Gorell et al., 1995).

In contrast to the increased iron content of the substantia nigra, our results suggest that iron deposition is reduced in the putamen of patients with Parkinson’s disease compared with matched control subjects. Such a finding has never been reported in studies that have examined the iron content of Parkinson’s disease brain tissue (Sofic et al., 1988; Riederer et al., 1989; Griffiths and Crossman, 1993), and many MRI studies actually report increased iron deposition in this area (Antonini et al., 1993; Ye et al., 1996; Bartzokis et al., 1999). However, our results are consistent with a recent investigation by Ryvlin et al., which found that the T2 relaxation time was increased in the putamen of patients with Parkinson’s disease of duration >10 years (Ryvlin et al., 1995). Disease duration may be pertinent to this finding since the previous conflicting studies used patient samples with mean disease duration up to 8 years. Figure 3, which illustrates the correlation between decreasing putaminal iron content and disease duration, also corresponds with the findings of Ryvlin et al. (1995) and provides further evidence for the importance of Parkinson’s disease duration.

Despite the role of disease duration, the severity of motor disability in the ‘off’ state was not associated with the alterations in iron deposition in the putamen or in the substantia nigra of our patients. The ‘off’ motor assessment was used for this analysis because when ‘on’, dopaminergic agents disguise the true extent of disease severity. Few studies have attempted to examine such an association and of those that do, only that of Gorell et al. used the ‘off’ state (Gorell et al., 1995); these authors found that iron content in the substantia nigra was related to disease severity. These conflicting results cannot readily be explained and further studies must be carried out for clarification.

The lower R2 relaxation rate in the globus pallidus of patients with Parkinson’s disease reflects intrinsic tissue differences, which are not relevant to our study of iron deposition. We can be confident that iron content is not altered in this region since the R2’ value does not differ between patients and controls.

The major findings of this MRI study are increased iron in the substantia nigra and reduced iron in the putamen of patients with Parkinson’s disease. Elevated brain iron is thought to be associated with cell damage through oxidative stress mechanisms (Wrigglesworth and Baum, 1988). However, since iron levels in the substantia nigra were found to be normal in pre-clinical cases (Dexter et al., 1994), such mechanisms are likely to contribute to the pathology of Parkinson’s disease, rather than being of direct aetiological relevance. We are uncertain of the implications of reduced iron levels in the putamen and recognize that further studies are required to corroborate our findings.

It is, however, interesting to speculate about a possible common factor between the increased nigral and reduced putamenal iron, based on other recent circumstantial evidence. It is generally accepted from rodent work that most iron enters the brain via transferrin (Swaiman and Machen, 1986), when blood levels of transferrin are normal. The putamen is a high-density region of transferrin binding sites and there is some evidence that the number of these binding sites is increased in Parkinson’s disease (Faucheux et al., 1995). However, the putamen is a region of low iron content. This mismatch between transferrin binding-site density and regions of high iron concentration has led two groups to propose that

**Fig. 4** Left: substantia nigra and red nucleus in a healthy control subject. Right: narrowing of the band of hyperintensity between the substantia nigra pars reticulata and the red nucleus in a patient with Parkinson’s disease.
iron is transported neuronally, particularly within GABAergic (Hill et al., 1985) or dopaminergic (Faucheux et al., 1995) neurones. The combination of elevated levels of transferrin binding sites in the putamen and increased iron deposition in the substantia nigra of patients with Parkinson’s disease is consistent with the idea of iron entering the putamen and being transported to the nigra by dopaminergic neurones. It is not known in what form the iron is transported. Ferritin seems an unlikely candidate, but the presence of high levels of neuromelanin in the nigrostriatal dopaminergic projection (Good et al., 1992; Jellinger et al., 1992; Zecca et al., 1996; Shima et al., 1997) means that this should be considered a possibility.

Once in the substantia nigra, the fate of the excess iron reported in patients with Parkinson’s disease is unknown. Our present study, and recent related studies (Griffiths et al., 1999), have not been able to localize iron to a particular cell type (neuronal or glial) or even to a precise anatomical region (substantia nigra pars compacta or pars reticulata). In contrast, rodent studies suggest that iron is stored in the oligodendrocytes (Hill and Switzer, 1984). If this were also the case in the human brain, our proposed mechanism would need to account for iron transfer from neurone to glia within the substantia nigra. One possible explanation is that the glia act as a scavenger system to mop up the iron released from degenerating dopaminergic neurones, both during normal ageing and, in an exaggerated fashion, in Parkinson’s disease. Loss of the nigrostriatal projection fibres through cell death would also result in a corresponding reduction in putaminal iron content, as observed in our study.

We concede that this mechanism is speculative. However, the mechanism is testable by studying both the levels of pre-synaptic dopaminergic terminals in the putamen, and by measuring putaminal iron content. Radionuclide methods are already available for measuring pre-synaptic dopaminergic receptor density (Kuikka et al., 1995; Wilson et al., 1996) and the methodology presented in the current paper provides a reliable and robust method of measuring brain iron deposition using a standard MRI system.

Conclusions
PRIME is a useful tool for assessing brain iron deposition in the basal ganglia of patients with Parkinson’s disease. In response to the inconsistent post-mortem and MRI findings published in the literature, we confirm that iron content is elevated only in the substantia nigra of such patients. Iron levels progressively decrease in the putamen with increasing disease duration, which suggests that transportation is occurring. Future studies should address this latter finding by investigating Parkinson’s disease samples of disease duration >10 years.

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References
PRIME imaging of brain iron in Parkinson’s disease


