



REVIEW

Region-Specific Iron Measured by MRI as a Biomarker for Parkinson's Disease

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Abstract The identification of sensitive and specific biomarkers for Parkinson's disease (PD) poses an important clinical challenge. A potential biomarker for early diagnosis and disease monitoring of PD is region-specific iron. Iron accumulation in the substantia nigra pars compacta is considered a main characteristic of PD. However, questions remain, such as the relationship between nigral iron and clinical indices of PD (motor impairment or disease duration). Further, previous studies have suggested the influence of iron on other nuclei. Iron quantification using magnetic resonance imaging (MRI) allows for studies of the relationship between regional iron and clinical symptoms *in vivo*. Thus, in this review we discuss the following topics: the technological development of MRI in measuring brain iron, nigral iron as a potential marker for PD in both clinical and prodromal stages, other influences of regional iron on PD, and clinical translation and future perspectives.

Keywords Iron · Biomarker · Parkinson's disease · Magnetic resonance imaging

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases and has heterogeneous clinical symptoms [1, 2]. The clinical diagnosis of PD lacking

objective evidence mainly depends on the occurrence of motor impairments, such as akinesia, rigidity, and resting tremor [2, 3]. Significant motor symptoms generally emerge only after 50%–70% of the dopaminergic neurons in the substantia nigra pars compacta (SNc) are irreversibly lost [4, 5], which indicates a pathologically advanced stage [6, 7]. In clinical practice, there are no sensitive and specific biomarkers for PD. Therefore, the rate of misdiagnosis is high, ranging from 12% to 74%, and the rates are markedly higher in patients with a shorter disease duration or without a clear response to dopaminergic medication [8]. Previous studies indicate little improvement in the diagnostic accuracy of PD over the past 20 years [8, 9], indicating an urgent need for a clinical biomarker to aid diagnosis.

Iron plays an essential role in physiological function during normal aging, including oxygen transport, DNA synthesis and repair, mitochondrial respiration, myelin synthesis, neurotransmitter synthesis and metabolism [10]. Dysfunction of iron homeostasis can contribute to the generation of free radicals, leading to the oxidation of proteins, lipids, lipoproteins, and other cellular components, which can result in neuronal death [10–12]. Pathological iron accumulation in the nigra has been reported in PD by previous histochemical studies [13–15]. A recent study also indicated that iron loading contributes to increasing the level of alpha-synuclein (the core pathology of PD) [16]. Therefore, nigral iron might be a potential marker for PD. However, these studies did not provide *in vivo* clinical verification or investigate the interaction between nigral iron and clinical symptoms.

To prompt clinical investigation, magnetic resonance imaging (MRI) has been developed to evaluate brain iron content *in vivo* and, with decades of progress, has reached a milestone in quantifying iron content. In this review, we discuss the technological development of MRI in assessing

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brain iron, nigral iron as a potential marker for PD in both clinical and prodromal stages, other influences of regional iron on PD symptoms, and clinical translation and future perspectives.

Technological Development of MRI in Measuring Brain Iron

Brain iron is mainly stored in the form of ferritin, which is reserved for the needs of the brain [17, 18]. In MRI, brain iron not only changes the relaxation behavior of tissue water surrounding ferritin, but also introduces susceptibility changes and microscopic field gradients. Iron levels *in vivo* have an effect on signal intensity, causing signal changes in T2 and T2* [19] and in phase values [20], enabling quantitative MRI iron mapping. However, these methods have limitations. First, both T2 ($R2 = 1/T2$) and T2* ($R2^* = 1/T2^*$) values are greatly influenced by the water content of diseased tissues, such as degenerating nuclei in PD. Second, the field-dependent R2 increase (FDRI) [21, 22], a difference in measures of brain R2 obtained with increasing magnetic field strength, is time-consuming and clinically challenging. Third, phase imaging is not easily reproducible because the signal phase is nonlocal and orientation-dependent [23, 24]. Recently, quantitative susceptibility mapping (QSM) gave rise to a major evolution in the quantification of iron content by converting phase shift to a localized magnetic susceptibility [23, 25, 26]. In past decades, field-dependent methods [21, 22], T2* mapping [19], T2' mapping ($R2' = 1/T2' = R2^* - R2$) [27, 28], phase imaging [29, 30] and QSM [31–33] for detecting iron content in healthy controls have been highly consistent with postmortem results. Therefore, MR iron mapping has promising potential for quantifying brain iron *in vivo* and for investigating the underlying pathological alterations in PD.

Nigral Iron as a Potential Biomarker for PD (Clinical and Prodromal)

Iron-related oxidative damage in the SNc is a common explanation for the loss of dopaminergic neurons in PD. The nigral degeneration leads to the depletion of dopamine in the striatum, which is assumed to be correlated with disease severity. In efforts to obtain a relevant biomarker for clinical-stage PD patients, extensive MRI studies have been performed to investigate the nigral iron changes in PD and their correlation with disease severity. A majority of studies using MRI techniques [34–65] (Table 1) support the accumulation of nigral iron in PD, which agrees with the previous histochemical findings. More interestingly,

many of the studies have also reported a significant correlation between nigral iron measured by MRI and part III of the Unified Parkinson's Disease Rating Scale (UPDRS III score, motor impairment) or Hoehn–Yahr stages (clinical disease stage) [36, 40–42, 49, 50, 53–60]. Moreover, it has also been reported that nigral iron accumulation has a good discriminative capacity for distinguishing PD patients from controls [63, 64]. Therefore, the quantification of nigral iron content by MRI is a promising biomarker for PD.

Concerning its use as a biomarker, it is crucial to understand whether nigral iron content increases or remains stable throughout the duration of disease. However, published studies have reported conflicting findings [35, 41, 49, 50, 52, 54, 60, 61, 64, 65]. Except for a few studies reporting a positive correlation between nigral iron content and disease duration [50, 52, 54], most studies, including some longitudinal analyses, have failed to find such a correlation [35, 41, 49, 60, 61, 64, 65]. Various sample sizes and techniques used by the studies likely contribute to the discrepancies (Table 1). Further, no study has analyzed the interaction of disease duration and nigral iron independent of the motor impairment in PD. Though the majority of studies support the conclusion that iron is elevated at the time of diagnosis and remains constant during the course of the disease, further studies are needed to confirm the relationship without the influence of motor impairment.

Nigrosome 1, located in the caudal and mediolateral SNc, plays an early and large role in PD [4, 5]. Recently, Blazejewska *et al.* [66] reported the loss of dorsolateral nigral hyperintensity (DNH) in a T2* map in PD patients, and confirmed correspondingly low neuromelanin in this region. These findings indicate that regional iron accumulation in nigrosome 1 mirrors the loss of dopaminergic neurons, which suggests that evaluating the level of DNH might provide a biomarker for PD. Several studies have also confirmed its application to differentiate PD from normal aging with high sensitivity and specificity [67–69]. However, only 13 of 35 normal subjects showed bilateral or unilateral DNH in a study by He and colleagues [54]. Intriguingly, De Marzi *et al.* [70] have reported that, as a majority of patients with idiopathic rapid eye movement sleep behavior disorder (iRBD) go on to develop PD, the loss of DNH in iRBD patients was found to be similar to that in PD patients. This indicates that evaluating DNH could be used to classify early-stage PD, referred to as *prodromal PD* [71]. As PD is one of the most common neurodegenerative disorders, low DNH in normal individuals [54] may indicate prodromal PD or high-risk cases. Studies with larger samples and different clinical subtypes, especially longitudinal studies, are still needed to confirm the usefulness of measuring DNH levels for future clinical

Table 1 Relationships between nigral iron accumulation and clinical phenotypes

Authors	Materials	Technique	Field strength	Nigral iron and motor impairment	Nigral iron and disease duration
Ryvlin <i>et al.</i> [34]	45 patients, 45 controls	T2	2.0 T	—	NG
Antonini <i>et al.</i> [35]	30 patients, 33 controls	T2	1.5 T	—	—
Gorell <i>et al.</i> [36]	13 patients, 10 controls	R2, R2*, R2'	3.0 T	+	NG
Kosta <i>et al.</i> [37]	40 patients, 40 controls	T2	1.5 T	—	NG
Graham <i>et al.</i> [38]	21 patients, 13 controls	R2, R2'	1.5 T	—	NG
Michaeli <i>et al.</i> [39]	8 patients, 8 controls	T2p	4.0 T	—	NG
Zhang <i>et al.</i> [40]	42 patients, 30 controls	SWI	1.5 T	+	NG
Martin <i>et al.</i> [41]	22 patients, 11 controls	R2*	3.0 T	+	—
Nestrasil <i>et al.</i> [42]	9 patients, 10 controls	T2p	4.0 T	+	NG
Gupta <i>et al.</i> [43]	11 patients, 11 controls	SWI	1.5 T	—	NG
Baudrexel <i>et al.</i> [44]	20 patients, 20 controls	T2*	3.0 T	—	NG
Du <i>et al.</i> [45]	16 patients, 16 controls	R2*	3.0 T	—	NG
Du <i>et al.</i> [46]	40 patients, 29 controls	R2*	3.0 T	—	NG
Peran <i>et al.</i> [47]	30 patients, 22 controls	R2*	3.0 T	—	NG
Wang <i>et al.</i> [48]	16 patients, 44 controls	SWI	1.5 T	—	NG
Jin <i>et al.</i> [49]	45 patients, 45 controls	SWI	3.0 T	+	—
Lewis <i>et al.</i> [50]	38 patients, 23 controls	R2*	3.0 T	+	+
Lotfipour <i>et al.</i> [51]	9 patients, 11 controls	QSM	7.0 T	—	NG
Du <i>et al.</i> [52]	47 patients, 47 controls	R2*, QSM	3.0 T	+	+
Langkammer <i>et al.</i> [53]	66 patients, 58 controls	R2*, QSM	3.0 T	+	NG
He <i>et al.</i> [54]	44 patients, 35 controls	R2*, QSM	3.0 T	+	+
Guan <i>et al.</i> [55]	60 patients, 40 controls	R2*, QSM	3.0 T	+	NG
Wieler <i>et al.</i> [57]	19 patients, 13 controls	R2*	3.0 T	+	NG
Wang <i>et al.</i> [58]	20 patients, 14 controls	ESWAN	3.0 T	+	NG
Ulla <i>et al.</i> [59]	Baseline: 27 patients, 26 controls Follow-up: 14 patients, 18 controls	R2*	1.5 T	+	+
Wallis <i>et al.</i> [60]	70 patients, 10 controls	R'	3.0 T	+	—
Rossi <i>et al.</i> [61]	Baseline: 32 patients, 19 controls Follow-up: 25 patients, 19 controls	R2*, SWI, T2	3.0 T	+	—
Murakami <i>et al.</i> [63]	21 patients, 21 controls	R2*, QSM	3.0 T	NG	—
Barbosa <i>et al.</i> [64]	20 patients, 30 controls	R2, R2*, QSM	3.0 T	NG	—
Zhang <i>et al.</i> [65]	40 patients, 26 controls	SWI	3.0 T	—	—
Acosta-Cabronero <i>et al.</i> [78]	25 patients, 50 controls	QSM	3.0 T	—	—

+ : Statistically significant;

— : No significant difference.

NG: Not given.

translation, especially in the identification of prodromal PD.

Because the main degenerative alterations in PD are limited to the SNc, some of the above studies have tried to distinguish the SNc from the SN. Martin *et al.* [72] have suggested that because the SN pars reticulata (SNr), which

has a low signal in T2 and phase imaging but a high signal in QSM, has a significantly higher iron content than the SNc; the SNc corresponds best to the high signal area that is interposed between the low signal structures of the SNr and the red nucleus (in T2 and phase imaging; opposite in QSM). Previous studies have confirmed the presence of iron

accumulation in the SNc in PD patients [39, 41, 42, 52, 55–59, 61, 62]. Guan *et al.* [56] have further confirmed that PD patients with different motor subtypes also show iron accumulation in the SNc. However, identification of the SNc remains a challenge with the available imaging resolution. Thus, we hope that future studies using ultrahigh field MRI will contribute to its precise delineation [51].

Other researchers have explored the possible physiochemical underpinnings of nigral iron accumulation. Jin *et al.* [49] have suggested that nigral iron content is highly correlated with the level of serum ceruloplasmin (an important anti-oxidative protein), and shown that PD patients with a decreased level of serum ceruloplasmin have significantly higher iron content than PD patients with a normal level. Although it is unclear how serum cholesterol levels and uric acid interact with nigral iron content, Du *et al.* have demonstrated a significant negative correlation between nigral iron content and total cholesterol, and Kim and Lee have confirmed both low serum uric acid levels and increased nigral iron content in PD, but without a correlation between them [73, 74]. Serum samples can be easily obtained and have a high potential to provide necessary biological information. New studies, especially those focusing on the relationship between anti-oxidative materials and nigral iron accumulation, will deepen our understanding. Test–retest studies will be important for translating these findings into clinical applications for classifying at-risk individuals.

In brief, nigral degeneration is a core pathology of clinical-stage PD. Although a single biomarker cannot definitively identify PD, we believe that quantification of nigral iron or qualitative analysis of DNH will contribute to recognizing high-risk individuals and possibly aid diagnosis.

Other Influences of Regional Iron on PD

Subcortical nuclei, like the globus pallidus (GP), putamen, caudate nuclei (CN), red nuclei (RN), and dentate nuclei (DN), are also rich in iron [17]. However, the influences of iron in these nuclei are not well understood in PD. Previous MRI studies have found significant iron accumulation in the GP [37, 53, 55, 75], especially in late-stage PD patients [55]. Martin *et al.* [41] and Ye *et al.* [75] have reported that the iron content in the GP is significantly correlated with disease severity. In a cohort of PD patients with a long disease duration (>10 years), Graham *et al.* and Ryvlin *et al.* [34, 38] have found significantly decreased iron content in the putamen while Ye *et al.* [75] have reported significantly increased iron content in their PD patients. In addition, in a *post-hoc* correlation analysis, Bunzeck *et al.* and Guan *et al.* [56, 76] have reported that iron content in the CN is significantly negatively correlated with the severity of akinesia/rigidity in PD. Iron content in these

nuclei plays an important role in maintaining physical function. Because of the degenerative changes in the basal ganglia in PD, the regional iron alterations may indicate abnormal metabolism. Sufficient evidence from basic research is still needed to explain these MRI findings.

It is thought that increased cerebellar function might contribute to the development of levodopa-induced dyskinesia in PD. Lewis *et al.* [50] have reported significant iron accumulation in the RN in patients with this form of PD, and suggested that increased RN iron might reflect structural changes associated with cerebello-thalamo-cortical compensation in PD. Guan *et al.* have also observed this phenomenon in late-stage PD patients [55], which likely reflects increased cerebellar compensation. The DN is another important region in the cerebellar circuit, and both He *et al.* and Guan *et al.* [56, 77] have reported significant iron accumulation in this region in tremor-dominant PD patients that correlates with tremor severity. Thus, iron content in the RN and DN possibly play roles in activating RN function (cerebellar compensation) and tremor generation, respectively.

Taken together, region-specific iron content shows complex regulation secondary to nigral degeneration in PD patients. Confirmation of these findings would greatly contribute to understanding the role of iron in PD and the search for promising biomarkers.

Clinical Translation and Future Perspectives

To improve the current diagnostic accuracy of PD, a biomarker with high sensitivity and specificity would be of great use. Reviewing the decades of effort toward this goal indicates that identification of a single biomarker is unlikely, whereas the use of multiple biomarkers may be beneficial. Iron-related biomarkers offer useful information about the disease mechanism and clinical diagnosis as the improved techniques (such as QSM) and increased field strength provide more precise measurements than previously available with high resolution and signal-to-noise ratios. Novel statistical methods, including voxel-wise analysis throughout the brain [78], would also contribute to a better understanding of the iron abnormalities in PD and provide potentially sensitive biomarkers. Of course, to determine their potential for clinical translation, test-retest reproducibility, the ability to monitor disease progression without age bias, and compensatory mechanisms or treatments still need to be investigated with larger cohorts or exclusive subtypes [79]. Once prodromal PD was defined [71], the first investigation of a nigral iron abnormality in iRBD patients (high-risk prodromal PD symptom) was reported [70]. Future efforts should aim to deepen understanding of the roles of regional iron in prodromal symptoms and also verify the candidate

biomarkers (to be used in combination with other biomarkers) longitudinally. The studies reviewed here indicate strong support for the clinical translation of iron-related biomarkers for future early diagnosis of PD and disease monitoring.

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