High Field MRI in Multiple Sclerosis: Novel multi-contrast protocols for detection of MS lesions and iron

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2012

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Download date: 10. May, 2022
7. MRI Assessment of Iron Deposition in Multiple Sclerosis


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Journal of Magnetic Resonance Imaging 2011, 34:13–21
Abstract

Iron deposition in the human brain tissue occurs in the process of normal aging and in many neurodegenerative diseases. Elevated iron levels in certain brain regions are also an increasingly recognized finding in multiple sclerosis (MS). The exact mechanism(s) for this phenomenon and its implication in terms of pathophysiology and clinical significance are still largely unknown and debated. Reliable methods to exactly quantify brain iron are a first step to clarify these issues. Therefore, the aim of this review is to present currently available magnetic resonance imaging (MRI) techniques for the assessment of brain iron. These include relaxation time mapping, phase imaging, susceptibility-weighted imaging, susceptibility mapping, magnetic field correlation imaging, and direct saturation imaging. After discussing their advantages and disadvantages, existing MRI clinical correlations with brain iron concentration in MS are summarized and future research directions are shown.

Iron is an essential trace element that plays a vital role in normal brain metabolism, oxygen transport, myelin production, neurotransmitter synthesis, and in the Fenton reaction, which is critical to oxidative stress (1–3). In brain tissue, iron is mainly stored in the proteins ferritin and hemosiderin, which serve as a buffer against harmful iron deficiency or iron overload (4). Early work by Hallgren and Sourander (5) demonstrated that ferritin bound iron accumulates in the brain until the 4th decade of life during the course of normal aging and that highest ferritin concentrations are typically found in the basal ganglia. Thereafter, the iron level is thought to remain fairly constant with the exception of the thalamus, where a decline after an age of about 35 years has been reported.

In many neurodegenerative and inflammatory diseases, including multiple sclerosis (MS), excess accumulation of iron has been observed. These insights have come from histologic examinations and increasingly from magnetic resonance imaging (MRI) with the application of techniques that allowed defining regional increases in iron concentration both visually and in a quantitative manner. The mechanism(s) behind the phenomenon of iron accumulation are not yet fully clear. On the one hand, it has been speculated that iron-mediated oxidative stress was the culprit and by the formation of cytotoxic protein aggregates might trigger or promote neurodegeneration (6,7). On the other hand, inflammatory processes such as in MS have been shown to cause local accumulation of iron by disrupting the blood–brain barrier (8) and by attracting iron-rich macrophages (8,9). Inflammation may also be responsible for reducing the axonal clearance of iron in MS brains (10,11). Recently, increased iron accumulation has been even contributed to a state of impaired venous drainage from the brain, termed chronic cerebrospinal venous insufficiency (CCSVI), which was diagnosed in MS patients and suggested as a possible cause of the disease by some (12,13). However, final evidence for all these mechanisms is lacking and the pathophysiologic and clinical consequences of increased iron accumulation such as for MS are still largely unknown.

Reliable and precise techniques for in vivo assessment of iron content are a prerequisite for further research in this direction. MRI offers several techniques that are based on the susceptibility and relaxivity effects of ferritin-bound iron. In this review we provide an overview of current and new approaches for iron mapping, their methodological restrictions, how they have been used to assess local iron accumulation in brain tissue, and finally, how iron accumulation may be related specifically to the clinical condition of MS patients.
MRI METHODS FOR IRON MAPPING

Relaxation Time Mapping

The transverse relaxation time $T_2$, also called the spin-spin relaxation time, of hydrogen protons is an intrinsic property of tissues and describes how fast the macroscopic transverse component of the magnetization decays after being excited by radiofrequency (RF) radiation at the Larmor frequency. The magnetization decay results from a loss of coherence (dephasing) due to random and time-dependent field variations induced by neighbouring spins, since not all spins have exactly the same precession frequency. When hydrogen protons diffuse through microscopic field gradients induced by iron, they accumulate a random phase shift which is not fully reversible; this results in an additional loss of coherence and consequently in $T_2$ shortening. It has been shown for gray matter that $R_2$, which is the inverse of $T_2$, scales linearly with iron concentration over the entire range of physiological concentrations (14-17). Whether this relationship also holds true for white matter is still unclear (14,17).

Figure 1. T2-weighted scans obtained from a 38-year-old primary progressive MS patient on a 3T (left) and 7T (right) scanner. The field dependent $T_2$ relaxivity of iron can be appreciated best in the globus pallidus (arrows) where a shorter $T_2$ results in a more pronounced hypointensity despite a shorter echo time. The echo time at 7T was 80 msec while the echo time at 3T was 112 msec.

In brain tissue, $T_2$ shortening due to iron accumulation can often be observed as hypointensity on T2-weighted images (18). As the $T_2$ shortening effect of iron increases with magnetic field strength (15,19) high field imaging offers a higher sensitivity in addition to the advantage of a higher signal-to-noise ratio (Fig. 1). A simple assessment of iron deposition, e.g., in the basal ganglia, can be achieved by means of visual rating (20) or by taking the signal intensity of the ventricular cerebrospinal fluid as internal reference (21).

However, such approaches are not sensitive enough for smaller regions or to detect more subtle changes in white matter. Relaxation time mapping is needed for a true quantitative assessment of iron deposition. This can be achieved by fitting a single exponential decay function to data obtained from a multiecho spin-echo sequence (16,22,23).
Dipolar relaxation is a further relaxation mechanism that occurs in the presence of paramagnetic compounds such as ferritin. Dipolar relaxation is caused by a fluctuation in the magnetic field sensed by water protons due to fluctuations in the direction of the magnetic moment of the iron as well as the diffusion of the protons in the vicinity of the iron compound (24). This relaxation mechanism affects T1, which is the relaxation time of the longitudinal component of the magnetization and describes how fast the magnetization recovers after RF excitation. R1, which is the inverse of the T1 relaxation time, shows a linear dependency on iron but the effect is weaker compared to R2 (14,25). It has been suggested that brain iron contributes to regional variations and age effects of T1 (25,26). However, for practical reasons T1 mapping is rarely used to assess brain iron concentration because of the weak effect and the long acquisition time needed for precise T1 mapping. Additionally, the sensitivity of this approach varies between brain regions (25) and does not significantly increase with higher field strengths (15).

In contrast to T1 and T2, T2* is not an intrinsic relaxation parameter but rather reflects the effective decay of transverse magnetization due to all effects that can cause loss of spin coherence (dephasing), i.e., microscopic changes of the precession frequency within a single voxel. While non-random and static dephasing effects can be refocused in a spin-echo sequence with its 180° refocusing pulse(s), this is not possible with a gradient-echo sequence when sampling the free induction decay (FID). It has been suggested that R2*, which is the inverse of T2*, can be considered the sum of all transverse relaxation rates according to 1/T2* = 1/T2 + 1/T20, where 1/T2 is associated with intrinsic tissue properties as outlined above and the rate 1/T20 is attributed to microscopic field gradients such as induced by iron loaded ferritin (27–29). However, 1/T20 is not always clearly defined, in particular if the decay of the transversal magnetization is not monoeponential (30,31). T2* mapping is expected to be more sensitive for iron than T2 mapping because the iron-induced field gradients are not refocused. T2* mapping is performed with a spoiled gradient-echo sequence with multiple echoes and by fitting these echoes to a single exponential decay function (Fig. 2). Such a sequence generally requires less than 10 minutes scan time and provides whole brain coverage. Limitations can arise from macroscopic susceptibility effects which cause a signal loss due to dephasing along the gradient between tissues with different magnetic susceptibility, which often makes it difficult to measure T2* in the cerebral cortex. Proximity to nasal sinuses aggravates artifacts in the frontobasal brain area. The artifacts due
to susceptibility effects increase with longer echo times and higher magnetic field strengths. Higher-order shimming and a smaller voxel size, i.e., a higher image resolution, can help to reduce such artifacts (Fig. 3). Similar to T2, the T2* sensitivity also linearly scales with magnetic field strength and favors iron mapping at higher field strengths (32).

Phase Imaging

Due to the nature of Fourier image encoding, MR images can represent the magnitude or the phase of the complex transversal magnetization, although the latter is virtually never used in clinical routine (apart from flow measurements). In contrast to MR magnitude images, phase images are not dependent on intrinsic relaxation parameters of the brain but represent local variations of the precession frequency. Iron induced changes of the magnetic susceptibility cause phase shifts that are proportional to the iron concentration (33). Unfortunately, even larger shifts can be induced by magnetic field inhomogeneities which typically occur at air–tissue interfaces but also may result from imperfect shimming and therefore have to be filtered with a highpass filter. In addition, phase images can only represent a phase range between -π and +π, which means that phase wrapping can occur for larger phase shifts. Phase unwrapping with an appropriate algorithm (34,35) is the first and most important step when processing phase images (Fig. 4). Recently, Hammond et al (36) proposed a procedure to obtain iron induced local field shifts (LFS) in ppm from filtered phase images. The image processing steps comprise the subtraction of a reference phase from a region such as the posterior internal capsule and the division by a term that includes the echo time and the field strength to make the LFS independent from scanner and sequence.

Susceptibility-Weighted Imaging (SWI)

SWI combines a corresponding set of phase and magnitude images from a gradient-echo sequence to form an enhanced contrast magnitude image (37–39). SWI requires a high-resolution, 3D spoiled gradient-echo with fully flow-compensating gradients. After phase unwrapping and filtering as described above, SWI images are calculated by multiplying the magnitude image with the phase image. To increase the susceptibility effect, phase values between -π and 0 are usually mapped to a range between 0 and 1 using a 4th power function. In the resulting SWI images, veins and structures containing iron appear dark. To better visualize vein connectivity and small susceptibility variations, a minimum intensity projection through a limited number of slices is performed (Fig. 5). In MS, SWI can reveal lesions that cannot be seen on conventional MRI and vice versa, which suggests that SWI provides independent tissue characterization (40). It is commonly believed that susceptibility changes in MS lesions result from iron deposition and from deoxygenated blood in smaller veins draining the lesions. However, due to the incorporation of an (arbitrary scaled) magnitude image, SWI is not a true quantitative method and therefore cannot be used as an indirect measure of iron.
Figure 3. Effect of field strength and image resolution on T2*-weighted gradient echo images. Left: spoiled 3D gradient echo sequence (TR: 30 msec, TE: 24.6 msec) at 3T with 1 mm in-plane resolution and 2-mm thick sections. Right: spoiled 3D gradient-echo sequence (TR: 19 msec, TE: 15 msec) of the same 38-year-old primary progressive MS patient at 7T with 0.8 mm isotropic resolution. The improved resolution at 7T allows removal of macroscopic susceptibility effects and to depict smaller venous vessels. Note that the lower signal intensity of the basal ganglia at 3T is mostly related to the longer echo time.

Figure 4. Magnitude (a) and corresponding phase image (b) acquired from a healthy volunteer with a gradient-echo sequence at 3T. The raw phase image is characterized by phase wraps and inhomogeneities. Mandatory image processing steps comprise phase unwrapping (c) and removing of global inhomogeneities. After high-pass filtering, a phase image can be derived (d) that directly represents susceptibility induced variations of the Larmor frequency.

Quantitative Susceptibility Mapping
Susceptibility-induced field shifts not only reflect local effects of iron but also depend on the spatial susceptibility distribution and its orientation with respect to the main magnetic field (41). The latter factor has recently been proven as a significant source of SWI contrast (42). Therefore, the relationship between iron concentration and SWI changes in highly oriented structures such as myelinated fiber bundles is not trivial. Quantitative susceptibility mapping (QSM) aims at extracting only the intrinsic local susceptibility from phase images as a more direct measure of iron concentration. A possible solution of this illposed inverse problem is the multi-
angle acquisition technique which requires that the orientation of the patients' head is slightly changed between subsequent acquisitions (43). Given the limited clinical applicability of such an approach, new techniques such as sophisticated harmonic artifact reduction for phase data (SHARP) seem to be more promising but await further validation (44).

**Magnetic Field Correlation Imaging**

Magnetic field correlation (MFC) imaging is another technique that allows assessing iron accumulation because the MFC is directly related to iron-induced microscopic (on a subvoxel scale) field variations. The MFC can be estimated from a series of asymmetric spin echo sequences where the 180° echo pulse is slightly shifted (45,46). While T2 and T2* are also affected by microscopic field variations, the MFC is expected to be independent from dipolar relaxation mechanisms and therefore less sensitive for the underlying tissue structure. When employing a singleshot EPI acquisition, MFC imaging can be done within a clinically reasonable acquisition time but at the cost of a limited image resolution. Similar to T2* mapping with gradient echo sequences, MFC imaging is also susceptible to macroscopic field variations and motion.

![Figure 5. Magnitude images (a) and corresponding SWI image (b) from a healthy volunteer with 3T, which was calculated by multiplying the magnitude image with the unwrapped and filtered phase image. A minimum intensity projection over a stack of five slices is shown in (c).](image)

**Direct Saturation Imaging**

As outlined above, iron shortens the T2 relaxation time of water protons, which in turn leads to a broadening of the saturation line shape. This effect is utilized by a recent development termed direct saturation imaging (DSI). Similar to conventional magnetization transfer (MT) imaging, DSI employs off-resonant RF saturation pulses that cause a reduction of the longitudinal tissue magnetization. However, in contrast to MT imaging, DSI aims to reflect the “direct” saturation of tissue water only. The reduction of the signal intensity relative to a reference measurement is expressed by a direct saturation ratio (DSR), which is expected to scale with iron concentration (47). Confounding effects due to MT between tissue water and bound protons can be minimized by applying longlasting (>200 msec) RF saturation pulses with low power. If the DSI maps are calculated from a series of examinations with different offset frequencies of the saturation pulse, it is also possible to correct the maps for magnetic field inhomogeneities. Although the DSI mechanism is mainly based on T2, DSI maps offer a sensitivity for iron detection that slightly differs from T2 or R2 maps (47).
**Validation of Iron Mapping Methods**

Relaxation rates and MFC scale with iron concentration. However, absolute quantification of iron with MRI remains difficult because relaxation characteristics may be confounded by variations of the water content, lipid content, magnetization transfer, and other minerals (e.g., calcium). Thus, only in vitro methods allow to measure iron concentration in brain tissue in absolute terms using colorimetry, x-ray fluorescence, or mass spectrometry. So far the largest study to quantify iron accumulation in brain tissue was done by Hallgren and Sourander (5). They measured iron concentration in postmortem tissue with colorimetry after adding ortho-phenanthroline to the iron solution that was washed out from the tissue samples with N-hydrochloric acid. A cohort of 81 subjects and samples from many brain regions allowed studying the strongly age-dependent iron accumulation in different brain regions. Although dated back to 1958, Hallgren and Sourander’s work is still frequently used as a look-up table to obtain age-corrected iron concentrations when validating new or existing iron-mapping techniques indirectly. Direct correlations between the results of MRI techniques and subsequent biochemical analyses of brain tissue specimens are scarce. Also, such correlative studies in post-mortem tissue may be affected by the fixation process and by changes in water content and temperature. To circumvent this problem, Langkammer et al (17) recently assessed transverse relaxation rates in situ and related them to chemically obtained iron concentrations after brain extraction. They confirmed a strong linear relationship between iron concentration and both \( R_2 \) and \( R_2^* \), where the latter exhibited a higher sensitivity for depicting differences in iron concentration. In another recent chemical correlation study, Hocq et al (48) measured \( R_2 \) relaxation rates in brain tissue samples at different field strengths up to 14 T. They found that \( R_2 \) increases quadratically with field strengths and depends on the interecho time of the multiecho sequence at high fields. However, their observations were based on fixed samples from deep gray matter structures only.

**CLINICAL IMPLICATIONS OF ABNORMAL IRON DEPOSITION IN MS**

*Brain Iron Detected by Conventional T2-Weighted MRI*

Reports of an increased concentration of iron in MS date back more than 20 years. Since then, virtually all attempts to assess iron concentration with MRI have focused on deep gray matter. Drayer et al (18,49) were the first to describe reduced signal intensities in the thalamus and putamen on T2-weighted images of MS patients, which they assumed to originate from increased ferritin levels. Since then, the vast majority of studies exploring the clinical implications of iron deposition in MS have used T2-weighted MRI to estimate brain iron levels (Table 1). The limitation of such an approach comes from the fact that T2 signal intensities do not scale linearly with iron concentration and strongly depend on sequence parameters.

Bakshi et al (20) provided a quite detailed investigation of the frequency, location, and clinical correlation of regional T2 hypointensity in 114 MS patients on a 1.5T system. Abnormal T2 hypointensity was defined against findings in 100 normal controls. To semiquantitatively rate the degree of iron deposition, the authors used a three-point ordinal visual grading system of T2 hypointensity in relation to the patients’ globus pallidus (20). Abnormal T2 hypointensity was most prevalent in the thalamus, putamen, the caudate nucleus, and the rolandic cortex. They found a weak correlation of disease duration with T2 shortening in thalamus, putamen, and caudate and more pronounced T2 shortenings in patients with advanced disability, such as when wheel-chair bound, and in secondary progressive MS (SPMS) compared to relapsing-remitting MS (RRMS). Age and gender did not significantly contribute to the finding of T2 hypointensity (20). The authors concluded that increased T2 hypointensity is present in MS and possibly related to neurodegeneration. Further work in this direction confirmed these findings.
and additionally established significant correlations between the hypointensity of deep gray matter structures and atrophy (21,50), T2 lesion load (21), enhanced disability status scale (EDSS) (51,52), the timed 25-foot walk (51), cognitive impairment (53), and clinical progression (54). No correlations were seen with the risk of developing clinically definite MS (CDMS) in patients presenting with a clinically isolated syndrome (CIS) (55). A recent study by Burgetova et al (22) is the only one of this kind that aimed at assessing iron accumulation by T2 relaxation time mapping with a multiecho sequence. Although quantitative T2 mapping provides a more sensitive and linear measure of iron accumulation than relative signal intensities on T2-weighted scans, these authors could not reveal any new insights but did confirm findings from previous semiquantitative studies.

Table 1
Clinical implications of increased iron Deposition in MS as Assessed With Classical MRI Methods

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients N</th>
<th>Course N</th>
<th>Controls N</th>
<th>Field strength [T]</th>
<th>Assessment of T2 effect</th>
<th>Clinical correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakshi et al (20)</td>
<td>114</td>
<td>RRMS 80 SPMS 34</td>
<td>100</td>
<td>1.5</td>
<td>Score (0-3)</td>
<td>Correlation with disease duration, advancing neurological disability</td>
</tr>
<tr>
<td>Bakshi et al (21)</td>
<td>60</td>
<td>RRMS 42 SPMS 18</td>
<td>50</td>
<td>1.5</td>
<td>Ratio to ventricular CSF</td>
<td>Deep gray matter T2 hypointensity associated with disability score and SPMS disease course</td>
</tr>
<tr>
<td>Tjoa et al (51)</td>
<td>47</td>
<td>RRMS 41 SPMS 6</td>
<td>15</td>
<td>1.5</td>
<td>Ratio to ventricular CSF</td>
<td>T2 hypointensity (dentate nucleus) associated with ambulatory dysfunction and overall physical disability</td>
</tr>
<tr>
<td>Brass et al (53)</td>
<td>33</td>
<td>RRMS 27 SPMS 6</td>
<td>14</td>
<td>1.5</td>
<td>Ratio to ventricular CSF</td>
<td>T2 hypointensity of globus pallidus correlated with neuropsychological composite score</td>
</tr>
<tr>
<td>Zhang et al (52)</td>
<td>17</td>
<td>RRMS 94%</td>
<td>17</td>
<td>3.0</td>
<td>Ratio to ventricular CSF</td>
<td>Normalized signal intensity of head of caudate and pallidum at 3T correlated with EDSS</td>
</tr>
<tr>
<td>Neema et al (54)</td>
<td>97</td>
<td>CIS 2 RRMS 64 SPMS 25 SPMS 6</td>
<td>-</td>
<td>1.5</td>
<td>Ratio to ventricular CSF</td>
<td>Baseline gray matter T2 hypointensity correlated with clinical progression</td>
</tr>
<tr>
<td>Ceccarelli et al (56)</td>
<td>61</td>
<td>BMS 35 SPMS 26</td>
<td>25</td>
<td>1.5</td>
<td>Ratio to ventricular CSF</td>
<td>T2 signal reduction similar in BMS and SPMS GM T2 hypointensity in BMS correlated with disability (weak to moderate)</td>
</tr>
<tr>
<td>Ceccarelli et al (55)</td>
<td>47</td>
<td>CIS 47</td>
<td>13</td>
<td>1.5</td>
<td>Ratio to ventricular CSF</td>
<td>Baseline T2 hypointensity of deep gray matter structures were not associated with increased risk of developing CDMS</td>
</tr>
<tr>
<td>Burgetova et al (22)</td>
<td>960</td>
<td>CDMS 970</td>
<td>117</td>
<td>1.5</td>
<td>T2 relaxometry</td>
<td>Increased iron in MS and associated with increased age</td>
</tr>
</tbody>
</table>

Besides providing an overview on reported clinical associations with increased brain iron levels as estimated by T2-weighted MRI, Table 1 shows the development of the analysis techniques over time. The first study published by Bakshi et al (20) used a rather semiquantitative visual grading system to measure the extent of iron deposition. Two years later the same authors described a semiquantitative method to obtain normalized T2 signal intensities (21). Signal intensity normalization was used by all following studies listed in Table 1, except for the study by Burgetova et al. In all studies expect one (52), MRI was done on a 1.5T scanner. Only two studies investigated the predictive value of T2 hypointensity in MS with regard to the clinical progression of the disease (54,55). Concerning disease stage and course, these investigations focused predominantly on RRMS and SPMS patients but one study also analyzed patients with benign MS (56) and another patients presenting with CIS (55). The study performed by Neema et al (54) also included CIS and primary progressive MS patients but with rather low numbers.
Brain Iron Detected by Advanced MRI Techniques

Recent years saw the advancement of methodological developments to assess brain iron in a more quantitative manner including MFC and T2* relaxation time mapping (Table 2). In addition, high field strengths have increased the sensitivity of these methods. This served not only to increase the sensitivity and specificity for a quantification of diffuse increases in iron deposition, such as in the deep gray nuclei, but to also extend the assessment towards MS lesions or plaques, although not yet in a quantitative manner.

**Table 2**

*Clinical Implications of Increased Iron Deposition in MS as Assessed With Classical MRI Methods*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Course</th>
<th>Controls</th>
<th>Field strength [T]</th>
<th>Assessment of T2-effect</th>
<th>Clinical correlations</th>
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<td>Balash et al (20)</td>
<td>114</td>
<td>RRMS</td>
<td>100</td>
<td>1.5 score (0-3)</td>
<td>Correlation with disease duration, advancing neurological disability</td>
<td></td>
</tr>
<tr>
<td>Balash et al (21)</td>
<td>60</td>
<td>RRMS</td>
<td>50</td>
<td>1.5 ratio to ventricular CSF Deep gray matter T2 hypointensity associated with disability score and SPMS disease course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tjoa et al (51)</td>
<td>47</td>
<td>RRMS</td>
<td>15</td>
<td>1.5 ratio to ventricular CSF T2 hypointensity (dentate nucleus) associated with ambulatory dysfunction and overall physical disability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brass et al (53)</td>
<td>30</td>
<td>SMPS 6</td>
<td>14</td>
<td>1.5 ratio to ventricular CSF T2 hypointensity of globus pallidus correlated with neuropsychological composite score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang et al (52)</td>
<td>17</td>
<td>RRMS 94</td>
<td>17</td>
<td>1.5 ratio to ventricular CSF Normalized signal intensity of head of caudate and pallidum at T1 correlated with the EDSS</td>
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<td></td>
</tr>
<tr>
<td>Neuma et al (54)</td>
<td>6</td>
<td>CIS 2</td>
<td>1.5</td>
<td>ratio to ventricular CSF Baseline grey matter T2 hypointensity associated with clinical progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coccia et al (55)</td>
<td>61</td>
<td>RRMS 94</td>
<td>25</td>
<td>1.5 ratio to ventricular CSF T2 signal reduction similar in BMS and SPMS. GM T2 hypointensity in BMS correlated with disability (weak to moderate)</td>
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<td>Coccia et al (55)</td>
<td>47</td>
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<td></td>
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</tr>
<tr>
<td>Burstein et al (52)</td>
<td>963</td>
<td>COMS 970</td>
<td>117</td>
<td>1.5 T1 T2 relaxometry Increased iron in MS and associated with increased age</td>
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</table>

Ge et al (57) were the first who applied MFC in MS patients at 3T and who also investigated iron accumulation in white matter. No significant differences between MS patients and healthy controls were observed with regard to the white matter, but deep gray matter MFC values were positively correlated with number of T2 lesions and cognitive performance.

The authors concluded that increased brain iron levels as detected by MFC might be associated with disrupted iron outflow pathways caused by MS lesions and may contribute to cognitive impairment in MS (57). Hammond et al (58) aimed at quantifying iron induced local field shifts (LFS) in MS patients with a 7T scanner. Compared to healthy controls, LFS were significantly higher in the caudate, putamen, and globus pallidus of MS patients. Putaminal LFS were positively correlated with MS disease duration. Furthermore, a close relation between MS lesions and veins was reported, indicated by the presence of well defined vessels penetrating the majority of lesions (36). Another recent study applied T2* relaxation time mapping in MS patients to assess brain iron levels (59). R2* relaxation rates were determined at 3T in seven deep gray matter structures (thalamus, caudate nuclei, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens) and the brainstem using a fully automated segmentation and registration algorithm based on deformable models from FSL (60). R2* relaxation rates were positively correlated with age and RRMS patients had significantly higher R2* relaxation rates in the basal ganglia compared to CIS. Putaminal R2* rates were independently predicted by the patients’ age, disease duration, and gray matter atrophy. Table 2 summarizes existing studies using more advanced methods for brain iron assessment in MS.

**SUMMARY AND OUTLOOK**

Many attempts have been made to assess disease related iron accumulation in MS. Most of these efforts were based on conventional T2-weighted spin echo sequences, where iron induced T2 hypointensity was assessed by visual rating or by signal intensity normalization.
More recent developments including quantitative relaxation time mapping, MFC, and assessment of LFS are expected to be more sensitive and specific for iron and additionally benefit from higher field strength, but these techniques have so far been applied to MS only to a limited extent. Additionally, they need implementation on different scanner platforms and further validation. Given the good availability of multi-echo gradient-echo sequences and the verified linear relationship between $R2^*$ and iron concentration in brain tissue, iron mapping with a gradient-echo sequence presently seems to be the most feasible and robust approach.

Existing data indicate that iron accumulation in MS is most pronounced in the deep gray matter structures and significantly extends beyond age-related effects. Iron accumulation in these regions seems to be associated with disease severity in terms of atrophy and disease duration. Future research should focus also on iron located in and surrounding MS lesions or plaques and how this relates to iron accumulation in deep gray matter. This would be an important step because it could disentangle disease mediated and possible disease-modulating effects. However, iron assessment in white matter is more challenging because the physiological iron concentration in this compartment is under the detection level of most methods. In addition, the contribution of iron to the relaxation mechanism in white matter is not fully understood and is smaller than in gray matter.

Work also needs to be done regarding the possible association of iron deposition and venous disease in MS and regarding the CCSVI hypothesis. Finally, it would be of great interest to also measure iron concentrations in the cortical gray matter, but this is not yet possible with sufficient reliability. New quantitative MRI approaches, such as QSM, which can serve to increase sensitivity by eliminating confounding relaxation effects, are promising. Much impact is also expected from the application of these techniques at high and ultrahigh field strengths, which provides a higher sensitivity for susceptibility-induced changes in addition to a higher resolution and signal-to-noise ratio (61).
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