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

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2. Inflammation High Field MR Imaging
Abstract / Synopsis
Multiple Sclerosis (MS) is the most common inflammatory demyelinating disorder of the central nervous system (CNS). It has been subject to high field magnetic resonance imaging (MRI) research to a great extent during the past years, and much data has been collected that might be helpful when investigating other inflammatory CNS disorders. This article reviews the value of high field MRI in imaging inflammatory MS abnormalities. Furthermore, it discusses possibilities and challenges for the future of high field MR imaging in MS.

Introduction
Inflammatory diseases in the central nervous system (CNS) include a wide and heterogenic spectrum of diseases entities. In general, data investigating the diagnostic value of higher magnetic field strengths in inflammatory CNS disease is rather limited. However, the most common inflammatory demyelinating disorder of the CNS, multiple sclerosis (MS), has been subject to high field magnetic resonance imaging (MRI) research to a great extent during the past years and much data has been collected that might be helpful when investigating other inflammatory CNS disorders. In this article we will give an overview of this data, focusing merely on MS. We will review the value of high field MRI in imaging inflammatory MS abnormalities by describing different imaging techniques. Furthermore, we will discuss possibilities and challenges for the future of high field MR imaging in MS.

MS is the most common inflammatory CNS disease in young adults leading to relevant chronic disability, and it is typified by both pathological and clinical heterogeneity. Pathologically, MS is described as multifocal areas of demyelination with loss of oligodendrocytes, astrogial scarring and axonal injury. Damage can be focal (plaques) or diffuse (in diffusely abnormal and normal appearing brain tissue), occurs in both white and gray matter, and can be characterized by a combination of inflammation, demyelination and neurodegeneration. Clinically, the disease displays heterogeneity in neurological disability between and within patients.

MRI has been used increasingly over the past decades to depict inflammatory and neurodegenerative abnormalities and it has been established as the most important paraclinical tool in diagnosing MS. This has led to the incorporation of MRI criteria for the demonstration of dissemination in space (DIS) and dissemination in time (DIT) into the International Panel (IP) diagnostic criteria for MS. Next to ascertaining the diagnosis, MR imaging is used to exclude other conditions with similar clinical profiles, and to monitor disease progression and treatment effects. Furthermore, MRI can be used to obtain prognostic information in the early course of the disease, being able to predict conversion to clinically definite MS (CDMS) and to predict long-term disability in patients with a clinically isolated syndrome (CIS) suggestive of MS.

Much progress has been made in improving the dissociation between imaging and clinical disability in MS patients, the so-called clinico-radiological paradox, particularly with the application of advanced MRI techniques. The assessment of brain atrophy can classify (gray versus white matter) and quantify tissue loss, whereas relaxation-time mapping, Magnetization Transfer Ratio (MTR), and Diffusion Tensor Imaging (DTI) are able to quantify the extent of structural changes within lesions and show ‘occult’ damage to MS brain tissue, i.e. outside focal lesions in normal appearing brain tissue (NABT). Proton MR spectroscopy (1H-MRS) provides information on the biochemical and metabolic nature of these changes and functional MRI (fMRI) shows that the brain is capable of limiting clinical consequences of irreversible damage by a process called neuronal adaptation.
Next to developing advanced sequences and techniques to improve the software of MR imaging, great strides have been made in improving the hardware. Besides improvement in gradient and receiver coils, an important development is the introduction of high field 3 Tesla (T) MRI scanners. Currently these are widely available and increasingly used in many hospitals, particularly in MS centers.

Although high field MRI seems a promising modality to depict and classify the heterogeneity of MS pathology, this article will not tackle the ongoing debate on the interrelation between inflammation, demyelination and neurodegeneration of the disease.

**High Field MRI in MS: Conventional imaging**

The search for the impact of increasing magnetic field strengths on the visibility of MS lesions has existed since the introduction of MR imaging, as shown in studies comparing 0.5T with 1.0 and 1.5T.\textsuperscript{17-19} Currently, 3T MRI is considered as high field for clinical purposes, and field strengths of 4T and above are considered ultra-high field.

One of the major advantages of moving to high field MRI is the increase in signal-to-noise ratio (SNR) that follows an almost linear relation with magnetic field strength.\textsuperscript{20} This gain in SNR can be used either to improve spatial resolution or to reduce scan time - or a combination of both - leading to higher image quality and faster image acquisition.

**Table 1**

**Standard imaging protocol for brain and spinal cord MRI in MS patients.**

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Orientation</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLAIR</td>
<td>Sagittal + Axial</td>
<td>Supratentorial brain, especially juxtacortical and periventricular lesions</td>
</tr>
<tr>
<td>FSE/ TSE PD/T2</td>
<td>Axial</td>
<td>Infratentorial lesions</td>
</tr>
<tr>
<td>T1 pregadolinium</td>
<td>Axial</td>
<td>Optional</td>
</tr>
<tr>
<td>T1 postgadolinium</td>
<td>Axial</td>
<td>Inflammatory lesions</td>
</tr>
<tr>
<td><strong>Spinal Cord</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSE/ TSE PD/T2</td>
<td>Sagittal</td>
<td>Focal demyelinating lesions</td>
</tr>
<tr>
<td>T1 postgadolinium</td>
<td>Sagittal</td>
<td>Inflammatory lesions</td>
</tr>
</tbody>
</table>

Modified according to Simon et al. (2006).\textsuperscript{21} MRI = Magnetic Resonance Imaging, MS = Multiple Sclerosis, FLAIR = Fluid Attenuated Inverse Recovery, FSE = Fast Spin Echo, TSE = Turbo Spin Echo, PD = Proton-density weighted, T2 = T2-weighted, T1 = T1-weighted, SE = Spin Echo

**Detection of inflammatory white matter pathology**

Imaging guidelines for conventional brain MRI in the diagnosis of inflammatory CNS disease recommend a multi-sequence protocol consisting of 3 sequences (table 1).\textsuperscript{21,22} The first is a sagittal (preferably 3D) fluid attenuated inverse recovery (FLAIR) image to depict the supratentorial brain, providing the highest sensitivity in detection of lesions close to the
cerebrospinal fluid (juxtacortical and periventricular lesions). Second is proton-density (PD)/T2-weighted fast spin echo (FSE) or turbo spin echo (TSE) imaging, being highly sensitive for detection of white matter (WM) lesions particularly in the infratentorial WM. Final recommendations in the protocol are pre- (optional) and post-contrast-enhanced T1-weighted images, which allow visualization of ‘active’ lesions, i.e. the ones associated with inflammatory activity and blood-brain-barrier breakdown. For patients who present with symptoms at spinal cord level, or when brain MRI analysis is equivocal, the protocol recommends MR imaging of the spinal cord (post-contrast T1-weighted and FSE/ TSE PD/T2 weighted sequences).

Images are evaluated for radiological findings as seen in inflammatory diseases, concentrating on focal and diffuse white and gray matter abnormalities. MR images obtained from patients with suspected MS are analyzed according to MRI criteria for DIS (Barkhof, Swanton),\textsuperscript{23,24} and the recently revised IP diagnostic criteria for MS, which are based on magnetic field strengths of 0.5 - 1.5T.\textsuperscript{6,25} With 3T MRI scanners being used more routinely in the clinical setting, one should question the accuracy of these criteria in determining lesion load in (suspected) MS. When comparing high (3T/ 4T) to lower (1.5T) field strength MRI in MS patients, conclusive finding is an improved detection of WM lesions and contrast-enhanced lesions (table 2).\textsuperscript{26-31} Another important finding is that at high field, more lesions are detected in anatomical regions important for establishing the diagnosis MS according to diagnostic criteria, such as periventricular, juxtacortical and infratentorial WM lesions (figure 1).\textsuperscript{31,32} The improvement in infratentorial lesion detection is also important to gain information on prognosis of the disease, since these lesions have important prognostic value in the prediction of long-term disability in patients with CIS suggestive of MS.\textsuperscript{8}

Detection of gray matter pathology
Gray matter (GM) pathology (cerebral cortex and deep GM structures) is a key feature of MS pathology. It is already present in the earliest stages of the disease and is accumulating and accelerating more in the later and progressive phases.\textsuperscript{33} GM damage can manifest as a mixture of focal demyelinating lesions and diffuse pathology. Early pathological studies already acknowledged the extensive involvement of GM in MS.\textsuperscript{14,35}
Fig. 1. Image examples of the higher sensitivity in the detection of inflammatory brain lesions at 3.0 T in comparison with 1.5 T (a–f). Top row (a, b): A 23-year-old male presenting with unilateral optic neuritis. An inflammatory lesion in the left hemisphere of the cerebellum (arrow) was clearly identified on the T2-weighted TSE images at 3.0 T but not on the corresponding 1.5 T examination. Middle row (c, d): Axial FLAIR sections of the same patient. A small lesion in the brain stem and a lesion in the right temporal lobe (arrows) could be visualized on the 3.0 T image but not on the corresponding 1.5 T image. Bottom row (e, f): Axial FLAIR sections of the supratentorial brain of a 45-year-old female presenting with optic neuritis of her left eye. A small juxtacortical lesion (arrow) was prospectively identified on the 3.0 T image but was missed on the 1.5 T examination. Another lesion, which is probably a mixed white matter-grey matter lesion (arrow), is sharply delineated on the 3.0 T image but more fuzzy and smaller on the 1.5 T image. (Images reproduced from: Wattjes MP, Lutterbey GG (2006) Higher sensitivity in the detection of inflammatory brain lesions in patients with clinically isolated syndromes suggestive of multiple sclerosis using high field MRI: an intraindividual comparison of 1.5 T with 3.0 T. Eur Radiol 16:2067-73; with permission)
Table 2

**MS Lesion detection using high field MRI, in White Matter and Gray Matter**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (n)</th>
<th>Field strength used (sequence)</th>
<th>Most important results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White Matter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keiper et al. (1998)</td>
<td>CDMS (15)</td>
<td>1.5T vs. 4T (T2w FSE)</td>
<td>WM lesion detection increase of 45%</td>
</tr>
<tr>
<td>Erskine et al. (2005)</td>
<td>SP (8)</td>
<td>1.5T vs. 4T (T1w, PD/T2w)</td>
<td>WM lesion detection increase 46% Total WM lesion volume increase 60%</td>
</tr>
<tr>
<td>Sicotte et al. (2003)</td>
<td>RR, SP (25)</td>
<td>1.5T vs. 3T (T1w +/-Gd)</td>
<td>Increase in detection of CE WM lesions of 21% Lesion volume CE WM lesion increase 30% Total WM lesion volume increase 10%</td>
</tr>
<tr>
<td>Bachmann et al. (2006)</td>
<td>RR, PP, SP (22)</td>
<td>1.5 vs. 3T (FLAIR)</td>
<td>3T imaging superior in lesion conspicuity and quality Significantly more artefacts at 3T Total WM lesion detection increase 42%</td>
</tr>
<tr>
<td>Nielsen et al. (2006)</td>
<td>Acute ON (28)</td>
<td>1.5T vs. 3T (T1w SE +/-Gd, PD/T2w TSE, FLAIR)</td>
<td>24% increase in detection of CE WM lesions, 26.5% increase in FLAIR lesions</td>
</tr>
<tr>
<td>Wattjes et al. (2006)</td>
<td>CIS (40)</td>
<td>1.5T vs. 3T (T1w SE +/-Gd, T2w TSE, FLAIR)</td>
<td>13% increase in WM lesion detection 7.5% increase in CE WM lesion detection Especially in the infratentorial, juxtacortical and periventricular anatomic region important for diagnosis</td>
</tr>
<tr>
<td><strong>Gray Matter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wattjes et al. (2007)</td>
<td>CIS, CDMS (26)</td>
<td>3T (2D-DIR, T2w TSE, FLAIR)</td>
<td>DIR detected a 7% and 15% increase in lesions compared to FLAIR and T2w imaging respectively Especially in infratentorial region</td>
</tr>
<tr>
<td>Simon et al. (2010)</td>
<td>CIS, CDMS (34)</td>
<td>1.5T vs. 3T (T1w SE +/-Gd, T2w TSE, FLAIR)</td>
<td>3T DIR detected 192% more intracortical lesions and 30% more mixed WM/WM lesions than 1.5T.</td>
</tr>
</tbody>
</table>

MS = Multiple Sclerosis, MRI = Magnetic Resonance Imaging, CDMS = Clinically Definite Multiple Sclerosis, T = Tesla, T2w = T2-weighted, FSE = Fast Spin Echo, WM = White Matter T1w = T1-weighted, PD = Proton-density weighted, SP = Secondary Progressive, RR = Relapsing Remitting, Gd = gadolinium, CE = Contrast-enhancing, PP = Primary Progressive, FLAIR = Fluid Attenuated Inverse Recovery, ON = Optic Neuritis, TSE = Turbo Spin Echo, CIS = Clinically Isolated Syndrome, SE = Spin Echo, DIR = Double Inversion Recovery

Notwithstanding the recent focus of MRI research on GM abnormalities, thus far GM (especially subpial intracortical) lesions are still vastly underdetected by conventional *in vivo* MRI studies when compared to pathological studies. The sensitivity of conventional imaging techniques (T1, PD/T2, FLAIR) in detecting GM damage is poor, because these techniques lack the necessary contrast and resolution to visualize cortical demyelination. The pathophysiology and histopathology of cortical lesions - less inflammatory cell infiltration, no complement activation or blood-brain-barrier damage - and low myelin content of GM, plus partial volume effects from cerebrospinal fluid (CSF) on MRI all contribute to this.

Improvement in the sensitivity of GM lesion detection was established with the introduction of the GM specific Double Inversion Recovery (DIR) sequence, higher resolution imaging of GM by the use of high field MRI and of course the combination of these two. The development of DIR, which is not included in the conventional MR imaging protocol on regular basis, leads to an improved (gray-white) contrast by depicting only GM. This is managed by employing two inversion pulses leading to an attenuation of both CSF and WM. Disadvantages are its rather
low SNR due to the double signal inversion pulses, and the propensity to (flow and pulsation) artefacts particularly in the posterior fossa. The development of multi-slab and later single-slab 3D-DIR applications meant a great improvement:

\[ \text{a fivefold increase in cortical lesions in MS patients compared to conventional T2-weighted sequences was detected.} \]

In addition, an improved distinction could be made between mixed gray-white matter lesions and purely intracortical lesions.

The introduction of high field imaging did not immediately lead to an increase in cortical lesion detection, when applied in post-mortem research using conventional proton-density (PD) sequences on a 4.7T MRI system. The majority of GM lesions were still missed; contrast between GM and GM lesions was found to be very low, independent of sequence or field strength. The combination of higher magnetic field strengths with DIR sequences in vivo appeared to be more successful in visualizing GM pathology. At 3T, DIR was superior to the standard sequences in the detection of WM, mixed WM/GM and intracortical GM lesions (table 2). Interestingly, one of these studies also demonstrated superiority of DIR at 3T compared to other sequences for infratentorial WM lesions, which is clinically highly important as stated above. Both studies made use of a 2D-DIR sequence; implementing 3D-DIR at higher magnetic field (3T) might result in further improvement of lesion detection by reducing artefacts, but will be accompanied by an increase in acquisition time.

Improved depiction of GM damage was achieved in studies using ultra-high field strengths (7T and higher), of which results will be described in more detail below.

The focus on how to depict GM damage has high clinical relevance, because cortical damage differs between MS disease types and stages, and shows a relation to physical as well as cognitive disability. Furthermore, when including the presence of intracortical GM lesions in MRI diagnostic criteria, an increase in accuracy of these criteria has been reported. However, an official introduction of GM lesions into the diagnostic criteria has not yet been made and needs further multicentre validation. A step in the right direction was recently made by developing consensus recommendations for MS cortical lesion scoring using DIR.

**Detection of active inflammatory pathology**

Magnetic field strength influences tissue relaxation times. At 3T MRI, T1 (spin lattice/longitudinal) relaxation time increases by 20-40%, whereas T2 (spin spin/ transverse) relaxation time decreases by about 5-10%. When using T1-shortening contrast agents at higher field strengths, e.g. paramagnetic gadolinium-based contrast agents, the overall longer high field T1 relaxation times will create a relatively stronger effect of T1-reduction by the contrast agent. This causes a greater post-contrast signal intensity difference at 3T when compared to 1.5T, which increases the detection of contrast enhancing inflammatory lesions in MS (figure 2). It may even allow dosage reduction at higher field strengths. Nonetheless, due to decreased GM-WM contrast with increasing magnetic field it remains challenging to develop a SE T1 sequence at high field MRI systems, which is the standard sequence to detect inflammatory lesions at lower field strengths.

Paramagnetic contrast agents based on iron oxides like (ultra) small particles of iron oxide ((U)SPIO), which have shown pluriformity of inflammatory MS pathology complementary to gadolinium-enhanced 1.5T MRI, have not yet been applied at higher magnetic fields.
Fig. 2. Image examples of increased detection of contrast-enhanced inflammatory brain lesions at 3T in comparison with 1.5T (A–C). Multiple lesions are seen in the 3T FLAIR image of a relapsing remitting MS patient. At (B) 3T post-contrast T1-weighted image, a contrast-enhancing lesion with a perivascular location can be visualized (arrow). This lesion could not be identified at corresponding 1.5T post-contrast images (C).

Detection of spinal cord pathology
MR imaging of the spinal cord has gained more importance in establishing the diagnosis of MS, particularly in the recent IP criteria. As we know from standard field strength studies, conventional MRI shows asymptomatic spinal cord lesions in 30-40% of CIS patients and in up to 90% of CDMS patients. Next to aiding in diagnosis and differential diagnosis, imaging of spinal cord abnormalities is relevant because they are related to clinical outcome. Advanced MR techniques are sensitive to tissue damage in the spinal cord, and are related to clinical outcome measures as well.

Fig. 3. Image examples of the higher sensitivity in the detection of brain lesions at 7T in comparison with 3T (A–D) Top row: Axial reformatted (A) 7T 3D-MP-FLAIR and (B) 3T 3D-FLAIR images of a 37-year-old female secondary progressive MS patient. A cortical lesion (closed arrowhead) can be identified at 7T, but not at the corresponding 3T image. A deep white matter lesion (open arrowhead) is visible at both field strengths. Bottom row: Sagittal (C) 7T 3D-MP-FLAIR and (D) 3T 3D-FLAIR images of a 50-year-old male primary progressive MS patient. Arrows indicate examples of lesions visible at 7T but not on the corresponding 3T image; the images also show multiple lesions that are visible at both 7T and 3T.
Post mortem studies at high field MRI showed a better visibility of MS spinal cord pathology including quantitative and GM abnormalities, but the in vivo use of higher magnetic field strengths for imaging spinal cord remains problematic, mainly due to susceptibility, CSF and pulsation artefacts. In contrast to brain MRI studies, in vivo comparison of 1.5T and 3T spinal cord MRI showed no significant differences in terms of lesion detection and correlations with clinical measures such as EDSS. A recent study investigating spinal cord volumes at 3T MRI described a decrease in cervical spinal cord volume in progressive forms of MS and a trend towards increased spinal cord volume in relapsing remitting (RR) MS/ CIS patients, which the authors refer to respectively as atrophy and inflammation/ oedema related expansion.

**Clinical value of conventional high field MRI in terms of diagnostic criteria**

As described, studies investigating the influence of higher magnetic field strengths on lesion load measurement showed an evident improvement in lesion detection. However, the crucial question remains if 3T MRI scanners are of added clinical value in terms of an earlier diagnosis of MS. High field 3T MRI scanning proved to be able to substantially influence classification of CIS patients according to Barkhof MRI criteria: 27.5% of the 40 patients studied fulfilled 1 additional criterion. Diagnostic classification in terms of DIS was mildly influenced: only 1 additional patient had DIS at 3T when compared to 1.5T examinations. During follow-up no additional patients showed DIT at 3T compared to 1.5T examination, neither to the revised IP criteria nor to the Swanton criteria. Hence using the 2005 IP criteria, 3T MRI does not lead to an earlier diagnosis of MS. When retrospectively applying the data of this cohort to the more liberal 2010 revised IP Criteria that are based on MRI criteria developed by the MAGNIMS group, again no earlier diagnosis of MS could be established at 3T when compared to 1.5T. From these studies can also be concluded that when using the revised IP criteria, 3T MR imaging is safe and does not lead to field strength influenced overdiagnosis of MS due to false positive detection of WM lesions. However, this conclusion together with the statement that in CIS patients there is no added clinical value of high field 3T MRI above standard 1.5T MRI, might be too premature, since it was only based on one rather small, single-centre and single-vendor dataset. Future studies might lead to new and improved criteria for the diagnosis of MS, based on (ultra) high field MR imaging in combination with novel sequences such as DIR.
Ultra-high Field strength MRI in MS

Although high field 3T MR imaging showed advantages over lower field strength imaging, the true future of MRI in MS might reside in ultra-high field MRI systems (>4T). Since 2000, when the US Food and Drug Administration (FDA) gave approval for in vivo high field imaging with magnetic field strengths up to 8T, researchers worldwide started moving up to ultra-high field MRI. In MS research the ultra-high field machine most commonly used for in vivo brain imaging is a 7T whole-body MRI scanner.

Implementation of in vivo 7T MR imaging is technically challenging, since disadvantages of scanning at high field are even more distinct when using ultra-high magnetic field. From our own experience we can state that sequences that are robust at 1.5 and 3T MRI do not result in high quality images at 7T. Main problems are practical issues related to heterogeneity of the magnetic field and maximum specific absorption rate (SAR) limitations, leading to artefacts that make full brain coverage seemingly difficult. At present, the major drawbacks of 7T MR imaging are solved and the first interesting observations of its application in MS research are being published. There are two crucial findings of ultra-high field MR imaging in MS: firstly, an increased detection of lesions when compared to lower field strengths, as would be expected from increased resolution and SNR. Secondly, the depiction of additional features of MS pathology, revealing a heterogeneity that is not visible at lower field strength.

Fig. 4. Example of a deep white matter lesion in a 43-year-old male MS patient, which showed a hypointense ring at (A) 7T 3D-MP-FLAIR (arrow) that can also be seen on (B) a SWI image (arrow), suggestive of iron deposition.
Fig. 5. Single-voxel 1H-MR spectra (TR/TE 2000/38 ms) at 3T from the centrum semiovale of a healthy control (A) and from an MS patient (B), where the MRS volume includes a white matter lesion (B). The most prominent finding in the patient’s spectrum is the strong decrease of the peak from N-acetyl components (tNAA), but also other metabolites like myo-inositol (MI) and choline compounds (Cho) show characteristic alterations (increase) in their peak intensities. Please note the multiplet of MI, which is not visible at lower field strengths because of overlap with glutamate and glutamine signals. (Provided by Dr. Frank Träber, Radiologische Klinik der Universität Bonn)
Increased MS lesion detection using ultra-high field MRI

Post mortem studies using ultra-high magnetic field strengths discovered cortical lesions at 8T that remained invisible at 1.5T. At histopathological verification often these cortical lesions could only be found after observing the 8T MR images. A recent post mortem study showed that 3D-T2* GRE and white matter attenuated TFE sequences at 7T were able to detect most cortical lesions verified by pathological examination. Unfortunately, both post mortem studies have used a limited amount of patients and further validation with a larger number of samples is warranted.

In vivo studies using ultra-high magnetic field strength show increased detection of MS lesions in WM as well as in cortical GM. Especially the improvement in detection of cortical GM lesions is important, since the depiction of this type of lesions has been difficult at lower field strengths. Mainero et al. found that 7T MR images were able to differentiate cortical lesions in accordance with histopathological lesion types (type 1: leukocortical, type 2: intracortical, type 3/4: subpial extending partly/ completely through cortical layers). Type 3/4 was found the most frequent type of cortical plaques (50.2%) and this type was also related to higher EDSS scores. In vivo studies comparing advanced sequences between 7T MRI and lower field strength do not exist, but our own data shows that 3D-FLAIR and 3D-DIR using magnetic preparation (MP) allows high quality T2-weighted MR imaging in MS at 7T, and improves lesion detection when compared to 3T (figure 3).
Table 3.
**MS lesion detection at ultra-high magnetic field strength MRI, post mortem and in vivo**

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Patients (n)</th>
<th>Field strength (sequence)</th>
<th>Most important results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kangarlu et al. (2007)</td>
<td>SP (1)</td>
<td>1.5T vs. 8T (GRE, T2w SE, FLAIR)</td>
<td>Detection of cortical lesions that remained invisible at 1.5T. At histopathological verification cortical lesions could only be found after observing 8T images.</td>
</tr>
<tr>
<td>Pitt et al. (2010)</td>
<td>SP (3)</td>
<td>7T (3D T2* GRE, WM attenuated TFE)</td>
<td>Detection of 93% (3D T2* GRE) and 82% (WM attenuated TFE) of cortical lesions compared to pathological examination.</td>
</tr>
</tbody>
</table>

**Post mortem**

**In vivo**

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Patients (n)</th>
<th>Field strength (sequence)</th>
<th>Most important results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolia et al. (2009)</td>
<td>(12)</td>
<td>1.5T vs. 7T (T1w, PD/T2w)</td>
<td>23% increased WM lesion detection at 7T. Better differentiation between juxtacortical and cortical lesions at 7T.</td>
</tr>
<tr>
<td>Mainero et al. (2009)</td>
<td>RR, SP (16)</td>
<td>7T (3D-T1w MPRAGE, FLASH T2* GRE, T2w TSE)</td>
<td>7T is able to classify cortical lesion according to histopathological lesion type: type 1 (36.2%), type 2 (13.6%), type 3-4 (50.2%). Cortical lesion type 3-4 was related to higher EDSS score.</td>
</tr>
</tbody>
</table>

**MS = Multiple Sclerosis, MRI = Magnetic Resonance Imaging, SP = Secondary Progressive, T = Tesla, GRE = Gradient Echo Sequence, T2w = T2-weighted, SE = Spin Echo, FLAIR = Fluid Attenuated Inverse Recovery, WM = White Matter, TFE = Turbo Field Echo, T1w = T1-weighted, PD = Proton-density weighted, RR = Relapsing Remitting, MPRAGE = Magnetization Prepared Rapid Gradient Echo, FLASH = Fast Low angle Shot, TSE = Turbo Spin Echo**

Visualizing heterogeneity of MS lesions at ultra-high field

The main focus of ultra-high field imaging in MS patients thus far has been on heterogeneity of lesions, which is studied by making use of the increased magnetic susceptibility at higher field. Susceptibility weighted imaging (SWI) identified the relationship between MS lesions and vasculature, and confirmed that MS lesions follow a strict perivascular distribution.\textsuperscript{45,78-81} That perivenular inflammation plays a role in MS was already identified in histopathological studies, but the possibility to visualize it in vivo provides opportunities to further investigate what determines lesion location (in a longitudinal setting) and it might help in differentiating MS from ischemic WM lesions.\textsuperscript{82}

Another specific feature discovered by ultra-high field SWI in a subset of MS lesions are hypointense rims (figure 4).\textsuperscript{45,47,79} Hammond et al. explained these rings to reflect iron-rich macrophages at the periphery of a lesion, which may indicate the site of active inflammation in tissue and might be of help in staging the disease.\textsuperscript{79} Post mortem pathology studies have identified this iron accumulation in MS plaques as well.\textsuperscript{83} Pitt et al. reported the hypointense rims to correspond to increased density of activated microglia.\textsuperscript{47} Hypointense rims have not been conclusively identified at 1.5T.\textsuperscript{45}
At even higher field strengths (9.4T) T2-weighted scanning was able to discriminate areas of remyelination and demyelination in post mortem MS lesions. More recently, the same authors investigated 21 tissue samples of multiple sclerosis motor cortex and found 28 GM cortical lesions that were visible both on T2-weighted MRI as well as on sections immunostained for myelin basic protein. Furthermore, a correlation between quantitative MR and quantitative histology was made, which suggested that in cortical GM T1 relaxation time differences may be a predictor of neuronal density and T2 relaxation time differences may predict myelin content. When these results can be translated into in vivo studies for instance at 3T or 7T, they might possibly have great impact on clinical translation of demyelination and neuronal loss.

**High Field MRI in MS: Quantitative imaging**

Several quantitative MRI modalities have been developed to gain more information concerning heterogeneity of pathological substrates of MS abnormalities, with respect to the extent of inflammation, demyelination, axonal injury, gliosis and remyelination as reported in pathological studies. These advanced techniques are also used to depict damage that is ‘occult’ on conventional MRI, and to narrow the clinico-radiological dissociation between clinical disability and imaging findings. The availability of high field MRI systems is beneficial to quantitative techniques such as proton magnetic resonance spectroscopy, diffusion weighted imaging and functional MRI in MS.

**High Field Proton Spectroscopy**

Proton magnetic resonance spectroscopy (1H-MRS) is a complementary modality to conventional MRI: it depicts and quantifies the biochemical and metabolic nature of tissue abnormalities. Measuring metabolite changes in brains of MS patients provided information on the pathogenesis and the natural history of the disease. The most important metabolites that are quantified in MS spectroscopy are N-acetyl-aspartate (NAA) being a measure of axonal integrity, Myoinositol (mI) reflecting glial cell activity and Choline (Cho) as an indicator of membrane turnover. In acute MS lesions ml and Cho are increased indicating myelin breakdown, whereas NAA is reduced reflecting axonal damage. In chronic MS lesions, Cho values have returned back to normal, whereas the elevated ml and reduced NAA remain evident. Next to metabolic changes in focal lesions, 1H-MRS also shows differences in metabolite concentrations in NABT (normal appearing WM and GM). The NAA reduction in MS lesions on H-MRS is related to greater clinical disability in MS patients. Moving to ultra-high field strength, these advantages become even more distinct: at 7T 1H-MRS a broad range of brain metabolites can be detected with increased sensitivity, total measurement time can be significantly reduced or the spatial resolution significantly increased, relative to 4T. In addition, new metabolites can be investigated, such as gamma amino butyric acid (GABA), as has been shown at 9.4T in rats.
The question remains what is the added value of better metabolic quantification at higher magnetic field strengths in MS patients? Despite the fact that high field $^1$H-MRS studies of MS patients are limited, the published results are promising. As assessed by 3T $^1$H-MRS, significant axonal damage (decreased NAA) already becomes apparent during the first demyelinating episode in patients with CIS, suggesting early neurodegeneration in MS. This in contradiction to glial cell activity (increased mi) at 3T, which was not increased in CIS patients until later on: in patients with a very early course of RRMS. The decrease in NAA reflecting axonal injury in CIS patients also has a prognostic function in predicting the conversion to definite MS.

The possibility to study glutamate metabolism at 3T $^1$H-MRS was used in MS patients and showed a significant elevation in glutamate in acute, gadolinium-enhanced lesions as well as in NAWM, whereas no glutamate elevation was visible in chronic lesions; this might render quantification of glutamate suitable as a marker for active inflammation.

Increasing magnetic field strength offers chances for new techniques, such as sodium 23 ($^{23}$Na) imaging, which showed deviant sodium values in lesions, NAWM and GM of RRMS patients. This might reflect changes in cellular and metabolic integrity and has the potential to provide insight into pathophysiological mechanisms of tissue injury.

The only study using $^1$H-MRS at 7T in MS patients quantified glutathione (GSH), a marker of oxidative status. Because of its low concentrations in the brain and its overlap with NAA, at lower field strengths this antioxidant is difficult to quantify. At 7T, MS patients compared to healthy controls showed a significant reduction in GSH concentration in GM lesions, implying a diminished protection against free radicals.

**High Field Diffusion Imaging**

Diffusion weighted imaging (DWI) measures Brownian motion of water molecules in tissues. Demyelination and remyelination in MS change the geometry of brain tissue orientation and thereby influence water diffusivity of tissues. Because of this, diffusion imaging has been widely used to study MS related tissue damage. If not only total diffusivity is measured, but the direction of the maximal diffusivity as well, diffusion weighted imaging is referred to as diffusion tensor imaging (DTI). DTI quantifies diffusivity in MS patients, by measuring apparent diffusion coefficient (ADC), mean diffusivity (MD) and fractional anisotropy (FA), as well as radial and axial diffusivity.

In MS patients, DTI at 1.5T provided information about tissue damage in focal lesions and in the NABT: a decrease in anisotropy (FA) and an increase in diffusivity (ADC and MD) were reported, compared to healthy controls. DTI abnormalities are more pronounced in focal lesions than in NAWM and are most severe in T1 hypointense lesions representing irreversible tissue damage. The characteristics of enhancing MS lesions are not well defined: although FA values are consistently lower in enhancing than in non-enhancing lesions, MD values in enhancing lesions vary or do not seem to differ between enhancing and non-enhancing lesions.

DTI alterations are more pronounced with increased disease duration and show a correlation with clinical disability. The strongest correlation was found to the diffusion characteristics of T2 lesions and GM, with GM abnormalities being more severe in progressive disease. Benedict et al. reported a significant correlation between DTI values and cognitive dysfunction.

Despite the promising results of the application of 1.5T DTI in MS research, the technique has shortcomings that can be amended by moving to higher magnetic field. Diffusion imaging
offers poor spatial resolution and marginal SNR since the use of diffusion gradients causes distortion and attenuation of signal. High field DTI should be beneficial because of an increased SNR, although stronger susceptibility artefacts at higher field strengths decrease image quality. The implementation of high field DTI faces several technical challenges. Firstly, the mapping of many different diffusion directions is time consuming, a problem that is slightly more pronounced at higher magnetic field strength because increased T1 relaxation times need longer repetition times. Secondly, to limit bulk motion DTI is in need of fast acquisition protocols. Rapid scanning is usually acquired by using spin echo single shot EPI sequences which, unfortunately, at higher field have the disadvantage of image blurring and geometric distortions near air/tissue transitions. These difficulties have been largely overcome by combining high field 3T MRI scanners with parallel imaging techniques that reduce EPI artefacts and reduce acquisition times.\textsuperscript{113-115}

The use of 3T DTI in the field of MS research focused on anatomical regions that are difficult to study at lower field strength, such as GM. Ceccarelli et al., who reported that 3T DTI is feasible and shows decreased FA and increased MD in NAWM, made the first observations of DTI at high magnetic field, and confirmed abnormalities (increased water diffusivity and decreased gray matter volume) in the GM of MS patients.\textsuperscript{116} In a second study the authors found that DTI at 3T shows regional differences in WM damage between subtypes of MS: benign MS and RRMS.\textsuperscript{117} In terms of global DTI metrics no differences were seen, which indicates that the topographical differences might be associated to clinical heterogeneity between different MS subtypes. Two other DTI studies at 3T were performed in MS patients related disability to corticospinal tract and optic tract abnormalities.\textsuperscript{118,119}

High Field Functional MRI
When neurons are activated, blood flow to this specific brain region is increased. The oxygenated-deoxygenated haemoglobin ratio changes with it, causing small variations in the local magnetic field (T2\textsuperscript{*}). Functional MRI (fMRI) measures these variations in blood oxygen level dependent (BOLD) contrast and creates an indirect measure of brain activity. At standard field strength fMRI has provided insight into different aspects of MS brain functioning focusing on visual, cognitive and motor networks. Compared to healthy controls, MS patients first show increased recruitment of brain regions for a specific task, followed by bilateral activation of these regions and at a later stage recruitment of additional brain regions.\textsuperscript{120} Comparing the results of brain function to structural MRI damage in MS patients suggested the existence of ‘brain plasticity’: the capability of the MS brain to compensate for irreversible structural damage, so-called cortical reorganization/ adaptation. That these cortical reorganization processes already occur in the earliest phases of the disease was shown in studies concerning CIS patients, in which functional changes were associated with the development to definite MS.\textsuperscript{121,122} Functional changes in MS brains vary between disease types and different stages of the disease.\textsuperscript{121-124} The inter-individual efficacy of brain reorganization might play a major role in clarifying clinical heterogeneity of MS.

Functional imaging benefits greatly from higher field strengths, in the first place because of the rise in SNR and secondly due to the stronger magnetic susceptibility effects. The BOLD contrast increases with magnetic field strength (BO),\textsuperscript{125,126} since the difference between deoxygenated blood (paramagnetic) and surrounding tissue (diamagnetic) increases with field strength, allocating a shorter TE and thus higher SNR and shorter acquisition times. Higher signal and higher spatial resolution on high field fMRI increase reliability in localising brain activity. But more importantly, high field fMRI enables the depiction of brain activity in additional (smaller) brain
regions, which cannot be visualized at lower field strengths. While studying cognitive function at 3T, Hoenig et al. detected additional activation in cortical areas involved in higher executive motor functions, when compared to functional 1.5T MR imaging.\textsuperscript{127}

High field fMRI in MS patients was used by Rocca et al., who focused on a part of the brain that could not be visualized with fMRI at standard field strength and reported increased activation of the mirror neuron system in patients with MS.\textsuperscript{128} These preliminary findings suggest a possibility that mirror neurons play a role in cortical reorganization. When the same study group focused only on PPMS patients using 3T fMRI, they saw an increased recruitment of cognition related networks with the potential to limit the severity of cognitive impairment.\textsuperscript{129}

Next to focusing on changes in the extent of brain activation or on the additional recruited regions, high field fMRI can also be used in combination with other modalities, to investigate functional and structural substrates of functional changes. Diffusion Tensor MRI tractography integrated with fMRI at 3T showed that functional connectivity is correlated to structural damage to some of the major brain WM bundles, when investigating motor and cognitive disability in MS patients.\textsuperscript{130-132} This association between damage to specific WM tracts and fMRI changes presents the opportunity for further investigation in a longitudinal setting to gain insight in functional reorganization of MS related structural damage.

Further advantages of fMRI at higher field strength are the reduction of acquisition time and the possibility to follow cortical stimulation in real time.\textsuperscript{133}

**High Field Relaxation Time Mapping**

At standard 1.5T MRI, T1 relaxation time mapping in MS has shown abnormalities in normal-appearing WM and GM that are not visible on conventional images.\textsuperscript{134,135} At (ultra) high field, increased T1 relaxation times together with increased SNR that enables the use of higher spatial resolution, are expected to enhance sensitivity of detecting abnormal brain tissue. An example of a high resolution T1 relaxation time map of an MS brain at 7T is shown in figure 7. Although T2 relaxation times are less dependent on the main magnetic field, higher SNR and spatial resolution reduce partial volume effects and are therefore expected to improve T2 relaxation time measurements at high field.
Fig. 7. High resolution T1 relaxation time map at 7T of a female primary progressive MS patient. Whole brain T1 maps with a spatial resolution of ca. 1 x 1 x 1.5 mm can be obtained in 5 minutes at 7T. Compared to lower field strengths, accuracy is increased because of higher SNR and higher spatial resolution reducing partial volume effects. This might help to detect damage to normal-appearing white and gray matter in MS.

Neurodegenerative aspects of neuroinflammation

Besides neuroinflammation MS also comprises neurodegenerative aspects, which can be visualized by (high field) MRI. Atrophy can be quantified by using T1-weighted imaging, and shows moderate correlation with clinical status of MS patients.\textsuperscript{11,136,137} While atrophy measurements in MS patients have not yet been applied much at high field strengths, they offer possibilities to look at specific regions like cortex or subcortical GM nuclei.

A second feature of neurodegeneration is pathological iron deposition in the brain of MS patients, which is thought to be triggered by iron mediated oxidative stress.\textsuperscript{138} Along with this, iron deposition in MS can also be linked to inflammatory processes that cause local blood-brain-barrier breakdown and promotion of macrophages to inflammation sites.\textsuperscript{139,140}

Iron deposition in the brain, predominantly in the basal ganglia, is a function of increasing age,\textsuperscript{141} but can also be a pathological phenomenon of neurodegenerative disease.\textsuperscript{142} High field MRI is a valuable tool in imaging and quantifying iron deposition in MS brains, since high field imaging is more sensitive to T2-shortening effects of iron-rich structures in the brain, causing hypointensities.\textsuperscript{143,144} Magnetic susceptibility of protons influenced by local iron concentrations increase with magnetic field strength as well. Hence, (ultra) high field studies using SWI lend itself well to image pathological iron deposition. Increased iron concentrations in deep GM nuclei of MS patients have been depicted and quantified at high field MRI (figure 8), and results were related to clinical parameters such as cognitive performance and disease duration.\textsuperscript{79,145,146}

For an overview of high field MR imaging in neurodegenerative diseases, we refer to the chapter in the current issue written by Luijten et al.
Summary and Future perspectives

Over the past years the impact of high field MRI has been subject of research in inflammatory CNS diseases as MS. Both conventional and non-conventional techniques take advantage of higher magnetic field strength. Using conventional high field sequences leads to an increased detection of focal MS lesions: WM lesions particularly in anatomic regions that are important for the diagnosis, prognosis and differential diagnosis of MS. Great strides have been made in the depiction of GM cortical lesions as well, by combining 3T MRI with novel sequences as DIR and by the introduction of ultra-high field systems. When adequate imaging of cortical abnormalities is feasible, this can be related with specific clinical symptoms. The use of high field quantitative sequences provides more insight in pathological processes that cause (subtle) diffuse MS damage and show improved correlation with clinical outcome measures.

One crucial question remains whether there is any added clinical value of high field imaging in MS and whether 3T MR imaging will therefore evolve to be gold-standard in imaging of MS patients in the future. 3T MRI scanners are gradually used more and more in the clinical setting, lacking explicit scientific foundation for this, which gives rise to some debate. Therefore future research should focus on clinical relevance of high field MRI in order to justify the higher costs of high field MRI scanners. As mentioned, the use of 3T MRI does not lead to a significant earlier diagnosis of MS using the current IP diagnostic criteria based on the available data defined by 1.5T. However, further studies are desired including a larger study population or even the use of ultra-high field strength (7T) MRI, which might lead to the development of more specific, high field 3T / 7T diagnostic criteria for MS.

In any case, high field MRI will aid in understanding the pathogenesis and heterogeneity of the disease MS, but more important is its role in individual patient care in diagnosing, monitoring disease progression, establishing prognosis, and monitoring treatment effects. The use of increasing field strengths will undoubtedly be part of this, and seems most promising if combined with other technical advancements such as refinements in quantitative techniques, development of new sequences and improvement in hardware such as better coil technology.
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38


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