“If I can’t picture it, I don’t understand it.”

(Albert Einstein)
Chapter 1

INTRODUCTION
1.1 General introduction: 7T MRI in multiple sclerosis
Multiple Sclerosis: incidence and clinical profile

Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative disease of the central nervous system (CNS), and one of the most common causes of chronic neurological disability in young adults. In the Netherlands, the prevalence of MS is about 1 per 1000, the incidence 3.5 per 100,000. The disease affects women twice as often as men. The exact cause of MS remains unknown, although it is acknowledged that a combination of environmental exposure and genetic susceptibility contribute to its pathogenesis.

MS patients experience physical disability, including motor and sensory symptoms, problems of gait and coordination, visual problems, bowel bladder and sexual dysfunction, fatigue and epilepsy. Furthermore, up to 40-65% of MS patients are cognitively impaired. The clinical course of MS varies from patient to patient, with a great diversity of disability and disease severity. Secondly, the clinical course of MS varies within patients, meaning a diversity of symptoms occurs throughout the disease course, depending on the location in the CNS. Based on the disease course, MS can be divided into several clinical subtypes. A large proportion (80%) of MS patients have a relapsing remitting (RR) disease course, characterized by relapsing attacks of neurological disability followed by longer periods of remission, where symptoms resolve fully or partly. Eventually, around 65% of these RRMS patients develop a slow deterioration of physical and cognitive disability, in which no remissions occur: the secondary progressive (SP) phase of MS. Approximately 10-20% of the MS patients have a progressive course from the start of the disease: primary progressive (PP) MS. The life expectancy of MS patients is 5-10 years shorter compared to healthy people, and when MS is the cause of death it is mostly because of infections (and their complications) of respiratory tract, skin and bladder.

Acute relapses, the so-called “schubs”, are frequently being treated with corticosteroids. In the relapsing-remitting course, immune modulating treatments are an option. Different types of interferon beta and glatiramer acetate decrease the frequency of attacks by approximately 30%, and decrease the formation of inflammatory lesions. For RRMS patients in whom these immune modulating therapies are not effective, newer immunosuppressive therapies such as natalizumab, alemtuzimab (intravenous administration), fingolimod, teriflunomid and dimethylfumarate (oral administration) are used. Unfortunately, still no treatment options for the progressive subtypes of MS are available.

Multiple sclerosis: diagnosis and differential diagnosis

Magnetic resonance imaging (MRI) is the most important tool for the establishment of MS diagnosis, in addition to clinical assessment. International consensus has led to a standardized MRI protocol of the brain and spinal cord (box 1). The macroscopically visible sclerotic plaques are seen on MRI as lesions, which can be detected in the corpus callosum, white matter (WM), cortical and deep grey matter (GM), optic nerves, brainstem, cerebellum and spinal cord. MS lesions appear hyperintense on T2-weighted and hypointense on T1-weighted images. The diagnosis MS on MRI is based on the frequency and distribution of these lesions throughout the CNS. The MRI diagnostic criteria, as recommended by the International Panel, are based on dissemination of the disease in space (DIS, multiple lesions in different regions) and in time (DIT, development of new lesions over time). The official formulation of the MRI criteria can be seen in box 2. In combination with the clinical symptoms, the MRI criteria form the diagnostic McDonald criteria, established in 2001, followed by revisions in 2005 and 2010.
The differential diagnosis of MS is wide and complex: many neurological diseases can mimic MS clinically and radiologically. In terms of radiology, the sensitivity of MRI to the detection of lesions in the WM of the brain is high. However, specificity remains low due to other disorders that show WM brain lesions as well, such as vascular disorders (ischemic small vessel disease, vasculitis) and neuroinflammatory disorders (Susac syndrome, Behcets disease, sarcoidosis). The addition of spinal cord imaging in the MRI protocol has improved specificity of MS differential diagnosis, since spinal cord lesions are uncommon in other neurologic diseases. Nevertheless, there is still a search for ways to further improve the differentiation of MRI-visible lesions in the brain. One of the largest challenges is the differentiation of MS lesions from age-related vascular WM lesions, which are presumably caused by cerebral small vessel disease (CSVD). WM lesions caused by CSVD are highly prevalent, even in the healthy middle-aged population. Starting in the third decade of life, prevalence increases with advancing age: in the age-group 45-55 years, WM signal changes occur in more than 50% of asymptomatic persons. For the differentiation between MS and vascular lesions we use specific characteristics of MS lesions: they stretch from the lateral ventricles into the WM, following the small vessels that run perpendicular to the ventricles, so-called Dawson’s fingers. Furthermore, juxtacortical lesions, i.e. lesions adjacent to the cortical GM involving the U-fibers, are specific for MS.

**Box 1. Standardized clinical MRI protocol for brain and spinal cord imaging in MS**

<table>
<thead>
<tr>
<th>Brain</th>
<th>Axial proton density (PD)/T2-weighted</th>
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<tr>
<td></td>
<td>Sagittal Flair (preferably 3D acquisition)</td>
</tr>
<tr>
<td></td>
<td>Axial T1- weighted (turbo/fast) spin-echo post contrast</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Sagittal PD-/T2-weighted</td>
</tr>
<tr>
<td></td>
<td>Sagittal T1-weighted</td>
</tr>
</tbody>
</table>

* Slice thickness of 3 mm and inplane spatial resolution of 1 x 1 mm² (voxel size 3x1x1mm) are recommended

**Box 2. 2010 McDonald MRI criteria**

**Dissemination in space (DIS)**

≥ 1 T2 lesion* in at least 2 of 4 areas of the CNS:

- Periventricular
- Juxtacortical
- Infratentorial
- Spinal cord**

**Dissemination in time (DIT)**

- A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of baseline MRI
- Simultaneous presence of asymptomatic gadolinium and non-enhancing lesions at any time

* Gadolinium enhancement of lesions is not required for DIS
** If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the criteria and do not attribute to lesion count
Multiple sclerosis: high-field and ultrahigh-field MRI

Since the introduction of the first 0.05 Tesla (T) MRI system in 1977, advances have been made in image acquisition and processing. The use of higher magnetic field strengths is one of those on-going developments, and the clinical relevance of this technological improvement has been a debate from the beginning. At present, 3T MRI systems are considered high field when compared to the standard-field 1.5 T, whereas systems above 4 T -mostly 7 T- are considered ultrahigh field. The first 7T system was installed in 1999, and at the moment there are approximately 40 whole-body 7T scanners in the world (2013). The main advantage of increasing field strength is the increased signal-to-noise ratio (SNR), which can be used to improve spatial resolution to visualize smaller anatomical structures, or to shorten acquisition time. Furthermore, at higher magnetic field strengths, greater chemical shift dispersion and increased susceptibility variations take place, which can be used to profit in magnetic resonance spectroscopy (MRS) and susceptibility weighted imaging (SWI).

In MS, moving from 1.5 T to 3 T has led to an increased detection of lesions. This held true for WM brain lesions and spinal cord lesions, including non-inflammatory (inactive, not gadolinium-enhancing) and inflammatory (active, gadolinium-enhancing) lesions. Increased lesion detection was particularly apparent in anatomical WM regions that are crucial for establishing the diagnosis and prognostic classification.

The implementation of ultrahigh-field 7T MRI in MS research demonstrated additional important aspects of the pathological features of MS, such as better visualisation of the perivenular distribution of lesions, lesion heterogeneity including the role of iron deposition, and improved detection and classification of GM abnormalities. However, these findings were demonstrated in studies with small samples, and with MRI sequences that are not (yet) used and recommended in the clinical routine setting, such as experimental phase imaging and T2*-weighted sequences.

For a more extensive discussion on the meaning of (ultra)high-field MR systems for MS research, I kindly refer to chapter 1.1, in which we have reviewed the use of (ultra)high-field MRI in MS.

Multiple sclerosis: neuroinflammation and neurodegeneration

The major pathological mechanisms leading to CNS damage in MS are inflammation, demyelination, plus neuronal and axonal degeneration. Multiple sclerotic plaques are macroscopically visible in the brain and spinal cord. Although MS was seen as a classical WM disease for a long time - including focal and diffuse WM changes - early histopathological studies already described lesions in the GM of the brain. During the past decade, a lot of effort was put in visualizing cortical GM lesions with MRI, but unfortunately sensitivity to cortical lesion detection remains low. Being able to depict cortical lesions is important, since cortical pathology has high clinical relevance: cortical lesions are common, present in the earliest stages of the disease, and relate better to physical and cognitive disability than WM lesions. It was even suggested that sensitivity of MRI diagnostic criteria will improve when taking cortical lesions into account.

Although inflammatory-mediated focal lesions are the pathological hallmark of MS, it is increasingly recognized that the disease has a strong neurodegenerative aspect, reflected by
increased brain atrophy in MS, that is more strongly associated with clinical disability. The coexistence of neuroinflammatory and neurodegenerative aspects of MS is a fact that cannot be ignored, however discussions about what actually triggers the disease are ongoing.

Besides the existing neuroinflammatory and neurodegenerative MRI markers of MS, new imaging characteristics have been described over the past years. One of these is increased iron levels, which occur in in specific areas of the MS brain, mainly in the deep gray matter. Increase in iron levels within MS lesions has also been suggested. The mechanisms behind iron deposition in MS brains are not very well understood. Furthermore, there are different techniques to detect iron deposition in MS patients that vary a lot in sensitivity. Another characteristic has been described on MRI scans of MS patients, namely enlarged perivascular spaces (PVS). PVS surround small cerebral vessels as they penetrate the brain parenchyma. When enlarged, PVS become visible on MRI, and are also known as Virchow-Robin spaces (VRS). VRS occur in the ageing brain, but are also found in many disorders mostly of vascular or neurodegenerative nature. In multiple sclerosis however, studies at standard field strengths have linked VRS to neuroinflammation rather than to neurodegeneration.

**Aims and outline of this thesis**

The general aim of the present thesis was to study the added value of moving to ultrahigh-field 7T MRI in MS: to explore the benefits from a technical perspective and the possible opportunities for clinical application. Although standard-field MRI has already proven its usefulness in the clinical setting for the diagnostics and monitoring of MS (mostly by monitoring the presence of WM lesions as T2/ Flair hyperintensities), there are several shortcomings that we hoped to tackle by moving to ultrahigh-field 7T MRI, including:

1) Detection of WM lesions correlates only modestly with the patient’s clinical status (the so-called clinico-radiological paradox). Cortical GM lesions correlate better with clinical and cognitive disability, but detection rates with MRI are low. There is a need for new MRI techniques that improve the detection of GM pathology in MS, to be able to further research the possible underlying pathogenic mechanisms, to better monitor disability of patients, and to be of aid in the development of future therapeutic options.

2) MRI has a high sensitivity for the detection of WM lesions, but low specificity. In other words, we detect WM lesions, but it is difficult to distinguish MS from other disorders that generate WM lesions, for instance vascular disorders. Furthermore, heterogeneity of WM lesions as is visible under the microscope, is not visible on MRI. There is need for more specific MRI markers of structural damage in and around WM lesions, more than only T2/ Flair hyperintensity, to be able to differentiate MS lesions from other WM lesions and help establishing an earlier and improved diagnosis.

Starting from a technological viewpoint, we explored the benefits of ultrahigh-field 7T MR systems compared with the clinically available high-field 3T MR system in **CHAPTER 2**. Firstly, we investigated whether 7 T detected more (cortical) MS lesions than 3 T, in a cohort of MS patients. Then, we examined which pulse sequence showed the highest lesion detection at 7 T. The last paper in this chapter verifies the sensitivities of a multicontrast protocol at 7 T versus 3 T to the detection of cortical lesions in MS in a postmortem setting, by comparing them to histopathology.
Proceeding to the exploration of clinical opportunities, we evaluated a special imaging technique at 7 T called FLAIR* (“flair star”), in CHAPTER 3. With this technique we combined FLAIR images for lesion detection with T2* images for visualisation of vessels. With 7T FLAIR* we explored new morphology characteristics of MS lesions and their relation to patient characteristics. Furthermore, we investigated if FLAIR* was able to increase specificity of MS lesion detection, by determining its capability to differentiate MS from vascular brain lesions.

Lastly, we used ultrahigh-field 7T MRI to look in the MS brain beyond lesions, in CHAPTER 4. Here we explored a phenomenon that was noticed during the analysis of our images for the first studies: a prominent presence of VRS at 7T MRI. We used the improved visibility of VRS at 7 T, to revisit the relation between VRS and neuroinflammatory or neurodegenerative aspects of the disease.

As sidestep to our 7T work, the last subchapter of this thesis took part at 3 T. With R2* mapping, we studied iron deposition in the brains of MS patients, and explored independent determinants of iron accumulation. This study was placed in a multicenter setting, within the Magnetic Resonance Imaging in MS (MAGNIMS) network (http://www.magnims.eu).
References

1.2

Review: Inflammation high-field magnetic resonance imaging


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Frederik Barkhof
Mike P Wattjes
Abstract
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 [NABT]), 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 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 0.5 T with 1.0 and 1.5 T. At present, 3T MRI is considered as high field for clinical purposes, and field strengths of 4T and above are considered ultrahigh 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. 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.

**Detection of inflammatory white matter pathology**

Imaging guidelines for conventional brain MRI in the diagnosis of inflammatory CNS disease recommend a multisequence protocol consisting of 3 sequences (table 1). 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 precontrast (optional) and postcontrast-enhanced T1-weighted images, which allow visualization of ‘active’ lesions, that is, those 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 (postcontrast T1-weighted and FSE/ TSE PD/T2 weighted sequences).

<table>
<thead>
<tr>
<th>Table 1. Standard imaging protocol for brain and spinal cord MRI in MS patients</th>
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<tbody>
<tr>
<td><strong>Sequence</strong></td>
</tr>
<tr>
<td><strong>Brain</strong></td>
</tr>
<tr>
<td>FLAIR</td>
</tr>
<tr>
<td>PD/T2w</td>
</tr>
<tr>
<td>T1w pregadolinium</td>
</tr>
<tr>
<td>T1w postgadolinium</td>
</tr>
<tr>
<td><strong>Spinal Cord</strong></td>
</tr>
<tr>
<td>PD/T2w</td>
</tr>
<tr>
<td>T1w postgadolinium</td>
</tr>
</tbody>
</table>

MRI = magnetic resonance imaging; MS = multiple sclerosis; FLAIR = fluid attenuated inverse recovery; PD = proton-density weighted; T2w = T2-weighted; T1w = T1-weighted

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), and the recently revised IP diagnostic criteria for MS, which are based on magnetic field strengths of 0.5 - 1.5 T. 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). 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). 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.

Table 2. MS Lesion detection in white matter and gray matter using high-field MRI

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Patients (n)</th>
<th>Field strength (sequence)</th>
<th>Most important results</th>
</tr>
</thead>
<tbody>
<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%</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% Total WM lesion volume increase 60%</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</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>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 (2D-DIR, 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; T2w = T2-weighted; FSE = fast spin echo; WM = white matter; SP = secondary progressive; T1w = T1-weighted; PD = proton-density weighted; 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

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. 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.

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 multislab and later singleslab 3D-DIR applications meant a great improvement: 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.

**Figure 1.** Image examples of the higher sensitivity in the detection of inflammatory brain lesions at 3 T in comparison with 1.5 T. (A, B) A 23-year-old man presenting with unilateral optic neuritis. An inflammatory lesion in the left hemisphere of the cerebellum (arrow) was clearly identified on the T2-weighted turbo spin echo images at 3 T but not on the corresponding 1.5 T examination. (C, D) Axial fluid-attenuated inversion recovery (FLAIR) sections of the same patient. A small lesion in the brainstem and a lesion in the right temporal lobe (arrows) could be visualized on the 3 T image but not on the corresponding 1.5 T image. (E, F) Axial FLAIR sections of the supratentorial brain of a 45-year-old woman presenting with optic neuritis of her left eye. A small juxtacortical lesion (arrow) was prospectively identified on the 3 T image but was missed on the 1.5 T examination. Another lesion, which is probably a mixed white matter–gray matter lesion (arrow), is sharply delineated on the 3 T image but is more fuzzy and smaller on the 1.5 T image.
The introduction of high-field imaging did not immediately lead to an increase in cortical lesion detection, when applied in postmortem 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 3 T, 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 3 T 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 (3 T) 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 ultrahigh field strengths (7 T 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 postcontrast signal intensity difference at 3 T when compared to 1.5 T, which

![Figure 2](image.png)
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.

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.

Postmortem 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/edema 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 3 T when compared to 1.5T examinations. During follow-up no additional patients showed DIT at 3 T 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, which are based on MRI criteria developed by the MAGNIMS group, again no earlier diagnosis of MS could be established at 3 T 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.

**Ultrahigh 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 ultrahigh-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 ultrahigh-field MRI. In MS research the ultrahigh-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 ultrahigh 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 7 T. 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 ultrahigh-field MR imaging in MS: firstly, an increased detection of lesions when compared to lower field strengths (table 3), 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.

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<tr>
<th>Table 3. MS lesion detection at ultrahigh magnetic field strength MRI, postmortem and in vivo</th>
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<td>Study, year</td>
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<td>Postmortem</td>
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<tr>
<td>Kangarlu et al., (2007)</td>
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<tr>
<td>Pitt et al., (2010)</td>
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<td>In vivo</td>
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<td>Kolia et al., (2009)</td>
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<td>Mainero et al., (2009)</td>
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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 inversion 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
Increased MS lesion detection using ultrahigh-field MRI

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

In vivo studies using ultrahigh 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. Mainiero 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 7 T, and that 7T 3D-FLAIR improves cortical lesion detection when compared to 3 T (figure 3).

Visualizing heterogeneity of MS lesions at ultrahigh field

The main focus of ultrahigh-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 strengths.
field. Susceptibility weighted imaging (SWI) identified the relationship between MS lesions and vasculature, and confirmed that MS lesions follow a strict perivascular distribution.\textsuperscript{55,78-81} 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 ultrahigh-field SWI in a subset of MS lesions are hypointense rims (figure 4).\textsuperscript{55,47,79} Hammond et al. explained these rims 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} Postmortem 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 1.5 T.\textsuperscript{45}

\textbf{Figure 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.

At even higher field strengths (9.4T) T2-weighted scanning was able to discriminate areas of remyelination and demyelination in postmortem MS lesions.\textsuperscript{84} 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.\textsuperscript{48} 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 3 T or 7 T, they might possibly have great impact on clinical translation of demyelination and neuronal loss.

\textbf{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.\textsuperscript{85} 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 mI 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 mI 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.

At higher magnetic field strengths there is an increase of the two main criteria upon which spectrum quality depends, namely SNR and chemical shift. The increase in SNR results in more signal (higher metabolite peaks in relation to background noise) and the increase in chemical shift improves spectral resolution (metabolite separation). This means that at high field a more precise metabolite quantification is possible. Increased spectral resolution at 3 T is capable of separating and individually quantifying glutamate, glutamine and mI, the peaks of which are overlapping at 1.5 T. Furthermore, metabolite quantification showed improved sensitivity and good reproducibility at 3 T.

**Figure 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. 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.
Moving to ultrahigh 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.\textsuperscript{96} In addition, new metabolites can be investigated, such as gamma amino butyric acid (GABA), as has been shown at 9.4T in rats.\textsuperscript{97}

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 1H-MRS studies of MS patients are limited, the published results are promising. As assessed by 3T 1H-MRS, significant axonal damage (decreased NAA) already becomes apparent during the first demyelinating episode in patients with CIS,\textsuperscript{98,99} suggesting early neurodegeneration in MS. This in contradiction to glial cell activity (increased mI) at 3 T, which was not increased in CIS patients until later on: in patients with a very early course of RRMS.\textsuperscript{98} The decrease in NAA reflecting axonal injury in CIS patients also has a prognostic function in predicting the conversion to definite MS.\textsuperscript{100}

The possibility to study glutamate metabolism at 3T 1H-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.\textsuperscript{101}

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.\textsuperscript{102}

The only study using 1H-MRS at 7T in MS patients quantified glutathione (GSH), a marker of oxidative status.\textsuperscript{103} Because of its low concentrations in the brain and its overlap with NAA, at lower field strengths this antioxidant is difficult to quantify. At 7 T, 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 1.5 T 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.\textsuperscript{104-106} DTI abnormalities are more pronounced in focal lesions than in NAWM and are most severe in T1 hypointense lesions, representing irreversible tissue damage.\textsuperscript{14,107} 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.\textsuperscript{107}
DTI alterations are more pronounced with increased disease duration and show a correlation with clinical disability.\textsuperscript{104,108} The strongest correlation was found to the diffusion characteristics of T2 lesions and GM, with GM abnormalities being more severe in progressive disease.\textsuperscript{109-111} Benedict et al. reported a significant correlation between DTI values and cognitive dysfunction.\textsuperscript{112}

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 of 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} An example of DTI at high-field 3 T can be seen in figure 6.

\textbf{Figure 6.} Coronal 3 T DTI overlay of a male MS patient showing main fiber directions with reconstructed resolution of 1.0 x 1.0 x 2.4 mm\textsuperscript{3}. The application of a higher main magnetic field increases the accuracy of determination of fiber direction by higher SNR and decreases partial volume effects.

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 3 T 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 3 T 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*). 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 function 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. 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. Functional changes in MS brains vary between disease types and different stages of the disease. 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 (B0), 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 3 T, Hoenig et al. detected additional activation in cortical areas involved in higher executive motor functions, when compared to functional 1.5T MR imaging.

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. 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.

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. DTI tractography integrated with fMRI at 3 T 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. 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.
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. 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 7 T 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.

![Figure 7. High-resolution T1 relaxation-time map at 7 T of a female primary progressive MS patient. Wholebrain T1 maps with a spatial resolution of approximately 1 x 1 x 1.5 mm$^3$ can be obtained in 5 minutes at 7 T. Compared with lower field strengths, accuracy is increased because of higher SNR and higher spatial resolution, reducing partial volume effects. This modality might help to detect damage to normal appearing white and gray matter in MS.](image)

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. 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. 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. Iron
deposition in the brain, predominantly in the basal ganglia, is a function of increasing age, but can also be a pathological phenomenon of neurodegenerative disease. 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. Magnetic susceptibility of tissue with higher iron concentrations increases 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.

**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 quantitative 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 ultrahigh-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 1.5 T. However, further studies are desired including a larger study population or even the use of ultrahigh-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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## References


Inflammation high-field MRI


Editorial: Ultrahigh-field MRI: looking through the ‘macroscope’


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The first publications about the in vivo application of ultrahigh-field MR imaging (MRI) in multiple sclerosis (MS) appeared in 2008. From then on, the number of studies performed at 7 Tesla (T) has rapidly increased. The main advantage of ultrahigh-field MRI is its higher signal-to-noise ratio, which can be used to increase spatial resolution greatly. This has led to improved detection of subtle MS pathology, particularly in clinically relevant regions like the gray matter (GM). Another advantage of 7T MRI is its increased sensitivity to susceptibility effects. This has been used to image additional morphological characteristics of MS lesions. For example, susceptibility-weighted MRI at 7 T has confirmed that MS white matter (WM) lesions are consistently oriented perivascularly and has furthermore shown that hypointense rims may appear around lesions and that some lesions appear hypointense whereas others do not.

In this issue, Filippi et al. provide an up-to-date overview of the major achievements of 7T MRI so far. The authors discuss improved detection of WM lesions, their particular morphology, improved visibility of GM lesions and the exact location of these lesions, quantification of (novel) brain metabolites, and sensitivity to iron accumulation. They conclude that ultrahigh-field MRI has improved our understanding of MS pathology, but that implementation in clinical practice is unfortunately still a bridge too far. Its role in the diagnostic process and the monitoring of disease progression and treatment response has not yet been sufficiently established.

Also, valid interpretation of the ultrahigh-field images can be challenging. For example, hypointense (rims around) lesions on T2*-weighted images have been generally proclaimed to reflect iron-laden macrophages, but a recent report showed that this may not always be true. Hypointense rims around WM lesions did not disappear over time at 7 T, decreasing their potential as a method for lesion staging. Moreover, several studies have focused on finding the 7T sequence that detects the highest number of cortical lesions. It was even suggested that T2*-weighted imaging at 7 T should be the new ‘gold standard’ for detection of cortical lesions in MS. However, when considering the set-up of these studies, at times simultaneously comparing different sequences and different field strengths, it might be too early to conclusively recommend any of the sequences investigated thus far. Comparison of sequences at 7 T needs to be more systematic and precise in future studies, and results should ideally be compared to the real gold standard, i.e. histopathology, at some point. Sensitivity and specificity of many (if not all) 7T sequences presented have yet to be determined. At 1.5 T, only the tip of the proverbial iceberg is visible when it concerns GM lesions. How much more of the iceberg do we see at 7 T? And do cortical hyper- or hypointensities as seen through the 7T ‘macroscope’ really reflect demyelination under the microscope? This has to be investigated carefully; with new fields and sequences new artifacts arise.

These issues aside for now, we look very much forward to the further development of ultrahigh-field MRI in MS. Better detection of subtle and diffuse pathology and the discovery of new imaging features of MS are likely to further improve the way we look at this complex disease.

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References