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

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4. Clinical application of multi-contrast 7-T MR imaging in multiple sclerosis: increased lesion detection compared to 3 T confined to grey matter


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Abstract

Objectives Seven-Tesla MRI demonstrated new pathological features of multiple sclerosis (MS) using $T2^*$-weighted sequences. However, a clinical MRI protocol at 7 T has never been investigated. We evaluated the clinical value of 7-T MRI by investigating the sensitivity of lesion detection compared with 3 T.

Methods Thirty-eight MS patients and eight healthy controls underwent multi-contrast MRI using 3D T1-weighted (3D-T1w), 2D dual-echo T2-weighted (2D-T2w) and 3D fluid-attenuated inversion recovery (3D-FLAIR) at 3 and 7 T. Images were analysed for focal lesions, which were counted and categorised according to anatomical location. The study was approved by the institutional review board. Results Lesion-wise analysis showed increased lesion counts in cortical grey matter (GM) at 7 T of 91, 75 and 238 % for 3D-T1w, 2D-T2w and FLAIR sequences, respectively. Patient-wise analysis confirmed this for 2D-T2w and FLAIR ($P<0.023$ and $P<0.001$). Seven-Tesla white matter (WM) lesion detection was not increased; 3D-FLAIR even detected significantly more WM lesions at 3 T.

Conclusions Using a clinical multi-contrast MRI protocol, increased lesion detection was observed in cortical GM but not in WM. Given the clinical relevance of GM abnormalities, this may have consequences for clinical outcome measures, prognostic classification and future diagnostic criteria incorporating GM abnormalities.

Key Points

• Standard multi-contrast 7-T magnetic resonance imaging in multiple sclerosis is feasible.

• Seven-Tesla MRI detects more cortical grey matter lesions than 3 T.

• Seven-Tesla MRI fares no better than 3 T in detecting white matter lesions.

• Grey matter abnormalities have high diagnostic and prognostic relevance in MS.
**Introduction**

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disorder of the central nervous system (CNS), clinically affecting both white and grey matter and leading to substantial long-term disability in young adults [1]. Magnetic resonance (MR) imaging is an important paraclinical tool for the detection of inflammatory abnormalities in MS, in the form of focal lesions as well as diffuse abnormalities in the brain and spinal cord [2, 3]. It has been established as a valuable and essential tool in diagnosing the pathological features of MS, which has led to the incorporation of MR imaging criteria for the demonstration of dissemination in space (DIS) and dissemination in time (DIT) into the International Panel (IP) diagnostic criteria for MS [4–6].

The introduction of high-field MR imaging has led to a successful application of whole-body 3-T MR systems in the clinical setting. Especially in the field of neuroradiology, the increased signal-to-noise ratio (SNR) and higher spatial resolution allowed by stronger magnetic field strength proved to be beneficial in the diagnosis of different disease entities. In MS, the sensitivity for grey matter (GM) and white matter (WM) lesion detection at 3 T is substantially better than at 1.5 T [7]. This is particularly apparent in anatomical WM regions that are crucial for establishing the diagnosis and prognostic classification [8–10].

In the past few years, high-field imaging applications beyond 3 T are increasingly being applied and investigated [11]. The use of 7 T in MS patients demonstrated additional important aspects of the pathological features of MS such as better visualisation of the perivenular distribution of lesions [11–14], lesion heterogeneity including the role of iron deposition [12–16], and improved detection and classification of GM abnormalities [12, 17–21]. However, these findings have been demonstrated with MR imaging sequences that are not (yet) used and recommended in the clinical routine setting, such as high-resolution phase imaging, T2*- or susceptibility-weighted imaging (SWI) sequences. Whether there are clinical benefits from 7-T compared with 3-T MR imaging considering the standard imaging protocol for clinical purposes (T1-weighted, T2-weighted and FLAIR images) [22] has not yet been investigated. Possible advantages of an increased sensitivity in lesion detection could have a substantial impact regarding the diagnosis, differential diagnosis and disease monitoring.

The aim of this study was to prospectively compare high-field 3- and 7-T MR imaging in terms of the sensitivity of lesion detection in MS-specific anatomical regions by using sequences as described in the standard brain imaging protocol for imaging of MS patients.
Materials and methods

Participants

In this prospective study, MS patients and healthy controls were imaged on a 3- and 7-T whole-body MRI system in two separate sessions within a 2-week period. The order of both imaging sessions was randomised. The study protocol was approved by the institutional review board, and all subjects gave written informed consent before participation in the study.

Patients were recruited from our neurology outpatient clinic and via an advertisement on the MS Center website. Inclusion criteria were clinical definite MS according to the 2005 revised McDonald criteria and age between 18 and 60 years old [5]. Exclusion criteria were the medical history of other neurological disorders (vascular and inflammatory pathological conditions, malignancies), recent relapses (< 3 months) and standard contraindications for undergoing MRI investigation, such as claustrophobia. In addition to these standard contraindications, local high-field MR safety regulations also excluded subjects with any (suspected) metal objects in or on the body as a result of medical interventions in the past.

MR imaging acquisition

All subjects were imaged on two whole-body MRI systems: 3 T (GE Signa HDXt, General Electric, Waukesha, WC, USA), slew-rate 150 T/m/s, maximum gradient strength 87 mT/m using an eight-channel phased array head coil; and 7 T (Philips Achieva, Philips Healthcare, Cleveland, OH, USA), slew-rate 200 T/m/s, maximum gradient strength 40 mT/m using a 16-channel phased array head coil. MR system- and field-strength-optimised sequence protocols were used at both field strengths: 2D dual-echo T2-weighted (2D-T2w), sagittal 3D T1-weighted (3D-T1w) and sagittal 3D fluid-attenuated inversion recovery (3D-FLAIR); detailed imaging parameters are given in Table 1.

The 3D-FLAIR sequence at 7 T included magnetisation preparation (MP) to prevent increased and unwanted T1 weighting, which accompanies higher magnetic field strength [23]. Total acquisition time was approximately 31 min at 7 T and 12 min at 3 T, using up to a 2.8-fold increase in spatial resolution for 3D-FLAIR at 7 T. No intravenous contrast agent was used in this study.

Image analysis and interpretation

Before image analysis, all sagittal 3D images were reconstructed in an axial plane (slice thickness is given in Table 1) corresponding to the 2D-T2w images that were also acquired in the axial plane, without any angulation. Image analysis was performed in consensus by three observers: IK and WG (respectively 2 and 5 years’ experience in MR image reading) and AL (neuroradiologist, 7 years’ experience). Images were presented in random order in terms of magnetic field strength, pulse sequence and patient identification number. All raters were blinded for any clinical and paraclinical (laboratory tests) information.

For each pulse sequence at both field strengths, the quality of images was assessed in terms of artefacts and image homogeneity. Subsequently, lesions were marked, counted and categorised according to their anatomical locations: periventricular (PV) WM lesions in contact with the ventricles; deep white matter (DWM) lesions not in contact with ventricles or cortex; juxtacortical (JC) WM lesions in contact with the cortex but located in white matter; mixed GM/WM matter (Mixed) lesions located in GM as well as in WM; intracortical (IC) lesions located completely in the cortical GM. Although a large field of view for the sagittal acquisition of 3D-FLAIR and 3D-T1w images was used, it was not possible to obtain sufficient signal from infratentorial
regions and deep GM for subjects with larger head size owing to the sensitivity of the receiver head coil. The same applied for the axially acquired 2D-T2w sequence. Therefore, deep GM and infratentorial lesions were not included in the analysis.

Lesions were defined as focal areas of hypointense (3DT1w images) or hyperintense (2D-T2w and 3D-FLAIR images) signal intensity compared with the surrounding WM and GM, with a minimum size of 3 voxels. Due to different voxel sizes, this definition is therefore field strength dependent. Pluriform abnormalities resulting from possible confluency of lesions were counted as one lesion when no obvious signal change could be observed between them. Particular care was taken not to include abnormalities that corresponded to normal structures, such as perivascular (Virchow-Robin) spaces. Cortical lesions were scored according to established guidelines developed by the MAGNIMS study group regarding double inversion recovery sequences [24].

A scoring tool developed in-house was used as a plug-in to MIPAV software (MIPAV version 5.1.1, CIT, NIH, Bethesda, MD, USA) to mark and label lesions per region for each sequence. The results for all subjects were collected by a Matlab script written in-house (Matlab 7.1, The Mathworks Inc., Natick, MA, USA) and transferred to an Excel spreadsheet (Microsoft Office Excel 2003, Microsoft Corp., Redmond, WA, USA). After analysis of the results, we compared the average number of PV and DWM lesions of the ten patients and controls with the highest and lowest scores to see if lesion confluence influenced results significantly.

Statistical analysis

Total lesion counts per region, sequence and field strength were collected and used for lesion-wise and patient-wise comparison. Results from healthy controls were assessed separately. Relative differences between field strengths for comparable sequences and locations were calculated for 7 T in percentages relative to the corresponding 3 T result. Furthermore, combinations were made of WM regions (periventricular, deep white matter and juxtacortical lesions) as well as GM regions (mixed and intracortical lesions).

Statistical analysis was performed using the SPSS software package, version 15.0 (SPSS, IBM, Chicago, IL, USA). As lesion counts are not normally distributed, patient-wise differences were analysed using the nonparametric Wilcoxon test for matched pairs. P values ≤0.05 were considered statistically significant.
**Table 1**

Sequence parameters per pulse sequence at 3T and 7T

<table>
<thead>
<tr>
<th>Contrast</th>
<th>3D-T1w</th>
<th>2D-T2w</th>
<th>3D-(MP-)FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Field Strength</strong></td>
<td>7T</td>
<td>3T</td>
<td>7T</td>
</tr>
<tr>
<td><strong>Sequence</strong></td>
<td>TFE</td>
<td>FSPGR</td>
<td>TSE</td>
</tr>
<tr>
<td><strong>TR [ms]</strong></td>
<td>7.0</td>
<td>7.8</td>
<td>4969</td>
</tr>
<tr>
<td><strong>TE (1/2) [ms]</strong></td>
<td>2.9</td>
<td>3.0</td>
<td>21 / 80</td>
</tr>
<tr>
<td><strong>TI [ms]</strong></td>
<td>1129</td>
<td>450</td>
<td>-</td>
</tr>
<tr>
<td><strong>Flip Angle [deg]</strong></td>
<td>8</td>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td><strong>Turbo Factor [-]</strong></td>
<td>312</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td><strong>Acquisition Resolution [mm3]</strong></td>
<td>0.8x0.8x.08 (sagittal)</td>
<td>1.0x1.0x1.0 (sagittal)</td>
<td>0.7x1.0x2.0 (axial)</td>
</tr>
<tr>
<td><strong>Reconstructed Resolution [mm3]</strong></td>
<td>0.5x0.5x0.4 (axial)</td>
<td>1.0x1.0x1.0 (axial)</td>
<td>0.5x0.5x2.0 (axial)</td>
</tr>
</tbody>
</table>

Note: 3D-T1w = 3 dimensional T1 weighted, 2D-T2w = 2 dimensional dual echo T2 weighted, FLAIR = fluid-attenuated inversion recovery; TFE = turbo field echo, FSPGR = fast spoiled gradient echo, TSE = turbo spin echo, TR = repetition time, TE = echo time, TI = inversion time

**Results**

**Clinical characteristics**

A total of 8 healthy controls (5 female, 3 male) with a mean age of 41.8 years, standard deviation (SD) 10.0, and 38 MS patients (24 women and 14 men), with a mean age of 44.2 years, SD 8.2, were included in the study. Twentyone MS patients had a relapsing remitting (RR), 11 a primary progressive (PP) and 5 a secondary progressive (SP) disease course; the median Expanded Disability Status Scale (EDSS) score [25] was 4 (range 0–7.5). Image examples of the pulse sequences used at both field strengths in an MS patient and a healthy control subject are presented in Figs. 1 and 2. Owing to technical failure, one sequence was occasionally missing in some subjects; we then excluded the corresponding sequence at the other field strength from our analysis as well. In total, the results included 33 3DT1w, 32 2D-T2w and 38 3D-FLAIR sequences at both field strengths. After quality assessment, no image series had to be excluded because of artefacts.
Figure 1. Image examples of a 42 years old female healthy control, using standard clinical pulse sequences at 3T and 7T MRI: a) 3T 3D-T1w, b) 3T 2D-T2w, c) 3T 3D-FLAIR, d) 7T 3D-T1w, e) 7T 2D-T2w*, f) 7T 3D-MP-FLAIR. Arrows indicate an incidental WM lesion.

*Note: slightly different angulation of the 7T 2D-T2w image

Figure 2. Image examples of a 44 years old female RR MS patient, using standard clinical pulse sequences at 3T and 7T MR imaging: a) 3T 3D-T1w, b) 3T 2D-T2w, c) 3T 3D-FLAIR, d) 7T 3D-T1w, e) 7T 2D-T2w, f) 7T 3D-MP-FLAIR.
**Lesion-wise analysis**

Detailed results of the regional analysis are presented in Tables 2 and 3. At 7 T, the 3D-T1w sequence detected fewer lesions in the periventricular WM (606 vs. 720 at 7 and 3 T respectively) and in the DWM (1,208 vs. 1,230), whereas more lesions were detected in the juxtacortical WM (846 vs. 631), mixed GM/WM (50 vs. 31) and intracortical GM (15 vs. 3) regions. For 2D-T2w, fewer lesions were found in the periventricular WM at 7 T compared with 3 T (531 vs. 611); the same was true for juxtacortical WM lesions (388 vs. 494). More lesions at 7 T were detected in the DWM (1,262 vs. 945), mixed GM/WM (81 vs. 41) and intracortical regions (33 vs. 24). On the 3D-FLAIR sequence at 7 T, fewer lesions were detected in the periventricular WM (625 vs. 754) and DWM (1,206 vs. 1,418), whereas more juxtacortical (828 vs. 769), mixed GM/WM (189 vs. 66) and intracortical (41 vs. 2) lesions were detected.

Regarding total lesion counts, total GM lesion detection is increased at 7 T for all sequences, with the FLAIR sequence detecting 238 % more GM lesions than 3 T; for the 3D-T1w and 2D-T2w sequences this increase amounted to 91 and 75 % respectively.

When comparing sequences per field strength, in general 2D-T2w sequences detect fewer lesions than 3D-T1w and 3D-FLAIR. At both field strengths, 3D-FLAIR showed the highest number of total WM lesions, as well as total GM lesions. At 7 T, WM lesions were seen equally at 3D-T1w and 3D-FLAIR (2,660 vs. 2,659). Different from other lesion categories, most IC lesions at 3 T were detected by 2D-T2w (24 compared to 3 for T1w and 2 for FLAIR).

**Table 2**

*Lesion-wise analysis MS patients: total lesion detection rates at 7- and at 3-T MRI, separated for the T1w, T2w and FLAIR pulse sequences, including relative differences between the two strengths*

<table>
<thead>
<tr>
<th></th>
<th>3D-T1w</th>
<th>2D-T2w</th>
<th>3D-FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7T* (n=33)</td>
<td>3T* (n=33)</td>
<td>7T vs. 3T* (%)</td>
</tr>
<tr>
<td>PV</td>
<td>606</td>
<td>720 -16</td>
<td>531</td>
</tr>
<tr>
<td>DWM</td>
<td>1208</td>
<td>1230 -2</td>
<td>1262</td>
</tr>
<tr>
<td>JC</td>
<td>846</td>
<td>631 34</td>
<td>388</td>
</tr>
<tr>
<td>Total WM</td>
<td>2660</td>
<td>2581 3</td>
<td>2181</td>
</tr>
<tr>
<td>Mixed</td>
<td>50</td>
<td>31 61</td>
<td>81</td>
</tr>
<tr>
<td>IC</td>
<td>15</td>
<td>3 400</td>
<td>33</td>
</tr>
<tr>
<td>Total GM</td>
<td>65</td>
<td>34 91</td>
<td>114</td>
</tr>
<tr>
<td>Total WM + GM</td>
<td>2723</td>
<td>2615 4</td>
<td>2295</td>
</tr>
</tbody>
</table>

*Data represent numbers of detected lesions per anatomical region

#Data represent relative differences in the numbers of lesions detected at 7T versus 3T

Note: PV = periventricular, DWM = deep white matter, JC = juxtacortical, WM = white matter, IC = intracortical, GM = gray matter
Patient-wise analysis

The detailed results of the patient-wise analysis are presented in Tables 4 and 5. This analysis showed a significant increase in lesion detection at 7 T for the 3D-T1w sequence in the juxtacortical WM (P<0.004). A significantly higher detection rate for the 7-T 2D-T2w sequence was found in DWM (P<0.001) and mixed GM/WM regions (P<0.011), whereas the 3-T 2D-T2w sequence showed significantly more lesions in periventricular (P<0.005) and juxtacortical WM (P<0.003) regions (examples shown in Fig. 3). On the 3D-FLAIR sequence, significantly more mixed GM/WM (P<0.001) and intracortical GM (P<0.003) lesions were detected at 7 T (examples shown in Fig. 4), whereas significantly more periventricular WM lesions (P<0.040) were detected at 3 T (Tables 4 and 5 and Fig. 5). In terms of total lesion counts, the patient-wise analysis shows a significantly higher WM lesion detection on the 3-T 3D-FLAIR sequence (P<0.040), and a significantly higher number of GM brain lesions on the 2D-T2w as well as the 3D-FLAIR sequence (P<0.023 and P<0.001) at 7 T. The overall total number of brain lesions did not show significant differences between 7- and 3-T MRI on 3D-T1w and 3D-FLAIR sequences; 2D-T2w showed significantly higher lesion detection at 7 T (P<0.030).

Table 3

Lesion-wise analysis healthy controls: total lesion detection rates at 7- and at 3-T MRI, separated for the T1w, T2w and FLAIR pulse sequences, including relative differences between the two strengths

<table>
<thead>
<tr>
<th></th>
<th>3D-T1w</th>
<th>2D-T2w</th>
<th>3D-FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7T* n=5</td>
<td>3T* n=5</td>
<td>7T vs. 3T* (%)</td>
</tr>
<tr>
<td>PV</td>
<td>5 0 -</td>
<td>9 4</td>
<td>125 7</td>
</tr>
<tr>
<td>DWM</td>
<td>7 6 17</td>
<td>18 11</td>
<td>64 26</td>
</tr>
<tr>
<td>JC</td>
<td>8 3 167</td>
<td>1 0</td>
<td>- 12</td>
</tr>
<tr>
<td>Total WM</td>
<td>20 9 122</td>
<td>28 15</td>
<td>57 55</td>
</tr>
<tr>
<td>Mixed</td>
<td>0 0 -</td>
<td>0 0</td>
<td>- 0</td>
</tr>
<tr>
<td>IC</td>
<td>0 0 -</td>
<td>0 1</td>
<td>-100 0</td>
</tr>
<tr>
<td>Total GM</td>
<td>0 0 -</td>
<td>0 1</td>
<td>-100 0</td>
</tr>
<tr>
<td>Total WM + GM</td>
<td>20 9 122</td>
<td>28 16</td>
<td>75 55</td>
</tr>
</tbody>
</table>

*Data represent numbers of detected lesions per anatomical region

#Data represent relative differences in the numbers of lesions detected at 7T versus 3T

Note: PV = periventricular, DWM = deep white matter, JC = juxtacortical, WM = white matter, IC = intracortical, GM = gray matter

Control subjects

Image examples of the pulse sequences used at both field strengths in a control subject are shown in Fig. 1. The 3DT1w, 2D-T2w and 3D-FLAIR sequences showed in total 20, 28 and 55 lesions at 7 T and 9, 16 and 26 lesions at 3 T (Table 3). When analysed patient-wise, no statistical differences between 7 and 3 T were found (Table 5). Most lesions were found in the WM of the control subjects and were described to be most probably of vascular origin. One intracortical lesion was found at 3-T 2D-T2w imaging.
### Table 4

**Patient-wise analysis of the sensitivity of brain lesion detection in MS patients at 7-T vs. 3-T MRI**

<table>
<thead>
<tr>
<th></th>
<th>3D-T1w More at 7T* More at 3T* P*</th>
<th>2D-T2w More at 7T* More at 3T* P*</th>
<th>3D-FLAIR More at 7T* More at 3T* P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>12 18 0.232 (n=33)</td>
<td>9 22 <strong>0.005</strong> (n=32)</td>
<td>10 25 <strong>0.019</strong> (n=38)</td>
</tr>
<tr>
<td>DWM</td>
<td>12 18 0.410 (n=33)</td>
<td>26 4 &lt;0.001* (n=32)</td>
<td>12 25 0.058 (n=38)</td>
</tr>
<tr>
<td>JC</td>
<td>20 7 <strong>0.004</strong> (n=33)</td>
<td>4 21 <strong>0.003</strong> (n=32)</td>
<td>15 18 0.957 (n=38)</td>
</tr>
<tr>
<td>Total WM</td>
<td>16 16 0.888 (n=33)</td>
<td>19 11 0.087 (n=32)</td>
<td>13 25 <strong>0.040</strong> (n=38)</td>
</tr>
<tr>
<td>Mixed</td>
<td>16 6 0.075 (n=33)</td>
<td>14 4 <strong>0.011</strong> (n=32)</td>
<td>24 6 <strong>0.001</strong> (n=37)</td>
</tr>
<tr>
<td>IC</td>
<td>7 2 0.058 (n=33)</td>
<td>11 7 0.278 (n=32)</td>
<td>11 0 <strong>0.003</strong> (n=37)</td>
</tr>
<tr>
<td>Total GM</td>
<td>13 6 0.059 (n=34)</td>
<td>16 6 <strong>0.023</strong> (n=32)</td>
<td>26 5 &lt;0.001 (n=38)</td>
</tr>
<tr>
<td>Total WM + GM</td>
<td>16 16 0.837 (n=33)</td>
<td>20 9 <strong>0.030</strong> (n=32)</td>
<td>15 21 0.432 (n=38)</td>
</tr>
</tbody>
</table>

* Data represents the number of patients with more detected lesions at 7T or 3T

# P Value obtained by the Wilcoxon test for matched pairs, ties are not shown

Note: PV = periventricular, DWM = deep white matter, JC = juxtacortical, WM = white matter, IC = intracortical, GM = gray matter

### Table 5

**Patient-wise analysis of the sensitivity of brain lesion detection in healthy controls at 7-T vs. 3-T MRI**

<table>
<thead>
<tr>
<th></th>
<th>3D-T1w More at 7T* More at 3T* P*</th>
<th>2D-T2w More at 7T* More at 3T* P*</th>
<th>3D-FLAIR More at 7T* More at 3T* P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>3 0 0.102</td>
<td>2 1 0.276</td>
<td>2 0 0.180</td>
</tr>
<tr>
<td>DWM</td>
<td>1 1 0.655</td>
<td>4 1 0.216</td>
<td>2 2 0.854</td>
</tr>
<tr>
<td>JC</td>
<td>1 0 0.317</td>
<td>1 0 0.317</td>
<td>2 0 0.157</td>
</tr>
<tr>
<td>Total WM</td>
<td>2 1 0.276</td>
<td>3 2 0.686</td>
<td>4 3 0.666</td>
</tr>
<tr>
<td>Mixed</td>
<td>0 0 1.000</td>
<td>0 0 1.000</td>
<td>2 0 0.180</td>
</tr>
<tr>
<td>IC</td>
<td>0 0 1.000</td>
<td>0 1 0.317</td>
<td>2 2 0.854</td>
</tr>
<tr>
<td>Total GM</td>
<td>0 0 1.000</td>
<td>0 1 0.317</td>
<td>2 0 0.157</td>
</tr>
<tr>
<td>Total WM + GM</td>
<td>2 1 0.276</td>
<td>3 2 0.786</td>
<td>4 2 0.666</td>
</tr>
</tbody>
</table>

* Data represents the number of patients with more detected lesions at 7T or 3T

# P Value obtained by the Wilcoxon test for matched pairs, ties are not shown

Note: PV = periventricular, DWM = deep white matter, JC = juxtacortical, WM = white matter, IC = intracortical, GM = gray matter

### Discussion

Standard imaging guidelines for conventional brain MRI in MS recommend the use of three pulse sequences (T1w, T2w and FLAIR) at a field strength of at least 1.5 T [21]. Over the years the use of these pulse sequences with high-field 3-T devices has been repeatedly investigated and has shown its value in the diagnosis and monitoring of MS [7]. It has long been technically...
challenging to implement this multicontrast protocol with ultrahigh-field 7-T MR systems; however, recent work in adjusting the pulse sequences proved it to be feasible [23, 26]. In the present study we investigated whether the use of 7 T has added clinical value compared with 3-T MR imaging according to standard diagnostic guidelines for MS. Our results show that moving from 3 T to 7 T, the number of grey matter lesions increased significantly, while no significant effect on total lesion detection (WM plus GM) was found. Unfortunately, because of lower sensitivity of the applied coil for infratentorial and deep GM lesions, in a number of patients with larger head size, these areas could not be assessed.

Figure 3. Image examples of a 32 yrs RR MS patient. Left: 7T images showing a juxta-cortical lesion that at 7T FLAIR may be mistaken for a mixed lesion, however less likely on T1w or T2w. Right: The same may occur at 3T.

Regarding WM lesion detection, 7-T MRI does not show significantly higher lesion detection compared with 3 T. Lesion-wise analysis showed that the total WM lesion load at 7 T was slightly increased at 3D-T1w and 2D-T2w sequences (3 and 6 %), whereas the 3D-FLAIR sequence showed a small decrease (10 %) of lesion detection compared with 3 T. These findings were reflected by the patientwise comparison, which even showed a statistically significant decrease in total WM lesion detection at 7 T on 3D-FLAIR. Surprisingly, these results are contrary to the earlier field-strength-dependent effect that was seen when 1.5- and 3-T MRIs were compared. These studies found an increased detection of WM lesions and contrast-enhancing lesions, particularly in the infratentorial, periventricular and juxtacortical WM, for all sequences [7–9].

Based on our results—although not formally tested—it is not likely that 7-T MR imaging will have a clinical impact in terms of a more sensitive or earlier diagnosis of MS, considering that MRI and diagnostic criteria are merely based on WM lesions. This trend was already reported when the standard MRI protocol was investigated at 3 T and has not led to an earlier diagnosis of MS so far [27, 28]. The stabilising total WM lesion count when moving beyond 3-T to 7-T MRI may indicate that a further increase in the sensitivity of WM lesion detection has reached its limits. Future studies including pathology have to show whether this hypothesis can be verified.
Figure 4. Image examples of a 37 years old female SP MS patient, showing a) 7T 3D-MP-FLAIR, b) 3T 3D-FLAIR, c) 7T 3D-T1w, d) 3T 3D-T1w, e) 7T 2D-T2w, f) 3T 2D-T2w images. Arrows depict cortical lesions that are best seen on 7T FLAIR.

We chose to categorise the WM lesions into anatomical locations that are important for the diagnosis of MS, as reflected by MR imaging and diagnostic criteria [6, 29]. Interestingly, this showed an even lower lesion count at 7 T for PV (for all three sequences) and DWM (for 3D-T1w and 3D-FLAIR sequences) compared with 3 T. When analysed patient-wise, the total WM lesion count was even significantly decreased on 7-T 3D-FLAIR compared with 3 T. Visual comparison of 3- and 7-T images showed that a possible explanation may be found in the image characteristics of 7 T: an “artificial” confluence of lesions was seen, caused by high signal intensity at 7 T in the centre of the brain. This would mostly affect PV and DWM lesions that already had the highest tendency to confluence. Lesions are displayed as strongly hyperintense on 7 T, and adjusting the window and level for sufficient background contrast can then easily result in loss of local contrast. According to our scoring guidelines, multiple lesions were counted as one confluent lesion when no obvious signal change could be observed between them. This progressive confluence of PV lesions at 7 T is depicted on an intensity line graph in Fig. 6. To verify if confluencing lesions had an influence on the lesion count in PV and DWM regions, we repeated the lesion-wise analysis at FLAIR for the ten patients with the lowest and highest number of lesions at 3 T; we expected the patients with the highest number of lesions to show the highest levels of confluence, whereas the possibility of confluencing lesions in patients with the least number of lesions is low. Analysis showed no significant difference between lesion scores at 3 and 7 T for patients with combined low numbers of lesions in PV and DWM areas (Table 6 and Fig. 7). However, in the ten patients with the highest number of combined PV and DWM lesions, a significant difference of 22 % fewer lesions was found for 7-T 3D-FLAIR.
Figure 5. Patient-wise analysis of the sensitivity of brain lesion detection in MS patients at 7T vs. 3T MRI. Top: 7T 3D-T1w vs. 3T 3D-T1w, Middle: 7T 2D-T2 vs. 3T 2D-T2, bottom: 7T 3D-MP-FLAIR vs. 3T 3D-FLAIR. Asterisks label significant differences.
This indicates that, as expected, confluent lesions may explain the lower lesion count at 7 T. To further verify this hypothesis that the lower lesion count at 7 T might be caused by lesions becoming confluent, we manually measured volumes from a sample of lesions in a randomly chosen subset of patients at 3- and at 7-T FLAIR (data not shown). The mean relative difference between 3- and 7-T lesion volume was not statistically significant. Hence, the lower WM lesion count at 7 T does not come with a lower lesion volume and might very well have been caused by WM lesions becoming confluent.

In vivo MR imaging at 3 T shows a substantial increase in the detection of cortical lesions in comparison to 1.5 T, when a GM-specific double inversion recovery (DIR) sequence was used [30]. Our results evidently show that, at 7 T, all standard clinical pulse sequences significantly increase lesion detection in cortical GM (mixed GM/WM plus intracortical lesions) compared with 3 T, without the use of GM-specific sequences. Lesion-wise analysis found a 91%, 75% and 238% higher total GM lesion detection for the 3D-T1w, 2D-T2w and 3D-FLAIR sequences respectively. Specifying these results per patient, the patient-wise analysis confirmed this higher sensitivity at 7 T for 2D-T2w and 3D-FLAIR sequences (P<0.026 and P<0.001). In general, the size of GM lesions is smaller than WM lesions. This, in combination with the fact that GM lesions show different aspects of inflammation in most cases, could influence conspicuity at lower field because of the applied minimum size restrictions and lower CNR, causing higher GM lesion detection at 7 T.

The depiction of cortical GM abnormalities in MS is of high clinical relevance, as cortical damage differs among disease stages and disease types [31–33]. In patients with early stage MS cortical pathological features are already frequent [31, 34]. Cortical pathological features also show a substantial relation to physical and cognitive disability [35, 36]. In addition, it has been shown that when the presence of cortical lesions is included in the diagnostic criteria for MS, this...
can lead to the increased accuracy of the criteria [37]. For the present diagnostic criteria, we expressed our reservations regarding the impact of 7-T MR imaging as these criteria are fully based on WM lesions, but when cortical lesions are incorporated, the influence of 7 T can be substantial.

Table 6, Comparison of means of 7-T and 3-T FLAIR lesions scores for PV and DWM lesions: total number of patients, ten patients with lowest and highest scores on 3 T

<table>
<thead>
<tr>
<th></th>
<th>Total (n=38)</th>
<th>n=10 lowest 3-T scores</th>
<th>3D-FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7T [Mean ± SD]</td>
<td>3T [Mean ± SD]</td>
<td>P</td>
</tr>
<tr>
<td>PV</td>
<td>16.5 (13.4)</td>
<td>19.8 (15.4)</td>
<td>0.010*</td>
</tr>
<tr>
<td>DWM</td>
<td>31.7 (27.2)</td>
<td>37.3 (35.2)</td>
<td>0.114</td>
</tr>
<tr>
<td>PV+ DWM</td>
<td>48.2 (36.5)</td>
<td>57.2 (46.0)</td>
<td>0.027*</td>
</tr>
</tbody>
</table>

*significant differences between 7T and 3T scores, P<0.05

PV = periventricular, DWM = deep white matter

The total number of intracortical lesions in our patient group seems low compared with other studies (41 at 7 T vs. 2 at 3 T) [36, 38]; this may be because these studies did not split purely intracortical and mixed GM/WM lesions. Furthermore the definition of the cortex differs among field strengths and sequences: the outer layer of the cortex on 7-T MP-FLAIR shows a hyperintense line as described earlier [23, 26], which may hinder the detection of intracortical lesions on FLAIR images.

Recent studies have already shown that 7-T imaging is a valuable tool to depict and classify cortical lesions by using T2*w GRE pulse sequences [12, 17–21] and that these sequences are able to depict most cortical lesions as verified by pathological examination [17]. The purpose of our study was to investigate sequences at 7 T that are used in routine clinical practice at standard field strengths as recommended by the standard MRI protocol for MS. In future 7-T studies, it would be interesting to compare cortical lesion detection on standard clinical sequences (T1w, T2w and FLAIR) with experimental sequences, such as T2*w or DIR.

Figure 7. Comparison of PV + DWM lesion numbers on 3T and 7T 3D-FLAIR. Patients are ranked for PV + DWM lesion scores on 3T and grouped. At 7T less lesions are scored for patients with high numbers of lesions, possibly due to artificial confluence of lesions.
The current study and earlier studies prove that 7-T MRI helps to depict features that are specific to MS, such as cortical GM abnormalities [12, 17-21, 26, 39], perivenular orientation of lesions [12-15, 39] and hypointense rims around lesions indicating iron deposition [15-17, 40].

Lesion-wise analysis in control subjects showed a small increase in the total amount of lesions at all pulse sequences at 7 T compared with 3 T, but this trend was not statistically significant when tested in a patient-wise analysis. The most WM lesions are presumed to be of vascular origin and show that even in MS patients some of the detected lesions may indicate vascular lesions that accompany aging.

Possible limitations of our study include the usage of different coils on the different devices as well as a small difference in spatial resolution (voxel size) between the two field strengths for some sequences and the increased effective echo time on the FLAIR sequence at 7 T. However, if we had used the same extreme high resolution at 3 T, the lower SNR and CNR would have resulted in low image quality with many small hyperintensities that could not be classified as lesions for size reasons, while at the same time this lowers the general conspicuity of lesions. The advantage of moving to higher field is that we were able to use the smaller voxel size without decreasing image quality because of the increased SNR at 7 T. But strictly speaking, our results should be interpreted as a combination of increasing field strength, increased resolution and coil type. However, it would be unnatural not to capitalise on the increased signal at 7 T.

In the future, the development of coils that show higher sensitivity for the lower part of the brain would help to assess performance of 7- compared to 3-T MR for infratentorial and deep GM lesions as well. Also a more uniform signal distribution is expected using a multitransmit setup.

In conclusion, at 7 T the use of a clinical multi-contrast MR imaging protocol according to the MS imaging guidelines [6, 22] increased the detection of cortical GM abnormalities substantially, but did not lead to a higher detection rate of total and WM lesions. As the current MR imaging and diagnostic criteria are based on WM lesion detection, we expect the added clinical value in terms of establishing a more sensitive diagnosis of MS to be limited. However, the increased detection of GM lesions at 7 T may lead to considerable consequences in terms of clinical outcome measures and prognostic classification of MS patients. Furthermore, if cortical abnormalities are to be included in diagnostic and MR imaging criteria, we expect a clinically relevant role for 7-T MR imaging in the diagnosis of MS.

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References


