Multicontrast MR imaging at 7 T in multiple sclerosis: highest lesion detection in cortical gray matter with 3D-FLAIR


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Abstract

Background and Purpose
7T MR imaging has lead to improved detection and classification of cortical MS lesions, mainly based on T2*w GRE sequences. Depiction of cortical GM by using the recommended MS imaging protocol has not yet been investigated at 7 T. We aim to investigate prospectively which recommended sequence for clinical use has the highest value at 7 T, in terms of GM and WM lesion detection.

Materials and Methods
37 MS patients (mean age 43.8 years, 25 female) and 7 healthy controls (mean age 40.4 years, 5 female) underwent multicontrast 7T MR imaging including recommended clinical 2D-T2w, 3D-T1w and 3D-FLAIR, and GM specific 3D-DIR. Lesions were scored and categorized anatomically, by 3 raters, in consensus. Value of sequences was evaluated lesion-wise and patient-wise (Wilcoxon signed rank test). The study was approved by the institutional review board.

Results
At 7 T, 3D-FLAIR detected the highest number of total cortical GM lesions (217), 89% more than 3D-DIR and 87 and 224% more than 2D-T2w and 3D-T1w. Patient-wise analysis showed that this difference between 3D-FLAIR and 3D-DIR was statistically significant (P<0.04), and most pronounced for the number of mixed lesions (P<0.03). 3D-FLAIR also detected the highest number of total WM lesions (2605), but the difference with 3D-DIR and 3D-T1w was not significant.

Conclusion
When using recommended sequences for clinical use at 7 T, the best way to detect cortical GM lesions is with 3D-FLAIR and not by GM specific 3D-DIR or by conventional 2D-T2w and 3D-T1w sequences.
Introduction

MS has been primarily regarded as a WM disease, which is reflected in current MR imaging and International Panel diagnostic criteria. However, early histopathology studies already recognized the involvement of cortical GM, and over the past years GM abnormalities in MS have been increasingly investigated. Histopathological studies report that up to 60% of total MS lesions affect the cortical GM. Unfortunately, the sensitivity of conventional MR imaging techniques to detect cortical lesions remains poor when compared with histopathological studies. In the clinical setting, it is highly relevant that GM abnormalities in MS can be visualized in vivo. Firstly, because GM abnormalities importantly explain cognitive and physical disability, and secondly because focal GM lesions are rather specific for MS. They occur in the earliest stages of the disease already, and it was suggested that McDonald criteria for the diagnosis of MS -at present completely based on WM lesion detection-will be of increased accuracy when cortical GM lesions are included. Due to a higher SNR with increased spatial resolution, MS lesion detection has improved by moving from 1.5T MR imaging to 3 T. At both field strengths, a common finding is that FLAIR detects the highest amount of WM lesions and DIR has the highest sensitivity in detecting cortical GM lesions. The introduction of ultrahigh-field 7T systems has lead to improved detection and classification of cortical lesions in MS patients, mainly by using experimental T2*w GRE sequences. The depiction of cortical GM by using the standard imaging protocol for MS, including T1w, T2w and FLAIR sequences has not yet been investigated at 7 T, nor has DIR at 7 T. This is mainly due to the fact that the application of 3D FLAIR and DIR sequences at a 7T system was challenging, due to, amongst others, SAR restrictions. Nonetheless, both sequences have been successfully implemented at 7 T recently. The aim of this prospective study was to investigate which sequence has the highest value at 7 T in terms of GM and WM lesion detection: recommended sequences for clinical use 2D-T2w, 3D-T1w and 3D-FLAIR, or 3D-DIR, a sequence that is developed to specifically depict the GM of the brain. Results of this study will be a preliminary finding for this multicontrast protocol at 7 T, according to our specific study design and sequence parameters.

Materials and Methods

Participants

37 Patients were prospectively recruited from our neurology outpatient clinic. Inclusion criteria were clinical definite MS according to 2005 revised International Panel (McDonald) criteria, and age between 18 and 60 years old. Exclusion criteria were the presence or past medical history of other neurological or vascular disorders, recent relapses (<3 months) and standard contraindications for MRI (e.g. claustrophobia). Next 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.

Seven healthy control subjects were also enrolled in this study from February 2009 till June 2011. A small part of the study population (10 MS patients and 5 healthy controls) has been incorporated in an explorative feasibility study, which was published earlier.
The institutional ethical review board approved the study and all subjects gave written informed consent prior to participation.

**MR Imaging acquisition**

All subjects were imaged on a whole-body 7T MR system (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 (Nova Medical, Inc. Wilmington, MA, USA). The protocol included the following pulse sequences: axial 2D-T2w, sagittal 3D-T1w, sagittal 3D-FLAIR and sagittal 3D-DIR. The 3D-FLAIR and the 3D-DIR sequences both used MP to reduce unwanted T1 weighting. Detailed sequence parameters are given in table 1.

Preceding image analysis, all sagittal 3D images were reconstructed in the axial plane corresponding to the 2D-T2w images, with the same slice thickness, using the same repositioning.

**Table 1.** Sequence parameters per pulse sequence at 7 T

<table>
<thead>
<tr>
<th></th>
<th>3D-DIR</th>
<th>3D-FLAIR</th>
<th>2D-T2w</th>
<th>3D-T1w</th>
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<tr>
<td>TR [ms]</td>
<td>8000</td>
<td>8000</td>
<td>4969</td>
<td>7.0</td>
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<tr>
<td>TE (1/2) [ms]</td>
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<td>303</td>
<td>21 / 80</td>
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<td>TI (1/2) [ms]</td>
<td>3150/550*</td>
<td>2325</td>
<td>-</td>
<td>1129</td>
</tr>
<tr>
<td>Flip Angle [°]</td>
<td>100</td>
<td>100</td>
<td>90</td>
<td>8</td>
</tr>
<tr>
<td>Echo Train Length [°]</td>
<td>128</td>
<td>125</td>
<td>8</td>
<td>312</td>
</tr>
<tr>
<td>Acquisition Resolution [mm³]</td>
<td>1.0x1.0x0.8 (sagittal)</td>
<td>0.8x0.8x0.8 (sagittal)</td>
<td>0.7x1.0x2.0 (axial)</td>
<td>0.8x0.8x0.8 (sagittal)</td>
</tr>
<tr>
<td>Reconstructed Resolution [mm³]</td>
<td>0.5x0.5x0.4 (axial)</td>
<td>0.49x0.49x0.4 (axial)</td>
<td>0.45x0.45x2.0 (axial)</td>
<td>0.5x0.5x0.4 (axial)</td>
</tr>
<tr>
<td>SENSE</td>
<td>2.0x3.0 (APxRL)**</td>
<td>2.5x2.5 (APxRL)**</td>
<td>2.1 (RL)</td>
<td>2.0 (RL)</td>
</tr>
<tr>
<td>Acquisition time [min:sec]</td>
<td>11:04</td>
<td>13:06</td>
<td>8:07</td>
<td>9:43</td>
</tr>
</tbody>
</table>

* The long inversion time (TI1) is the interval between the first 180° inversion pulse and the 90° excitation pulse, and the short inversion time (TI2) is the interval between the second 180° inversion pulse and the 90° excitation pulse
** SENSE applied in 2 dimensions (AP: Anterior-Posterior, LR: Left-Right)

**Image analysis**

Images were interpreted by 3 raters in consensus: IK and WG (PhD students with 2 and 5 years experience in MR image reading respectively) and AL (neuroradiologist, 7 years experience). While scoring, images of pulse sequences per subject were separated and presented in random order, to avoid recall bias. Raters were blinded for patient identification and (para)clinical information.

Prior to the evaluation of lesions, quality of images (artifacts and image homogeneity) was assessed for each pulse sequence. Contrast ratios of the sequences were reported elsewhere. For each subject and pulse sequence, lesions were counted and categorized according to their anatomical location: PV WM lesions in contact with the ventricles; DWM lesions not in contact with ventricles or cortex; JC WM lesions in contact with the cortex; mixed lesions located in GM as well as in WM; IC lesions located completely within the cortical GM. Only supratentorial WM and cortical GM were included in the analysis, since the sensitivity of the coil did not cover infratentorial regions in all subjects. Besides specific anatomical locations, combined regions were defined: total WM (PV + DWM + JC), total cortical GM (mixed + IC) and total lesion numbers (total WM + total GM). Focal areas of hypointense (3D-T1w images) or hyperintense (2D-T2w, 3D-FLAIR and 3D-DIR images) signal intensity compared to the surrounding WM
and GM, with a minimum size of 3 voxels were classified as lesions. Scoring of cortical GM lesions was performed using consensus guidelines developed by the MAGNIMS study group regarding DIR sequences (although these were not primarily designed for 7T scorings).

Lesions were marked by a scoring tool developed in-house, which was used as a plug-in in MIPAV software (MIPAV version 5.1.1, CIT, NIH, Bethesda, MD, USA). Results per subject were collected by a Matlab script (Matlab 7.1, The Mathworks Inc., Natick, MA, USA) written in-house. After analysis of the results, we reviewed a subset of patients and compared 3D-FLAIR and 3D-DIR side-by-side to explain our results, mostly because they are conflicting with earlier studies at lower (1.5 and 3T) field strengths.

**Statistical analysis**

For each subject, numbers of lesions per anatomical location and sequence were assessed and analyzed by SPSS version 15.0 (SPSS, IBM, Chicago, IL, USA). In a lesion-wise analysis total number of lesions per anatomical region for each sequence are presented, as well as the mean lesion count per patient. Results were compared patient-wise by a Wilcoxon signed rank test, as total lesion numbers showed a non-normal distribution that could not be transformed into normality. Results from the pair-wise comparison were Bonferroni corrected for multiple (six pairwise) comparisons. Corrected P-values ≤ 0.05 were considered statistically significant.

**Figure 1.** Axial 3D-DIR, 3D-FLAIR, 3D-T1WI, and 2D-T2WI at 7T MR imaging of a 50-year-old healthy male control. Note the hyperintense visualization of both the outer (subpial) layers of the cortex and perivascular spaces on both 3D-DIR and 3D-FLAIR images.

**Results**

**Demographic data**

Thirty-seven MS patients (25 female, 12 male) and 7 healthy controls (5 female, 2 male) were included in the study. Mean age of the MS patients at time of the MR examination was 43.8 years (standard deviation [SD] 8.3) and median EDSS was 4 (range 0 – 7.5). 22 Patients had RRMS, 9 PPMS and 6 had SPMS. Mean age of the healthy controls was 40.4 years (SD 8.9).
Healthy control subjects
In the healthy control subjects a total number of 40 lesions was found on the 3D-FLAIR images, 26 on 3D-DIR, 24 on 2D-T2w and 21 on 3D-T1w. Of these lesions, 79% were PV and DWM lesions, presumably of vascular ischemic origin. No IC lesions were identified in any of the healthy control subjects; only one mixed lesion was found in one healthy control on 3D-DIR. An example of the 7T sequences in a healthy control subject can be found in figure 1.

MS patients: Lesion-wise analysis
Overall, the 3D-FLAIR sequence detected the highest number of lesions when compared to other sequences. In total GM, 217 lesions were detected at 3D-FLAIR, which was 89% more compared to 3D-DIR (115), 87% more compared to 2D-T2w (116), and 224% more compared to 3D-T1w images (67). The difference was largest for the detection of mixed lesions at 3D-FLAIR, where 147% more mixed lesions were detected than at 3D-DIR (72), 117% (82) more than at 2D-T2w and 242% (52) more than at 3D-T1w images. The highest number of purely IC lesions was detected at 3D-DIR (43), a 10% increase compared to 3D-FLAIR (39) and a 27% and a 187% increase when compared to 2D-T2w (34) and 3D-T1w (15) images. Images of intracortical lesion detection with the different 7T sequences used in the study are shown in figure 2.

In WM, 3D-FLAIR also detected the highest number lesions (2605), a relative gain of 12% compared to 2D-T2w images (2321); the difference with both 3D-DIR and 3D-T1w images was small: 1% (2582 and 2583 respectively). In total, 3D-FLAIR detected the highest number of lesions: 2822 lesions meant a relative gain of 16% compared to 2D-T2w images (2437), 7% compared to 3D-T1w images (2650), and 5% compared to 3D-DIR (2697) images. For more detailed information on lesion counts per anatomical WM region we refer to table 2.

MS patients: Patient-wise analysis
In this analysis, every sequence was compared to the 3 other sequences, per patient. In terms of total GM lesion detection, patient-wise analysis showed significantly improved lesion detection at 3D-FLAIR when compared to 3D-DIR (P<0.04) and 3D-T1w (P<0.01) sequences. This was mostly due to a higher detection of mixed lesions at 3D-FLAIR, which was statistically significant when compared to 3D-DIR (P<0.03) and 3D-T1w (P<0.01) images.

Concerning the WM, JC lesion detection at 3D-DIR was significantly higher than at 2D-T2w images (P<0.01), which also held true for 3D-FLAIR and 3D-T1w images compared to 2D-T2w images (P<0.01 and P<0.01). Total WM lesion detection did not differ significantly between all sequences, nor did the number of PV and DWM lesions.
Discussion

Our results show that 3D-FLAIR detects the highest number of MS lesions at 7 T, in total cortical GM as well as in total WM. On FLAIR images, signal from CSF is nulled, which increases contrast between lesions and adjacent CSF. At standard field strength (1.5 T) this meant an increase in MS lesion detection compared to conventional T2w sequences, especially for juxtacortical lesions. Moving to 3 T, FLAIR showed an increased lesion detection compared to 1.5 T, and it showed superiority over conventional T2w and T1w sequences for WM lesion detection. Regarding cortical GM lesions at lower field strengths, highest lesion detection was found by DIR, which at 1.5 T and at 3 T, suppresses the signal of both CSF and WM improving the visibility of the cortex and cortical abnormalities. This improved visibility of cortical abnormalities at DIR did not hold in our 7T dataset. The detection of total GM lesions was higher on 3D-FLAIR than on 3D-DIR, mostly due to a considerably superior detection of mixed lesions. The higher total GM and mixed lesion detection at 3D-FLAIR was statistically significant when tested in a patient-wise analysis. Although the detection of purely IC lesions was higher at 3D-DIR compared with the other sequences, this did not reach statistical significance in the patient-wise comparison. The 10% gain in purely IC lesion detection on 3D-DIR compared to 3D-FLAIR concerned only 4 lesions.

In the present literature there are several studies that focus on the detection of cortical GM lesions at 7 T, mostly reporting that T2*w GRE sequences improve detection. One of these studies using T2*w GRE images even suggests that this sequence should be the new gold standard for detection of cortical lesions in MS patients. Another recent study described that white matter signal attenuation at 7 T is feasible, and able to detect cortical abnormalities at 7 T. To our knowledge, the value of recommended sequences for clinical use at 7 T had not yet been investigated, nor has the use of DIR. Our results show that the highest total cortical lesion detection at 7 T is gained with 3D-FLAIR. Future studies should compare the difference between these experimental T2*w GRE or white matter attenuated sequences, and clinical 3D-FLAIR sequences and elucidate which sequence has the highest sensitivity in terms of 7T cortical lesion detection. At even higher field strength (9.4T) T2w sequences were able to discriminate demyelinated and remyelinated areas in postmortem MS lesions.

The results of our 7T study are promising, because in vivo imaging of cortical abnormalities in MS has high clinical relevance. Cortical lesions correlate with cognitive impairment, and

| Table 2. Lesion-wise analysis in MS patients: total lesion detection and mean lesion count per patient |
| --- | --- | --- | --- | --- |
| Region | 3D-DIR* (mean±SD) | 3D-FLAIR* (mean±SD) | 2D-T2w* (mean±SD) | 3D-T1w* (mean±SD) |
| PV | 692 (18.7±16.5) | 594 (16.1±13.5) | 584 (15.8±16.8) | 621 (16.8±16.7) |
| DWM | 1162 (31.4±32.3) | 1197 (32.4±27.3) | 1323 (35.8±34.2) | 1109 (30.0±34.6) |
| JC | 728 (19.7±29.7) | 814 (22.0±29.4) | 414 (11.2±16.8) | 853 (23.1±30.1) |
| Total WM | 2582 (69.8±7.1) | 2605 (70.4±8.2) | 2321 (62.7±13.1) | 2583 (69.8±6.6) |
| Mixed | 72 (1.9±3.0) | 178 (4.8±7.9) | 82 (2.2±3.8) | 52 (1.4±1.9) |
| IC | 43 (1.2±2.4) | 39 (1.1±2.7) | 34 (0.9±1.9) | 15 (0.4±0.9) |
| Total cortical GM | 115 (3.1±0.6) | 217 (5.9±2.7) | 116 (3.1±0.9) | 67 (1.8±0.7) |
| Total WM+GM | 2697 (72.9±12.9) | 2822 (76.3±12.7) | 2437 (65.9±14.1) | 2650 (71.6±13.1) |

*Data represent numbers of detected lesions per anatomical region
could be used as an outcome measure in MS research, or be of help in the development and monitoring of treatment. Furthermore, the detection of GM abnormalities has prognostic relevance and will help to identify CIS patients who will eventually convert to CDMS. It has been proposed that sensitivity of the criteria for the diagnosis of MS will increase when GM lesions are included. These McDonald criteria are at present based on WM abnormalities solemnly, but GM abnormalities might be introduced in the criteria in the future. 7T MR imaging of cortical lesions can play a role in these different aspects, and can be of additional value in MS patient care. However, only a limited number of 7T scanners are available, worldwide around 40 7T systems, as mentioned in a recent review on 7T MR imaging.

As opposed to 1.5 T and 3 T, the highest total cortical GM lesion detection at 7 T was found by the 3D-FLAIR sequence. To investigate this finding further, we reviewed a subset of patients and compared 3D-FLAIR and 3D-DIR sequences side-by-side (figure 3). This comparison suggested several possible explanations, involving the design of both sequences as well as our rating process. First, the design of sequences at our 7T system causes a multiple-layered appearance of the cortex which differs between 3D-DIR and 3D-FLAIR, and has recently been described to differ between anatomical regions in the brain. The cortex is often relatively more

Figure 3. Examples of scoring differences at 7T MR imaging: 3D-FLAIR versus 3D-DIR, found while reviewing a subset of images retrospectively. A, A juxtacortical lesion (closed arrows) that was scored on 3D-FLAIR but not on 3D-DIR because of differences in contrast between the lesion and the cortical gray matter. On 3D-DIR, the cortex looks relatively hyperintense compared with 3D-FLAIR because of the attenuation of white matter, which might have hindered lesion detection. The open arrows show a juxtacortical lesion that was detected at both sequences. B, The closed arrows show a mixed lesion that was scored on 3D-FLAIR but not on 3D-DIR because of conservative scoring/distraction by many small hyperintensities and its smaller size on 3D-DIR. C, A juxtacortical lesion that was scored on 3D-FLAIR but not on 3D-DIR images (closed arrows) because tissue was attenuated too much by using the DIR sequence, which decreases the size of the lesion.
hyperintense at 3D-DIR than at 3D-FLAIR, because of attenuation of WM at DIR (figure 3). This might have caused diminished visibility of cortical lesions at 3D-DIR. Furthermore, due to the combination of two inversion pulses at 3D-DIR, additional tissue components besides CSF and WM are partly attenuated as well, including lesions, particularly the periphery of a lesion. This did not make small lesions completely invisible, but often too inconspicuous to score, a phenomenon which has also been described at lower field strength. As T1-values are field strength dependent, this effect could be different at high field, and should be further investigated. In addition to these aspects, the resolution of 3D-FLAIR was better than that of 3D-DIR, 0.51 mm\(^3\) vs. 0.64 mm\(^3\) voxel volumes respectively, which might affect the ability to detect small lesions. Second, the scoring process might also have hampered lesion detection at 3D-DIR. There is an abundance of small signal abnormalities, mostly perivascular spaces, on 3D-DIR (figure 1). This may have caused too much distraction whilst scoring lesions, so that they were overlooked or not specified as being a lesion. Furthermore, a rather conservative scoring system was used: focal hyperintensities were only specified as lesions if they were in line with the consensus guidelines for scoring of cortical lesions on DIR, which were developed by the MAGNIMS study group. Hyperintensities or inhomogeneities in the cortex were interpreted as artefacts or as small vessels more easily on the 3D-DIR sequence than on the 3D-FLAIR sequence, which may have caused an underrepresentation of lesions at 3D-DIR.

Contrast ratios of our 7T 3D-FLAIR have been reported to be lower compared to 3D-DIR: GM/WM 0.40 and 0.35 in healthy controls and patients respectively for FLAIR, compared to 0.93 and 0.87 for DIR. Lesion/WM contrast in FLAIR was 0.86, whereas 2.92 in DIR, lesion/GM 0.91 in FLAIR and 1.40 in DIR. Hence contrast ratios are unlikely to have advanced lesion detection at 3D-FLAIR. Despite the higher relative contrast in DIR, the absolute contrast in terms of contrast-to-noise ration could be less, due to the overall reduction in SNR by the extra inversion pulse.

The lower lesion counts detected by the 3D-DIR sequence cannot be explained by a reclassification phenomenon; i.e. the shift from one anatomical region to another because of improved visibility of the cortex. This was the case at 1.5T and 3T DIR, when a slightly lower sensitivity in JC lesion detection was counterbalanced by an increased detection of mixed or purely IC lesions. However at 7 T, with higher spatial resolution and different image contrast, visibility of the cortex is improved at all sequences, hence a reclassification phenomenon was not evident in our data.

Concerning WM lesion detection at 7 T, our results show statistically significant differences in the juxtacortical region. At 3D-FLAIR, 3D-DIR and 3D-T1w images a higher number of JC lesions was detected when compared to 2D-T2w images. Total WM lesion detection was highest at 3D-FLAIR when analysed lesion-wise, although the difference with 3D-DIR and 3D-T1w images was negligible (1% higher). When tested patient-wise, this increased WM lesion detection of 7T 3D-FLAIR compared to other sequences was not statistically significant.

Limitations of the study are that we could have taken more advantage of the multicontrast protocol by scoring lesions one-on-one on all 4 sequences simultaneously. The goal of this study however, was to evaluate the performance of the different sequences regarding overall lesion counts in different anatomical regions between the different sequences, so we chose to score the sequences separately. The scoring process was done by three raters in consensus, because of the novelty of 7T MR images. A possible limitation could be that we have no intra- or inter-observer
comparison. In the future, it is interesting to study this, possibly in addition to comparing inter observer agreement between different field strengths and between raters of different levels of experience. And most importantly, the results in this study are specific for our MR system and our sequences with mentioned parameters. Whether results can be generalised to other 7T MR systems, remains a matter for future research.

Conclusion
The results of the present study show that - according to our study set up and our sequence designs - when using recommended sequences for clinical use at 7 T, the best way to detect focal cortical GM abnormalities is with 3D-FLAIR and not by a GM specific 3D-DIR sequence or by conventional 2D-T2w and 3D-T1w sequences.

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References


