“It’s not what you look at that matters, it’s what you see.”

(Henry David Thoreau)
Chapter 3

LESION MORPHOLOGY AT ULTRAHIGH FIELD
Opportunities for clinical application
Morphological features of MS lesions on FLAIR* at 7 T and their relation to patient characteristics

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Abstract

Recently, a new MRI technique was developed at 3 Tesla (T), called fluid attenuated inversion recovery* (FLAIR*). In this study, we implemented FLAIR* in an existing MS cohort at 7 T, to investigate whether we could corroborate results of previous 7T studies that introduced specific MS lesion characteristics. Furthermore, we aimed to investigate the meaning of these lesion characteristics by relating them to clinical characteristics of the MS patient. 3D-FLAIR and T2*-weighted images of 33 MS patients and 7 healthy controls were fused into FLAIR* images. Lesion type, signal intensity, and morphology were analysed on FLAIR*, side-by-side with the original FLAIR and T2*, and correlated to clinical characteristics using Spearman's rho. Three morphological features of MS lesions were visualised: (1) central vessel (CV) within lesions, present in 78% of total MS lesions; (2) hypointense rims around MS lesions, present in 8 patients; (3) FLAIR* lesions that were hypointense at T2*, present in 13 patients. The presence of hypointense (rims around) lesions was not related to clinical characteristics. The simultaneous presence of rimlike lesions and hypointense lesions within MS patients was significantly correlated (ρ=0.52, P<0.01). We conclude that the implementation of the new MRI technique FLAIR* at ultrahigh-field 7 T, combines and corroborates results of preceding 7T research, by showing three morphological features of MS lesions. In addition, our study shows that these phenomena do not show a relation to patient’s clinical characteristics and cannot be allocated to certain MS disease subtypes.
Introduction

The introduction of high-field magnetic resonance imaging (MRI) at 3 Tesla (T) and more recently ultrahigh-field 7T MRI has shown to be beneficial for multiple sclerosis (MS). A higher signal-to-noise-ratio (SNR) and the possibility to improve spatial resolution have lead to increased lesion detection, in white matter (WM) and grey matter (GM) of the brain.\textsuperscript{1–4}

In addition to lesion detection alone, ultrahigh-field 7T MRI studies focussed on new aspects of MS pathology on MRI. Based on increased susceptibility effects that accompany increasing field strength, in combination with higher SNR, 7T imaging makes it possible to study morphology of MS lesions in a more precise way. Susceptibility weighted imaging (SWI) at 7 T has improved the visibility of the small parenchymal veins with without the use of intravenous contrast media,\textsuperscript{5} and demonstrated the perivascular distribution of MS lesions.\textsuperscript{6,7} Perivascular inflammation, which is the histopathological hallmark of MS white matter (WM) lesions, leads to a characteristic perivascular lesion distribution pattern in the periventricular and deep white matter, forming the typical Dawson's fingers on MRI.\textsuperscript{8} Furthermore, phase imaging at 7 T has shown specific lesion characteristics beyond the morphology of classical lesions on T2- and T1-weighted images, including hypointense rims around lesions, and hypointense lesions themselves.\textsuperscript{9–12}

Recently at 3 T, Sati et al. described a technique that combines T2-weighted fluid attenuated inversion recovery (FLAIR) contrast with T2*-weighted (T2*W) contrast into one image called FLAIR*.\textsuperscript{13} At 3 T, this FLAIR* contrast offered cerebrospinal fluid attenuation, plus a high conspicuity for lesions and parenchymal veins, ideal for imaging MS lesions.

To build upon this, we aim to implement the new FLAIR* technique in an existing 7T MS cohort. With this, we take the expected benefits from 7T imaging when compared with 3T imaging, namely a higher sensitivity of 7T FLAIR in MS lesion detection,\textsuperscript{3} and an improved visibility of small cerebral veins at 7T T2* images,\textsuperscript{5} without the need of contrast administration, as was necessary with 3T FLAIR*.\textsuperscript{13} Furthermore, with 7T FLAIR* we can try to corroborate results of previous 7T studies that introduced specific MS lesion characteristics such as perivascular MS lesion orientation, rimlike and hypointense lesions. Lastly, we aim to investigate what is the meaning of these distinct lesion characteristics, which has not been investigated so far. In other words: Are these hypointense lesions related to clinical characteristics of the MS patient or linked to of one of the MS disease subtypes?

Methods

Subjects

MS patients were selected from our on-going study “7T high-field in MS study”, who had underwent both FLAIR and T2* imaging. This study includes patients from our outpatient neurology clinic, diagnosed with clinically definite MS according to the 2005 revised McDonald criteria.\textsuperscript{14} Exclusion criteria were other neurological, vascular and malignant comorbidity, recent clinical relapses (< 3 months), and contraindications for MRI (i.e., metal objects, claustrophobia). Healthy control subjects without neurological, vascular and malignant comorbidity were selected from this database too. The study protocol was approved by the local institutional ethical review board. Written informed consent was obtained from all participants prior to inclusion.
Clinical Evaluation

The following demographic and clinical variables were collected for every participant: age, sex, disease type, disease duration and clinical disability as measured by the Expanded Disability Status Score (EDSS).15

Imaging Protocol

Subjects were scanned on a whole-body 7T MR system (Achieva, Philips Healthcare, Best, The Netherlands), slew rate 200 T/m/s, gradient strength 40 mT/m and a 16-channel phased array headcoil (Nova Medical, Wilmington, MA). The following sequences were acquired: sagittal 3 dimensional (3D) FLAIR (echo time (TE) 300 ms, repetition time (TR) 8000 ms, inversion time (TI) 2325 ms, flip angle 100°, acquired resolution 0.8x0.8x0.8mm³, sensitivity encoding 2.5x2.5 APxRL, acquisition time 13:06min) and a dual-echo transversal T2*W sequence with a built-in phase correction, partial echo-filter and homogeneity correction of the MR system (TE1/2 2.5/15 ms, TR 20 ms, flip angle 20°, acquired resolution 0.39x0.45x0.6mm³, sensitivity encoding 2.5 RL, acquisition time 8:50 min). The FLAIR sequence made use of magnetisation preparation (MP), to reduce unwanted T1-effects.16,17 No intravenous contrast agent was administered.

Image processing

Calculation of FLAIR* images was performed by one of the authors (JPK, physicist 15 years of experience in image processing), and consisted of 3 main steps. At first, with a custom Matlab script (R2011a, Matworks, Natick, MA, USA), a thin-slab axial minimum intensity projection (MinIP) was made from the second echo of the T2*W images. This was done over 11 slices with 4 slices overlap, yielding a MinIP slice spacing of 7*0.3=2.1mm. In addition, an axial thin-slab multiplanar reconstruction (MPR) was made from the first echo of the T2*W images, which was averaged over 7 slices (MPR slice spacing of 7*0.3=2.1mm). Secondly, we registered the 3D FLAIR images to the 3D T2* MPR by using FMRIBs Linear Registration Tool (FLIRT) as part of FSL (FSL, 4.19; FMRIB Software Library, available at fsl.fmri.ox.ac.uk). To correct for motion that might have occurred between the sequences, six degrees of freedom and mutual information cost function were used. After this, all images were visually inspected to check for correctness of the registration. The third step included voxelwise multiplication of the registered FLAIR with the MinIP images, yielding final 7T FLAIR* images with a resolution of 0.4x0.4x2.1mm³ (figure 1).
Image Analysis
Images were read in consensus, by two raters (IDK, 3 years experience in image reading and AL, neuroradiologist 8 years experience), using MIPAV software (Medical Image Processing, Analysis & Visualization, National Institute of Health; mipav.cit.nih.gov). We analysed all three sequences in a side-by-side manner; divided over multiple screens we opened and synchronised the registered axial FLAIR, T2*W MinIP and FLAIR* images.

On FLAIR*, lesions were classified as: periventricular (PV), deep white matter (DWM), juxtacortical (JC), mixed gray matter and white matter (MIX) and intracortical (IC) lesions.\textsuperscript{18} A lesion was defined as a hyperintensity on FLAIR*, extending over at least 5mm. Per lesion, the presence of a central vessel (CV) was analysed. We applied the following definition of a CV: (1) a continuous hypointense line on FLAIR* and T2*W MinIP, (2) oriented along the long axis of the lesion, (3) traversing more than 50% of the lesion, (4) located in the center, i.e. there is lesional tissue symmetrically at both sides of the vessel. Furthermore, differences in signal intensity of the lesions were analysed at all three sequences aside. Most commonly, MS lesions are hyperintense on FLAIR, isointense/hyperintense on T2*W and, hence, hyperintense on FLAIR*. We also considered lesions at FLAIR* that were hypointense at T2*W MinIP, compared to the surrounding normal appearing WM. The presence of a hypointense rim around an MS lesion was considered on FLAIR* and T2*W MinIP images. The (signal in the) field of view did not reach to the infratentorial part of the brain in every MS patient, so infratentorial lesions were not taken into account in our official analyses.

Statistical analysis
Statistical analysis was performed using the SPSS software package, version 20.0 (SPSS, IBM, Chicago, IL, USA). Kolmogorov-Smirnov tests and visual inspection of the histogram were used to assess normality of the variables. Morphological features of MS lesions: (1) presence of CV, (2) hypointense rim and (3) presence of hypointense lesions at T2*, were related to patient characteristics (as described in clinical evaluation) and lesion counts, using Spearman’s rank correlation coefficient. P-values of <0.05 were considered as statistically significant.

Results
Demographic Data
FLAIR and T2*W images from 33 MS patients were collected: 20 females and 13 males, mean age 44.2 years (SD 8.4). There were 19 relapsing remitting (RR), 9 primary progressive (PP) and 5 secondary progressive (SP) MS patients, with a median EDSS of 4.0 (range 0-7.5) and a mean disease duration of 9.6 years (SD 5.9). We also included 7 healthy control subjects, 4 females and 3 males, mean age 41.0 years (SD 10.0).

Central vessel
All MS patients had brain lesions; in total 1004 lesions were detected on FLAIR*, mean 30.4 lesion per patient (SD 25.8). From the total amount of lesions, 78% were located around a vessel. Most lesions were found in the DWM (372). Of these DWM lesions, 311 showed a perivascular distribution pattern (84%). The highest proportion of lesions with a perivascular orientation was found in the PV area, where 266 out of 282 lesions (94%) had a CV. In the juxtacortical region, 66% of the lesions had a CV, just as 52% of the MIX and 25% of the IC lesions. Examples of different lesion types with a CV are shown in figure 2. In healthy controls, 1 DWM lesion was
detected, without a CV. Detailed information on lesion numbers, lesion location and presence of a CV is displayed in Table 1.

**Table 1.** Lesion distribution and presence of central vessel in MS patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>PV</th>
<th>DWM</th>
<th>JC</th>
<th>MIX</th>
<th>IC</th>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No. lesions</td>
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<td>282</td>
<td>372</td>
<td>222</td>
<td>104</td>
<td>24</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>30.4 (25.8)</td>
<td>8.6 (9.1)</td>
<td>11.3 (10.4)</td>
<td>6.7 (7.9)</td>
<td>3.2 (5.2)</td>
<td>0.7 (1.6)</td>
</tr>
<tr>
<td>No. CV</td>
<td>782</td>
<td>266</td>
<td>311</td>
<td>147</td>
<td>54</td>
<td>6</td>
</tr>
<tr>
<td>% CV</td>
<td>77.9</td>
<td>94.3</td>
<td>83.6</td>
<td>66.2</td>
<td>51.9</td>
<td>25.0</td>
</tr>
<tr>
<td><strong>HC (n=7)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. lesions</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean (SD)</td>
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<td>-</td>
<td>0.1 (0.4)</td>
<td>-</td>
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<tr>
<td>% CV</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

PV = periventricular; DWM = deep white matter; JC = juxtacortical; MIX = mixed grey matter/white matter; IC = intracortical; MS = multiple sclerosis; CV = central vessel; HC = healthy controls

**Figure 2.** Examples of MS lesions with central vessel as seen on FLAIR, T2* MinIP and FLAIR* at 7 T. Lesions are most commonly hyperintense on FLAIR, iso- or hyperintense at T2*MinIP, and hence hyperintense at FLAIR.
The proportion of total lesions with a CV was not related to any of the clinical measures including age, sex, disease type and duration, or EDSS. After dichotomization of the ages of MS patients using a cut-off of 40 years, results showed a significantly lower proportion of DWM lesions with a CV in patients older than 40 (ρ=-0.457, P=0.01). MS patients aged 40 years and younger had DWM lesions with a CV in 92%, whereas MS patients older than 40 had a CV in 73%.

Although not the primary focus of this study, 5 thalamic lesions were detected in the MS patient group, all of which contained a CV (figure 3). The same goes for infratentorial lesions, in 24 MS patients the field of view reached the cerebellar peduncles and in this group 13 pons lesions were found, 12 of which contained a CV (figure 4). Furthermore, one cerebellar lesion was detected with a CV.

**Hypointense rim**

With FLAIR*, we detected lesions that were surrounded by a hypointense rim in eight MS patients (24%) (figure 5). Three of these patients had one single rimlike lesion; the other 5 patients had more (range 1-17). The 33 rimlike lesions represented 3% of the total lesions. Details of the MS patients with rimlike lesions are presented in table 2.

The presence of rimlike lesions was not related to sex or age of the patients. Of the patients with rimlike lesions, 3 had a progressive disease start and 5 a relapsing onset (3 RR, 2 SP at present). There was no significant influence of disease type, or MS onset type on the presence of rimlike lesions. Neither was the presence of hypointense rims in MS patients related to disease duration or EDSS. The presence of rimlike lesions was significantly related to a higher number of total MS lesions (P=0.006), GM lesions (P=0.006) and WM lesions (P=0.012).

**Figure 3.** MS lesion in the thalamus with a central vessel as seen on FLAIR, T2∗ MinIP and FLAIR* at 7 T

**Figure 4.** MS lesion in the pons with a central vessel as seen on 7T FLAIR, T2∗ MinIP and FLAIR* at 7 T

**Figure 5.** Hypointense rim lesion with a central vessel as seen on FLAIR, T2∗ MinIP and FLAIR* at 7 T
Hypointense lesions

In the side-by-side comparison of the 3 sequences, 13 MS patients (39%) showed FLAIR* lesions that appeared hypointense at T2*, instead of the hyper- or isointensity that is more common (figure 2). Four patients had a single hypointense lesion; the rest had more (range 1-9). In total, 38 hypointense lesions (4%) were detected: 8 PV, 9 DWM, 15 JC and 6 MIX (table 3). None of the tested clinical variables were significantly associated with the presence of hypointense lesions. The numbers of total (P=0.027) and WM (P=0.032) lesions were significantly related to the presence of hypointense lesions.

A surprising finding was the presence of hypointensities at T2*W MinIP, where no abnormality was seen at corresponding FLAIR and thus FLAIR*. We did not score these T2* hypointensities as lesions at FLAIR*, since they were not hyperintense and hence not classified a lesion according to our own criteria (most were smaller than 5 mm as well). Examples of different lesion intensities are presented in figure 6. None of the healthy controls showed hypointense lesions at T2*W MinIP. Within patients, the presence of rimlike lesions at FLAIR* and hypointense lesions were significantly related (ρ=0.52, P=0.001).

### Table 2. Clinical characteristics of MS patients with rimlike lesions

<table>
<thead>
<tr>
<th>PT</th>
<th>Rimlike lesions (n)</th>
<th>Distribution</th>
<th>Sex (M/F)</th>
<th>Age (year)</th>
<th>Disease type</th>
<th>Disease duration (year)</th>
<th>EDSS</th>
<th>Patient has hypointense lesions?</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>4 PV, 1 DWM, 1 MIX</td>
<td>M</td>
<td>52</td>
<td>PP</td>
<td>12</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1 PV, 1 JC, 1 MIX</td>
<td>M</td>
<td>43</td>
<td>RR</td>
<td>9</td>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2 MIX</td>
<td>M</td>
<td>47</td>
<td>PP</td>
<td>12</td>
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<tr>
<td>4</td>
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<td>F</td>
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<td>15</td>
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<td>1 PV</td>
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<td>1 JC</td>
<td>M</td>
<td>50</td>
<td>PP</td>
<td>5</td>
<td>6</td>
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PT = patient; EDSS = Expanded Disability Status Scale; PV = periventricular; DWM = deep white matter; JC = juxtacortical; MIX = mixed grey matter/white matter; IC = intracortical; M = male; F = female; RR = relapsing remitting; SP = secondary progressive; PP = primary progressive
Discussion

The new MRI technique FLAIR*, which was described recently at 3 T, was implemented in an existing MS cohort at 7 T. The expected benefits of 7T imaging, as mentioned in the introduction, offered a high-resolution simultaneous depiction of MS lesions and intralesional veins within one single image.

Perivascular orientation of MS lesions

Our results show that 78% of total MS lesions were oriented perivascularly. Previous studies that depicted the relation between MS lesions and vessels in vivo, made use of 7T T2*W and phase imaging,\(^6,19-21\) or lower field strengths in combination with contrast agents.\(^13,22\) In these studies, 25-92% of MS lesions were associated with CV, which is in concordance with our results. This wide range is caused by use of different field strengths, sequences and criteria for scoring a CV, as well as different MS lesion types that are included in the analysis. In our study, we focussed on the presence of a CV in multiple WM and GM lesion types, and the results show the highest numbers of perivascular lesions are located in PV and DWM regions. The proportion of lesions with a CV is decreasing towards the cortex and intracortical lesions hardly show a CV (25%), which might be due to the fact that cortical lesions evolve in a different way.

Table 3. Clinical characteristics of MS patients with hypointense lesions

<table>
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<tr>
<th>PT</th>
<th>Rimlike lesions (n)</th>
<th>Distribution</th>
<th>Sex (M/F)</th>
<th>Age (year)</th>
<th>Disease type</th>
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<td>F</td>
<td>38</td>
<td>RR</td>
<td>?</td>
<td>2.5</td>
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</table>

PT = patient; EDSS = Expanded Disability Status Scale; PV = periventricular; DWM = deep white matter; JC = juxtacortical; MIX = mixed grey matter/white matter; IC = intracortical; M = male; F = female; RR = relapsing remitting; SP = secondary progressive; PP = primary progressive.
It is known that increasing age is accompanied by the development of asymptomatic lesions on brain MRI, most commonly located in the DWM and most likely of vascular origin. Patients older than 40 had a significantly lower percentage of perivascular DWM lesions (73%) when compared to younger MS patients (92%), which is probably caused by the development of age-related vascular DWM lesions besides MS lesions, and those are not necessarily associated with a CV.

Morphological features of MS lesions: hypointense rims and lesions

Hypointense rims around lesions and hypointense MS lesions have been reported in previous 7T SWI and phase imaging studies, and were also visible in our 7T FLAIR* data. These morphological aspects of MS lesions were not seen at standard 1.5T MRI images.

We detected lesions with hypointense rims in a small subgroup of 8 MS patients. From the total number of MS lesions, only 3.3% had a rim. Using 7T T2* FLASH sequences, two other studies found higher numbers of 23 and 41% MS lesions with rims. It was not
mentioned on how much of their patients these percentages were based. In a study that fused 3T FLAIR with 7T SWI images, 7% of MS lesions were surrounded by a hypointense rim, which is closer to our results. Thirteen out of 33 MS patients had hypointense lesions (figure 6), which made up 3.8% of total lesions. Other 7T studies have shown hypointense MS lesions at SWI and phase images or by quantitative measurements of R2*-times.10,12,25–29

The interpretation of the underlying histopathological and pathophysiological background of these hypointense rims and hypointense lesions, as seen on 7T imaging, has been extensively studied, but remains matter of debate.30 Initially the rims were believed to reflect active iron-laden macrophages and hence, active MS lesions,10,12 however serial in vivo 7T imaging showed the rims did not disappear overtime.31 Postmortem studies suggest hypointensities on 7T phase imaging are due to abnormal iron deposition in the MS brain.26,28,32 However, in a recent publication Walsh et al claim that hypointense phase MS lesions cannot always be interpreted as lesions that contain iron.33

To our knowledge, no study has investigated why only a small subgroup of the MS patients shows these rimlike and hypointense lesions. Where most ultrahigh-field 7T studies focus on their pathological substrate, we are more interested in whether these lesions with different morphology features are associated with specific clinical characteristics. For instance, are rimlike lesions or hypointense lesions a feature of one of the MS disease subtypes? That is why we related the presence of rimlike and hypointense lesions to clinical variables of the MS patients. The resulting absent influences of disease type, disease onset, disease duration or clinical disability on the presence of rims and hypointense lesions indicate that these morphology features do not apply to one of the established subgroups of MS. Therefore, the appearance of rimlike lesions and hypointense lesions appears to be an MS-broad phenomenon, irrespective of clinical status of the patient, or disease subtype. Hypothetically, the hypointense rims and lesions resemble a different subtype of lesions or just a different phase in lesion development, which were not visible at lower field, but this has to be further investigated. The presence of rimlike and hypointense lesions was related to the lesion load of MS patients. Additionally, the presence of rimlike lesions was related to the presence of hypointense lesions within patients, which suggests a common underlying pathophysiological mechanism, although this has to be further investigated in a prospective study setting with larger patient groups.

The lesion that was found in one of the healthy control subjects did not show the three morphological features. It is too preliminary to say that a CV and hypointense (rims around) lesions are specific for MS. However, here are other studies suggesting this, when MS lesions were compared to other neuroinflammatory diseases as Susac and neuromyelitis optica.20,21

A serial imaging study at 7 T, showed that there are hypointense lesions at phase images that precede magnitude images lesions.31 Our interest goes out to the small hypointensities that we discovered at T2*MinIP, but that were not scored as lesions since they were too small and not hyperintense at FLAIR* (because there was no lesion visible at FLAIR) (figure 6). It warrants future follow up studies to investigate whether these small hypointensities develop to be lesions, and are so-called preactive lesions, as described elsewhere.34,35 Future research could furthermore investigate the hypointense (rims around) lesions with quantitative image sequences such as T1-mapping or MTR to obtain more information about these different lesion types. Main limitation of our study is that it concerns a small patient group, with even less patients when the group is subdivided into different MS subtypes.
In conclusion, we implemented a new technique FLAIR* at ultrahigh-field 7T MRI. Our 7T FLAIR* images combine and corroborate results of preceding 7T research, by showing three major morphological features of MS lesions: (1) the presence of a CV within a lesion, (2) the presence of hypointense rims around lesions, and (3) the presence of hypointense lesions at T2*. When these morphological features are related to the patient’s clinical characteristics, it was shown that the presence of a CV in DWM lesions was significantly lower for patients older than 40 years, presumably due to increasing age-related DWM hyperintensities. More importantly in terms of clinical purposes, the presence of hypointense (rims around) lesions was not related to any of the patient’s clinical characteristics or allocated to one of the established MS disease subtypes.

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References


