Multiple Sclerosis Lesions and Irreversible Brain Tissue Damage

**A Comparative Ultrahigh-Field Strength Magnetic Resonance Imaging Study**

Tim Sinnecker; Paul Mittelstaedt; Jan Dörr, MD; Caspar F. Pfueller, MD; Lutz Harms, MD; Thoralf Niendorf, PhD; Friedemann Paul, MD; Jens Wuerfel, MD

**Background:** In current clinical practice, T2-weighted magnetic resonance imaging (MRI) is commonly applied to quantify the accumulated multiple sclerosis (MS) lesion load, whereas T1-weighted sequences are used to differentiate edema, blood-brain barrier breakdown by contrast enhancement, and irreversible brain tissue damage (commonly called “black holes” owing to the loss of signal intensity in T1-weighted sequences). Black holes are histopathologically associated with axonal loss and severe tissue destruction. In addition, double inversion recovery techniques were developed to improve the sensitivity to cortical lesions.

**Objective:** To demonstrate the potential of ultrahigh-field 3-dimensional T1-weighted imaging using magnetization-prepared rapid acquisition and multiple gradient-echoes (MPRAGE) to detect and characterize white and gray matter pathology in MS.

**Design:** Comparative study.

**Setting:** The patients with MS were recruited from the outpatient clinics of the NeuroCure Clinical Research Center and underwent 7-T brain MRI at the Berlin Ultrahigh Field Facility, both of which are in Berlin, Germany.

**Patients:** Twenty patients with relapsing-remitting MS and 14 healthy controls underwent 7-T brain MRI, using a 24-channel receive head coil, and a subgroup of 18 patients with relapsing-remitting MS also underwent 1.5-T brain MRI. The imaging protocol included 2-dimensional T2-weighted fast low-angle shot (FLASH) and turbo inversion recovery magnitude (TIRM) sequences. For 3-dimensional T1-weighted imaging, the MPRAGE sequence was used. Each sequence was initially examined independently in separate analyses by an investigator blinded to all other data. In a second study, all detected lesions were retrospectively analyzed in a side-by-side comparison of all sequences.

**Results:** By use of 7-T T2-weighted FLASH imaging, 604 cerebral lesions were detected in the patients with relapsing-remitting MS (mean, 30.2 lesions per patient [range, 2-107 lesions per patient]), but none were detected in healthy controls. Cortical pathology was visible in 10 patients (6 cortical lesions and 37 leukocortical lesions). Within the 7-T acquisitions, each lesion detected at T2-weighted sequences and/or double inversion recovery sequences was also clearly delineated on corresponding MPRAGE sequences in side-by-side analysis. However, at 1.5 T, the MPRAGE images depicted only 452 of 561 lesions visualized in T2-weighted sequences and/or double inversion recovery sequences. In contrast, when analyzing each sequence separately, we found that the 7-T MPRAGE depicted more lesions than the 7-T FLASH (728 lesions vs 584 lesions), and almost twice as many as the 1.5-T MPRAGE (399 lesions). The 7-T MPRAGE also improved the detection of cortical and leukocortical lesions (15 lesions vs 58 lesions).

**Conclusions:** At ultrahigh-field strength, T1-weighted MPRAGE is highly sensitive in detecting MS plaques within the white and the gray brain parenchyma. Our results indicate structural damage beyond demyelination in every lesion depicted, which is in accordance with postmortem histopathological studies. The 7-T MPRAGE clearly delineated every cortical lesion that was visualized by any other MRI sequence at 1.5 or 7 T.

therapies. However, the correlation of the T2 lesion load with clinical parameters such as relapse rate and neurological disability is modest, which is referred to as the so-called clinico-radiological paradox. On spin-echo T1-weighted images, a proportion of T2 hyperintense lesions (hereafter referred to as “black holes”) appears hypointense to the surrounding normal-appearing white matter for a long period of time. These black holes are associated with clinical worsening and cerebral atrophy. Besides edema and demyelination, histopathological studies demonstrated severe tissue destruction as the morphologic correlate of black holes. It has also been demonstrated that remyelination processes may reverse plaque hypointensity. Such ex vivo data are corroborated by in vivo magnetic resonance spectroscopy findings of decreased N-acetylaspartate levels in black holes as a further surrogate marker of axonal injury and loss.

Black holes are reported to correlate better with clinical disability compared with T2 lesion load and are therefore suggested as outcome parameters in clinical studies. However, during conventional MRI, only a small proportion of T2-hyperintense lesions appears hypointense at T1-weighted imaging. With increasing recognition of gray matter pathology in MS based on postmortem studies, efforts have been undertaken to improve the in vivo detection of cortical lesions by the use of novel neuroimaging techniques. Despite the development of double inversion recovery (DIR) techniques, the depiction of cortical lesions still remains challenging, partially owing to limitations of low signal-to-noise ratio at conventional field strengths. Consequently, many cortical lesions still remain undetected in vivo.

Recently, the application of ultrahigh-field strengths in small MS cohorts was able to improve the detection rate of cortical, leukocortical, and white matter lesions in comparison with lower field strengths. Against the background of the unresolved dispute over the clinical significance of black holes, and the increasing appreciation of gray matter pathology in MS, we investigated whether the visibility of T1 and T2 lesions in both gray and white matter would be influenced by the improved signal-to-noise ratio at 7 T. In particular, we hypothesized that the application of magnetization-prepared rapid acquisition and multiple gradient echoes (MPRAGE) would facilitate the detection of hypointense lesions in comparison with conventional MRI. Moreover, we performed a longitudinal substudy to investigate whether hypointense lesions detected at 7 T are a transient or permanent phenomenon.

MRI DATA ACQUISITION

Ultrahigh-field magnetic resonance images were acquired using the 7-T Siemens Magnetom, applying a 24-channel receive head coil (Nova Medical). The imaging protocol included the 2-dimensional T2-weighted fast low-angle shot (FLASH) sequences (echo time [TE], 25.0 milliseconds; repetition time [TR], 1820 milliseconds; acquisition time, 12 minutes and 11 seconds; spatial resolution, 0.5 × 0.5 × 2 mm³) and the turbo inversion recovery magnetization (TIRM) sequences (TE, 90 milliseconds; TR, 16000 milliseconds; inversion time, 2925.5 milliseconds; acquisition time, 12 minutes and 50 seconds; spatial resolution, 1.0 × 1.0 × 3.0 mm³). For 3-dimensional T1-weighted imaging, the MPRAGE sequence (TE, 2.98 milliseconds; TR, 2300 milliseconds; inversion time, 900 milliseconds; acquisition time, 9 minutes and 14 seconds; spatial resolution, 1.0 × 1.0 × 1.0 mm³) was used. The image acquisition time of this protocol was 39 minutes.

For comparison, 18 patients underwent MRI of the brain using a 1.5-T system (Siemens Avanto), including a MPRAGE sequence (TE, 3.09 milliseconds; TR, 7100 milliseconds; flip angle, 15°; resolution, 1.52 × 1.52; field of view, 256 mm × 256 mm) and a 3-dimensional T2-weighted turbo spin-echo sequence (TE, 198 milliseconds; TR, 1900 milliseconds; flip angle, 120°; resolution, 256 × 256; field of view, 256 mm × 256 mm). In 13 patients, a DIR sequence (TE, 103 milliseconds; TR, 7100 milliseconds; flip angle, 180°; resolution, 256 × 160; field of view, 310 mm × 193 mm) was performed during the same session. A subgroup of 8 patients was reassessed after a median interval of 13.8 months (one patient at month 7 and the other patients after more than 13 months [range, 13.1-15.9 months]), applying the identical magnetic resonance protocol, in order to evaluate the persistence of T1 hypointense lesions.

CHARACTERIZATION OF LESIONS

To achieve a high level of objectivity, the following criteria were established in accordance with previously published classifications. A lesion in both 1.5-T and 7-T MPRAGE sequences was defined as follows: hypointensity relative to the surrounding normal-appearing white or gray matter, a distinction in the maximum gray-scale level of at least 15%, and a volume of at least 3 voxels. Lesions with a distance of less than 5 mm from the ventricle and a diameter of at least 2 mm in T2-weighted FLASH sequences were defined as periventricular lesions. Lesions with a distance of less than 1.5 mm from the cortex and a diameter of at least 2 mm in T2-weighted FLASH sequences were defined as juxta cortical lesions. White matter lesions not meeting the previously described criteria and with a diameter of at least 2 mm were defined as other white matter lesions. Cortical lesions were characterized according to the histopathological criteria of Peterson et al into lesions affecting the white matter and at least 1 layer of the cortex (leukocortical lesions [type I]), perivascular purely cortical lesions (type II), and subpial lesions (type III).

STUDY PARTICIPANTS

We enrolled 20 patients suffering from MS (11 male patients with a mean [SD] age of 42.0 [7.8] years, a mean [SD] disease duration of 3.1 [5.0] years [range, 0.5-14.4 years], and a median Expanded Disability Status Scale score of 1.5 [range, 1.0-4.5]) with a relapsing-remitting disease course fulfilling the current panel criteria. All patients underwent 7-T MRI, and a subgroup of 18 patients was additionally examined at 1.5 T. Neurological disability was assessed with the Expanded Disability Status Scale. Fourteen healthy volunteers (7 men with a mean [SD] age of 31.1 [10.5] years) underwent 7-T MRI of the brain as controls to assess 7-T–specific artifacts. Our study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki in its currently applicable version, the guidelines of the International Conference on Harmonisation of Good Clinical Practice, and the applicable German laws. All participants gave informed written consent.

METHODS

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ANALYSIS AND QUANTIFICATION OF LESIONS

The MRI data were processed using OsiriX version 3.8.1 (OsiriX Foundation). During the first approach, each sequence was analyzed individually by an observer blinded to any other data.

During the second approach, the 27-in (68.6-cm) screen (resolution, 2560 × 1100/1440) was split into two windows to ensure the most convenient visual colocalization of all data “side by side” at the same time. Individual images could be freely zoomed into. The 7-T T2 lesion load was determined at first on TIRM sequences. Every single lesion depicted at 7-T T2-weighted FLASH sequences was subsequently colocated and characterized with high diligence in each other magnetic resonance sequence. Thus, in the second analysis, T1 hypointense lesions were assessed with prior knowledge of the corresponding T2-weighted FLASH sequences. The use of TIRM sequences improved the differentiation from Virchow-Robin spaces.

RESULTS

In accordance with previous reports, 27,28 7-T MRI was well tolerated. We detected 604 cerebral lesions in patients with MS on 7-T FLASH images, but none in healthy controls. In a side-by-side analysis, each cerebral lesion seen on a 7-T FLASH image was also visualized at 7-T MPRAGE, but with even greater distinction concerning shape and appearance of the plaques on MPRAGE images (Figures 1 and 2). In contrast, at 1.5 T, the MPRAGE images were only able to depict a proportion (452 lesions) of those lesions seen on 1.5-T T2-weighted images (561 lesions; Table 1).

Looking at the individual lesion count in each sequence separately, we found that an advantage to the 7-T MPRAGE sequences in detecting MS lesions became even more evident: 7-T FLASH revealed 584 cerebral lesions. The 7-T MPRAGE sequences detected a total number of 728 lesions, depicting more lesions than 7-T FLASH and almost twice as much as 1.5-T MPRAGE (Table 1). Each of the 217 T1 hypointense lesions detected by the 7-T MPRAGE sequences in the longitudinal subgroup persisted without major change in formation or size for at least 1 year and could thus be classified as a black hole.

Despite the fact that the predominant localization of MS lesions was the periventricular white matter, 7-T FLASH could also depict 37 leukocortical plaques and 6 purely cortical plaques, 3 of which were of a perivascular type (type II) and another 3 of which were of a subpial type (type III). Each of these lesions was also visible at the 1.5-T T2-weighted turbo spin-echo sequence and clearly delineated by the 7-T MPRAGE sequence, which, however, revealed an additional 21 leukocortical (type I) lesions not visible on any other sequence investigated. On the other hand, 3 subpial cortical lesions were delineated weakly by the 7-T MPRAGE sequence but were much more pronounced at the 7-T FLASH sequence (eFigure [http://www.archneur.com]). In contrast to the 7-T MPRAGE sequence, the lesion-to-cortex contrast was weaker at the 1.5-T MPRAGE sequence owing to a lower signal-to-noise ratio, and, consecutively, none of the cortical lesions and only 21 leukocortical lesions could be detected at 1.5 T (Table 2). Within these lesions, only

Figure 1. Characteristics of 7-T magnetic resonance imaging. At 7 T, each neuroinflammatory lesion is clearly marked with great distinction in the T1-weighted magnetization-prepared rapid acquisition and multiple gradient echo (T1 MPRAGE) image (A). At the same field strength, the T2-weighted fast low-angle shot (T2 FLASH) image reveals a perivascular location (black arrow) for the majority of lesions (B). Some of the lesions that express a hypointense rim are believed to be chronic plaques (white arrows).
minor parts of the individual lesion area could be differ-
entiated from the surrounding brain tissue (Figure 3).

In our study, DIR imaging at 1.5 T was prone to move-
ment artifacts and therefore did not improve the detec-
tion rate of cortical and mixed lesions (Table 1). 

To our knowledge, the present study is the first to dem-
onstrate that, at ultrahigh-field strength, every T2 hy-
perintense lesion detected on T2-weighted FLASH se-
quences directly corresponds to a T1 hypointense lesion
on a MPRAGE sequence. Our finding challenges previ-
ous studies11-13,32 as well as our own data obtained at 1.5-T
MRI, in which only 80% of T2, TIRM, or DIR hyperin-
tense lesions were visible on MPRAGE images. In the past,
the prevalence and natural evolution of black holes were
assessed in longitudinal studies using spin-echo se-
quences. A 4-year natural history follow-up study re-
vealed that, of 966 contrast-enhancing lesions, 22.9%
evolved into persistent black holes.13 Van Waesberghe
et al33 demonstrated cross-sectionally that, of 126 contrast-
enhancing lesions, only 80% appeared hypointense on
T1-weighted images. After a follow-up period of 6 months,
36% of these initially hypointense lesions remained persistent black holes.33 Similar results were reported by van den Elskamp et al30 within a shorter follow-up duration.

In contrast to conventional field strengths, at ultrahigh magnetic field, MPRAGE visualized significantly more lesions compared with T2 (FLASH). Furthermore, our results indicate the structural damage of every lesion depicted, which is in accordance with postmortem histopathological studies demonstrating axonal transection in each MS lesion, visualized as terminal axonal ovoids.34 Moreover, bearing in mind individual variations between different types of lesions, axonal density is generally reduced compared with the normal-appearing white matter.35 Schmierer et al22 demonstrated in a postmortem study that T1 hypointensity at 9.4 T is a predictor of neuronal density in cortical lesions. For reasons of comparability, the 1.5-T MPRAGE sequence was also used in that study.22 Different contrast mechanisms at ultrahigh field, combined with sequence-specific characteristics of MPRAGE (eg, the intrinsic sensitivity to proton density and T28 contrast),36 may support the improved capability of MPRAGE to differentiate and delineate neuroinflammatory plaques. In our longitudinal study, we demonstrated that 7-T MPRAGE hypointense lesions do not change their appearance over the course of more than 1 year and thus may well express brain parenchymal destruction rather than, for example, temporary edema. However, at ultrahigh-field strengths, stronger artifacts and/or susceptibilities, especially of small lesions, need to be taken into consideration. Principally, the possibility of misclassification (eg, of vascular lesions) exists, even in the relatively young cohort investigated herein, and should be further evaluated in future as well as postmortem studies.

A further key aspect of our study was the detection of cortical pathology in patients suffering from MS. Peterson et al31 histopathologically defined 3 subtypes of cortical lesions: leukocortical lesions (type I), purely cortical circumscribed lesions (centered by a blood vessel; type II), and subpial lesions (type III). In our retrospective analysis, we detected 37 type I lesions, 3 type II lesions, and 3 type III lesions. However, in contrast to the 7-T FLASH sequence, the T1-weighted MPRAGE sequence was able to depict every cortical and leukocortical lesion visible on any other 1.5-T and 7-T sequence. In addition, the 7-T MPRAGE sequence was able to depict every cortical and leukocortical lesion compared with any of the other sequences. In the individual analysis of each sequence, this advantage became even more obvious. Only subpial cortical lesions (type III lesions) could be delineated clearer on 7-T T2-weighted FLASH (7-T T2 FLASH) images. The percentages are derived by using the 7-T T2 FLASH values as the reference values (ie, the denominators).

Table 2. Data on Distribution of Lesions in Patients With Relapsing-Remitting Multiple Sclerosis\(^a\)

<table>
<thead>
<tr>
<th>Type of Multiple Sclerosis Lesion</th>
<th>Type of Image</th>
<th>Periventricular</th>
<th>Other White Matter</th>
<th>Juxtacortical</th>
<th>Leukocortical</th>
<th>Cortical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%</td>
<td>Mean (SD</td>
<td>[Range]</td>
<td>No. (%</td>
<td>Mean (SD</td>
<td>[Range]</td>
<td>No. (%</td>
</tr>
<tr>
<td>Separate and Blinded Analysis</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7-T T2 FLASH 249 (100)</td>
<td>14 (15)</td>
<td>186 (100)</td>
<td>[0-60]</td>
<td>12 (9)</td>
<td>123 (100)</td>
<td>[0-30]</td>
<td>3 (100)</td>
</tr>
<tr>
<td>7-T T1 MPRAGE 231 (93)</td>
<td>13 (13)</td>
<td>318 (171)</td>
<td>[0-60]</td>
<td>18 (17)</td>
<td>121 (98)</td>
<td>[0-17]</td>
<td>6 (200)</td>
</tr>
<tr>
<td>1.5-T T2 TSE 224 (90)</td>
<td>12 (16)</td>
<td>160 (86)</td>
<td>[0-60]</td>
<td>9 (7)</td>
<td>140 (114)</td>
<td>[0-25]</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1.5-T T1 MPRAGE 159 (64)</td>
<td>9 (11)</td>
<td>142 (76)</td>
<td>[0-60]</td>
<td>8 (8)</td>
<td>83 (67)</td>
<td>[0-18]</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

| Side-by-Side Comparison         | Mean (SD | [Range] | No. (% | Mean (SD | [Range] | No. (% | Mean (SD | [Range] | No. (% | Mean (SD | [Range] | No. (% | Mean (SD | [Range] |
| 7-T T2 FLASH 230 (100)           | 13 (15) | 153 (100) | [0-60] | 9 (8) | 143 (100) | [0-25] | 6 (100) | 0.3 (0.8) | [0-3] | 569 (100) | 32 (29) |
| 7-T T1 MPRAGE 230 (100)          | 13 (15) | 153 (100) | [0-60] | 9 (8) | 143 (100) | [0-25] | 6 (100) | 0.3 (0.8) | [0-3] | 569 (100) | 32 (29) |
| 1.5-T T2 TSE 229 (99)            | 13 (15) | 150 (98) | [0-60] | 8 (8) | 141 (99) | [0-25] | 4 (67) | 0.2 (0.6) | [0-2] | 561 (99) | 31 (29) |
| 1.5-T T1 MPRAGE 202 (88)         | 11 (14) | 118 (77) | [0-55] | 7 (7) | 110 (77) | [0-23] | 1 (17) | 0.1 (0.2) | [0-1] | 452 (79) | 25 (26) |

Abbreviations: FLASH, fast low-angle shot; MPRAGE, magnetization-prepared rapid acquisition gradient echo; TSE, turbo spin-echo.

\(^\text{a}\)In side-by-side comparisons, the 7-T T1-weighted MPRAGE (7-T T1 MPRAGE) sequence proved to be clearly superior in the differentiation of cortical and leukocortical lesions compared with any of the other sequences. In the individual analysis of each sequence, this advantage became even more obvious. Only subpial cortical lesions (type III lesions) could be delineated clearer on 7-T T2-weighted FLASH (7-T T2 FLASH) images. The percentages are derived by using the 7-T T2 FLASH values as the reference values (ie, the denominators).
sequences proved to be useful for routine clinical imaging as well.

In conclusion, our study indicates that there was structural and permanent damage to every MS plaque depicted on T2-weighted MRI. Every white or gray matter plaque visualized by any other sequence corresponded to a distinct hypointensity on 7-T MPRAGE images, indicating a higher degree of tissue degradation as estimated from conventional MRI at lower field strengths. The use of the MPRAGE improved the detection of cortical pathology and facilitated the differentiation between cortical and leukocortical lesions. A fast acquisition time and a relatively low vulnerability to image susceptibility make it particularly suitable for clinical studies.

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Author Contributions: Dr Wuerfel had full responsibility for the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Sinnecker, Harms, Wuerfel, and Paul. Acquisition of data: Sinnecker, Mittelstaedt, Dorr, Pfueller, Harms, Niendorf, Wuerfel, and Paul. Analysis and Interpretation of data: Sinnecker, Niendorf, Wuerfel, and Paul. Drafting of the manuscript: Sinnecker, Niendorf, and Wuerfel. Critical revision of the manuscript for important intellectual content: Sinnecker, Mittelstaedt, Dorr, Pfueller, Harms, Niendorf, Wuerfel, and Paul. Statistical analysis: Sinnecker. Administrative, technical, and material support: Dorr, Pfueller, Niendorf, and Paul. Study supervision: Harms, Niendorf, Wuerfel, and Paul.

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