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Ultra high field 7T imaging in multiple sclerosis

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Key points

- Seven Tesla MRI provides increased sensitivity compared to 3T MRI to detect multiple sclerosis cortical lesions, especially subpial lesions the most common cortical lesion type.
- Quantitative cortical mapping at 7T allows to investigate cortical damage, showing diffuse abnormalities expanding beyond cortical lesions.
- Morphological details of white matter lesions can be visualized by 7T MRI including the presence of a central vessel in most lesions and an iron-rich paramagnetic rim in a subset of lesions.
- Seven Tesla MRI allows for a better delineation of multiple sclerosis lesions in the thalamus, cerebellum and spinal cord.

Abbreviation:

CL: cortical lesion; CSF: cerebrospinal fluid; CVS: central vein sign; DIR: double inversion recovery; FLAIR: fluid-attenuated inversion recovery; GM: gray matter; MRI: Magnetic Resonance Imaging; MPRAGE: magnetization-prepared rapid-acquisition gradient-echo; MS: Multiple Sclerosis; MP2RAGE: Magnetization-prepared 2 inversion-contrast rapid gradient-echo; MTR: magnetization transfer ratio; NAWM: normal appearing white matter; qT2*: quantitative T2*; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; WM: White Matter

Abstract

Purpose of the review: Ultra-high field 7 Tesla (7T) magnetic resonance imaging (MRI) has multiple applications for the in vivo characterization of the heterogeneous aspects underlying multiple sclerosis (MS) pathology including the i.) identification of cortical lesions (CL), ii.) characterization of the different types of white matter (WM) plaques, iii.) evaluation of structures difficult to assess with conventional MRI (thalamus, cerebellum, spinal cord, meninges).

Recent findings: The sensitivity of CL detection at 7T is twice than at lower field MRI, especially for subpial lesions, the most common CL type in MS. Cortical lesion load accrual is independent of that in the WM and predicts disability progression. Seven Tesla MRI provides details on tissue microstructure that can be used to improve WM lesion characterization. These include the presence of a central vein, whose identification can be used to improve MS diagnosis, or the appearance of an iron-rich paramagnetic rim on susceptibility weighted images, which corresponds to iron-rich microglia at the periphery of slow expanding lesions. Improvements in cerebellar and spinal cord tissue delineation and lesion characterization have also been demonstrated.

Summary: Imaging at 7T allows assessing more comprehensively the complementary pathophysiological aspects of MS, opening up novel perspectives for clinical and therapeutics evaluation.

Introduction

The recent advent of ultra-high-field strength 7 Tesla (7T) magnetic resonance imaging (MRI) has enabled substantial advantages in image signal-to-noise ratio (SNR), contrast and spatial resolution over lower field strength system, providing increased sensitivity to different aspects of brain tissue anatomy and pathology. In multiple sclerosis (MS) 7T imaging has provided both novel and improved identification of important in vivo radiological markers of the disease, whose detection and monitoring could help a better understanding of disease mechanisms and explain a large part of the interindividual variability and heterogeneous prognosis of the disease course. The main advances discussed herein relate to the improved visualization and characterization of cortical lesions (CL), the identification of specific features of white matter (WM) plaques that have been used for improving diagnosis sensitivity and specificity and monitoring of the disease burden (Table 1). Further applications for studying other brain structures and the spinal cord are also discussed (Figure 1).

Cortex

- Cortical lesion detection

In vivo 7T imaging using T2*-weighted gradient-echo and magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) T1-weighted sequences allows enhanced identification of the cortical layers that, in turn, leads to improved visualization of CL/subtypes relative to lower field MR strength¹⁻³. The different CL subtypes described by neuropathology⁴ can be visualized in vivo at 7T: Type I, leukocortical, lesions extending across the cortical gray matter (GM) and adjacent white matter (WM); Type II, purely small intracortical lesions confined within cortex; Type III-IV, subpial lesions, extending from the pial surface downwards through different cortical layers and sometimes along several gyri leading to a phenomenon termed the “general subpial demyelination”⁵.

Other contrasts have been tested and optimized at 7T⁶⁻⁸ to identify sequences with the highest value for detecting CL in clinic. The comparison of T2* contrast at 7T with 3T double inversion recovery⁹ sequence or multicontrast data¹⁰ that are more accessible in clinic demonstrated the superiority of the T2*-sequence at 7T in detecting intracortical, especially subpial, lesions. Despite this, leukocortical lesion identification at 7T remains similar to that achieved at 3T¹⁰.

The sensitivity of CL detection, however, cannot be inferred from imaging alone without histopathology validation. Concurrent histological/MRI correlations have demonstrated that regardless of the pulse sequence, 7T MRI detects more than twice as many CL compared to 3T MRI and that, overall, fluid-attenuated inversion recovery sequence shows the highest sensitivity of CL detection¹¹. The same study found, however, that the subpial lesions, the most frequent and broad CL type in MS, are still suboptimally identified even at 7T, and that T2*-weighted contrast detects the highest amount of subpial lesions at ultra high field (32% at prospective and 79% at retrospective scoring, respectively). Further improvements could be obtained by using the two inversion-contrast magnetization-prepared rapid gradient echo (MP2RAGE) technique that can advance overall intracortical lesion detection and especially that of the small lesions¹² by increasing the tissue contrast while minimizing the field inhomogeneities¹³.

Nevertheless, to date, there is no perfect sequence for CL detection at 7T and probably the best approach would be a combination of MR sequences as different techniques may provide complementary information in the definition of cortical tissue.

- Cortical lesion evolution and relation to clinical outcome

At 7T, CL are detected in the majority (97%)¹⁴, if not in all patients¹⁵. The detailed development and evolution of CL across cortical width, sulci and gyri was recently assessed in a longitudinal study at 7T¹⁵.

At 7T, the CL accrual rate is high (relapsing-remitting MS (RRMS): 1.1/patient/year; secondary-progressive MS (SPMS): 3.6/patient/year), being almost twice as high as that previously reported at 1.5-3T (RRMS:0.8 /patient/year SPMS:1.6 patient/year)^{16,17}. Most importantly, the overall rate of CL development does not correlate with and exceeds that of WM lesions (0.6/patient/year), suggesting that cortical pathology is largely independent of WM damage, as also observed in post-mortem studies¹⁸. The dynamics of lesion formation within cortex and WM show a different path according to the MS phenotype: while CL accrual rate is higher in SPMS than in RRMS, the opposite is true for WM lesions. Another interesting aspect is that CL preferentially develop within cortical sulci than in the gyri, with the highest percentage of total surface area filled by new CL located in the sulci of patients with RRMS. These findings may indicate a possible link between CL development and an ongoing neuroinflammatory process mediated by cerebrospinal-fluid (CSF).

The enhanced CL detection at 7T can potentially provide an early and more specific tool for MS diagnosis¹⁹ as well as increased diagnostic accuracy in clinically isolated syndrome at presentation²⁰, since subpial demyelination is highly specific to MS^{21,22}. The presence of CL has, therefore, been recently included in the MRI diagnostic criteria of MS²³.

The usefulness of CL identification is also linked to disease prognosis, given that “benign MS” is characterized by a mild cortical pathology²⁴ while extensive cortical damage at disease onset predisposes to rapid occurrence of disease progression²⁵. The association of CL with high levels of intrathecal immunoglobulins also identifies patients with a poorer outcome at three years follow-up²⁶.

Only few studies have investigated the contribution of CL load assessed at 7T to clinical MS disability. Even if derived from relatively small cohorts (up to 36 patients), the data obtained from cross-sectional studies^{27,28} confirm the findings observed at lower field strength²⁹⁻³³ regarding the relationship between high CL load and higher Expanded Disability Status Scale (EDSS) scores and cognitive impairment. Furthermore, the same studies have shown that CL subtypes might have a different clinical relevance. While intracortical lesion load mainly relates to neurological disability, leukocortical lesions show the greatest effect on cognition. Additionally, in line with previous reports at lower field strength^{16,34}, CL volume at baseline predicts EDSS at follow-up independently from WM damage and cortical atrophy¹⁵.

- Cortical quantitative T2* mapping

General subpial demyelination has been shown to be estimated in vivo by surface-based mapping of T2* relaxation time (qT2*) within cortical layers, along the entire cortex³⁵. Longer T2* relaxation time has been pathologically related to iron and myelin loss^{36,37}, while a shorter T2* to iron accumulation³⁸, likely reflecting iron-rich in microglia/macrophages³⁹.

Using this technique, a previous study⁴⁰ has provided in vivo evidence of abnormally increased qT2* in a heterogeneous cohort of 41 people with MS. In early disease, q-T2* changes were mainly confined to iuxtameningeal cortical layers and cortical sulci, while in later stages involved deeper cortical laminae and gyri. These findings constitute radiological evidence that adds to histopathological findings⁴¹⁻⁴³ that cortical demyelination in MS may be driven from the pial surface by organized meningeal inflammation. Furthermore, qT2* analysis revealed a significant association between qT2* increase and worse EDSS and MS severity score⁴⁰ as well as cognitive impairment⁴⁴.

The qT2* mapping can also enable a more accurate assessment of microstructural changes in normal appearing cortex, beyond the visible CL⁴⁵. Interestingly, while changes in qT2* in

CL seem to be of the same magnitude, regardless of the CL subtype or disease phenotype, changes in the perilesional cortex are wider for leukocortical lesions in progressive patients than in RRMS. This suggests that this CL subtype may in fact be more destructive than the intracortical lesion subtype.

Surface-based estimation of $qT2^*$ at 7T⁴⁶ can be combined with quantitative indices of magnetization transfer imaging⁴⁷ resulting in a multivariate statistical model⁴⁸ that can be used to extract in vivo the shared information from these different contrasts likely related to myelin content, excluding confounding factors such as iron, cortical thickness. A study that applied this model to integrate myelin-related information from 7T $qT2^*$ and T1 maps demonstrated that this technique has a better specificity to MS pathology compared to $qT2^*$ and T1 metrics alone⁴⁹.

White matter

- Lesion detection

The contribution of 7T MRI for detecting MS WM lesions is currently less marked than for the cortex. The sequences traditionally used at 3T for following WM lesion load, including FLAIR and T2 spin echo, are hampered by high specific absorption rate (SAR) and B1 field inhomogeneities at 7T, leading to an overall decreased image signal. Technical improvements of these sequences have been proposed to decrease SAR limitations including approaches using “T2-weighted gradient and spin echo” (GRASE) sequence⁵⁰, or to reduce the radio-frequency field inhomogeneities by parallel transmission (PTx)⁵¹. Currently, the best sequences used at 7T for visualizing WM lesions are T2*, FLAIR but also magnetization transfer imaging⁵² and MP2RAGE⁵³.

- The central vein sign

Seven Tesla MRI can provide details on the morphology and tissue microstructure of WM lesions that can be used to improve their characterization⁵⁴. The presence of a central vessel in WM lesions (central vein sign, CVS) is a specific radiological feature that can be used to differentiate MS from other diseases that mimic this condition. A study⁵⁵ using a 7T fast low angle shot T2* sequence determined that 92% of MS lesions show a CVS, compared with only 54% of lesions of in a cohort of 5 patients with Susac syndrome.

Another study⁵⁶ using susceptibility weighted imaging coregistered with FLAIR determined that a threshold of 67% of CVS positive lesions allows to discriminate MS subjects from controls with non-pathological WM hyperintensities, with a sensitivity of 94 % and specificity of 100%.

- Slow expanding lesions

Studies using 7T gradient echo-T2* sequences have identified a subset of WM plaques displaying a paramagnetic rim on phase reconstructions, which was found to correspond to iron-enriched activated macroglia/macrophages at the lesion periphery. These lesions may correspond to the so-called “chronic active lesions” described by neuropathology³⁸.

It has been demonstrated that presence of at least 4 rim lesions either at 3T or 7T is associated with a more aggressive phenotype in MS⁵⁷. Moreover, rim lesions tend to extend over time unlike rimless lesions⁵⁸.

Interestingly, paramagnetic phase changes within and around WM lesions seem to be specific of MS, as they were only rarely observed (<2%) in a cohort of 10 NMO spectrum disorder patients scanned at 7T⁵⁹.

- Diffuse WM damage quantification

Diffuse normal appearing WM (NAWM) abnormalities known from pathological and 3T MRI studies have been quantified at 7T. Recently, a study⁶⁰ using maps of T1 relaxation time and magnetization transfer ratio made it possible to identify NAWM abnormalities in MS and neuromyelitis optica (NMO) compared to controls, whereas these abnormalities have not been described in NMO at lower field strength.

Other quantitative sequences evaluating the myelin content in the lesional and non-lesional compartments have been validated recently at 7T including Selective Inversion Recovery quantitative MTI⁶¹.

Leptomeningeal inflammation

Using post-contrast FLAIR MRI, a few investigations have reported the presence of foci of leptomeningeal enhancement (LME) in the brain of people with MS^{62,63}. Leptomeningeal enhancement, however, is not specific to MS, since it has been observed to occur with a high frequency in other non-MS inflammatory neurological conditions and systemic inflammatory diseases with WM MRI abnormalities⁶⁴. Additionally, LME is thought to represent an indirect sign of meningeal inflammation consequent to trapping of gadolinium in fibrotic meningeal tissue, which is thought to form after repetitive episodes of inflammation⁶². This might explain the reason why LME tends to be fixed in time and space, and seems to be not modified by treatment⁶⁵.

The in vivo association between the LME sign and CL development also remains controversial^{62,66}, as some investigators reported a statistical association between the number of LME foci and the number of thalamic and CL in MS patients⁶⁷, while others have not observed such association but a only positive relation between LME foci and GM atrophy⁶⁸.

Thalamus

Currently, few studies have specifically analyzed the radiological changes within the thalamus using ultra-high field MRI. Harrison et al⁶⁹ investigated a cohort of 34 MS patients to visualize and quantify thalamic lesions. Some lesions were described as nodular and ovoid while other were confluent at the edge of the ventricles and associated with a more severe clinical phenotype.

In a cohort of 41 MS patients⁷⁰, a quantitative analysis using qT2* mapping outside focal lesions showed qT2* increase suggesting diffuse demyelination within the thalamus. In RRMS, there was a gradient of qT2* abnormalities originating from the ventricles, suggesting that this diffuse demyelinating process may be driven by CSF-mediated immune factors.

Cerebellum

Demyelination affects the WM and GM of the cerebellum both in RRMS and SPMS, although cerebellar cortex is more widely involved in the progressive phase. Imaging of the cerebellum is challenging because of its convoluted structure, and lesion detection is hampered, especially in the cortex, by the low MRI contrast in this structure. At 7T MP2RAGE acquisitions proved better sensitivity for cerebellar cortical and WM lesion detection and higher contrast-to-noise ratio between normal-appearing cortical GM and CL than 3T MP2RAGE⁷¹. Moreover, high-resolution 7T MP2RAGE permitted to anatomically localize cerebellar lesions, better distinguishing leukocortical from WM lesions. Imaging of

the MS cerebellum at 7T has also been applied to guide selective analysis of lesions to measure neuroinflammation⁷². Future application of 7T MP2RAGE will allow a more detailed in vivo study of cerebellar cortical and subcortical pathology in MS through the application of T1 relaxometry maps to study microstructural tissue alterations.

Spinal cord

The increased SNR at 7T allows high-resolution anatomical imaging, with good visualization of spinal cord parenchyma, nerve roots, blood vessels and ligaments.

High-resolution 7T imaging also demonstrated improved visualization of cervical spinal cord lesions in MS, with an increase of 52% of lesion detected from axial 7T T2* images compared to 3T T2-weighted sequence in the cervical spinal cord⁷³. The same study has demonstrated that the combination of T2* and T1 sequences at 7T allows classification of spinal cord lesions according to their stage.

Contrast-to-noise ratio (CNR) between GM and WM has also proved to be better at 7T compared to 3T imaging⁷³, allowing optimal segmentation of spinal cord GM and WM. This is of great interest for the characterization of MS pathology, since the localization of MS lesions along the parenchyma can give useful information on their tropism based, for example, on disease stage⁷⁴.

Some limitations come with the application on ultra-high field in the spinal cord.

The high SNR in the cervical cord at 7T is inhomogeneous around the spinal cord and has limited longitudinal coverage⁷⁵. The CNR between spinal cord WM and cerebrospinal fluid might be in some cases suboptimal⁷³.

So far, due to lack of dedicated coils, only the cervical spinal cord has been examined at 7T that limits the disease staging and monitoring.

Also, further comparison between 7T imaging and novel 3T methods for spinal cord lesion detection including Phase-Sensitive Inversion Recovery⁷⁶ could be performed in future research studies.

Conclusion

Seven Tesla imaging has provided a broad improvement in assessing various physiopathological processes in MS. Cortical lesion load can be assessed with a reasonable sensitivity and since the changes in CL counts can be observed even in a short follow-up interval, it may represent a valid outcome in addition to WM lesions to assess disease activity and treatment response.

Quantitative sequences applied on several CNS compartments could be used as an imaging marker to monitor remyelination in vivo, during follow-up and in therapeutic trials. However, several technical challenges will have to be overcome before the implementation of 7T imaging in routine medical practice.

Table 1. Advantages of MS lesion detection at 7T vs 3T MRI

MS lesion type	Detection sensitivity		Advantages of using 7T vs 3T MRI
	3T	7T	
Cortical lesions	10-20% ¹¹	27-35% ¹¹	<p>Better discrimination between juxtacortical and leukocortical lesions due to improved gray-white junction delineation at 7T</p> <p>Earlier and more specific MS diagnosis^{19-21,23,77}</p> <p>Better prognostication of the disease progression^{14,15,78}</p>
Type I	33-83% ¹¹	50-100% ¹¹	
Type II	0-7% ¹¹	0-11% ¹¹	
Type III-IV	0-46% ¹¹	7-64% ¹¹	
White matter lesions	No significant improvement		<p>Increased diagnostic accuracy at 7T due to:</p> <ul style="list-style-type: none"> increased capacity of identification of the “central vein sign” (in 87% vs 45% lesions)⁷⁹ better discrimination of the paramagnetic rim on phase images⁸⁰ <p>Detection of 4 or more rim lesions on phase images at 7T is a poor prognostic factor¹²</p>
Cerebellar lesions	Increased up to 134% at 7T ⁷¹		<p>Better delineation of cerebellar cortical and white matter lesions</p> <p>Accurate discrimination between cerebellar leukocortical and white matter lesions⁷¹</p>
Spinal cord lesions	Increased by 52% at 7T ⁷³		<p>Increased detection can help in MS diagnosis</p> <p>Can identify the lesional gray matter involvement when present⁷³</p>

Legend to the Figure

Figure 1. 7T MRI identification and characterization of MS lesions at different levels.

Axial 7T T2* images show examples of leukocortical (A) intracortical type II (B) and subpial type III-IV (C) lesions as well as extensive subpial demyelination that involves the parasagittal frontal cortices (D) of a relapsing-remitting MS patient.

White matter lesion with a peripheral hypointense rim on phase images (E). A central vessel is visible in most T2* hyperintense white matter lesions (F). Leukocortical cerebellar lesion shown as a hypointensity on MP2RAGE sequence (G). Hyperintense T2* lesion affecting the right lateral column of the white matter of the spinal cord (H).

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Conflicts of interest:

None

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

▪▪Junker A, Wozniak J, Voigt D, et al. Extensive subpial cortical demyelination is specific to multiple sclerosis. *Brain Pathol.* 2020.

Extensive ribbon-like subpial demyelination was only observed in MS even if cortical oxidative injury was detected in both demyelinating and non-demyelinating CNS disorders.

▪▪Treaba CA, Granberg TE, Sormani MP, et al. Longitudinal Characterization of Cortical Lesion Development and Evolution in Multiple Sclerosis with 7.0-T MRI. *Radiology.* 2019;291(3):740-749.

In patients with MS 7T MRI detects more cortical lesions compared to lower-field MRI and shows a relationship between cortical lesions subsequent disease progression.

Cortical preferentially develop in cortical sulci, indicating a possible link with an ongoing cerebrospinal fluid-mediated neuro-inflammatory process.

▪Maranzano J, Dadar M, Rudko DA, et al. Comparison of Multiple Sclerosis Cortical Lesion Types Detected by Multicontrast 3T and 7T MRI. *AJNR Am J Neuroradiol.* 2019;40(7):1162-1169.

The detectability of subpial lesions at 7T is increased relative to 3T and it is not related with the degree of demyelination. Detection of leukocortical lesions at 7T is about the same with that at 3T and is influenced by the demyelination degree.

▪▪Beck ES, Sati P, Sethi V, et al. Improved Visualization of Cortical Lesions in Multiple Sclerosis Using 7T MP2RAGE. *AJNR Am J Neuroradiol.* 2018;39(3):459-466.

A combination of MP2RAGE and T2*-weighted imaging at 7T can improve cortical lesion detection.

▪▪Mangeat G, Badji A, Ouellette R, et al. Changes in structural network are associated with cortical demyelination in early multiple sclerosis. *Hum Brain Mapp.* 2018;39(5):2133-2146.

The study investigates the relationship between structural connectivity and cortical demyelination in early multiple sclerosis. The study shows an association between cortical myelin loss and changes in white matter connectivity.

▪▪Scalfari A, Romualdi C, Nicholas RS, et al. The cortical damage, early relapses, and onset of the progressive phase in multiple sclerosis. *Neurology.* 2018;90(24):e2107-e2118.

Extensive cortical damage at onset, the earlier the age at onset and an increased number of early attacks predispose to a rapid occurrence of the progressive phase of the disease.

▪▪Absinta M, Sati P, Masuzzo F, et al. Association of Chronic Active Multiple Sclerosis Lesions With Disability In Vivo. *JAMA Neurol.* 2019.

White matter lesions surrounded by a paramagnetic rim are frequent in multiple sclerosis, and are associated with disease severity. They expand slowly over time compared to lesions without a rim that overall shrinks during follow-up.

■Bagnato F, Hametner S, Franco G, et al. Selective Inversion Recovery Quantitative Magnetization Transfer Brain MRI at 7T: Clinical and Postmortem Validation in Multiple Sclerosis. *J Neuroimaging*. 2018;28(4):380-388.

Selective Inversion Recovery Quantitative Magnetization Transfer imaging provides a quantitative measure of myelin integrity.

■Zurawski J, Tauhid S, Chu R, et al. 7T MRI cerebral leptomeningeal enhancement is common in relapsing-remitting multiple sclerosis and is associated with cortical and thalamic lesions. *Mult Scler*. 2020;26(2):177-187.

At 7T MRI, cerebral leptomeningeal enhancement was observed in 2/3 of MS patients in a cohort of 30 patients and was independently associated with grey matter injury as related to cortical lesion and thalamic volume.

■Ighani M, Jonas S, Izbudak I, et al. No association between cortical lesions and leptomeningeal enhancement on 7-Tesla MRI in multiple sclerosis. *Mult Scler*. 2020;26(2):165-176.

At 7T MRI, cerebral leptomeningeal enhancement was observed in 65,8% of MS patients in a cohort of 41 patients. Although it was associated with mean cortical thickness, it was not associated with cortical lesion count in this cohort.

■Louapre C, Govindarajan ST, Gianni C, et al. Heterogeneous pathological processes account for thalamic degeneration in multiple sclerosis: Insights from 7 T imaging. *Mult Scler*. 2018;24(11):1433-1444.

At 7T MRI, thalamic lesions were mainly located next to the ventricles. Quantitative T2* mapping within the thalamus demonstrated thalamic damage next to the white matter in RRMS, while homogenously distributed in SPMS.

■Fartaria MJ, O'Brien K, Şorega A, Bonnier G, Roche A, Falkovskiy P, Krueger G, Kober T, Bach Cuadra M, Granziera C. An Ultra-High Field Study of Cerebellar Pathology in Early Relapsing-Remitting Multiple Sclerosis Using MP2RAGE. *Invest Radiol*. 2017 May;52(5):265-273.

MP2RAGE at 7T showed higher cerebellar lesion detection and contrast-to-noise ratio compared to 3T. High-resolution 7T MP2RAGE also proved optimal description of cerebellar white and grey matter pathology.