7 Tesla MRI will soon be helpful to guide clinical practice in multiple sclerosis centres: yes

Céline Louapre, Ysoline Beigneux

7 Tesla MRI will soon be helpful to guide clinical practice in multiple sclerosis centres: yes

Céline Louapre[1], Ysoline Beigneux[1]

1. Sorbonne Université, Institut du Cerveau, ICM, Assistance Publique Hôpitaux de Paris APHP, Department of neurology, Hôpital de la Pitié Salpêtrière, Inserm, CNRS, CIC neuroscience, Paris, France

Over the past 10 years, 7 Tesla (7T) MRI has brought many advances in the *in vivo* exploration of the pathophysiological mechanisms of multiple sclerosis (MS). Thanks to increased signal-to-noise ratio and contrast-to-noise ratio, as well as increased spatial resolution (voxel size below 500 μm^3), 7T MRI provides access to precise anatomical details, not or barely visible at 3T MRI, some of which being strongly associated with MS prognosis. Although routine use of 7T imaging is still limited due to cost, engineering time required, and technical challenges (more severe B_0 and B_1 inhomogeneities compared to lower field strength, long scan time), it is very likely that 7T MRI will soon be an additional tool to guide clinical practice.

Assessment of cortical lesion load at 7T: a future parameter for routine monitoring

The central nervous system compartment that benefits the most from 7T imaging in terms of clinical impact is surely the cortex. Cortical demyelination in patients with MS has been described from the first neuropathological observations in the 19th century, it is particularly widespread in progressive forms of MS (up to 90% of the cortical surface). Subpial demyelination is hardly visible on 3T MRI, even using Double Inversion Recovery sequence, which mainly allows to visualize leukocortical lesions. Thus, thanks to gradient recalled echo T_2*-weighted sequence at 7T, the number of visible subpial lesions more than doubles relative to 3T[1]. The anatomo-radiological correlations show that such acquisition enables to detect two-thirds of the subpial lesions visible in histology. Importantly, cortical lesion detection can also be achieved using 3D-T1-weighted acquisition with a scan time of less than 7 minutes with whole brain coverage[2].

The monitoring of subpial demyelination is all the more important as in progressive forms of MS, white matter (WM) lesion load is a poor prognostic marker. Treaba et al[3] recently quantified the progression of cortical lesion load over a 2-year longitudinal follow-up. In this study, patients with secondary progressive MS (SPMS) had the highest cortical lesion accrual, while the WM lesion load remained almost stable. Increase in cortical lesion volume during follow-up mainly concerned intracortical lesions, those reaching the pial surface. Interestingly, most of these patients with SPMS were receiving immunosuppressive therapy. Therefore, it clearly appears that the current MRI monitoring at 1.5T or 3T in patients with MS completely ignores this pathophysiological process affecting the cortex. A possible therapeutic effect of molecules that specifically target subpial cortical demyelination should call for ultra-high field MRI monitoring.

7T imaging using fluid-attenuated inversion recovery (FLAIR) sequence after gadolinium injection can detect leptomeningeal enhancement in nearly two-thirds of patients with MS[4].

Even if the spatial link with cortical demyelination and leptomeningeal enhancement remains difficult to establish, this marker is associated with grey matter injury.

The assessment of cortical lesions in MS is not limited to advanced or progressive forms only. Visualization of cortical lesions is frequent from the first clinical manifestations as observed in 92% of patients in a cohort of early relapsing remitting MS (within 5 years from onset)[5]. In relapsing-remitting patients, most of the new lesions appear in the sulci[3], supporting the hypothesis that cortical tissue injury may be related to immune-mediating factors originating from the CSF.
This observation of cortical lesions in patients with early MS is in line with the recent addition of this criterion for the definition of dissemination in space in the revised McDonald 2017 criteria.

Apart from the currently limited access to 7T scanners, visualization and quantification of cortical lesions remains difficult as it requires some experience, and a significant amount of time given the number of slices in these high-resolution images. To circumvent this challenge, quantitative parameters that reflect cortical involvement may be helpful. In cross-sectional studies, quantitative measures of T_2* relaxation time have been associated with neurological disability[6], as well as cognitive impairment[7]. Even if the prognostic value has not been evaluated longitudinally, one could imagine that having a quantitative measure of microstructural cortical damage, preferably at 7T to limit partial volume effect, will be useful to stratify patients according to initial severity.

Beyond cortical pathology, which 7T imaging markers will be likely to guide routine clinical practice?

The central vein sign, also detectable at 3T, is defined by the presence of a vessel within a WM lesion. This sign provides a strong argument (without being specific) for the diagnosis of MS in certain difficult cases[8]. It is not clear, however, that 7T is superior to 3T imaging apart from more precise anatomical details. Ongoing clinical trials aiming to determine the diagnostic value of this sign are being performed using 3T MRI.

The presence of a hypointense rim around WM lesions in phase imaging, visible both at 3T and 7T MRI, corresponds to ferromagnetic deposits, which has been linked to the presence of activated microglial cells and is associated with a more severe clinical phenotype.

Although still under development, 7T imaging of the spinal cord could provide a considerable gain for the assessment of the spread of lesions in this territory. Indeed, at 7T, the lesion detection sensitivity is increased by 52% compared to 3T, and small lesions can be identified[9]. This is particularly relevant in early MS like clinically isolated syndrome when dissemination in space criteria are not fulfilled on brain MRI and 3T spinal cord MRI. In addition, a recent study has highlighted the importance of the topography of cervical spinal cord lesions as a function of clinical phenotype[10], which opens up interesting perspectives for the identification of prognostic markers.

Conclusion

Recent technical developments allowed to improve some limitations linked to high-resolution acquisitions: they include for example parallel transmission to mitigate radiofrequency field inhomogeneity, echo-planar imaging or simultaneous multislice imaging to reduce scan time. Future longitudinal studies should also investigate more deeply the long-term prognosis value of 7T imaging markers in MS. Altogether, we can expect that the use of 7T scanners will expand in clinical practice in the coming years for a more comprehensive and systematic assessment of MS lesions, particularly in areas that could not be monitored until now.

Conflict of interest
None declared.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Kilsdonk ID, Jonkman LE, Klaver R, et al. Increased cortical grey matter lesion detection in multiple sclerosis with 7 T MRI: a post-mortem verification study. *Brain*. 2016; 139: 1472-81.
2. Cocozza S, Cosottini M, Signori A, et al. A clinically feasible 7-Tesla protocol for the identification of cortical lesions in Multiple Sclerosis. *Eur Radiol*. 2020; 30: 4586-94.
3. 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: 740-9.
4. 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: 177-87.
5. Granberg T, Fan Q, Treaba CA, et al. In vivo characterization of cortical and white matter neuroaxonal pathology in early multiple sclerosis. *Brain*. 2017; 140: 2912-26.
6. Mainero C, Louapre C, Govindarajan ST, et al. A gradient in cortical pathology in multiple sclerosis by in vivo quantitative 7 T imaging. *Brain*. 2015; 138: 932-45.
7. Louapre C, Govindarajan ST, Gianni C, et al. The association between intra- and juxta-cortical pathology and cognitive impairment in multiple sclerosis by quantitative T2* mapping at 7 T MRI. *Neuroimage Clin*. 2016; 12: 879-86.
8. Suthiphosuwan S, Sati P, Guenette M, et al. The Central Vein Sign in Radiologically Isolated Syndrome. *AJNR Am J Neuroradiol*. 2019; 40: 776-83.
9. Dula AN, Pawate S, Dortch RD, et al. Magnetic resonance imaging of the cervical spinal cord in multiple sclerosis at 7T. *Mult Scler*. 2016; 22: 320-8.
10. Ouellette R, Treaba CA, Granberg T, et al. 7 T imaging reveals a gradient in spinal cord lesion distribution in multiple sclerosis. *Brain*. 2020.