Advanced Structural and Functional Brain MRI in Multiple Sclerosis

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Abstract

Conventional magnetic resonance imaging (MRI) of the central nervous system is crucial for an early and reliable diagnosis and monitoring of patients with multiple sclerosis (MS). Focal white matter (WM) lesions, as detected by MRI, are the pathological hallmark of the disease and show some relation to clinical disability, especially in the long run. Gray matter (GM) involvement is evident from disease onset and includes focal (i.e., cortical lesions) and diffuse pathology (i.e., atrophy). Both accumulate over time and show close relation to physical disability and cognitive impairment. Using advanced quantitative MRI techniques such as magnetization transfer imaging (MTI), diffusion tensor imaging (DTI), proton MR spectroscopy (^{1}H-MRS), and iron imaging, subtle MS pathology has been demonstrated from early stages outside focal WM lesions in the form of widespread abnormalities of the normal appearing WM and GM. In addition, studies using functional MRI have demonstrated that brain plasticity is driven by MS pathology, playing adaptive or maladaptive roles to neurologic and cognitive status and explaining, at least in part, the clinicoradiological paradox of MS.

Keywords

- multiple sclerosis
- magnetic resonance imaging lesions
- normal-appearing brain
- atrophy
- magnetization transfer
- diffusion tensor imaging
- proton magnetic resonance spectroscopy
- iron
- susceptibility weighted imaging
- functional magnetic resonance imaging
- resting state networks
- brain connectivity
- high-field magnetic resonance imaging
- demyelination
- neurodegeneration

Given its sensitivity in revealing focal white matter (WM) abnormalities, magnetic resonance imaging (MRI) has become an indispensable tool for the assessment of patients with multiple sclerosis (MS) in the diagnostic workup. It is also extensively used in monitoring of abnormalities over time and elucidating the mechanisms of disease progression and disability.

There are established MRI guidelines that incorporate WM lesions into the diagnosis of patients with a clinically isolated syndrome (CIS) suggestive of MS,[1] and specific MRI acquisition protocols have been suggested for longitudinally monitoring WM lesion changes in patients with established disease.[2] Moreover, in MS research, conventional MRI has been significantly improved by quantitative and advanced MRI techniques, which

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have shown greater sensitivity and specificity to the heterogeneous pathological substrates of the disease, not only in focal T2-visible WM lesions, but also in normal-appearing white matter (NAWM) and gray matter (GM).[3]

Efficiency or dysfunction of brain cortical reorganization in the different stages of MS might play an important role in explaining heterogeneity of the clinical manifestations across patients, and several studies have used functional MRI (FMRI) to evaluate functions of brain network in patients with MS.[4,5]

More recently, new MRI methods capable of measuring pathological processes that have been overlooked in the past (e.g., iron deposition) and the advent of high- and ultrahigh-field magnets, have provided further insight into the pathophysiology of MS.[2]

This review aims at elucidating and discussing the role of advanced MRI in the central nervous system (CNS) of patients with MS for the appraisal of focal and diffuse tissue damage, abnormalities in the normal-appearing brain and functional brain changes. Future directions and challenges, with an emphasis on high-field MRI, will be also pointed out.

Focal Tissue Damage

Conventional Magnetic Resonance Imaging

The pathological hallmark of MS is demyelination in circumscribed regions (lesions), which nonetheless are also characterized by various degrees of other tissue abnormalities. An acute active lesion contains a large proportion of infiltrated macrophages with myelin debris, lymphocytes, and reactive astrocytes, some axonal swelling (a sign of axonal injury), and oligodendroglia (a sign of remyelination). A chronic inactive lesion, on the other hand, appears with sharp margins and is characterized by marked axonal and oligodendrocytes loss, fibrillary gliosis, few signs of perivascular inflammation, and absence of active demyelination.[6]

The identification of CNS lesions by MRI is a critical component of the diagnostic workup of patients with CIS, as well as one of the most important tools for monitoring treatment response to disease-modifying treatments (DMTs). According to the revised 2010 McDonald Criteria for the diagnosis of MS,[7] dissemination in space (DIS) is defined as the presence on MRI of one or more asymptomatic T2 lesions in at least two of four typical anatomical locations, such as juxtacortical, periventricular, infratentorial, or spinal cord. Dissemination in time (DIT) is defined as the presence on MRI of one or more asymptomatic gadolinium- (Gd-) enhancing lesions on the baseline scan, or one or more new T2 and/or Gd-enhancing lesions on follow-up MRI.[1] Alternative neurologic conditions need to be excluded.[8]

MS lesions typically have an oval or elliptical shape[9] and are commonly located in the periventricular and juxtacortical WM, corpus callosum, and infratentorial areas (especially pons and cerebellum) and can be found in the optic nerves of patients with optic neuritis.[10] In terms of MRI sequences, fluid-attenuated inversion recovery (FLAIR), T2-weighted, and postcontrast T1-weighted images are fundamental for the diagnosis and monitoring of MS. Moreover, they provide overtime information on subclinical disease activity (i.e., asymptomatic lesions), which occurs at a rate 5 to 10 times higher than that observed by simple clinical assessment.[11,12]

T2-hyperintense lesions can variably represent inflammation, edema, demyelination, gliosis, and axonal loss, while T1-enhancing lesions (after Gd intravenous injection) indicate the presence of acute inflammation.

In terms of prognosis, the role of MRI lesions has been demonstrated in patients with CIS. Indeed, various MRI measures at disease onset have demonstrated the best predictive value for the subsequent development of clinically definitive (CD) MS, such as brain T2 lesions (number and volume),[13,14] infratentorial lesions,[15] and T1-enhancing lesions.[16] In the longest follow-up studies to date, in patients with CIS and brain MRI lesions, the risk of developing CDMS in the very long term (14–20 years) was over 80%. Moreover, in these patients T2-lesion volume (LV) at baseline was a strong predictor of worsening disability over time.[13,14] In a large cohort of CIS patients with optic neuritis, infratentorial, T1-enhancing, and spinal cord lesions developing within 3 months of onset and new T2 lesions after 3 months were able to predict physical disability 6 years later.[17]

Unlike patients with CIS, in individuals with an established diagnosis of MS, a relationship between T2-lesion load and subsequent worsening disability is less recognized.

In a large cohort of placebo-treated relapsing-remitting (RR) MS patients, the multivariate analysis indicated that Expanded Disability Status Scale (EDSS) score and T2-LV together accounted for only a 3% probability of having an EDSS increase over short-term follow-up.[18] Such findings are in line with those of previous cross-sectional and longitudinal studies performed on smaller cohorts of MS patients with various clinical characteristics, which have shown the limited role of MRI lesions for predicting subsequent disability worsening.[19,20]

Indeed, T2 lesions are a simple expression of general and macroscopic tissue damage. Although new or enlarging T2 lesions reflect disease activity and thus areas of additional tissue damage, they are actually nonspecific to the actual pathological changes occurring in MS lesions.

A greater specificity is provided by the lesions appearing dark on T1-weighted images and thus defined as "black holes."[21] Most of these lesions ("acute black holes") originate from areas of Gd enhancement and resolve over a period of approximately 6 months. The remaining lesions, called "persistent black holes," constitute only approximately 36% of all T1-enhancing lesions, and are believed to represent severe demyelination and irreversible axonal loss.[22] The degree of lesion hypointensity, ranging from mild (i.e., similar to GM) to severe (i.e., similar to cerebrospinal fluid [CSF]), seems to correlate with the degree of pathological severity.[23] In general, the black hole LV is low in the early MS stage and increases during the disease course, ranging from 5% to 20% of the total T2-LV in RRMS and secondary progressive (SP) MS. In some studies, correlation between black hole LV and physical disability is closer than that of T2 lesions. In a recent study on RRMS, EDSS worsening in the long term (i.e., 10 years) was best correlated, among different lesional measures, with the combination of black hole number at baseline and increasing

black hole LV over the same period.[24] The clinical relevance of black holes in the long term has been shown also for cognition. Indeed, black holes (number and LV) at baseline and new T2 lesions at 3-month follow-up were able to predict, respectively, the severity of executive deficits and slowed information processing 7 years later.[25]

More recently, MRI-derived lesion probability maps (LPMs), by pooling information from MRI datasets, allowed the assessment of spatial patterns of focal pathology that would be much less evident in single-patient studies (►**Fig. 1**). Through LPMs, it was demonstrated the relevance of focal damage to specific WM regions for short- and long-term prognosis in CIS,[26,27] for clinical status and cognition in various MS phenotypes,[28–32] for distinguishing RRMS from PPMS,[33] benign MS,[34] and seropositive neuromyelitis optica spectrum disorder,[35] and for showing similar brain lesion distribution and frequency in patients with RRMS and in subjects with radiologically isolated symptoms (RIS), an asymptomatic condition suggestive of MS.[36]

Cortical Lesions

Very interesting—and to some extent—revolutionary was the evidence that focal lesions also occur in the cerebral GM of patients with MS, which is an aspect of MS that has not been fully studied until recently. Neuropathological studies have shown that cortical demyelination is present and common since the early stages of disease, and that early cortical lesions (CLs) are topographically associated with meningeal inflammation.[37]

The introduction of special MRI sequences such as double-inversion recovery (DIR)[38] and phase-sensitive inversion recovery (PSIR)[39] has greatly contributed to imaging CLs, which have been demonstrated in all MS phenotypes[40–43] and in RIS.[44] In general, CLs tend to accrue over time; they are found more frequently in patients with SPMS than in those with CIS or RRMS.[45] However, they are so frequently present in CIS that they are proposed as a further element of DIS for patients at risk of evolution to CDMS. In fact, the presence of CLs in patients with CIS is felt to have predictive value, and forecasts conversion to CDMS.[46] Relationships of CLs with physical disability and cognitive impairment have been reported. Indeed, a high number of CLs is present in patients with the poorest prognosis who show early and severe cortical atrophy and cognitive impairment.[47] Moreover, in a 5-year longitudinal study of different MS phenotypes, the CL volume at baseline correlated with the progression of cortical atrophy and with clinical worsening 5 years later.[48]

Several strategies have been proposed to improve the detection of CLs and to allow a reliable classification of them, including the use of three-dimensional (3D) DIR sequences and the combination of DIR, PSIR, and other MRI sequences.[39,49] However, drawbacks include the possible presence of false-positives and the limited ability of these sequences to detect subpial lesions, which according to histopathologic studies, represent a large proportion of CLs.[50]

A standard protocol for the acquisition of DIR has not been developed yet. However, multicenter consensus criteria have been proposed for scoring CLs.[51]

Magnetization Transfer Imaging

Magnetization transfer imaging (MTI) is based on the interactions between free-water protons and protons bound to macromolecules, and provides an index of general tissue integrity called magnetization transfer ratio (MTR).[52,53] Variable degrees of MTR decrease have been found in acute and chronic WM lesions, and obviously the most-marked abnormalities are present in black holes. Magnetization transfer ratio follows a distinct pattern in the development and evolution of MS lesions. Months before a Gd+ lesion, MTR declines in the prelesional WM, and at the time of enhancement, MTR strongly declines due to inflammation and demyelination.[54,55] Partial or complete MTR recovery may then follow, reflecting remyelination of remaining axons as well as resolution of edema or inflammation.[56,57] Through a method able to monitor the evolution of MTR changes in individual lesion voxels, changes of lesional MTR have been shown, consistent with demyelination and remyelination.[56] Changes in lesion MTR over time may depend upon the MS phenotype and may even give some clue on the subsequent disease evolution. Indeed, new lesions over 3 years demonstrated more severe MTR decrease in SPMS than in RRMS.[58]

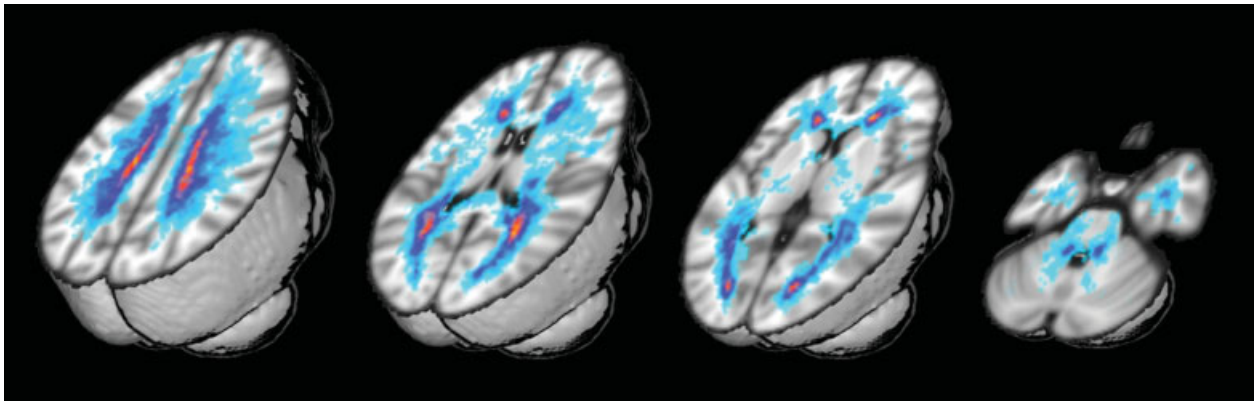

Fig. 1 Three-dimensional rendering of a T2-lesion probability map (LPM) in standard space in a group of patients with multiple sclerosis ($n = 20$). The color overlay created on top of the Montreal Neurological Institute (MNI) standard brain represents the probability of lesion occurrence (lesion frequency: low in *blue/light blue*, high in *red-yellow*) in a particular anatomical location.

Moreover, change in lesion MTR after 1 year was able to predict disability worsening in patients with RRMS.[59]

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) allows the assessment of the microstructural integrity of WM tracts by exploiting the different directionality of water diffusion across the brain.[60] The DTI findings in MS lesions appear to relate to different pathological features of tissue damage. However, conflicting results have been achieved when comparing DTI values in acute versus chronic MS lesions. In general, studies have reported lowest fractional anisotropy (FA), a sensitive index of microstructural integrity, in acute Gd+ lesions[61–63] and highest apparent diffusion coefficient (ADC) values, a measure of bulk diffusivity and general tissue integrity, in black holes.[61,63–65] Moreover, longitudinal studies have demonstrated that DTI is sensitive to the evolution of tissue damage within MS lesions over relatively short periods, with diffusion changes reported in T2 lesions of patients with RRMS and progressive disease after 15 to 18 months.[66,67]

Proton MR Spectroscopy

Proton MR spectroscopy (^{1}H-MRS) is an MR technique that records signals from metabolites that are present in tissues at low concentrations. Resonances in MR spectra are identified primarily by their frequency (i.e., position in the spectrum), and the resonance intensity is proportional to the concentration (or density) of the metabolite in the voxel.[68] ^{1}H-MRS studies demonstrated metabolic changes in different brain compartments. Indeed, this technique has the ability to discern between active and chronic MS lesions based on metabolite profile.[69] In general, a marked decrease in N-acetyl aspartate (NAA) is constantly present in acute lesions. NAA reflects neuronal number, health, and viability, and although its biochemical functions are not fully clear, it might have a bioenergetic role in neuronal mitochondria, thereby representing a unique marker for neuronal structure and neuronal (mitochondrial) metabolism in the CNS.

Since the early stages of an MS lesion, ^{1}H-MRS also shows an increase of choline, reflecting membrane phospholipids released during active myelin breakdown, and sometimes of lactate, which may be a primary sign of hypermetabolism of the inflammatory cells.

Special editing MRS imaging techniques allow the quantification of other interesting brain metabolites including glutamate. Glutamate-mediated excitotoxicity is an important process in the pathogenesis of MS.

Glutamate concentration (estimated at 3 Tesla [3T] MRI) usually increases in active, enhancing lesions, whereas it is normal in chronic lesions.[70] Increased glutamate probably relates to inflammation because active MS lesions show high expression of glutaminase, a marker of glutamate production, in macrophages and microglia in close proximity to dystrophic axons.[71]

As for the lesion evolution over time, the signal intensity of NAA may remain low or show partial recovery, starting soon after the acute phase and lasting for many months.[72] The partial recovery in NAA concentration correlates with the extent of clinical improvement,[73] in line with the hypothesis that increased mitochondrial function might be a mechanism of repair in MS.

Iron Imaging

Susceptibility weighted imaging (SWI) by using a velocity-compensated, high-resolution, 3D gradient-echo sequence that creates magnitude and phase images, enhances the effects of local magnetic susceptibility variation, thus creating a new source of MRI contrast.

One of the most interesting applications of SWI in MS is the demonstration of a central vein in a large proportion ($> 40\%$) of MS lesions, but not in other non-MS-related focal WM lesions.[74–77] This finding is due to the strong paramagnetic properties of deoxyhemoglobin within veins or to the presence of non-heme iron, particularly when acquired at high-field MRI ($\geq$ 3T). The "central vein sign"[78] may potentially discriminate MS from other neurologic conditions presenting with MRI WM lesions. However, the specificity of this biomarker has been evaluated only in a few cases thus far, and future studies are needed.

SWI is also able to identify ring-like hypointensities around lesions or nodular hypointensities in the WM that seem to be relatively specific to MS.[76,79] The mechanisms of this signal change are not completely understood, and although deposition of non-heme iron seems to be a major contributor, demyelination and free radicals related to inflammation may also play a role.[80] A recent longitudinal SWI study on MS lesions at different stages using quantitative susceptibility mapping, a new sophisticated postprocessing technique, showed that these signal changes followed, consistent with histochemical studies, a characteristic temporal pattern (i.e., iron deposition in chronic-active lesions, but not in active and chronic-inactive lesions).[79] This suggests that rapid iron accumulation could represent a potential hallmark of MS lesion formation.

The iron found in MS lesions derives from the destruction of iron-rich oligodendrocytes caused by phagocytosis or sequestration by microglia or macrophages. A specific interest in assessing iron through imaging in MS derives from the fact that this released iron may promote inflammatory activity and may propagate neurodegeneration through mechanisms of oxidative damage.[81,82]

Overall, SWI is a promising MRI technique for MS diagnosis and for monitoring the focal inflammatory process in MS. However, several technical challenges remain to be addressed before its introduction in clinical practice, such as optimization and standardization of the technique across the different MR scanners, and a clear demonstration of the specificity of these features to MS.

Diffuse Tissue Damage

Several lines of evidence suggest that MS is not simply a focal disease of the CNS and that macroscopic lesions are just the most evident aspect of MS pathology. Indeed, in MS a widespread pathological process occurs, which is partially independent from pathological abnormalities within WM lesions.[83]

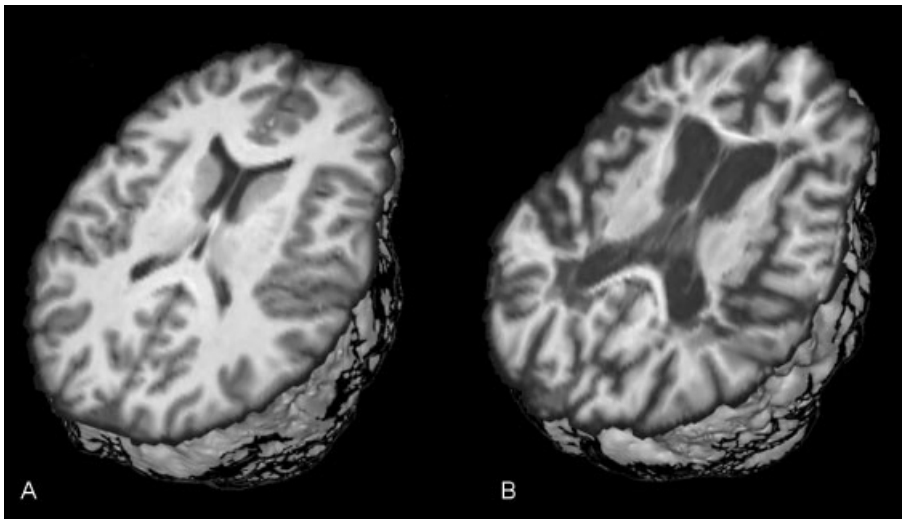

Fig. 2 Illustrative three-dimensional renderings of high-resolution T1-weighted magnetic resonance images (axial orientation) in a healthy male subject (**A**) and in a male patient with multiple sclerosis of similar age (**B**). Note in (**B**) the enlargement of the ventricles and subarachnoid spaces, consistent with widespread brain volume loss.

Brain atrophy, which is usually evaluated through MRI (on T1-weighted images), is the expression of such diffuse damage (►**Fig. 2**).[84]

In MS, brain atrophy is largely due to neurodegeneration, although in such a complex disease, other pathological processes, including demyelination, inflammation, and microglia activation, come into play. The rate of whole-brain atrophy is higher in MS (0.5–1% per year) than in healthy subjects (0.1–0.3% per year),[85,86] with a value of −0.4% per year representing a suggested threshold for "pathological" brain volume loss.[87] However, it needs to be considered that high rates of brain volume loss can also arise from resolution of inflammatory edema ("pseudoatrophy," either spontaneous or induced by anti-inflammatory treatment) or from other causes of shifts in tissue water content.[88]

Global brain atrophy starts at the earliest stage of MS and progresses throughout the disease course, probably at a constant rate, as demonstrated in a study on a large cohort of untreated MS patients.[89] It tends to correlate better with physical disability and cognitive impairment than measures of MRI lesions in both cross-sectional and longitudinal studies.[90,91] A recent multicenter study showed that, after correction for imaging protocol, global brain atrophy in the first 2 years was a good predictor of EDSS at 10 years.[92] Moreover, in an ongoing study of MS patients with 10-year follow-up, multivariate analysis identified combined MRI measures of focal (increased black hole LV) and diffuse tissue damage (global brain volume at baseline and on-study percent brain volume change) as a predictor of long-term disability worsening ($r = 0.65$, $p < 0.001$).[93] Further results in predicting disability progression have been obtained by the regional analysis of global brain atrophy. A study suggested that atrophy of central brain regions was related to a decline in ambulatory function, whereas atrophy of both central and peripheral brain regions was associated with worsening performance in complex tasks (e.g., hand dexterity).[94]

Important insights into the mechanisms of brain atrophy have been obtained by the separate assessment of GM and WM volumes. GM but not WM atrophy was demonstrated in CIS patients who developed CDMS over the subsequent 3 years.[95] Atrophy of the deep GM structures seems to occur early, whereas cortical atrophy develops later on. In RRMS, GM atrophy in the long term was predicted by focal (WM LV and MTR) and diffuse (NAWM MTR) damage. In terms of dynamics of atrophy in different brain tissue types, GM atrophy seems to mainly drive global brain atrophy, and its rate increases over the disease course, whereas a lower rate of WM atrophy appears constant across all MS stages.[96] Compared with WM, GM atrophy is more closely associated with the progression of MS in the long term.[97] Interestingly, a close correlation has recently been shown between periventricular lesions and cortical thinning, suggesting that common CSF-mediated factors might play a role in the accumulation of damage to GM and WM in MS.[98]

Interestingly, recent work has pointed out the role of GM tissue loss as a predictor of future clinical disability in studies with follow-up periods as long as 9,[99] 10,[92] and 13[100] years.

Finally, due to the clinical relevance and the relative ease of measurement, brain atrophy has been used as an outcome in several clinical trials of MS.[101,102] Most DMTs seem to have a delayed effect on reducing the rate of brain atrophy.[102]

Abnormalities in Normal-Appearing Brain

The advent of new, quantitative MRI methodologies has prompted the focus of investigations on the so-called normal-appearing brain tissue (NABT; i.e., without visible lesions on conventional MRI). In this setting, MRI techniques such as MTI, DTI, ^{1}H-MRS, and iron imaging have been extensively applied, providing important results.

Magnetization Transfer Imaging

In predicting the worsening of disability over time, the first MTI studies focused on NAWM. Patients with CIS

demonstrated reduced MTR in NAWM at the level of the corpus callosum, fronto-occipital tracts, external capsule, and optic radiations. These regional MTR abnormalities were associated with physical disability as well as with cognitive performance (PASAT).[103] Although a seminal study suggested that the extent of NAWM MTR abnormalities might be an independent predictor of subsequent disease evolution,[104] other studies did not confirm this observation.[105–107]

More recently, a relevant role of MTR abnormalities in GM has been recognized. Lower MTR values have been shown in both NAWM and GM of patients with various MS phenotypes, including those at the earliest clinical stages.[52] In patients with benign MS, MTR in NAWM and cortex was similar to that of healthy controls and significantly higher than in early RRMS patients, suggesting the presence of mild tissue damage.[108] Moreover, the subtle brain tissue damage detected by MTR was milder in RIS than in RRMS, especially in NAWM and GM of clinically relevant brain regions, providing a possible explanation for the lack of clinical manifestations in subjects with RIS.[36] Patients with CIS showed abnormalities in GM MTR histogram parameters[106,109] and in a voxel-based MTR study, GM MTR decrease was more evident in the basal ganglia.[110] A large cohort of patients studied within 6 months of isolated optic neuritis showed a selective MTR reduction in the visual cortex bilaterally.[111] In general, regarding clinical correlations, MTR changes in GM were associated with both physical disability and cognitive impairment, and were more evident in progressive MS.[112–114]

The role of GM MTR in MS has been particularly highlighted in prognostic studies. In patients with relapse-onset MS, baseline GM MTR, together with disease duration, independently predicted cognitive deterioration 13 years later.[100] In PPMS, GM MTR was associated with the rate of clinical worsening over 5 years[115] it turned out to be the best predictor of poor cognition after a similar period.[116] Finally, in patients followed prospectively, a multivariable model identified GM MTR at baseline, alongside average lesion MTR percentage change after 12 months, as independent predictors of disability worsening at 8 years.[59]

MTR is also able to assess the demyelination process at the cortical level as demonstrated in a postmortem study.[117] However, MTI is currently hindered in imaging subpial lesions; thus, some alternative strategies have been recently proposed. Through a method able to segment the cortex into outer and inner bands, reduced MTR values have been detected in the outer cortical band in the various MS phenotypes, being more pronounced in SPMS.[118] In another study, which implemented parametric surface models, MTR abnormalities were preferentially located in the cingulate cortex, the insula, and the deep sulci, consistent with pathological findings of subpial GM lesion distribution.[119]

Recently, MTR has been incorporated as an exploratory endpoint in a few large-scale multicenter clinical trials to assess treatment efficacy.[120,121] However, the presence of intersubject and interscanner variability has so far hampered its widespread use in this setting.

Diffusion Tensor Imaging

Histopathological studies showed close associations of abnormal DTI indices (i.e., FA and mean diffusivity [MD]) with myelin content and axonal count not only in WM lesions, but also in NAWM.[122,123]

In general, associations of DTI measures in MS brains with measures of disease activity or clinical disability have been investigated, although with conflicting findings. In patients with CIS, DTI abnormalities were found in NAWM,[124,125] although they were not able to predict DTI at 3 and 12 months.[124] Moreover, CIS patients showed a significant increase in GM diffusivity over 3 years, which was unrelated to clinical activity.[126] In a longitudinal study on PPMS patients, GM MD at study entry was able to identify patients with a high risk of progression over the following 5 years.[127] In a more recent prospective study (3 years), NAGM FA and T2 LV were independent predictors of EDSS score, while change in NAGM FA and disease duration were independent predictors of on-study EDSS change.[128]

More recently, DTI was used in conjunction with tract-based and voxel-wise analyses to better understand the processes underlying the various clinical characteristics of patients with MS. Using tract-based spatial statistics (TBSS) in early RRMS, T2-LV showed correlation with FA not only in lesions but also in NAWM, and FA decrease in internal capsule and corpus callosum was associated with higher EDSS.[129] Moreover, in MS patients with low lesion load, a relationship between abnormal FA in the corpus callosum and processing speed was found.[130] In patients with early PPMS, the same methodology showed that lower FA in the corpus callosum at baseline was associated with worse cognition in different domains and with higher accrual of physical disability 5 years later.[131] Moreover, in cognitively impaired MS patients 76% and 50% of WM tracts were more damaged compared with, respectively, healthy controls and cognitively preserved patients, and this occurred particularly in the corpus callosum, inferior and superior longitudinal fasciculus, corticospinal tract, forceps minor, cingulum, and fornix.[132]

Overall, these findings obtained with voxel-wise DTI analyses suggest that damage to NAWM of clinically eloquent WM tracts, especially those providing interhemispheric communication in the brain, and partially independent of GM atrophy and lesion load, may lead to a lower performance on both cognitive and motor tasks, possibly through a mechanism of "disconnection" between different GM regions.[133]

Finally, the very recent application of a topology-based brain network analysis to DTI images has demonstrated that general structural network efficiency was reduced in MS patients, especially in sensorimotor, visual, default-mode, and language areas, and was associated with total WM LV and disability scores.[134]

The relationship between reduced WM tract integrity and GM atrophy has been explored with the combined use of TBSS of DTI data and voxel-based morphometry analysis of T1-weighted high-resolution scans. Indeed, in early PPMS an anatomical and quantitative correlation between NAWM tract damage and volume reduction in specific GM regions anatomically connected to these tracts has been found.[135] In

SPMS patients, only regional deep GM atrophy, but not cortical atrophy, was explained by pathology in connected WM tracts.[136] However, in RRMS no correlation was found between global GM volume and TBSS-derived measures of WM damage.[137] Altogether, these findings point toward a link between the mechanisms of WM and GM damage, although this may be restricted to specific brain regions and differ across MS phenotypes.

Proton MR Spectroscopy

As mentioned earlier for MS lesions, ^{1}H-MRS has the unique ability to provide chemicopathological characterization of a tissue. Using ^{1}H-MRS, various metabolic changes such as reduced concentrations of NAA and choline and increased concentrations of myo-inositol have been observed in the NABT of MS patients,[69] indicative of axonal damage, glial cell activity, and increased membrane turnover, respectively. More recently, decreased NAA was also found in the brain of RIS patients, indicating that axonal damage can be significant even at the very early disease stage.[138]

Recent ^{1}H-MRS studies have focused on metabolic abnormalities in the GM, confirming the important contribution of GM pathology in MS.[139] A decrease in NAA in the cerebral cortex may be small or absent in the early stages, but seems to be marked in patients with progressive disease.[140–143] By contrast, a NAA decrease in the deep GM is more consistently found since the early stages of disease.[144–146]

By using a spectral editing method of ^{1}H-MRS, which is able to reliably separate gamma-aminobutyric acid (GABA), a product of glutamate, from other more abundant metabolites, it was demonstrated that decreased GABA levels in the sensorimotor cortex is associated with impaired motor performance in patients with progressive MS, suggesting a possible role of this metabolite in the mechanisms of neurodegeneration.[147]

In general, longitudinal studies exploiting the unique properties of ^{1}H-MRS are limited, probably because of technical challenges, which could be overcome by following appropriate guidelines.[148]

Iron Imaging

The measurement of iron in MS brains was made possible thanks to a novel MRI technique named R2* relaxometry. It provides quantitative data that, at least for the deep GM, scale linearly with iron levels and has therefore been proposed as a reliable method of determining iron concentration within this structure.[149,150] Most deep GM structures of MS patients show elevated R2* values compared with healthy controls, indicating increased iron accumulation in association with duration and severity of the disease.[151–153]

Functional Brain Changes

FMRI measures blood-oxygen-level dependent (BOLD) signal in regions of GM involved in the performance of a task or during a rest condition.

Studies of task-FMRI probing the visual, cognitive, and sensorimotor systems have consistently demonstrated functional cortical changes in all MS phenotypes in comparison with healthy controls, with hyperactivation of regions normally recruited for performing a specific task and/or the recruitment of additional areas.[4] Functional MRI abnormalities in MS patients during the performance of a task occur early in the course of disease (►**Fig. 3**).[154] Interesting results have been obtained by the few longitudinal FMRI studies performed so far. In a 1-year study, CIS patients who developed CDMS had a higher cortical activation when compared with those who did not, suggesting that the extent of early cortical reorganization following tissue injury might be among the factors influencing disease progression.[155] Another longitudinal study showed that in CIS patients, the increased activation in the right dorsolateral prefrontal cortex was associated with improved performance in working memory and processing speed 1 year later.[156]

In general, increased recruitment of cortical regions, also described as functional adaptation or reorganization, helps limit the functional impact of MS-related structural damage and might in part explain the suboptimal correlation between MRI findings and clinical findings (clinicoradiological paradox). An extensive and bilateral functional cortical reorganization has been found during a simple motor task in patients with benign MS; this may in part explain the favorable clinical expression of disease in these patients.[157] However, increased cortical recruitment does not proceed indefinitely, and a lack and/or exhaustion of adaptive mechanisms has been considered as a possible factor responsible for clinical worsening in the advanced stages of MS.[5]

Resting-state FMRI investigates spontaneous modulations in the BOLD signal by identifying temporal correlations between remote areas of the cerebral GM with similar functional properties (resting state networks [RSNs]).[158] In more recent years, several resting-state FMRI studies investigating the MS brain have been performed, due to easier data acquisition and better interpretability with respect to task-FMRI. The synchronization of cerebral activity found at the earliest stage of MS (CIS) is subsequently lost as brain damage progresses (RRMS), indicating that cortical reorganization in RSNs might be an early, but finite compensatory phenomenon in MS.[159] A study on a large sample of RRMS patients demonstrated complex functional abnormalities (both increases and decreases) within and between RSNs in patients with RRMS, with decreases related to the extent of T2 lesions and the severity of disability.[160]

Functional connectivity of the default-mode network (DMN), a relevant RSN for cognition, has been explored in MS, with a reduction of the anterior component (anterior cingulate cortex) in progressive patients with cognitive impairment[161] and a complex reorganization in RRMS, with a decrease in the anterior cingulate cortex and core of the posterior cingulate cortex and an increase at the periphery of the latter, reflecting a possible compensatory effect.[162] In relapse-onset MS patients, better cognitive performance (sustained attention) was associated with increased functional connectivity of the anterior cingulate cortex to the cerebellum, middle temporal gyrus, occipital pole, and angular gyrus, interpreted as adaptive changes.[163]

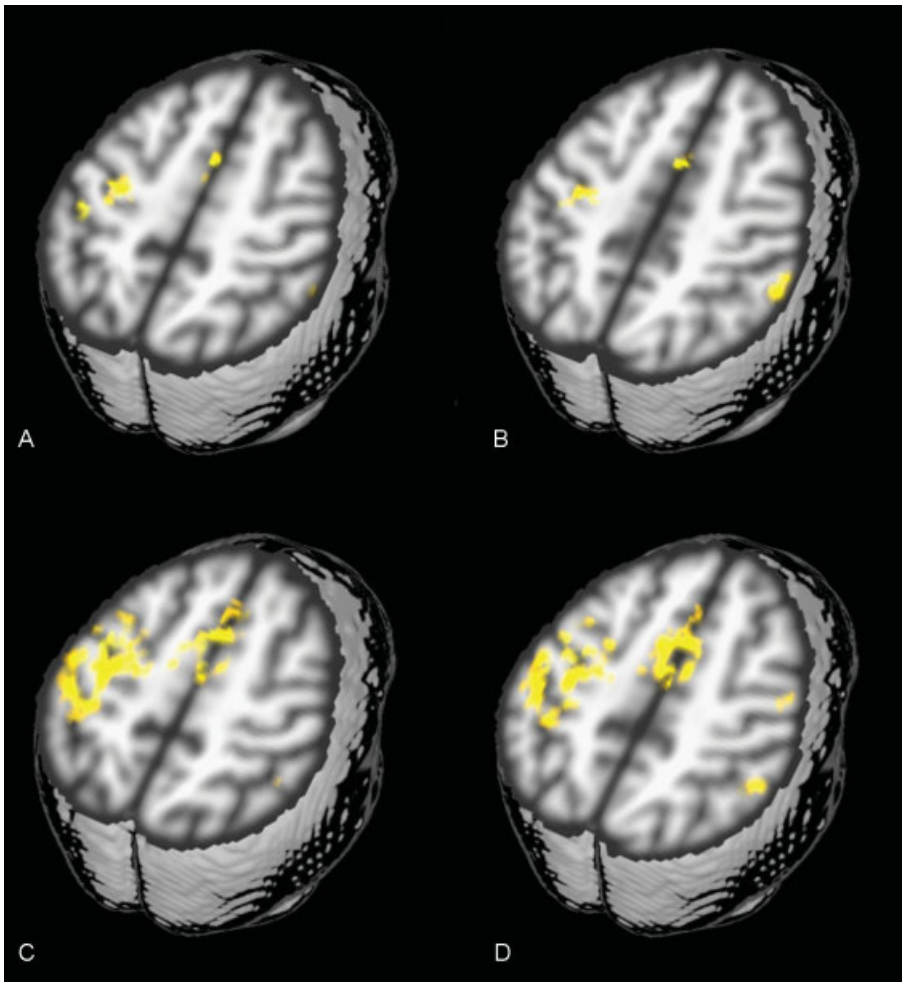

Fig. 3 Three-dimensional rendering showing brain areas that were activated ($Z > 4$, $p < 0.05$, cluster corrected for multiple comparisons) during right-hand tapping in a group of healthy subjects ($n = 10$) (**A, B**) and of patients with early relapsing-remitting multiple sclerosis ($n = 10$) (**C, D**) overlaid on the Montreal Neurological Institute (MNI) standard brain. Note the more widespread and bilateral activation in (**C**) and (**D**) compared with (**A**) and (**B**).

However, the prevailing adaptive/compensatory theory described thus far for increased cortical activation is contradicted by some other studies of resting-state FMRI. Indeed, in early RRMS, the increased connectivity in some RSNs was negatively correlated with the MS Functional Composite (MSFC).[164] Moreover, in another study of early-stage MS patients, increased functional connectivity of the DMN and areas involved in attention and cognitive control correlated with a poorer cognitive performance.[165] Overall, these studies propose that increased RSN functional connectivity might also reflect maladaptive mechanisms, which may contribute to the worsening of cognitive functions. Very recently, functional organization was demonstrated to be absent in two key brain networks (sensorimotor and working memory) of RIS patients, suggesting that brain "functional reserve" may come into play only in case of clinical deficit.[166]

Independently of disease phenotype and disease burden in different MS stages, part of the variability observed in RSN studies of MS might also reflect patient features, including genetic background and cognitive reserve, which are likely to impact patient ability to compensate efficiently.

As for the possible application of FMRI in clinical practice, a predictive model based on alterations of RSN connectivity and suitable for distinguishing MS patients from healthy controls on individual basis has recently been proposed, with a sensitivity of 82% and a specificity of 86%.[167]

Finally, the potential of FMRI in a multicenter setting has been demonstrated by the MAGNIMS (Magnetic Resonance Imaging in Multiple Sclerosis) group in various studies of the sensorimotor and cognitive networks.[168–172]

Future Directions and Challenges: The Promise of High-Field MRI

The main promise of MRI lies in the use of high-field and ultra-high field scanners, which have the potential to improve quantitative and FMRI studies. Indeed, there are advantages in terms of signal-to-noise ratio and image contrast and resolution, although they can be obtained only by using the appropriate radiofrequency coils and intensity-uniformity correction.

There is growing evidence that MRI at 3T, compared with 1.5T, improves detection of T2-hyperintense and Gd-enhancing lesions.[173,174] Thus, high-field MRI might, in principle, determine a better characterization of patients with CIS, although it has not demonstrated a significant gain in terms of DIS.[175–177] High-field MRI is also beneficial for SWI by

providing better sensitivity to localized iron deposition, and by revealing that iron content is closely associated with disease duration.[178] The images also show distinct peripheral rings, which may be consistent with histological data demonstrating iron-rich macrophages at the periphery of MS lesions.[179] Very recently, 3T MRI demonstrated through postcontrast T2-FLAIR sequences the frequent presence in MS (both RR and progressive) of focal leptomeningeal contrast enhancement, which was proposed as an in vivo marker of inflammation and associated subpial demyelination.[180] Moreover, a novel combined MR contrast technique called FLAIR* has recently demonstrated on 3T imaging the ability to produce high-resolution images, yielding high contrast for WM lesions and parenchymal veins.[181] The potential use of such a technique in a clinical setting needs further investigation.

A few preliminary studies performed at 7T showed the ability of MRI to capture the morphological features of MS lesions in both WM and GM, including subpial demyelination, almost resembling pathological assessment.[178,182–185] Moreover, phase imaging combined with dynamic contrast enhancement at 7T demonstrated high sensitivity to tissue abnormalities in acute versus chronic MS lesions, suggesting different inflammatory processes in the two lesion types.[180] Finally, the use of FLAIR* at 7T led to improved differentiation between MS and vascular lesions.[179] Noticeably, imaging at 7T was demonstrated to be safe and well tolerated.

Conclusions

Magnetic resonance imaging is very sensitive for the detection of focal lesions in the WM of MS brains; thus, it is an important tool for the diagnostic workup of patients suspected of having MS, for disease monitoring over time and also with respect to treatment response, as well as for obtaining early prognostic information. MRI criteria are updated on a regular basis to demonstrate DIS and DIT of MS lesions. However, several factors related to MRI examination, such as patient positioning, sequence parameters, image resolution, and MR field strength, may have a major influence on MS lesion detection[186]; hence, guidelines for the standardization and optimization of MRI in clinical practice are mandatory.[2]

Conventional MRI lacks specificity to the heterogeneous pathological substrates of the disease. The last decade or so has seen an impressive development and application of several advanced MRI techniques, which provide higher specificity for MS pathology. These modern techniques have improved our understanding of MS pathophysiology and the mechanisms responsible for the accumulation of irreversible neurologic disability. It is now well established that MS brain abnormalities are much more widespread than we used to assume from the hallmark finding of MS lesions. Among the various MRI measures, brain atrophy has been used as a marker of neuroprotection in several MS clinical trials. Unfortunately, nonconventional MRI techniques have been applied only in selected research centers for the evaluation of relatively small patient cohorts; thus their added value in the diagnostic workup of single patients is still elusive and needs to be further investigated.[2,186]

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