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Imaging Cortical Damage and Dysfunction in Multiple Sclerosis

Massimo Filippi, MD; Maria A. Rocca, MD; Mark A. Horsfield, PhD; Simon Hametner, MD; Jeroen J. G. Geurts, PhD; Giancarlo Comi, MD; Hans Lassmann, MD

In line with pathological investigations, in vivo magnetic resonance imaging has consistently shown both focal and diffuse damage in the cerebral cortex of patients with multiple sclerosis. Cortical injury tends to progress over time and is only partially related to white matter abnormalities. This review summarizes the main findings from studies using both conventional and modern quantitative magnetic resonance–based techniques for the assessment of cortical damage and dysfunction in patients with multiple sclerosis.

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The notion that multiple sclerosis (MS) is a white matter (WM) disease of the central nervous system has been challenged by several pathological and magnetic resonance imaging (MRI) studies that have consistently revealed both focal and diffuse damage in the cerebral cortex of patients with MS.[1-3] The clinical relevance of measures of cortical damage has been shown by several studies demonstrating that its extent differs between the principal MS disease phenotypes and that it correlates better with clinical disability and cognitive impairment than do measures of focal T2 lesion load or normal-appearing WM damage.[1-3] Furthermore, some symptoms of the disease, such as epilepsy and fatigue, are likely to be related to cortical involvement.[1-3] However, imaging the cortex is technically difficult because of its morphology and location and the nature of the pathology within this structure. Over the last decade, advances in MRI technology have helped to improve significantly our ability to quantify focal and diffuse cortical damage in patients with MS. Additionally, the use of functional magnetic resonance (MR) techniques has improved our understanding of cortical reorganization in response to tissue injury at different stages of the disease. After a summary of the features of MS-related cortical pathology, this review discusses findings from studies using both conventional and modern quantitative MR-based techniques for the assessment of cortical damage and dysfunction in patients with MS.

Author Affiliations: Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience (Prof Filippi and Dr Rocca), and Department of Neurology (Profs Filippi and Comi and Dr Rocca), San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy; Department of Cardiovascular Sciences, University of Leicester, Leicester, England (Dr Horsfield); Center for Brain Research, Medical University of Vienna, Vienna, Austria (Dr Hametner and Prof Lassmann); and Department of Anatomy and Neurosciences, VU University Medical Center Amsterdam, Amsterdam, the Netherlands (Prof Geurts).

CORTICAL PATHOLOGY

The pathological hallmark of MS is the demyelinated WM plaque with relatively well-preserved axons and astrocytic scar formation. However, it has been recognized since the 19th century that the cerebral cortex of patients with MS is also affected by demyelination. Although cortical pathology is by no means restricted to chronic MS, extensive demyelination of the cortex is undoubtedly typical of chronic, long-standing disease.[4] Three types of cortical lesions (CLs) are commonly distinguished: type 1 refers to leukocortical lesions involving the cortex and adjacent subcortical WM; type 2 refers to purely intracortical lesions; and type 3 la-

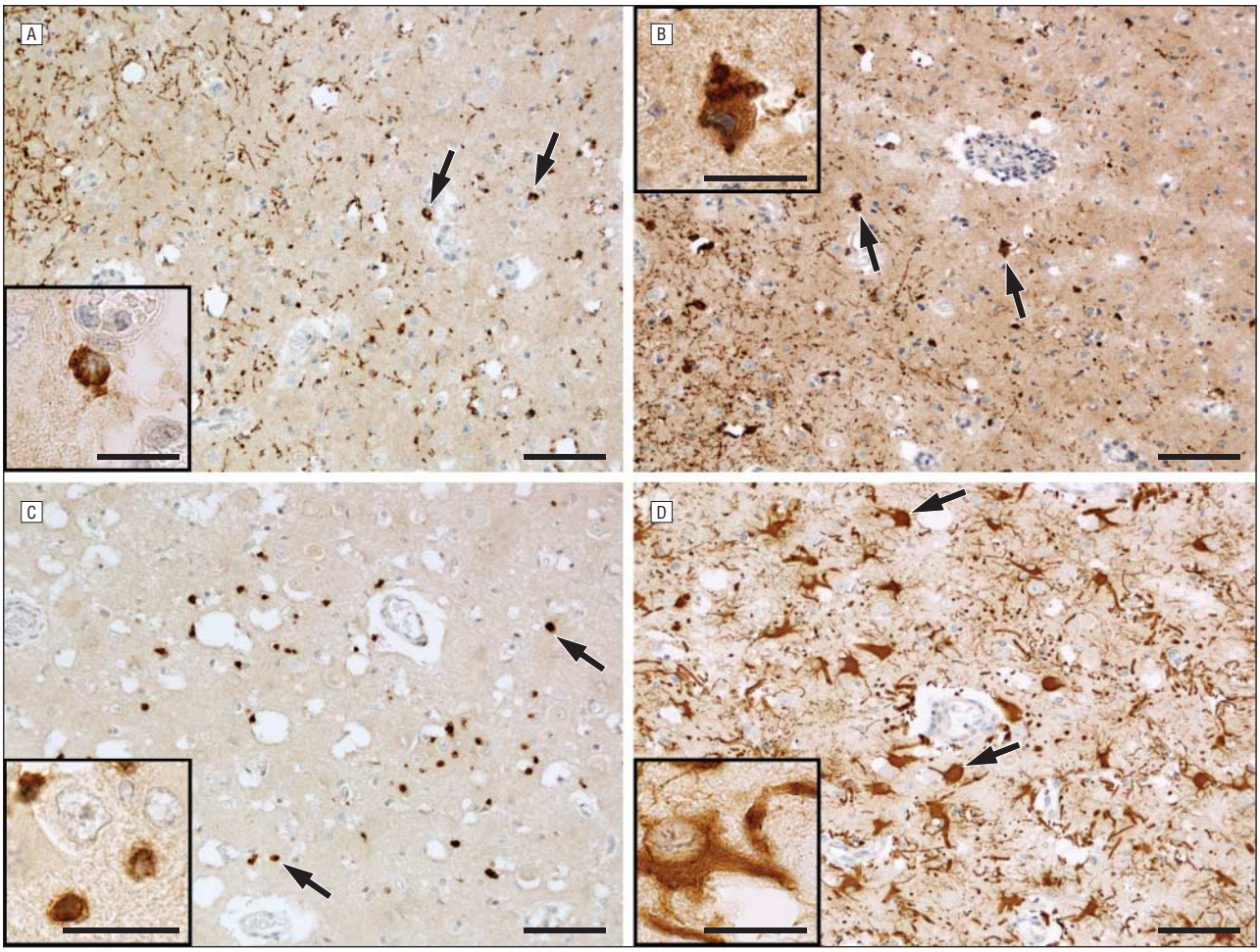

Figure 1. Pathological findings in an acute multiple sclerosis case with severe cortical involvement. A, Proteolipid protein immunohistochemical (IHC) staining shows macrophages in the cortex containing myelin degradation products (arrows), indicating active demyelination. B, Immunohistochemical staining for 2'3'-cyclic-nucleotide 3'-phosphodiesterase shows macrophages containing early myelin degradation products (arrows), indicating early active demyelination. C, CD3 IHC staining reveals cortical parenchymal infiltration of T lymphocytes (arrows). D, Glial fibrillary acidic protein IHC staining shows severe cortical protoplasmic astrogliosis with reactive astrocytes (arrows). Scale bars represent 100 μm or 25 μm (insets).

bels subpial demyelination.[5] Type 3 lesions are most common in the neocortex of patients with chronic MS.[4] While demyelination may in fact involve any part of the cortex, and comparison of different studies using different sampling procedures is generally difficult, the cingulate gyri and temporal cortex seem to be most frequently affected.[6] However, the degree of cerebellar cortical demyelination, where plaques often involve multiple adjacent folia, may even exceed that in the neocortex.[7] Demyelination of the hippocampus[8] and deep gray matter (GM), especially the thalamus and caudate nuclei,[9] is also frequently found in patients with MS.

Compared with WM plaques, cortical plaques are characterized by fewer inflammatory infiltrates, less gliosis, and milder tissue loss, which is mainly due to synaptic and axonal pathology.[5,10] However, the concept that cortical demyelination does not take place on an inflammatory background, which arose mainly from studies of cases with late and progressive stages of MS, has been challenged in the last few years; cortical demyelination is frequently oriented toward meningeal inflammatory infiltrates composed of B cells and dendritic cells, suggesting cytokine diffusion into the underlying cortex that might lead to microglial activation.[11] Recently, a study of biopsy material from 138 patients presenting with early-stage MS found inflammatory lymphocytic infiltrates in 82% and macrophages laden with myelin debris in 41% of all the observed CLs (**Figure 1**).[12] The study also found a strong spatial association of CLs with diffuse inflammation in the overlying meninges and emphasized the early onset of cortical pathology in MS.

Global cortical thinning of around 10% has been found in patients with MS compared with controls.[13] This finding could only partly be explained by focal neuronal or glial loss within CLs, suggesting that diffuse cortical pathology is present outside such lesions. The relative contributions of focal and diffuse pathology to neocortical thinning remain to be determined. Mitochondrial injury has been suggested to be an important contributor to diffuse cortical MS pathology,[14] since reactive oxygen species and nitrogen intermediates are abundantly produced in inflamed tissues and have the capacity to interfere with the mitochondrial respiratory chain, thus leading to energy deficiency and further perpetuation of radical production.[15] Consistent with this, a recent study found evidence for oxidative damage to neurons and transected neurites, suggesting that cortical pathology is at least partly due to related oxidative pathogenesis.[16]

IMAGING THE CORTEX: TECHNICAL ISSUES

Imaging of focal pathology in the cortex is hampered by the similarity of the relaxation times in CLs to those of adjacent WM and cerebrospinal fluid. This had led to the development of specialized pulse sequences that can suppress the signal from these 2 tissue compartments simultaneously, named *double inversion recovery* (DIR).[17] These sequences have 2 inversion pulses timed so that the longitudinal magnetization from 2 compartments (normally cerebrospinal fluid and WM) is passing through zero when the readout radiofrequency (RF) pulse is applied.

Cortical atrophy, the long-term outcome of inflammatory demyelination and tissue loss, can be visualized and measured on MRI scans. This requires the images to be partitioned, or segmented, into the separate tissue compartments (GM, WM, and cerebrospinal fluid) using images with a suitable contrast, normally T1 weighting. Some of the most popular and successful segmentation schemes use an "atlas" of the brain derived from many individual subjects, where the separate compartments have been segmented and then averaged. The patient's scan is distorted, or registered, so that it occupies the same space as the atlas, and the presegmentation is used as "prior knowledge" to assist in the correct assignment of the tissue class.[18] Registration requires the resampling of an image by interpolating the intensities at the pixel grid positions of the original image. Image resampling is generally less prone to artifacts when the images are acquired with a 3-dimensional phase-encoded pulse sequence rather than with a multislice sequence.[19]

Because the cortex is a thin "ribbon" and because of the subtlety of the pathology, both focal and diffuse, high spatial resolution is a great advantage. However, reducing the pixel size and slice thickness also reduces the signal to noise ratio in the images, with a rapid degradation in image quality being seen with only modest reduction in the pixel dimensions. An obvious way to increase the signal to noise ratio is to use higher–field strength magnets, since the magnitude of the measured signal is proportional to the square of the polarizing magnetic field strength. While 3 T is the maximum field strength normally found in routine clinical installations, magnets of 7 T and beyond are becoming more common in dedicated research environments, yielding significant improvements in the detection and categorization of CLs (**Figure 2**). However, increased field strength brings its own technical challenges. First is the increased cost and size of high-field magnets, which makes them more difficult to site. Second, it is more difficult to make the RF field uniform at high field, where the wavelength of the RF field is closer to the size of structures in the human body. This is being mitigated by the development of parallel transmission technology, whereby multiple RF transmitter coils are arrayed around the subject, with independent control of the phase and amplitude of the field generated by each of them. The overall field can then be "shimmed" to the individual patient, making the flip angles more uniform, leading to more consistent contrast over the whole field of view. The signal to noise ratio is further improved by the now common use of arrayed receiver coils, which have particular benefits for imaging the cortex because of the proximity to the coil elements.

Unfortunately, the amount of energy deposited in the subject also increases as the square of the Larmor frequency, which can be a limiting factor at high field in pulse sequences where RF pulses are applied in rapid succession (such as multiecho sequences) or where large flip angles are used. High specific absorption rate can be mitigated by lowering the flip angle of the pulses or by extending their duration. However, care must be taken to avoid changing the image contrast or unduly lengthening the scan time. Magnetization transfer (MT) sequences are particularly prone to a high specific absorption rate, because they use multiple high flip angle pulses to saturate the magnetization in the "bound" water pool. Nevertheless, with careful design, MT MRI can still be used at higher-field strengths, yielding significant improvements in image quality.[21]

FOCAL CORTICAL LESIONS

The use of DIR sequences has enabled substantial improvements in CL detection in MS when compared with conventional T2-weighted and fluid-attenuated inversion recovery sequences[22] (**Figure 3**). Double inversion recovery imaging confirmed earlier histopathology reports: CLs develop early in MS and increase in number and size with progression of the disease.[23] Using DIR, it was also found that CLs are very important in explaining both locomotor disability and cognitive impairment[24] and that their presence is associated with other MRI indicators of damage such as T2 lesion load and WM and GM atrophy.[25] It was also found that CLs are sparse in benign forms of the disease[26] and in children with MS.[27] Importantly, the accuracy of MRI diagnostic criteria for MS increases when considering CLs on baseline scans in patients who present with a clinically isolated syndrome suggestive of MS.[28]

Images acquired using DIR sequences are inherently noisy, and different DIR sequences are applied at different centers. Because of this, guidelines for CL scoring on DIR have been defined and the first interrater data were obtained in a multinational consensus meeting.[29] Postmortem verification of lesions scored according to these guidelines showed that DIR has a high pathological specificity even though its sensitivity is quite low.[30] To translate DIR results reliably from single centers to broader research, and possibly a clinical setting, further sequence optimization and development of guidelines are needed. Given the moderate overall sensitivity of DIR, other techniques, such as T1 mapping and T2* and phase-sensitive imaging[31,32] or the use of higher field strengths[31,32] should also be evaluated in an attempt to further improve the sensitivity of CL detection in MS without losing specificity. High-field MRI systems seem to be especially useful for detecting subpial CLs, which are notoriously difficult to detect at standard field strengths.[33]

Finally, in addition to improving the sensitivity of MRI for detecting CLs, future studies should investigate the relative contributions of WM lesions and diffuse WM abnormalities, as well as CLs and GM and WM atrophy, to the development of clinical and especially cognitive impairment in MS. For example, in the postmortem setting, the location of WM lesions was not necessarily

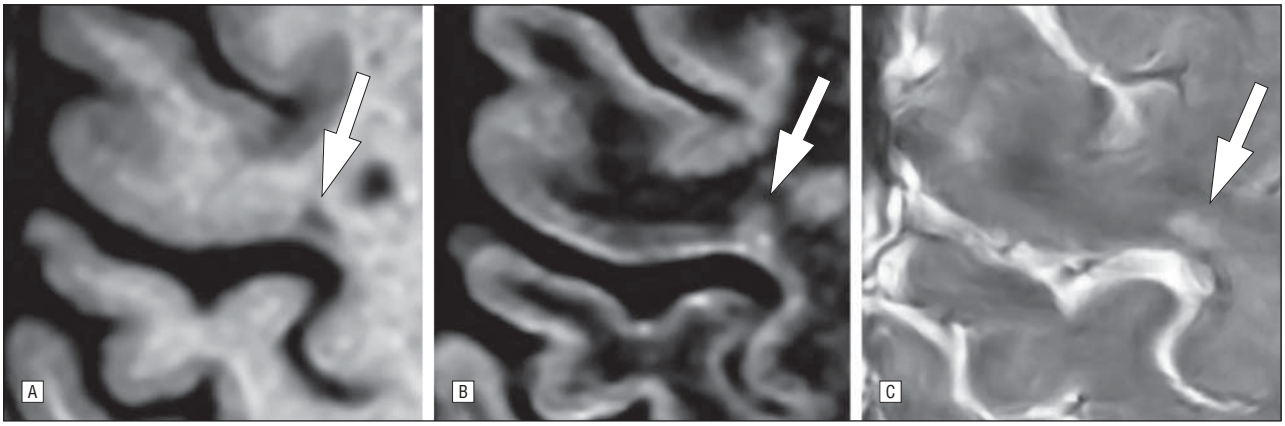

Figure 2. Comparison of cortical lesion detection and classification using 3- and 7-T magnetic resonance imaging. A and B, Three-Tesla T1-weighted magnetization-prepared rapid acquisition with gradient echo (A) and double inversion recovery (B) sequences disclosed a juxtacortical lesion (arrow). C, Seven-Tesla fast low-angle shot–T2*-weighed imaging categorized the lesion as type 1 (arrow). Adapted from Nielsen et al[20] with permission.

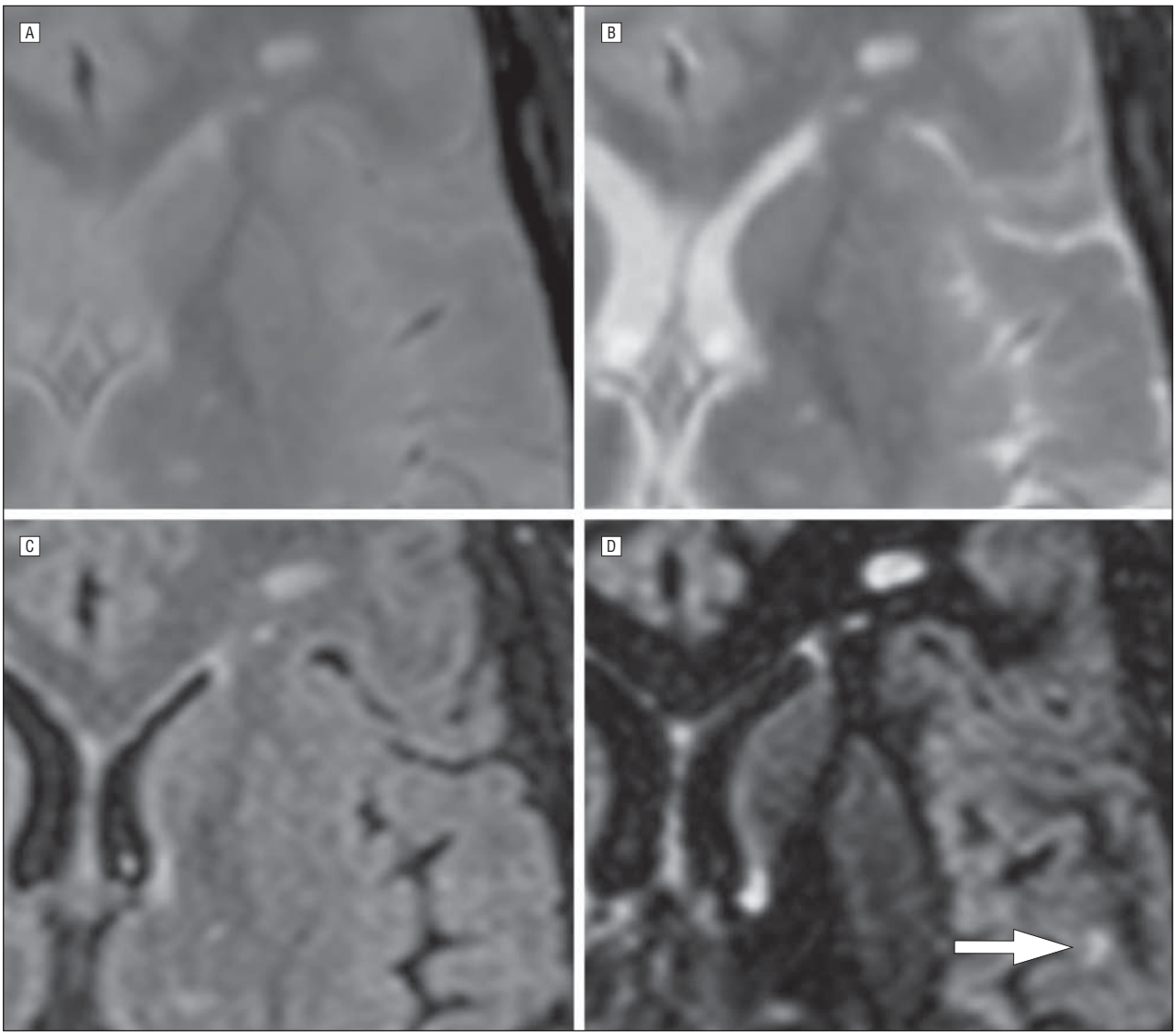

Figure 3. Cortical lesions in multiple sclerosis using double inversion recovery sequences. A and B, Increased cortical multiple sclerosis lesion visibility on double inversion recovery short echo time (A) and long echo time (B) T2-weighted magnetic resonance images. C, Multislab 3-dimensional fluid-attenuated inversion recovery image. D, Multislab 3-dimensional double inversion recovery image showing a cortical lesion (arrow) that is not visible on the other, more conventional, magnetic resonance sequences. White matter lesions around the ventricles are visible on all sequences. Adapted from Geurts et al[17] with permission.

related to that of CLs,[34] and the two may therefore differentially influence clinical measures over the course of the disease. Furthermore, cortical atrophy was found to be present throughout the entire cortex in MS and was partly independent of the presence of CLs.[13]

DIFFUSE CORTICAL DAMAGE

Several factors are likely to contribute to diffuse cortical damage in MS, including the presence of focal CLs beyond the resolution of current MR scanners, degenerative phenomena secondary to local discrete areas of demyelination, and retrograde and transynaptic degeneration of fibers passing through damaged WM. The application of modern MR techniques can contribute to the assessment of different aspects of cortical damage, including the presence of diffuse disease-related abnormalities (measured using quantitative techniques such as MT and diffusion tensor MRI), metabolic abnormalities (measured by means of proton MR spectroscopy), irreversible tissue loss (atrophy), and iron deposition (quantified using T2- and T2*-weighted imaging), thought to reflect neurodegeneration.

Several studies have demonstrated reduced MT ratio and increased mean diffusivity in the cortex of patients with different MS phenotypes[35-37] including those at the earliest clinical stages of the disease.[38,39] These abnormalities are more severe in patients with the progressive disease phenotypes.[35,37,40] Analogous findings have been shown when measuring cortical atrophy.[41] Using proton MR spectroscopy, metabolite abnormalities, including reduced concentrations of *N*-acetylaspartate and choline and increased concentrations of *myo*-inositol, have been found in the cortex[42,43] and subcortical GM tissue[44,45] from patients with MS.

Diffuse cortical damage is not stable but tends to worsen over time, independent of the progression of damage within the WM.[36,46,47] The clinical relevance of measures of such a damage has been demonstrated by several studies showing correlations with clinical disability[39,48,49] and cognitive impairment.[50-52] A longitudinal study showed an increased rate of cortical tissue loss in patients with progressing disability compared with those with stable disease,[53] whereas another study demonstrated that progressive neocortical loss is relevant to MS-associated cognitive impairment.[54] Fisher et al[55] compared atrophy rates over 4 years across the main MS clinical phenotypes and found that GM atrophy rate increases with disease stage, from 3.4 times greater than normal in patients with clinically isolated syndrome converting to relapsing-remitting MS to 14 times normal in secondary progressive MS. These important findings now await further confirmation in independent data sets.

Analysis of the spatial distribution of cortical damage has demonstrated that different regions might have different vulnerabilities to MS-related pathological processes. Overall, MRI studies have agreed in identifying the frontal, temporal, and parietal lobes as the most affected cortical regions in patients with MS.

However, the patterns of GM loss differ between the major MS clinical phenotypes.[56] In patients with clinically isolated syndrome, GM atrophy involves the thalamus, hypothalamus, putamen, and caudate nucleus.[57] Cortical atrophy in patients with relapsing-remitting MS affects preferentially the frontotemporal lobes,[58,59] and volume reduction in these regions over 1 year is correlated with WM lesion progression.[59] The evaluation of the regional patterns of cortical involvement has undoubtedly improved the correlation with disease clinical manifestations. Reduction of cortical volumes of regions associated with working memory and executive functions is correlated with cognitive task performance,[60] temporal lobe atrophy is associated with auditory/verbal memory and visual/spatial memory performance,[61] and hippocampal atrophy is related to a poor performance on a memory encoding task.[62] Fatigued patients with MS experience cortical atrophy in frontal regions,[63] while those with cerebellar dysfunction have a reduced cerebellar GM volume compared with those without.[64] In patients with MS with long-standing disease or severe disability, focal thinning of the primary sensorimotor cortex has been reported.[65] More recently, Riccitelli et al[66] showed that the pattern of regional cortical and subcortical GM atrophy differs among cognitively impaired patients according to their clinical phenotype (**Figure 4**).

Voxelwise analysis of MT and diffusion tensor MRI data can also be used to assess the distribution of diffuse cortical damage. Khaleeli et al[67] showed, in patients with primary progressive MS, a significant correlation between a decrease of the MT ratio of cortical motor areas and an increased Expanded Disability Status Scale score, as well as between the MT ratio in the right inferior parietal cortex and performance of the Paced Auditory Serial Addition Task. Similarly, using a voxel-based analysis of diffusion tensor MRI maps, Ceccarelli et al[68] showed diffusivity abnormalities in cortical areas associated with motor and cognitive functions in primary progressive MS.

The quantification of diffuse GM damage provides robust prognostic measures of disease progression. In patients with relapsing-onset MS, GM MT ratio was found to be an independent predictor of the accumulation of disability over the subsequent 8 years,[69] while in primary progressive MS, GM mean diffusivity predicted the accumulation of disability over a 5-year period.[46]

CORTICAL REORGANIZATION

Using functional MRI, modifications of brain activation have been demonstrated consistently in all MS phenotypes, with different experimental paradigms. Functional MRI abnormalities in patients with MS occur relatively early in the disease, even in patients with clinically isolated syndrome and pediatric MS,[70] and tend to vary over the course of the disease, not only after an acute relapse but also in clinically stable patients.[71]

The correlations found between functional and structural MRI abnormalities in patients with MS have suggested that increased recruitment of "critical" cortical networks may help to limit the functional impact of MS-related damage. However, increased cortical recruitment cannot continue indefinitely and a lack or exhaustion of the "classic" adaptive mechanisms has been sug-

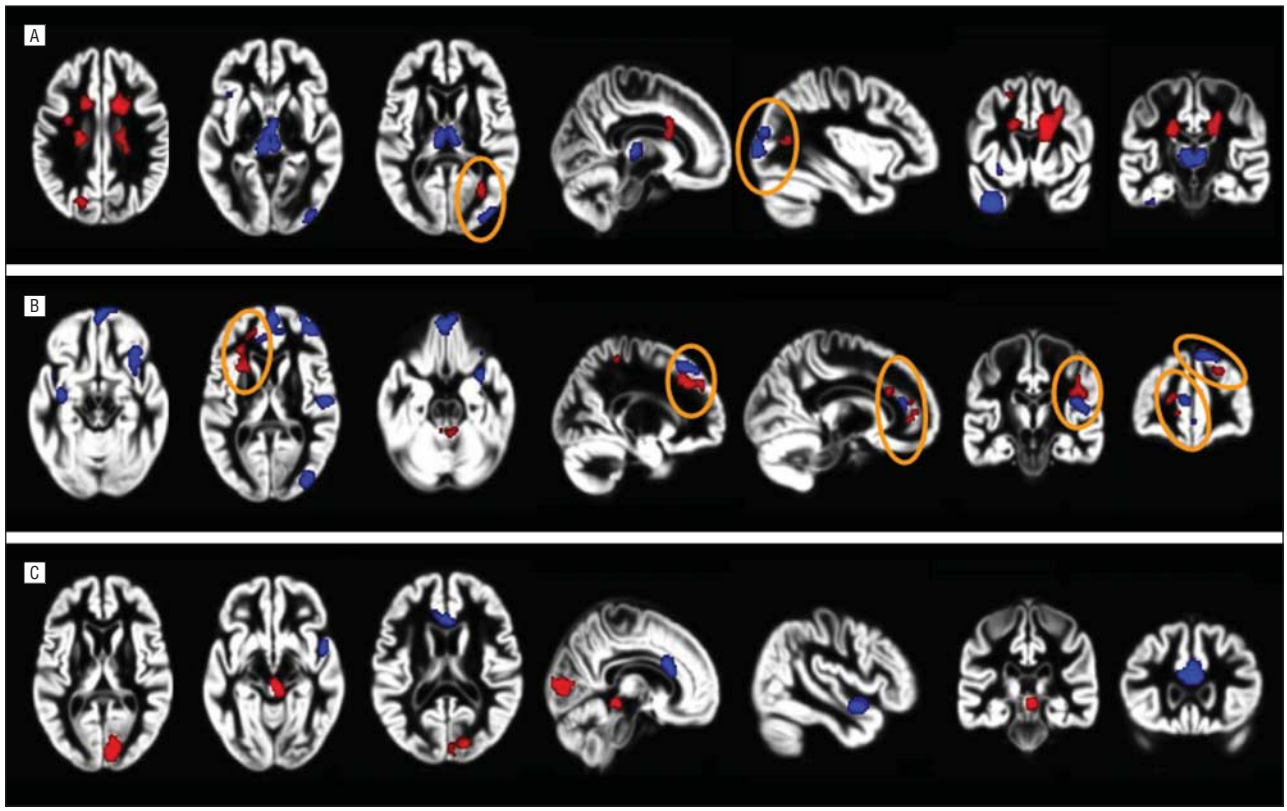

Figure 4. Distribution of regions of significant cortical and subcortical atrophy ($P < .05$, familywise error corrected) (blue) and T2 visible lesions (red) in patients with multiple sclerosis (MS) with cognitive impairment vs cognitive preservation according to the clinical phenotype. A, Relapsing remitting MS. B, Secondary progressive MS. C, Primary progressive MS. Orange circles identify regions with a correspondence between the presence of T2 visible lesions and cortical atrophy. The comparison between patients with cognitive impairment vs cognitive preservation in the 3 clinical phenotypes, analyzed separately, shows several areas with significant tissue loss in the former groups. Differences between patients with cognitive impairment vs cognitive preservation are more prominent when considering patients with secondary progressive MS. The analysis of regional distribution of T2 visible lesions shows that while in patients with relapsing-remitting MS and secondary progressive MS there is a correspondence between location of focal white matter lesions and cortical atrophy, in primary progressive MS such an association is not found. Images are oriented in neurological convention. From Riccitelli et al[66] with permission.

gested as a possible factor responsible for an unfavorable clinical evolution (as in patients with the progressive forms of the disease),[72] accelerated cognitive decline[73,74] (**Figure 5**), and development of specific disease-related symptoms, such as fatigue.[75]

Several studies have attempted to develop sophisticated statistical approaches to establish the strength of activations and the synchrony between specific cortical areas through the analysis of functional and effective connectivities.[76] The optimization of these methods might help to explain abnormalities of function of specific brain networks and their relationship to clinical symptoms. The combination of measures of functional connectivity with measures of structural damage to specific WM fiber tracts is also likely to improve our understanding of the relationship between structural and functional abnormalities, as suggested by 2 studies in patients with relapsing-remitting MS[76] and benign MS.[77] More recently, the analysis of brain function at rest has shown a reduced activity of the anterior regions of the default-mode network in patients with progressive MS, which correlates with cognitive impairment.[78]

CONCLUSIONS

Developments in methods of acquisition and analysis have undoubtedly allowed in vivo assessment of at least some aspects of cortical pathology in patients with MS. This has resulted in a better understanding of the heterogeneity of the clinical manifestations of the disease. Several factors are likely to contribute to cortical damage in patients with MS, including focal macroscopic lesions, diffuse changes beyond the resolution of current MR scanners, and irreversible tissue loss. All of these abnormalities become more severe over time and are only partially associated with the location and extent of WM pathology. The cortex has great potential to aid recovery by synaptic reorganization following injury, thus helping to counteract the progressive accumulation of structural damage due to disease. However, the ability to reorganize is likely limited, and its exhaustion might be an additional factor in the clinical manifestation of disease progression.

One challenge that still remains is to gain a better understanding of the dynamics of damage progression within the cortex and the WM, and the relationship between them. The use of ultra-high-field MRI scanners should aid the visualization of CLs, and quantitative MR assessment of cortical damage may improve our understanding of MS pathobiology, resulting in the identification of additional markers of disease evolution. Accurate evaluation of cortical damage might not only be important per se but also because of the impact that this damage can exert on the capacity of

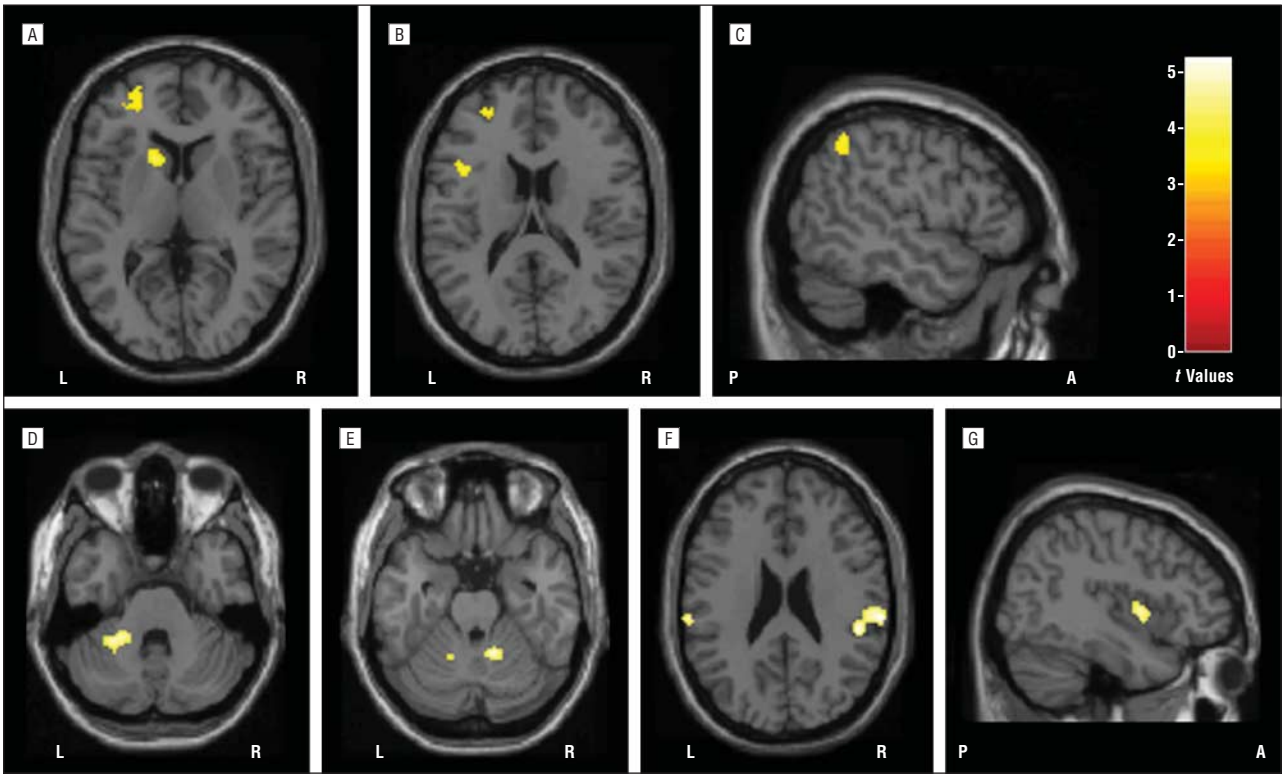

Figure 5. Areas showing increased activation in patients with primary progressive multiple sclerosis with cognitive preservation in comparison with those with cognitive impairment (A-C) and vice versa (D-G) during the analysis of the 2-back task (random effect analysis, analysis of variance, $P<.05$, corrected for multiple comparisons). Compared with patients with cognitive impairment, patients with cognitive preservation have more significant activations of the head of the left caudate nucleus, left prefrontal cortex, and left inferior parietal lobule. Conversely, compared with patients with cognitive preservation, those with cognitive impairment have more significant activations of the bilateral secondary sensorimotor cortex, bilateral cerebellum, and right insula. The color-encoded activations have been superimposed on a rendered brain and normalized into the standard Montreal Neurological Institute space (neurological convention). From Rocca et al[74] with permission.

the cortex to readapt functionally after MS-related tissue injury.

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Correspondence: Massimo Filippi, MD, Neuroimaging Research Unit, Department of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, via Olgettina, 60, 20132 Milan, Italy (filippi.massimo@hsr.it).
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