

Speciality area: Multiple Sclerosis

Gray Matter Damage and Dysfunction in MS

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Highlights

- Patients with multiple sclerosis (MS) experience focal and diffuse damage to the gray matter (GM).
- Advances in imaging technology have contributed to improve significantly our ability to quantify GM damage and dysfunction in MS patients.
- The extent and regional distribution of GM damage differ between the main MS disease phenotypes and correlate with clinical disability and cognitive impairment.
- GM damage can influence the capacity of the cortex to readapt functionally after MS-related tissue injury.

The notion that multiple sclerosis (MS) is a white matter (WM) disease of the central nervous system (CNS) has been challenged by several pathological and magnetic resonance imaging (MRI) studies that have consistently revealed both focal and diffuse damage to the gray matter (GM) of MS patients.¹

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 GM of MS patients is also affected by demyelination.² In the cortex, three types of cortical lesions (CLs) are commonly distinguished: type I refers to leukocortical lesions involving cortex and adjacent subcortical WM; type II refers to purely intracortical lesions; and type III labels subpial demyelination.³ Type III lesions are most common in the neocortex of patients with chronic MS, in particular the cingulate gyri and temporal cortex seem to be the most frequently affected structures.⁴ However, it has been shown that the degree of cerebellar cortical demyelination, where plaques often involve multiple adjacent folia, may even exceed that in the neocortex.⁵ Demyelination of the hippocampus,⁶ deep GM (especially the thalamus and caudate nuclei),⁷ and GM of the spinal cord is also frequently found in MS patients.

Although imaging of the cortex is technically challenging, due to its morphology, and the nature of pathology occurring in this structure, the development of specialized MRI sequences that can suppress the signal from WM and cerebrospinal fluid (CSF) simultaneously, named “double inversion recovery” (DIR), has enabled substantial improvements in CLs detection.⁸ Using DIR, MRI studies revealed that CLs develop early in MS and increase in number and size with

progression of the disease.⁹ On the other hand, they are rare in benign forms of the disease¹⁰ and in children with MS.¹¹ CLs explain a large proportion of variance in locomotor disability and cognitive impairment,¹² and their presence is associated with other MRI indicators of damage such as T₂ lesion load and WM and GM atrophy.¹³ Recently, it has been demonstrated that the accuracy of MRI diagnostic criteria for MS increases when considering CLs on baseline scans in patients who present with a clinically isolated syndrome (CIS) suggestive of MS.¹⁴

Global cortical thinning of around 10% has been found in MS patients compared to controls.¹⁵ This finding is only partially explained by focal neuronal or glial loss in CLs, suggesting that diffuse cortical pathology is present outside such lesions.

The application of modern MR techniques can contribute to the assessment of different aspects of GM damage, including the presence of diffuse disease-related abnormalities (measured using quantitative techniques such as magnetization transfer [MT] and diffusion tensor [DT] MRI), metabolic abnormalities (measured by means of proton MR spectroscopy [¹H-MRS]), irreversible tissue loss (atrophy) and iron deposition (quantified using T₂/T₂^{*}-weighted and susceptibility-weighted imaging), thought to reflect neurodegeneration.

Several studies have demonstrated reduced MT ratio (MTR) and increased mean diffusivity (MD) in the GM of patients with different MS phenotypes including those at the earliest clinical stages of the disease. These abnormalities are more severe in patients with the progressive disease phenotypes. Similar findings have been shown when measuring cortical atrophy.¹

Using ¹H-MRS, metabolite abnormalities, including reduced concentrations of N-acetylaspartate and choline and an increased concentration of myo-inositol, have been found in the cortex¹⁶ and subcortical GM tissue¹⁷ from MS patients.

Diffuse cortical damage is not stable, but tends to worsen over time, independent of the progression of damage to the WM.¹⁸ The clinical relevance of measures of such a damage has been demonstrated by several studies which have shown correlations with clinical disability and cognitive impairment.¹ A longitudinal study has found an increased rate of cortical tissue loss in patients with progressing disability compared to those with stable disease,¹⁹ whereas another study demonstrated that progressive neocortical loss is relevant to MS-associated cognitive impairment.²⁰ In addition, a recent long-term study demonstrated that GM damage is one of the key factors associated with accumulation of disability and cognitive impairment in MS patients after 13 years of follow up.²¹

Analysis of the spatial distribution of GM 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

MS patients. However, the patterns of GM loss differ between the main MS clinical phenotypes.²² The evaluation of the regional patterns of GM involvement has allowed to improve the correlation with disease clinical manifestations. Reduced GM volume of regions associated with working memory and executive functions is correlated with cognitive task performance, temporal lobe atrophy to auditory/verbal memory and visual/spatial memory performance, and hippocampal atrophy with a poor performance in memory encoding task.¹ Fatigued MS patients experience cortical atrophy in frontal regions,²³ and those with cerebellar dysfunction have a reduced cerebellar GM volume compared to those without.²⁴

The quantification of diffuse GM damage provides robust prognostic measures of disease progression. In patients with relapsing-onset MS (RRMS), GM MTR was found to be an independent predictor of the accumulation of disability over the subsequent 13 years²¹, while in primary progressive MS, GM MD predicted the accumulation of disability over a five-year period.¹⁸ Dual-echo spin echo MRI can detect spinal cord abnormalities in MS patients with a high sensitivity. Although significant reduction of cervical cord size can also be observed in the early phase of MS, cord atrophy is more severe in the progressive forms of the disease. Changes in cord cross-sectional area, both at a given time point and over time, correlate better with clinical disability than changes of T2 lesion burden. The development of phased-array receiver coils and fast imaging techniques has led to a more reliable imaging of the cord and has improved quantification. Advances in MRI analysis methods have also enabled quantification of cervical cord injury at a subregional level, either through quantification of damage to GM and WM separately,²⁵ or through use of voxel-based methods to define the precise topographical distribution of tissue damage in different cervical cord levels and compartments.

The use of functional MRI (fMRI) has improved our understanding of CNS reorganization in response to tissue injury at different stages of the disease. Indeed, modifications of the patterns of brain and cervical cord activations have been demonstrated consistently in all MS phenotypes, with different experimental paradigms. The cortex has a great potential to aid recovery through synaptic reorganization following injury, thus helping to counteract the progressive accumulation of structural damage due to disease. However, the ability to reorganize cortical functions is likely limited, and its exhaustion might be an additional factor responsible for disease progression, accelerated cognitive decline and development of specific disease-related symptoms, such as fatigue.^{1,26}

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.²⁷ The combination of measures of functional connectivity

(FC) 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. More recently, the analysis of brain function at rest has shown a distributed pattern of abnormalities within and between resting state networks in patients with different MS clinical phenotypes, which correlate with disability and the severity of cognitive impairment.^{28,29}

In conclusion, several factors are likely to contribute to GM damage in MS patients, including focal macroscopic lesions, diffuse changes beyond the resolution of current MR scanners, and irreversible tissue loss. One challenge which is still in front of us is to achieve a better understanding of the dynamics of damage progression in the GM 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 and spinal damage may improve our understanding of MS pathobiology, resulting in the identification of additional markers of disease evolution. Accurate evaluation of GM damage might not only be important *per se*, but also because of the impact that it can exert on the capacity of the cortex to readapt functionally after MS-related tissue injury.

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