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We read with great interest the article by Filippi and Rocca entitled "MR Imaging of Gray Matter Involvement in Multiple Sclerosis: Implications for Understanding Disease Pathophysiology and Monitoring Treatment Efficacy."[1] The authors reported on how advances in MR imaging technology and methods of analysis are contributing to the detection of focal lesions and occult pathology and atrophy in multiple sclerosis (MS). They concluded that the application of quantitative MR imaging–based techniques has shown consistently that gray matter (GM) is not spared by MS and that GM damage is present in all MS phenotypes since the earliest clinical stages of the disease, affects various GM compartments, and is associated with the main clinical manifestations of MS. They discussed several aspects of GM pathology, including focal macroscopic lesions, intrinsic diffuse changes, and irreversible tissue loss.

To date, relatively little is known about the spatiotemporal relationship of regional white matter (WM) and GM changes. A recent cross-sectional study using MR imaging–based lesion probability maps (LPMs) showed that retrograde damage of the perikarya from axonal injury within MS plaques might be crucial to the genesis of GM atrophy.[2] In this study, an association of focal WM damage in the optic radiations with upstream GM atrophy of the lateral geniculate nucleus and visual cortex in the calcarine sulcus of the occipital lobe was found. To develop a better understanding of the longitudinal spatiotemporal relations between regional GM and WM changes in patients with MS, our group studied the associations of regional WM lesion changes and regional GM volume reductions in patient groups with either "progressive" or "nonprogressive" WM lesion load. Voxel-wise regional brain volume changes were assessed by using voxel-based morphometry (VBM), a structural image analysis method that avoids an a priori knowledge about the relationship among these anatomic structures and queries the entire brain.[3] We also used LPMs, obtained from T2-weighted or T1-weighted structural MR imaging of a large sample of patients with MS and applied "optimized" VBM to compare WM and GM changes.[4]

By using LPMs, we demonstrated a more widespread regional distribution pattern of WM lesions in the progressive group compared with the nonprogressive group of patients with relapsing-remitting MS.[4] This might be a central issue predicting further lesion development as well as development of GM atrophy in patients with MS. Furthermore, the longitudinal VBM analysis revealed spatial T2 lesion changes in parts of the cerebral projection, commissural, and association fiber systems only in the progressive group. These changes were accompanied by GM volume reductions in specific cortical regions predilected for atrophy. Multiple disconnections between different areas of cortical networks could relate to widespread cortical atrophy and cognitive impairment, commonly observed in MS. A small number of nonprogressive lesions located in WM tracts (ie, of the associative cortex) might have interrupted relatively few connections with little or no effect on regional GM volumes in the nonprogressive group. A larger number of progressive lesions, however, accompanied by a widespread spatial distribution, could have interrupted a higher number of associative connections, thereby contributing to the progression of GM atrophy in the progressive group. Further large-scale studies using VBM or other measures for estimation of regional brain volumes may help to disentangle the spatiotemporal relations between regional GM and WM pathology and could impact current views on MS pathogenesis.

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