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Central Nervous System Disorders?**

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Regional Assessment of Brain Atrophy: A Novel Approach to Achieve a More Complete Picture of Tissue Damage Associated with Central Nervous System Disorders?

The progressive development of brain atrophy is a well-known feature of many central nervous system (CNS) disorders and can be measured in vivo accurately and reliably using MR imaging. Therefore, during the last decade or so, a number of MR imaging-based methods and postprocessing analysis tools have been developed for quantifying global and regional brain tissue loss associated with neurologic conditions. In general, there has been a move from seminal methods based on subjective visual ratings, which were time-consuming, labor-intensive, and poorly reproducible, to the use of sophisticated computerized tools that have made brain atrophy measurements reproducible and potentially applicable to routine clinical activity. The massive body of work performed in this field has convincingly shown that there is a strict correlation between the extent of overall brain tissue loss with the clinical manifestations, in terms of both neuropsychologic impairment and locomotor disability, detected in patients affected by various neurologic diseases. This has been shown to be the case not only in neurodegenerative diseases, such as Alzheimer disease (AD),¹ but also in inflammatory-demyelinating disorders, such as multiple sclerosis (MS).² However, given the fact that neurologic disorders may affect the brain unevenly, and given the availability of novel technical approaches, a large amount of research work has been devoted to achieve a more complete picture of the extent of brain tissue loss on a regional basis, with the ultimate goal of developing more sensitive neuroimaging markers of disease-related pathology.

The initial strategy to define the topography of brain tissue loss with MR imaging in neurologic patients was based on region-of-interest analysis, which, however, is extremely time-consuming and poorly reproducible, especially when a cross-sectional assessment is performed. Recently, these limitations have been overcome, at least partially, by the development and application of fully automated techniques, such as “voxel-based morphometry” (VBM).³ VBM involves a comparison, on a voxel-by-voxel basis, of the regional “attenuation” of gray matter (GM) and white matter of the brain among groups of subjects. VBM is relatively insensitive to large-scale volumetric differences in gross anatomy and is based on a spatial normalization of high-resolution images from all study subjects into the same stereotactic space, which removes spatial and volume differences among individual subjects. Furthermore and most importantly, VBM does not require any a priori hypothesis on the localization of group differences, and this has led to a series of “unexpected” findings that might prove to be central in the reshaping of our understanding of the pathobiology of CNS damage with potentially important implications for the development of novel treatment strategies. For

instance, the use of VBM in the assessment of topographic patterns of irreversible brain tissue loss in patients with AD has shown that areas of decreased GM attenuation extend well beyond the classic targets of this disease (ie, the hippocampus and the entorhinal cortex) and involves several regions of the frontal and parietal lobes.⁴ Similar patterns of regional brain atrophy changes, albeit at a lower magnitude, were also found in patients with mild cognitive impairment and were shown to have the potential to contribute to the identification of those patients with an increased risk to convert to AD in a short time frame.⁵

Against this background, the study by Mezzapesa et al⁶ published in the present issue of *AJNR* represents an additional piece of evidence that, though human neurodegenerative conditions show a marked regional “preference,” they tend to involve the brain more globally than previously thought. Indeed, Mezzapesa et al⁶ show elegantly that in nondemented patients with amyotrophic lateral sclerosis (ALS), mild volume loss over the whole brain can be detected as well as a pattern of regional atrophy that involves several areas in the frontal and temporal lobes, outside the classic motor network. Therefore, this study strengthens the notion that ALS is a multisystem disorder of the CNS, which is more pronounced in the motor/premotor cortices and along the corticospinal tracts, but not limited to them. Because reduced GM densities of areas located in the frontal and temporal lobes seem to be more severe in cognitively impaired ALS patients,⁷ the study by Mezzapesa et al⁶ raises the intriguing question of whether subtle GM changes in these regions, which can be disclosed by VBM, might have a prognostic value in the identification of patients at high risk to develop frontotemporal dementia.⁷ Longitudinal VBM studies of ALS patients are now warranted to respond to this clinically important question.

Another intriguing aspect of the study by Mezzapesa et al⁶ is that they did not find selective tissue loss in the primary motor cortex of their patients. Previous MR imaging studies did not reach firm conclusions regarding the presence of motor and premotor cortex atrophy in ALS, and 2 possible factors are readily apparent to explain such a discrepancy. First, the intrinsic heterogeneity of the pathologic process should be considered.⁸ Second, the different clinical characteristics of the cohorts of patients studied may be responsible for the conflicting results. Because Mezzapesa et al⁶ studied patients with a moderately disabling ALS and a reduced GM attenuation was found in ALS patients with more severe disability,⁷ a tempting speculation is to suggest that reactive gliosis might have occurred in the sample of Mezzapesa et al⁶ at a degree enough to “mask” tissue loss in this cortical region. The progressive loss of tissue might then counterbalance the “pseudonormalizing” effect of gliosis in the extremely disabled cases.⁷ This again calls for longitudinal MR imaging studies of ALS patients with a multiparametric MR approach (eg, VBM analysis might be applied not only to define patterns of reduced GM attenuation but also to map diffusivity changes in the remaining tissue) to gain additional insights into the nature of the GM damage associated to this condition as well as on the timing of the different CNS structure involvement and its impact on the disease-related neurologic manifestations.

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