Reply:

The recent development of advanced automated 3D MR imaging analysis provides new tools aimed at defining the entity and topography of brain tissue loss in neurodegenerative diseases. The application of voxel-based analysis in amyotrophic lateral sclerosis (ALS) has recently produced several reports of evidence of a brain involvement beyond the motor areas.[1-5] Moreover, discordant results emerge from the comparison of these studies. In particular, the pattern and extent of volume loss in frontal and temporal areas vary widely among studies. Also 2 studies did not show atrophy in the primary motor cortex.[1,5]

The main explanation of these discrepancies could derive from the combination of 2 factors: the heterogeneity of ALS-related brain pathology and the high sensitivity of the voxel-based analysis (in particular voxel-based morphometry [VBM]). The presence of regional atrophy in the frontal and temporal lobes supports the current opinion of a continuum between ALS and frontotemporal dementia. Each single subject could belong to a wide range of combinations of pathology inside this continuum. Unfortunately VBM is not able to depict tissue loss in individual brains but only recognizes differences among groups of subjects. Despite the effort to select homogeneous subjects in the study groups, particularly considering the neuropsychological profile, the relatively rapid course of ALS could prevent the appearance of extramotor symptoms and mask an understanding subclinical heterogeneity.

On the other hand, VBM seems extremely sensitive and could depict a small amount of intergroup difference in terms of regional volume loss, especially in gray matter, even in the presence of very low global brain atrophy. Indeed, only brain parenchymal fraction (BPF) was able to discover global brain atrophy in ALS, as detected in 2 studies.[4,5] Therefore, we agree with the opinion that among whole-brain measures, BPF is the most sensitive as a biologic marker in neurodegenerative diseases. Again, the high sensitivity of automated 3D MR imaging analysis calls for a selection of homogeneous patient groups to provide compelling results.

Another aspect that must be kept in mind when volumetric analyses are performed is that brain pathology in neurodegenerative diseases is not reducible exclusively to volume loss. For example, reactive gliosis may occur to mask tissue loss, particularly in the primary motor cortex, as speculated by Filippi et al.[6]

For all these reasons, further longitudinal studies are required with a multiparametric MR imaging approach, adding MR spectroscopy and diffusion tensor imaging, to investigate both tissue volume and tissue attenuation.[6] In addition, an intriguing finding, which was not investigated enough, is the hemispheric asymmetry of atrophy in ALS subjects, with a right lateralization reported by 2 studies.[4,5]

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