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What Causes Deep Gray Matter Atrophy in Multiple Sclerosis?

Multiple sclerosis is a chronic neuroinflammatory and neurodegenerative disease of the central nervous system. Patients often experience a complex combination of physical and cognitive symptoms, both of which are strongly disabling. Unfortunately, progression of disability and cognitive decline has been difficult to understand using neuroinflammatory markers such as lesion volumes. Neurodegenerative components of MS and especially deep gray matter (DGM) atrophy continue to progress with time[1] and have a strong predictive potential for disability[2] and cognitive impairment.[3] Thalamic atrophy occurs very early[4] and continues linearly during the disease course,[5] with especially strong clinical correlations.[6] Therefore, it is clear that deep gray matter and especially thalamic atrophy is of great relevance for MS, and its measurement may even become reliable enough to include in routine neuroradiologic practice. What drives this typical neurodegenerative pattern in MS, however, remains unclear, probably including a combination of network disconnection,[7] Wallerian degeneration, and local damage.[8]

The study by Pontillo et al,[9] published in the current issue of the *American Journal of Neuroradiology*, represents a comprehensive way to investigate the possible correlates of deep gray matter atrophy. The authors apply several MR imaging measures of diffusion, perfusion, and susceptibility in the DGM in relapsing-remitting MS (RRMS, $n = 52$) and progressive MS ($n = 25$), which were compared with those in healthy controls ($n = 44$). Results show that white matter lesion burden was the main correlate of DGM atrophy in RRMS, possibly indicating a role for Wallerian degeneration of connected fiber bundles, resulting in structural network disconnection and atrophy. In progressive MS, however, the most important correlates of atrophy were local microstructural damage and thalamic susceptibility, while lesion volumes did not strongly relate to atrophy.

These results highlight an important point, namely that the cause and consequence of atrophy could vary among the different MS phenotypes and that these should be studied separately.[10] This point is supported by recent findings that while some therapeutic options that target neuroinflammation in the white matter may impact thalamic atrophy in RRMS,[11] these do not impact disease progression in progressive MS.[12] Nonetheless, recent studies have shown that thalamic atrophy rates are similar in all phenotypes,[5] indicating that neurodegeneration continues in progressive MS even when the formation of new neuroinflammatory lesions may become less apparent. These findings could reflect an entirely different local pathologic process or may indicate a second-order disconnection effect[10] induced by an accelerated cortical degeneration of important networks such as the default mode network,[2] causing additional waves of disconnection leading to a so-called network collapse.[13]

This notion of network disconnection was also supported by a recent study using experimental autoimmune encephalomyelitis, showing inflammation and demyelination in the spinothalamic tracts to be related to thalamic neuronal loss, while lesions within the thalamus itself were scarce.[14] In MS, focal lesions within DGM structures also do not seem to be that common and appear to be poorly related to DGM atrophy.[15] In fact, neuronal loss in nondemyelinated DGM tissue can be as severe as 35%.[16] Other work[17] has also indicated that the DGM has a less severe neuroinflammatory profile than the white matter. However, diffuse microglial activation within the thalamus has also been noted using PET research, especially in progressive MS,[18] which was also related to cortical thinning and clinical dysfunction,[19] again indicating a network effect. It remains unclear, however, whether microglial activation is a cause of neurodegeneration or a consequence of it, or both. Susceptibility-weighted imaging as used in the present study by Pontillo et al[9] has also been indicated to reflect both microglial activation (ie, through changes in iron levels) and myelin content, further complicating matters.[20]

As Pontillo et al[9] note, future longitudinal multimodal studies are now required to disentangle the causal chain of events for these different local and network-based pathologic processes. It seems apparent, however, that the cause and consequence of DGM atrophy will remain a complex combination of primary and second-order effects. Thus, future treatment strategies aiming to impact DGM atrophy may need to impact the disease early, to prevent the network collapse from happening altogether.

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