Mapping Deep Gray Matter Iron in Multiple Sclerosis by Using Quantitative Magnetic Susceptibility

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See also the article by Zivadinov et al in this issue.

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At the onset of multiple sclerosis, the focus is on early diagnosis and treatment. MRI is a cornerstone of the diagnosis by depicting focal demyelinating lesions in the central nervous system to demonstrate dissemination of lesions in space and time (1). Patients presenting with a clinically isolated syndrome may fulfill diagnostic criteria for multiple sclerosis based on the finding of inflammatory demyelinating lesions on MR images and be treated as early as possible. Multiple sclerosis is considered an autoimmune disease; more than 10 drugs are currently registered for the treatment of multiple sclerosis, typically targeting the immune system. MRI is widely used to monitor the efficacy (and safety) of these drugs, with the goal of preventing development of new focal lesions (2,3). Despite an expanding armamentarium of immunomodulatory drugs available for first- and second-line treatment that effectively suppress clinical relapses and development of new focal MRI lesions, patients may still develop progressive disability.

The mechanisms of progression of disability in multiple sclerosis are incompletely understood. Potential mechanisms include low-grade inflammation, small new lesions that remain undetected at MRI (eg, in the cortex), or independent mechanisms leading to neuronal damage. Simple neurodegenerative measures such as whole brain atrophy or spinal cord atrophy independently contribute to disability progression. Of special interest is damage in the gray matter, which may occur as a direct result of gray matter lesions or secondary to damage in axons. The latter mechanism is undoubtedly relevant for deep gray matter structures such as the thalamus and basal ganglia that are heavily interconnected. Possible MRI measures to determine damage to these deep gray matter regions include simple volume measurements and also quantitative MRI techniques that probe their structural integrity and measures of iron accumulation. A novel approach is the use of quantitative susceptibility mapping. Quantitative susceptibility mapping measures susceptibility changes related to paramagnetic and diamagnetic moieties in brain. For the basal ganglia, iron accumulation seems to be the main determinant for quantitative susceptibility mapping alterations. Iron accumulation is important as a measure of neurodegeneration in multiple sclerosis, as well as in other disorders (4).

In this issue of *Radiology* (5), Zivadinov et al investigate the use of quantitative susceptibility mapping as a biomarker for iron accumulation in deep gray matter structures of patients with multiple sclerosis. By using three-dimensional susceptibility-weighted imaging, advanced processing methods were applied to the phase images to generate quantitative maps of tissue susceptibility. A large convenience cohort of 600 participants with multiple sclerosis with relatively long disease duration was compared with 250 healthy control participants by using region of interest and voxelwise comparison methods. Groupwise differences were observed in the thalamus (participants with multiple sclerosis had lower susceptibility values relative to control participants) and the basal ganglia (where susceptibility was higher in the participants with multiple sclerosis) regions. Lower thalamic susceptibility was associated with longer disease duration, higher disability degree, and secondary progressive course; higher susceptibility in the globus pallidus was associated with higher disability. The authors' quantitative susceptibility mapping findings confirm in a large sample that abnormal deep gray matter iron content impacts disease evolution of multiple sclerosis and disability accrual.

Quantitative susceptibility mapping has two principal advantages over susceptibility-weighted imaging as a biomarker of disease: quantitative susceptibility mapping provides quantitative values of a physical parameter, and provides spatial localization of the source of tissue changes.

The methods for quantitative susceptibility mapping processing and quantification are still an active area of research (6). However, the current study uses state-of-the-art data processing approaches that are able to provide precise and robust measurements of tissue susceptibility. The quality of quantitative susceptibility mapping depends on the various steps applied during its reconstruction, including combination of the raw data acquired with multichannel array coils to ensure accurate phase information, phase unwrapping, background field removal, and inversion of the field maps to susceptibility maps. Suboptimal performance of any of these stages can result in severe artifacts in the resulting quantitative susceptibility mapping images, obscuring their interpretability; translation of the current implementation into clinical practice will need to address this. By using offline reconstruction tools (5), this study shows clear regional differences in susceptibility values of participants with multiple

sclerosis relative to control participants, and demonstrates an association between clinical disability and susceptibility in (subnuclei of) the thalamus and globus pallidus. These results highlight the potential of quantitative susceptibility mapping as a biomarker of neurodegenerative disease.

Future developments in methodology of quantitative susceptibility mapping may improve its usefulness further. Imaging at 7.0 T increases the contrast-to-noise ratio and sensitivity of the phase measurements (7). The improved results at 7.0 T can be used to increase spatial resolution or to achieve higher measurement precision. Multiecho acquisition protocols, which acquire several image volumes over a range of echo times, will enable more accurate field estimation through linear or nonlinear fitting. Last, advances in postprocessing methods of quantitative susceptibility mapping will further reduce the level of image artifacts, enabling more accurate measurements on a per-patient level. For clinical use, it will be important for postprocessing of quantitative susceptibility mapping to be fully automated and integrated into clinical workflow. Currently, the reconstruction time for quantitative susceptibility mapping takes too long to be feasibly performed in real time with the imager, and therefore alternative processing software will need to be established.

A fundamental question is the relevance of iron deposition in multiple sclerosis and whether it outperforms other MRI measures of neurodegeneration. Iron is an important element in metabolic pathways that has both beneficial as well as detrimental effects in the central nervous system. Although too much iron is undesirable, iron is also involved in repair mechanisms (8). In addition, iron accumulation in deep gray matter is not specific for multiple sclerosis. Iron deposition also occurs in many other diseases, including Parkinson disease, Alzheimer disease, and other neurodegenerative disorders (9). In fact, it seems that iron accumulation in the lentiform nucleus plateaus early in multiple sclerosis, which may explain its weak clinical relevance. More work is needed to understand the value of quantitative susceptibility mapping for determining patient prognosis and monitoring treatment in multiple sclerosis. In particular, iron accumulation in the thalamus seems to have clinical relevance beyond simple measures of atrophy (5).

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