Research Highlights

Highlights from the latest articles in imaging

Treatment of multiple sclerosis (MS) has benefited from the development of MRI methods that improve our understanding of the pathophysiology of the disease. Here we offer examples of recent applications of functional and structural MRI methods to study damage to gray and white matter, as well as potential protective and reparative mechanisms in MS.

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Detecting cortical pathology in MS using high-field MRI

Evaluation of: Schmierer K, Parkes HG, So P-W *et al.*: High field (9.4 Tesla) magnetic resonance imaging of cortical grey matter lesions in multiple sclerosis. *Brain* 133, 858–867 (2010).

Previous studies have identified axonal damage and neuronal loss in the cortical gray matter of MS patients. Until recently, cortical gray matter pathology could only be seen histologically; however, with higher-field MRI, it may be possible to reliably visualize and characterize cortical lesions.

This study compared cortical lesion detection in 21 postmortem MS brains using a 9.4 T MRI scanner and histological sections. The aim was to identify MRI methods that were both sensitive and specific to the detection of cortical lesion pathology.

Regions containing cortical gray matter lesions were dissected and scanned to obtain T_1, T_2 and magnetization-transfer ratio maps, as well as T_2-weighted images. Histological staining was performed on these regions and sections were visually matched to the corresponding slice in the T_2-weighted MRI scan.

Out of the 36 cortical lesions identified on histological sections, 28 were subsequently identified on T_2-weighted MRI. As seven of the eight missed cortical lesions were missed owing to inadequate coverage of the MR coil and the visible lesions had excellent morphological correspondence to histological sections, the authors concluded that MRI scans at 9.4 T field strength improved the detection of histologically defined cortical gray matter lesions.

Significant correlations were found between the neuronal density and T_1, and the intensity of myelin basic protein (iMBP) and T_2, as well as between the intensity of phosphorylated neurofilament staining and iMBP. Previous research has demonstrated T_1 to be related to macromolecule concentration (which will decrease with neuronal loss). The difference in T_2 can be detected more easily at the border of lesioned and nonlesioned cortical tissue, probably owing to the demyelination of the lesion (which is then reflected in a decreased iMBP). The strength of these correlations indicate that T_1 and T_2 maps collected with high-field MRI have potential use as markers of neuronal density and myelin content, respectively.

Evolution of myelin pathology in MS lesions

Evaluation of: Levesque IR, Giacomini PS, Narayanan S *et al.*: Quantitative magnetization transfer and myelin water imaging of the evolution of acute multiple sclerosis lesions. *Magn. Reson. Med.* 63, 633–640 (2010).

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Although MRI is commonly used to detect white matter lesions in MS, methods to examine the process of demyelination and remyelination are still needed. Two methods may improve specificity in the examination of myelin pathology compared with other MRI sequences:

- Quantitative magnetization transfer imaging (QMTI) uses variation in the T_2 signal to divide tissue into free (liquid) and restricted (semisolid) components;
- Myelin water imaging (MWI) uses multicomponent T_2 relaxation to obtain T_2 distributions of each voxel and calculate the fraction of the T_2 distribution below 40–50 ms. This fraction reflects the amount of water trapped between layers of myelin and is called myelin water fraction (MWF).

This study compared the sensitivity of these techniques in evaluating the evolution of acute gadolinium-enhancing MS lesions over 1 year.

Five women with relapsing remitting MS and with a gadolinium-enhancing lesion on postcontrast T_1-weighted MRI were studied. For each patient, MRI scans were performed at baseline and at 1–5, 8 and 11 months. Five healthy controls were also scanned at least four separate times. Quantitative data, including QMTI and MWI measures, were collected in one oblique slice that intersected with the lesion. Analysis of QMTI and MWI measures was performed at all timepoints within the lesion area and in contralateral homologous normal-appearing white matter (NAWM) regions.

In the NAWM of MS patients, both QMTI and MWI parameters were abnormal compared with controls, indicating diffuse disease. The QMTI parameters were also abnormal in acute lesions compared with controls, with all of the parameters moving towards control levels after resolution of the enhancement. The authors propose that these findings are reflective of acute demyelination, inflammation and edema, followed by a period of remyelination over 2–3 months.

Using MWI, the mean of the T_2 distribution within enhancing lesions was initially higher than NAWM or control white matter and it decreased in subsequent scans, which the authors propose is an indication of resolution of inflammation. However, there was no difference in the MWF between lesions and NAWM. The authors speculate this was caused by the large variability in the MWF and underpowering of the study owing to a small sample size.

Results from both myelin imaging techniques suggest that there is a resolution of inflammation in the first month after enhancement, with a slower remyelination continuing for 2–3 months. However, the high variability in the MWF resulted in reduced sensitivity to detect these changes.

Imaging cognitive reserve in MS

Evaluation of: Sumowski JF, Wylie GR, DeLuca J, Chiaravalloti N: Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: functional magnetic resonance imaging evidence for cognitive reserve. *Brain* 133, 362–374 (2010).

Previous studies in Alzheimer's disease and MS patients have demonstrated that higher levels of intellectual enrichment provide a cognitive reserve, which allows patients to withstand more disease-related damage before suffering from cognitive impairment. This study used functional MRI to explore the patterns of brain activation in patients with varying levels of intellectual enrichment.

A total of 18 patients with MS were enrolled in the study. Estimates of brain atrophy, intellectual enrichment and current cognitive status were obtained for each patient. Blood-oxygen-level-dependent (BOLD) functional MRI of brain activations were studied in response to the n-back working memory task using 0-back, 1-back and 2-back levels (with the cognitive demand increasing for each level).

Results demonstrated three main findings:

- There was a significant positive correlation between intellectual enrichment and brain atrophy when controlled for cognitive status. In other words, patients with a higher intellectual enrichment were able to withstand greater brain damage before experiencing the same cognitive decline as patients with a lower intellectual enrichment;
- Patients with higher intellectual enrichment had less deactivation of the default resting network and less recruitment of the frontal cortex while performing the n-back tests. This pattern of activation during cognitive tasks has been reported

in previous studies to indicate increased cerebral efficiency. The authors propose that this pattern of activation represents the neural basis of the cognitive reserve;

- The proposed cognitive reserve network was found to account for approximately 97% of the relationship between intellectual enrichment and cognitive status, indicating that the activation of this network was the primary component in the effects of intellectual enrichment on cognitive status.

Previous studies have not found a relationship between intellectual enrichment and cerebral efficiency in healthy adults, indicating that the cognitive reserve network does not lead to increased cognition, but, rather, is protective against disease-related damage. Future results could extend this study to other neurological diseases and determine where rehabilitation activities targeting cognitive efficiency could improve the cognitive reserve in patients already diagnosed with a neurological disease.

Assessing the role of mitochondrial metabolism for recovery in MS

Evaluation of: Ciccarelli O, Altmann DR, McLean MA *et al.*: Spinal cord repair in MS: does mitochondrial metabolism play a role? *Neurology* 74, 721–727 (2010).

^{1}H-magnetic resonance spectroscopy can be used to study acute spinal cord inflammation and repair in MS by measuring the concentration of *N*-acetyl-aspartate (NAA), which indicates both mitochondrial metabolism and axonal density. Measurement of the cross-sectional area of the spinal cord can inform on the degree of demyelination and atrophy.

In this study, the authors examined the NAA levels and cross-sectional area of the spinal cord in 13 controls and 14 MS patients with an acute lesion in their spinal cord between levels C1 and C3. The clinical condition of the patients was assessed using the Expanded Disability Status Scale. The subjects were examined longitudinally at baseline, 1, 3 and 6 months after their attack. For analysis, patients were divided into those with an improvement in their disability status over the 6 months and those with no improvement.

Cord swelling was seen in patients at baseline. Both groups showed a significant decline in spinal cord cross-sectional area compared with controls over 6 months. In the patients who recovered during follow-up, NAA levels were found to steadily increase over 6 months, while patients who did not recover showed a general trend towards decreasing NAA levels over time. Additionally, a longer disease duration predicted a worse clinical outcome and smaller increases in NAA concentration.

As both groups of patients demonstrated a decrease in the cross-sectional area of the spinal cord, which would indicate demyelination or atrophy, the increased NAA levels in the patients who recovered are probably caused by increased mitochondrial metabolism. The fact that increased NAA levels correlated with clinical recovery may support the role of mitochondria in re-establishing axonal conduction after a demyelinating event.