

Using MRI to assess brain pathology in multiple sclerosis

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Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS), affecting over two million people, mainly in the Northern hemisphere (1). MRI has become the most valuable tool to support the clinical diagnosis of MS, and to rule out other conditions that can mimic MS (2). Apart from helping clinicians to establish the diagnosis, MRI is used as tool to (i) predict the course and severity of MS and (ii) support research into the aetiology and pathogenesis of this condition. Predicting the course of individual people with MS (pwMS) using MRI remains challenging not least due to considerable between-patient variability of the association between clinical and MRI 'burden of disease'. This shortcoming of MRI is particularly cumbersome when treatment with disease modifying drugs is being considered as such decisions rely – at least in part – on MRI evidence of disease activity (3). To understand the pathological basis of MRI, studies have been pursued to explore the histological substrate of changes detected on MRI. There are three principal approaches to do this, (i) animal models (4), (ii) brain biopsies (5), or (iii) *post mortem* MS tissue. Here, we focus on the associations between MRI changes and histopathological features in *post mortem* MS brain.

Imaging MS white matter myelin

The ability to accurately estimate myelin content in the MS brain is of particular interest given the likely significance of remyelination for axonal preservation and functional recovery. As treatment strategies facilitating remyelination emerge, accurate non-invasive techniques are needed to monitor remyelination in patients with MS. It is feasible to assess directly whether a white matter lesion (WML) is de- or remyelinated on T₂ weighted images provided they are acquired at ultra-high field (9.4T) strength using a small field of view and a sufficiently long acquisition time (6).

Only a minority of current clinical MR systems operates at field strengths beyond 1.5T though, and quantitative MRI is therefore the preferred option to try and assess specific tissue features such as the 'myelination status' in the brain white matter. A

number of studies using *post mortem* MS brain have consistently reported strong association between magnetization transfer (MT) indices and myelin content (7-10). Two large studies – each including over 100 WML – revealed significant differences in MT ratio (MTR) between remyelinated WML and (i) demyelinated WML and (ii) normal appearing white matter (NAWM) (7;10). However, there are limitations of the myelin specificity of MTR, particularly outside lesions (11).

Whereas 'T₂ weighted' MRI is generally non-specific for the severity of tissue damage studies investigating *post mortem* MS tissue suggested strong association between T₂ relaxation time and myelin content. Multi-component T₂ relaxation enables the proton signal to be separated into different water compartments. Evidence suggests of the three described water compartments the one with the shortest T₂ (sT₂; <30ms) is associated with protons in water trapped between myelin by-layers (12;13). This hypothesis has been underpinned by studies of *post mortem* brain, in which the density of luxol fast blue staining (indicating myelin phospholipids) in histological sections was strongly associated with sT₂ (r²= 0.67 to 0.79) (13;14).

Imaging MS grey matter

Lesions in the grey matter (GML) are common and extensive in MS. They are already present early in the disease and increase with disease duration (15). However, the visualization of MS pathology in the cortical grey matter has been difficult using standard MRI. Causes include the often relatively small lesion volume, a – again relative – lack of inflammation and contrast between lesions and non-lesional grey matter, and partial volume effects at the interface between tissue and cerebro-spinal fluid. Compared to WML detection of lesions is generally also more challenging in deep grey matter structures such as thalamus, basal ganglia and hypothalamus, the hippocampus, cerebellum and spinal cord. MRI techniques such as double inversion recovery (16) and phase-sensitive inversion recovery have been tuned into promising tools for GML detection and assessment. Yet even using these techniques most lesions remain undetected when compared with the number and size of GML reported histologically. Ultra-high-field MRI (7, 8 and 9.4 T) has been

shown to be superior compared to standard 1.5T MRI to image GML and study their characteristics (17).

References

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