

# Magnetic Resonance Imaging in Multiple Sclerosis – A Brief Review

## MS pathology

Our concept of pathology in multiple sclerosis (MS) has recently evolved from one of relatively focal white matter (WM) inflammatory demyelination, to one of a more global process affecting the whole central nervous system (CNS), both WM and grey matter (GM), with spatially variable inflammation, demyelination and remyelination, glial proliferation, and neurodegeneration.<sup>1,2,3</sup> It has also become clear that focal WM lesions explain only a fraction of the disability accrued by patients; changes in regions not overtly abnormal on conventional magnetic resonance imaging (MRI) scans contribute at least as much to clinical outcomes.<sup>4</sup> Indeed, it is thought that widespread neurodegeneration, which seems to be only partly related to focal WM inflammation, is a key factor determining long term clinical outcomes in MS.

## Conventional magnetic resonance imaging

Conventional structural MRI is readily able to detect focal WM lesions, but is not so good for spotting GM lesions or diffuse changes. WM lesions may be seen on both T2 (as hyper-intensities) and T1 (as hypo-intensities) weighted images, with more lesions usually seen on the T2-weighted scans. This mismatch between lesion visibility on T2 and T1 weighted images is thought to reflect differences in pathological specificity; persistent lesion hypo-intensity on T1 images seems to correlate with axonal loss, while T2 hyper-intensity is pathologically non-specific.<sup>5</sup>

The differentiation of acute inflammatory from non-inflammatory lesions is aided by contrast-enhancing MRI scans with gadolinium chelates; these agents non-specifically mark regions where the blood brain barrier is compromised through a variety of processes, including inflammation.<sup>6</sup> Iron based contrast agents have the potential to illuminate different aspects of inflammatory activity in the CNS: ultra-small particles of iron oxide given

intravenously are taken up by phagocytic monocytes and macrophages, tagging them even after they have entered the CNS;<sup>7</sup> and antibody-conjugated micro particles of iron oxide can target specific CNS molecules, with a recently developed vascular cell adhesion molecule marker hinting at the potential value of such labels in MS.<sup>8</sup> However, use of MR contrast media is not without potential risk; nephrogenic systemic fibrosis has been described in people who have received gadolinium based contrast agents, and this has led to a re-evaluation of its use, particularly in people with pre-existing renal impairment.<sup>9</sup>

## Quantitative magnetic resonance imaging

MRI is moving from a paradigm of photography to one of cartography, requiring ever more technically demanding acquisition and processing protocols that, at present, limit the use of many quantitative MRI measures to research projects rather than routine practice; perhaps those nearest to application in the clinic are measures of brain atrophy. Brain atrophy is thought to reflect neuronal and axonal loss, and as such has been of particular research interest recently. Measurement of brain atrophy relies on high quality structural images, with sufficient contrast to reasonably define tissues. Broadly, methods can be divided into registration or segmentation-based measures, although most combine elements of both. Registration-driven approaches seek to determine how much a region defined on one scan has to be stretched or crushed to fit an equivalent region on another scan; when applied to serially acquired MRI data, differences between scans approximate the degree of atrophy; when applied to single scans registered to a reference image, estimates of relative volume differences, i.e. normalisation factors, are obtained. Segmentation-powered techniques seek to deliver absolute measures of tissue volumes, but results are often presented as ratios to concurrently determined

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**Table 1: Main currently available MRI techniques and their routine clinical applications in MS**

MRI modality	Main pathological substrate and localisation of abnormalities in MS	Clinical Application
T1 and T2 weighted structural imaging	Visualises mostly white matter lesions. Not pathologically specific, but T1 hypo-intensity appears correlate better than T2 hyper-intensity with axonal damage.	Core element of the current McDonald MS diagnostic criteria, and monitoring disease course.
Gadolinium chelates contrast imaging	Localised non-vascular enhancement represents disruption of the blood brain barrier; in MS this is associated with active inflammation, mostly seen in white matter lesions.	Core element of the McDonald MS diagnostic criteria, and monitoring disease course.
Volumetric imaging	Brain and cord atrophy represents a combination of cellular atrophy and loss, and appears to mirror irreversible neuronal loss. Atrophy has been observed in both grey and white matter.	Not routinely used.
Diffusion tensor imaging	Assesses tissue, in particular tract, integrity; it is usually abnormal in white matter lesions, but may also be subtly abnormal in normal appearing tissues.	Not routinely used in MS, but increasingly used to determine the age of vascular lesions.
Magnetisation transfer imaging	Assesses tissue myelination; it is usually abnormal in white matter lesions, but may also be subtly abnormal in normal appearing tissues.	Not routinely used.
Spectroscopy	Provides relatively cell specific measures of neuronal damage (as represented by concentrations of N-acetyl-aspartate) and glial activation or proliferation (as represented by concentrations of myo-inositol). Reductions in N-acetyl-aspartate concentrations have been detected in grey and white matter, and lesions; increases in myo-inositol have been seen in normal appearing and lesional white matter.	Not routinely used.

**Table 2: McDonald criteria (2005) for establishing a diagnosis of MS.**

<i>Relapse onset MS, after a single clinical event and with initial signs of one focal abnormality in the CNS, so requiring further evidence of both dissemination in space and time.</i>	
<b>Dissemination in space</b>	<b>Dissemination in time</b>
<p><i>If unmatched CSF oligoclonal bands are not detected, or have not been tested for, at least three out of the following:</i></p> <ul style="list-style-type: none"> <li>• One or more gadolinium enhancing lesions in the brain or spinal cord;</li> <li>• If no gadolinium enhancing lesions are seen, then nine or more brain and/or spinal cord lesions visible on T2-weighted scans;</li> <li>• One or more infratentorial or spinal cord lesions;</li> <li>• One or more juxtacortical lesions;</li> <li>• Three or more periventricular lesions;</li> </ul> <p>Or</p> <ul style="list-style-type: none"> <li>• Objective clinical evidence consistent with at least one further focal CNS lesion.</li> </ul> <p><i>If unmatched CSF oligoclonal bands are detected:</i></p> <ul style="list-style-type: none"> <li>• Two or more MRI visible lesions consistent with the diagnosis.</li> </ul> <p>Or</p> <ul style="list-style-type: none"> <li>• Objective clinical evidence consistent with at least one further focal CNS lesion.</li> </ul>	<p><i>Any of the following on MRI:</i></p> <ul style="list-style-type: none"> <li>• Compared with a reference T2-weighted scan undertaken at least 30 days after the onset of the index clinical episode, any new lesions seen on any subsequent T2-weighted scans;</li> <li>• Three or more months after the initial clinical event, any gadolinium enhancing lesion observed in any CNS region to which the original symptoms and signs cannot be attributed;</li> </ul> <p>Or</p> <ul style="list-style-type: none"> <li>• A further clinical event, lasting at least 24 hours, consistent with the diagnosis.</li> </ul>
<i>Primary progressive MS, after at least one year of clinical disease progression as determined retrospectively or prospectively.</i>	
<p><i>Two of the following:</i></p> <ul style="list-style-type: none"> <li>• If visual evoked potentials are normal, or have not been tested, nine or more brain lesions visible on T2-weighted images;</li> <li>• If visual evoked potentials are abnormal and consistent with demyelination, four or more brain lesions visible on T2-weighted images;</li> <li>• Two or more focal spinal cord lesions visible on T2-weighted images;</li> <li>• Unmatched oligoclonal bands detected in the CSF.</li> </ul>	
<i>The criteria assume that no viable alternative explanation for a person's symptoms and signs has been found after appropriate investigation.</i>	

intracranial volumes; this adjustment yields measures which are naturally less variable between people, and which are less susceptible to scanner calibration drift, which can be a problem with serial MRI studies. GM specific measures may be of added value in MS, offering better surrogate markers of disease progression compared with WM or whole brain parameters.<sup>10</sup> In clinical trials of potential neuroprotective agents, the inclusion of MRI brain atrophy measures may reduce both the number of participants and the follow-up period required to show a significant treatment effect, when compared with studies relying purely on clinical outcome measures.<sup>11</sup>

As presently acquired, conventional structural MRI is designed to maximise spatial clarity but not to serve as an objective quantifiable measure of a tissue's intrinsic characteristics; however a suite of newer MRI techniques are able to provide such information. Magnetisation transfer (MT) imaging offers insight into myelination,<sup>12</sup> estimating the proportion of membrane associated macromolecular protons (not readily seen with conventional MRI) in a region; abnormalities in MT have been detected in both lesional and non-lesional tissues in MS, and such measures have been recommended for use in studies of treatments aimed at promoting remyelination.<sup>13</sup> Diffusion tensor imaging yields a measure of tissue integrity, with changes again seen in both MS lesional and non-lesional tissues,<sup>14</sup> and has demonstrated potential in the assessment of MS associated WM tract damage.<sup>15</sup> Proton spectroscopy allows the estimation of brain chemical concentrations: N-acetylaspartate, which is found almost exclusively in neurons and their axonal projections in the adult brain, offers a measure of neuronal

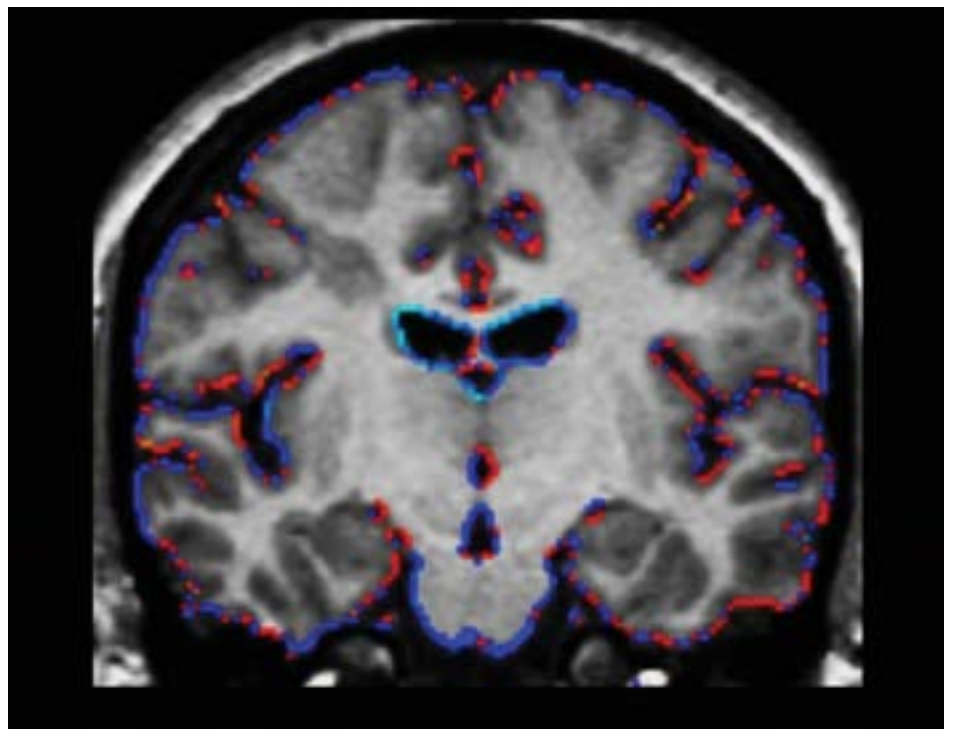


Figure 1: Brain volume loss in MS demonstrated using the 'Structural Image Evaluation, using Normalisation, of Atrophy' technique applied to two MRI scans acquired one year apart. A coronal brain slice is presented, rendered with a colour overlay, where blue indicates volume loss and red indicates gain. For further details see Anderson et al.<sup>10</sup> Image courtesy of Valerie Anderson.

health and density, and has been found to be reduced early in the clinical course of MS, in WM and GM; myo-inositol, which is preferentially concentrated in glia, has been found to be elevated in lesions and normal-appearing WM, suggesting glial activation and or proliferation.<sup>16</sup> Using MRI, it is also possible to quantitatively measure T1 and T2 relax-

ation times, and tissue perfusion, although these measures have been less extensively employed in MS, compared with those mentioned previously.

The functional impact of MS is also being addressed with MRI, beyond that of simply associating measures of tissue damage with clinical outcomes; recent functional MRI studies

suggest that cortical plasticity may attenuate the effects of focal damage in MS, and promote recovery beyond that achievable through localised innate tissue repair mechanisms alone (for example <sup>17</sup>).

### McDonald diagnostic criteria and other clinical applications

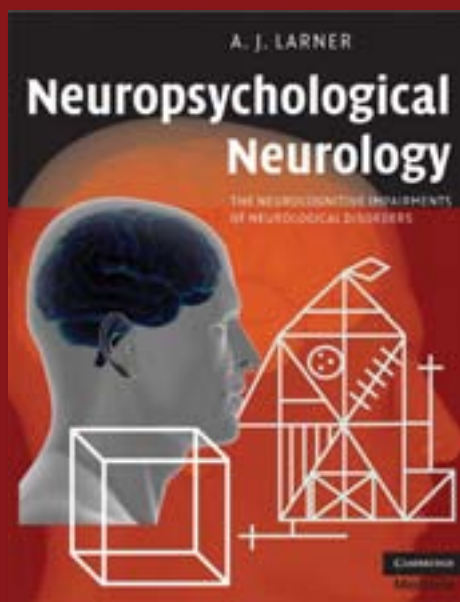
Technical limitations and the complex data processing required to derive quantitative MR measures have meant that routine clinical application of MRI has focused mainly on identifying lesions to support the diagnosis of MS, and excluding or confirming alternative diagnoses. MRI on its own cannot be used to establish a diagnosis of MS, but can provide key evidence for evolving multifocal pathology. The latest diagnostic guidelines in MS, the revised McDonald criteria,<sup>18</sup> allow the diagnosis of MS after a single clinical event, where there are sufficient MRI visible brain and cord lesions, and lesion accrual is demonstrated on scanning undertaken after the index clinical event. A very recent study suggests that in people who have had no episodes suggestive of CNS demyelination, the incidental detection on MRI of MS-like lesions is associated with a relatively high risk of a person having a clinical event consistent with MS within five years.<sup>19</sup> However, while lesions do appear to predict onset of MS, they are not so good at predicting subsequent disability, even in the longer term, i.e. they mark the process better than its effects.<sup>20</sup> While MRI has established itself in a diagnostic role in MS, it is only just beginning to find a clear place in treatment decisions; lesion activity measures form part of the National Institute for Clinical Excellence (2007) recommended criteria for the prescription of natalizumab in rapidly evolving severe relapsing-remitting MS.

### Where next?

MRI has already made invaluable contributions to our understanding of MS. In the short term, it remains for quantitative MRI measures to realise their potential in clinical practice: such measures may help make the diagnostic criteria even more sensitive and specific; may yield more reliable prognostic indicators; and provide timely and effective surrogates of pathological progression, in a way that can usefully inform treatment decisions, preferably before such progression becomes clinically manifest. In the long term, it may be possible to deliver truly cell and process-specific information from MRI, and integrate such measures with immunological and genetic data to better characterise the disease's genesis and evolution. From this it is to be hoped that we can develop a range of more effective disease specific treatments, optimise their use on a person-by-person basis, and observe their effectiveness dynamically with a view to eliminating, or at least markedly curtailing, the clinically apparent effects of MS.

### References

- Dhib-Jalbut S. Pathogenesis of myelin/oligodendrocyte damage in multiple sclerosis. *Neurology*. 2007 May 29;68(22 Suppl 3):S13-21.
- Dutta R, Trapp BD. Pathogenesis of axonal and neuronal damage in multiple sclerosis. *Neurology*. 2007 May 29;68(22 Suppl 3):S22-31.
- Miller RH, Mi S. Dissecting demyelination. *Nat Neurosci*. 2007 Nov;10(11):1351-4.
- Neema M, Stankiewicz J, Arora A, Guss ZD, Bakshi R. MRI in multiple sclerosis: what's inside the toolbox? *Neurotherapeutics*. 2007 Oct;4(4):602-17.
- van Walderveen MA, Kamphorst W, Scheltens P, van Waesberghe JH, Ravid R, Valk J, Polman CH, Barkhof F. Histopathologic correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis. *Neurology*. 1998 May;50(5):1282-8.
- Essig M, Weber MA, von Tengg-Kobligh H, Knopp MV, Yuh WT, Giesel FL. Contrast-enhanced magnetic resonance imaging of central nervous system tumors: agents, mechanisms, and applications. *Top Magn Reson Imaging*. 2006 Apr;17(2):89-106.
- Petry KG, Boiziau C, Dousset V, Brochet B. Magnetic resonance imaging of human brain macrophage infiltration. *Neurotherapeutics*. 2007 Jul;4(3):434-42.
- McAteer MA, Sibson NR, von Zur Muhlen C, Schneider JE, Lowe AS, Warrick N, Channon KM, Anthony DC, Choudhury RP. In vivo magnetic resonance imaging of acute brain inflammation using microparticles of iron oxide. *Nat Med*. 2007 Oct;13(10):1253-8.
- Penfield JG, Reilly RF Jr. What nephrologists need to know about gadolinium. *Nat Clin Pract Nephrol*. 2007 Dec;3(12):654-68.
- Anderson VM, Fox NC, Miller DH. Magnetic resonance imaging measures of brain atrophy in multiple sclerosis. *J Magn Reson Imaging*. 2006 May;23(5):605-18.
- Kapoor R. Neuroprotection in multiple sclerosis: therapeutic strategies and clinical trial design. *Curr Opin Neurol*. 2006 Jun;19(3):255-9.
- Schmierer K, Scaravilli F, Altmann DR, Barker GJ, Miller DH. Magnetization transfer ratio and myelin in postmortem multiple sclerosis brain. *Ann Neurol*. 2004 Sep;56(3):407-15.
- Filippi M, Rocca MA. Magnetization transfer magnetic resonance imaging of the brain, spinal cord, and optic nerve. *Neurotherapeutics*. 2007 Jul;4(3):401-13.
- Pagani E, Bammer R, Horsfield MA, Rovaris M, Gass A, Ciccarelli O, Filippi M. Diffusion MR imaging in multiple sclerosis: technical aspects and challenges. *AJNR Am J Neuroradiol*. 2007 Mar;28(3):411-20.
- Ciccarelli O, Toosy AT, Hickman SJ, Parker GJ, Wheeler-Kingshott CA, Miller DH, Thompson AJ. Optic radiation changes after optic neuritis detected by tractography-based group mapping. *Hum Brain Mapp*. 2005 Jul;25(3):308-16.
- De Stefano N, Filippi M, Miller D, Pouwels PJ, Rovira A, Gass A, Enzinger C, Matthews PM, Arnold DL. Guidelines for using proton MR spectroscopy in multicenter clinical MS studies. *Neurology*. 2007 Nov 13;69(20):1942-52.
- Forn C, Barros-Loscertales A, Escudero J, Belloch V, Campos S, Parcet MA, Avila C. Cortical reorganization during PASAT task in MS patients with preserved working memory functions. *Neuroimage*. 2006 Jun;31(2):686-91.
- Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinschenker BG, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol*. 2005 Dec;58(6):840-6.
- Lebrun C, Bensa C, Debouverie M, De Ze J, Wiertlewski S, Brochet B, Clavelou P, Brassat D, Labauge P, Rouillet E; CFSEP. Unexpected multiple sclerosis: follow-up of 30 patients with magnetic resonance imaging and clinical conversion profile. *J Neurol Neurosurg Psychiatry*. 2008 Feb;79(2):195-8.
- Fisniku LK, Brex PA, Altmann DR, Miszkal KA, Benton CE, Lanyon R, Thompson AJ, Miller DH. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain*. 2008 Jan 29.



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