Research Highlights

Highlights from the latest articles in multiple sclerosis MRI

Advanced MRI and multiple sclerosis

Emilia Sbardella[1,2] & Valentina Tomassini*[1,3]

[1]IRCCS Santa Lucia Foundation, Rome, Italy
[2]Department of Psychology, Sapienza University of Rome, Rome, Italy
[3]Institute of Psychological Medicine & Clinical Neurosciences, Cardiff University School of Medicine, Cardiff, UK
**Author for correspondence:*
Tel.: +44 29 2074 5118
Fax: +44 29 2074 4394
tomassiniv@cardiff.ac.uk

These Research Highlights focus on applications of advanced MRI methods that aim to overcome the 'clinical–radiological paradox', namely, the dissociation between apparent MRI damage and clinical disability in multiple sclerosis (MS). Indeed, advanced MRI methods for image acquisition and analysis have substantially improved our ability to detect subtle microstructural damage hidden to conventional approaches, as well as to understand its functional consequences.

Sensitivity of 3D-fluid attenuated inversion recovery in detecting MS cortical lesion on 7 T MRI

Evaluation of: Kilsdonk ID, de Graaf WL, Lopez Soriano A *et al.* Multi-contrast MR imaging at 7T in multiple sclerosis: highest lesion detection in cortical gray matter with 3D-FLAIR. *AJNR Am. J. Neuroradiol.* doi:10.3174/ajnr.A3289 (2012) (Epub ahead of print).

Conventional MRI can detect MS white matter (WM) lesions and thus is fundamental in the diagnosis of MS. However, it shows poor sensitivity in detecting cortical damage that is specific to MS and it is responsible for physical and cognitive impairments in patients. Therefore, there is growing interest directed towards MRI acquisitions able to identify grey matter (GM) lesions.

From earlier studies using 1.5 and 3 T scanners, fluid attenuated inversion recovery (FLAIR) sequences have revealed the most WM lesions, while double inversion recovery (DIR) acquisitions have shown the highest sensitivity to GM lesions. In this study, the authors assess the capability of 2D-T2 weighted imaging (WI), 3D-T1 WI and 3D-FLAIR, which are MRI sequences recommended in clinical settings, to detect WM and GM MS lesions at 7 T by investigating the lesion-sensitivity of these sequences in comparison with the GM-specific 3D-DIR [1].

For this purpose, 37 MS patients and seven healthy volunteers were enrolled. First, lesions were counted and classified according to the anatomical location as periventricular, deep and juxtacortical WM; mixed lesions, located both in WM and GM; and intracortical lesions. Second, lesions were classified as 'total WM lesions', including periventricular, deep and juxtacortical; 'total GM lesions', including mixed and intracortical; and 'total lesions', including WM and GM lesions.

No intracortical lesions were identified in any of the healthy controls.

3D-FLAIR was more sensitive than 3D-DIR and the other sequences in detecting both total GM lesions and total WM lesions. The difference was particularly significant for the total GM lesions, with 3D-FLAIR showing a higher proportion of lesions when compared with 3D-DIR (+89%), 2D-T2 WI (+87%) and 3D-T1 WI (+224%). This result was driven by the higher sensitivity of 3D-FLAIR in detecting mixed lesions.

The authors conclude that 3D-FLAIR at 7 T can detect cortical GM lesions more sensitively than 3D-DIR. They suggest

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that this higher sensitivity is achieved through an increased contrast between lesions and surrounding tissues. This finding has important implications for the development of MRI acquisitions that may improve the correlation between visible damage and disability in MS.

Reference

1 Kilsdonk ID, de Graaf WL, Lopez Soriano A *et al*. Multi-contrast MR imaging at 7T in multiple sclerosis: highest lesion detection in cortical gray matter with 3D-FLAIR. *AJNR Am. J. Neuroradiol.* doi:10.3174/ajnr.A3289 (2012) (Epub ahead of print).

Perfusion changes in MS cortical lesions as markers of inflammation and neurodegeneration

Evaluation of: Peruzzo D, Castellaro M, Calabrese M *et al.* Heterogeneity of cortical lesions in multiple sclerosis: an MRI perfusion study. *J. Cereb. Blood Flow Metab.* doi:10.1038/jcbfm.2012.192 (2012) (Epub ahead of print).

Studies of pathology have demonstrated the involvement of the circulatory system in the formation of MS lesions. Techniques evaluating brain perfusion have been used to investigate changes in blood circulation in MS. The most frequently applied technique to the study of brain perfusion is dynamic susceptibility contrast MRI (DSC-MRI), which uses an exogenous tracer (gadolinium-DTPA), under the assumption that this tracer is not diffusible into the extracellular space. DSC-MRI quantifies cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time.

In MS, perfusional changes have been shown in the normal-appearing WM and in lesions. These changes are usually represented by CBF and CBV increases in active lesions and can occur even before the blood–brain barrier breaks down. They can also appear as CBF and CBV decreases within areas of chronic degeneration. Given the clinical relevance of GM damage in MS, the authors of this study investigated cerebral perfusion in cortical lesions of MS patients using DSC-MRI, with the aim of improving the characterization of pathological processes occurring within the GM.

A total of 44 relapsing–remitting MS patients were studied using DSC-MRI. CBF, CBV and mean transit time were calculated in the cortical lesions and compared with perfusion parameters within the normal-appearing GM [1]. In comparison with perfusion within normal-appearing GM, cortical lesions showed reduced CBV and CBF, but normal mean transit time. Only in a few patients did cortical lesions show increased CBV and/or CBF values.

The authors interpret the finding of hypoperfusion of cortical lesions as a potential marker of neurodegeneration or reduced metabolic activity within the lesions. They hypothesize that lesions showing increased perfusion may reflect areas of increased metabolism during the inflammatory phase. The authors conclude that different aspects of pathology may be reflected in perfusional changes and that perfusion changes might be used as markers of lesion evolution, thus complementing information coming from conventional MRI sequences.

Reference

1 Peruzzo D, Castellaro M, Calabrese M *et al*. Heterogeneity of cortical lesions in multiple sclerosis: an MRI perfusion study. *J. Cereb. Blood Flow Metab.* doi:10.1038/jcbfm.2012.192 (2012) (Epub ahead of print).

A novel method to improve the neuropathological characterization of MS WM lesions

Evaluation of: Yiannakas MC, Tozer DJ, Schmierer K *et al.* ADvanced IMage Algebra (ADIMA): a novel method for depicting multiple sclerosis lesion heterogeneity, as demonstrated by quantitative MRI. *Mult. Scler.* doi:10.1177/1352458512462074 (2012) (Epub ahead of print).

Areas of inflammatory demyelination within the CNS characterize MS. Conventional MRI sequences, such as proton density-weighted and T2-WI can detect this damage in the WM, but they cannot identify the different pathological substrates that underlie WM lesions and that can range from inflammation and demyelination to axonal loss and gliosis. Therefore, the volume of WM lesions often does not correlate with clinical disability.

In this study, the authors aim to introduce a new method to improve the characterization of tissue damage within individual WM lesions that appear otherwise similar using conventional sequences [1]. They use a postprocessing method called ADvanced IMage Algebra (ADIMA), which, after registration steps, combines

proton density-weighted and T2-WI sequences to obtain a new image with different levels of intensities within the WM lesions. Areas of WM damage can appear to be bright (ADIMA-b) or dark (ADIMA-d), according to different structural substrates. These lesions can be segmented to create a lesion mask and calculate the lesion volume.

The authors studied ten MS patients. For each patient, they calculated ADIMA-b, ADMA-d and total or combined ADIMA lesion volumes, beyond the lesion volumes on T1-WI and T2-WI. To compare microstructural damage within ADIMA lesions and conventional T2-WI or T1-WI lesions, they obtained a magnetization transfer ratio, and T1 and T2 relaxation times.

ADIMA-derived volumes correlated with conventional lesion volumes. The ADIMA-d and ADIMA-b regions showed microstructural characteristics that were similar to T2-WI and T1-WI lesions, respectively, although both ADIMA-d and ADIMA-b lesion maps were only partially overlapping with T2-WI and T1-WI maps, respectively.

The authors suggest that the ADIMA method may detect more widespread damage than that identified by conventional T1-weighted and T2-weighted images. They also propose that ADIMA may identify neuropathological heterogeneity within WM lesions, highlighting lesions with greater microstructural damage. This may help to improve the relationship between damage revealed by MRI and disability in MS.

Reference

1 Yiannakas MC, Tozer DJ, Schmierer K *et al.* ADvanced IMage Algebra (ADIMA): a novel method for depicting multiple sclerosis lesion heterogeneity, as demonstrated by quantitative MRI. *Mult. Scler.* doi:10.1177/13524585 12462074 (2012) (Epub ahead of print).

Functional abnormalities within and between large-scale neural networks in MS as detected by resting state functional MRI

Evaluation of: Rocca MA, Valsasina P, Martinelli V *et al.* Large-scale neuronal network dysfunction in relapsing–remitting multiple sclerosis. *Neurology* 79(14), 1449–1457 (2012).

Resting state (RS) functional MRI (fMRI) investigates spontaneous fluctuations in brain activity to identify spatial patterns with similar temporal coherence. These patterns are thought to represent neural networks and the level of their temporal correlation is thought to reflect the strength of functional connectivity (FC) between regions. In clinical studies, RS-fMRI is used to map the functional connectivity of distinct neural networks without the confounding effects of altered performance.

In this study, the authors used RS-fMRI to investigate the functional integrity of the principal brain RS networks in MS and to relate it to clinical disability [1]. For this purpose, they identified the main resting neural networks in 85 relapsing–remitting MS patients and 40 healthy volunteers and quantified the associated FC. They related measures of FC to clinical disability and lesional damage. They obtained measures of functional network connectivity between different networks. Independent component analysis applied to RS-fMRI data could identify ten RS networks. FC was quantified and compared between the two groups. Similarly, functional network connectivity was calculated and compared between the groups.

When compared with controls, patients showed decreased RS FC in the sensory–motor and visual networks and in cognitive-related networks – that is, salience, executive control network, working memory network and default mode network. The decreased FC correlated with increasing levels of disability and T2 lesion volume. Patients also showed increased FC in some regions of the executive control network and auditory networks when compared with controls. Functional network connectivity analysis showed diffuse abnormalities in the patients when compared with controls. The connectivity of the executive control network was higher with salience network and lower with default mode network in patients than in controls. In patients, working memory network connectivity with sensory–motor networks was lower, while working memory network connectivity with visual networks was higher than in controls.

The authors conclude that, in MS, RS-fMRI provides evidence of functional abnormalities within and between large-scale neural networks. This network disruption relates to MS pathology and may constitute the functional basis of adaptive reorganization underlying recovery, as well as of insufficient or maladaptive reorganization supporting clinical disability.

Reference

1 Rocca MA, Valsasina P, Martinelli V *et al.* Large-scale neuronal network dysfunction in relapsing-remitting multiple sclerosis. *Neurology* 79(14), 1449–57 (2012).