HHS Public Access

Author manuscript

J Neurol. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

J Neurol. 2016 October ; 263(10): 1893–1902. doi:10.1007/s00415-016-8060-0.

SPRING CLEANING: TIME TO RETHINK IMAGING RESEARCH LINES IN MS?

Martina Absinta, MD[1,2], **Daniel S. Reich, MD, PhD**[2], and **Massimo Filippi, MD**[1]

[1]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

[2]Translational Neuroradiology Unit, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Bethesda, MD, USA

Abstract

Together with recently advanced MRI technological capability, new needs and updated questions are emerging in imaging research in multiple sclerosis (MS), especially with respect to the identification of novel in vivo biomarkers of MS-relevant pathological processes. Expected benefits will involve approaches to diagnosis and clinical classification. In detail, three main points of discussion are addressed in this review: (1) new visible imaging biomarkers (centrifugal/centripetal lesion enhancement, central vein, paramagnetic rims at the lesion edge, subpial cortical demyelination); (2) thinking about high-resolution MR from a pathological perspective (from postmortem to in vivo staging); and (3) the clinical utility of quantitative MRI. In this context, research efforts should increasingly be focused on the direct in vivo visualization of “hidden” inflammation, beyond what can be discerned with conventional gadolinium-based methods, as well as remyelination and repair, since these are likely to represent critical pathological processes and potential therapeutic targets. Concluding remarks concern the limitations, challenges, and ultimately clinical role of non-conventional MRI techniques.

Keywords

multiple sclerosis; neuroimaging; biomarkers

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder that extensively affects the central nervous system (CNS) of young people. Foci of perivenular demyelination with relative axonal preservation, and subtle pathological changes in the remaining white

Correspondence to: Prof. Massimo Filippi, Neuroimaging Research Unit, Institute of Experimental Neurology, Scientific Institute and “Vita e Salute” University, San Raffaele Hospital, Via Olgettina, 60, 20132 Milan, Italy. Telephone number: #39-02-2643-3033; Fax number: #39-02-2643-5972; filippi.massimo@hsr.it.

Competing interests Martina Absinta reports no actual or potential conflict of interest.
Daniel S. Reich received research support from the Myelin Repair Foundation and Vertex Pharmaceuticals. Massimo Filippi received personal compensation for activities with Merck-Serono, Genmab, Biogen-Dompé, Bayer-Schering, and Teva Neuroscience as a consultant, speaker, and advisory board member. He received also research support from Merck-Serono, Biogen-Dompé, Bayer-Schering, Teva Neuroscience and Fondazione Italiana Sclerosi Multipla (FISM).

and gray matter characterized by a variable degree of tissue loss, are the historical pathological hallmarks of the disease. Inflammatory and overlapping neurodegenerative processes are thought to be responsible for overall tissue damage and disability accrual, however their interaction still needs to be fully unraveled [1].

The diagnostic approach and clinical management of this condition have been revolutionized in the last 30 years by the introduction of magnetic resonance imaging (MRI), which allows the in vivo detection of demyelinated white matter lesions on T2-weighted sequences. Lesions' spatial location (periventricular, juxtacortical, infratentorial, spinal cord) and temporal assessment (development of new lesions) dominate the current diagnostic criteria [2], form the basis for clinical management, and serve as endpoints for clinical trials (mostly of anti-inflammatory treatments). However, the correlation with disability and variable clinical evolution of MS patients (the so-called “clinical-radiological paradox”) remains disappointing.

Identification of the clinical-radiological paradox led to several imaging research lines that mainly focused on the in vivo demonstration of subtle pathological changes outside visible T2-lesions, as these were thought to better correlate with prognosis and treatment effectiveness. For example, a multitude of MRI strategies (magnetization transfer, diffusion, spectroscopy, volumetric assessment) were quite successful in quantifying abnormalities outside visible T2-lesions, including those in eloquent pathways, as well as irreversible tissue loss (atrophy) [3]. To date, however, technical issues and, perhaps, physiological variability, have led to poor reproducibility of these biomarkers over time and prevented their clinical application to individual cases. Thus, all the outstanding qualities of MRI in lesion detection (applicability to individual cases, high sensitivity and reproducibility, ease of use) simply do not apply directly to quantitative imaging biomarkers. Additionally, the pathological origin and specificity of the MRI signal within and outside discrete lesions are still debated [4].

As MRI is an effective tool for the investigation of MS pathobiology in vivo, this might be the right time to rethink imaging research lines in MS and to update our research questions. Here, we discuss three main points:

1) New visible imaging biomarkers: should we revert to a semi-qualitative approach and look for directly visible radiological biomarkers that take advantage of the introduction of ultra-high-field (7T) MRI and pulse sequence optimization?

2) Thinking about high-resolution MR from a pathological perspective: is this our chance to image specific and relevant pathological processes with the ultimate aim to treat them in the near future?

3) The space for quantitative MRI: among existing quantitative MRI techniques, which should be kept and finally moved to clinical practice?

A syndrome called MS: time for new subgroup classification?

MS is a heterogeneous disease in terms of clinical and radiological manifestations as well as immunological background. Two major phenotypes describe the clinical course of MS: a relapsing-remitting disease (exacerbations and remissions of neurologic deficits) and a progressive disease (unceasing accumulation of disability without discrete clinical events) [5]. The progressive disease may manifest after a relapsing-remitting course (secondary progressive MS) or at onset (primary progressive MS). The latter course is commonly considered a neurodegenerative disease [6], though there is incontrovertible evidence for inflammatory activity that is now recognized in the new clinical classification [5]. Even if MRI is highly sensitive in detecting demyelinated lesions within the white matter (WM), no specific MRI patterns correlate with clinical phenotypes and reliably predict the disease course. In addition, the fact that the clinical perception of disease activity, by both patients and neurologists, generally underestimates the actual amount of inflammation in the brain and spinal cord [7] necessarily causes discrepancies between MRI features and clinical classification, not to mention a great deal of uncertainty about the time of biological onset of both the inflammatory and neurodegenerative components of the disease [8]. Paradigmatic is the case of primary progressive MS, in which MRI commonly suggests extensive silent inflammatory disease activity (sometimes with a high brain lesion load), often indistinguishable from secondary progressive MS.

To complicate this picture, in clinically identical MS patients, four different immunopathological mechanisms can lead to myelin injury and lesion formation [9, 10]. Even if remains a matter of debate, the immunological heterogeneity among patients supports the notion that MS is a syndrome more than a unique pathological entity. Typically, an MS lesion arises around a small parenchymal vein, where myelin-reactive T-lymphocytes induce a macrophage/microglial myelin-phagocytic response (immunopatterns I and II, ~75% of MS patients). A prominent B-lymphocyte response and complement deposition distinguish immunopattern II from I. On the other hand, primary or secondary (toxic, metabolic, hypoxic) oligodendrocyte dysfunction and death characterize immunopatterns III and IV. Of note, in a given case, the immunopattern has the propensity to remain constant over time, suggesting an intra-individual specificity of the events leading to the demyelinating process [11, 12]. To date, immunopathological phenotypes can only reliably be defined histologically (from biopsy and autopsy), preventing their use for classification purpose in clinical practice.

Take-home message: Our clinical classification approach may benefit from the definition of MS imaging phenotypes.

Back to lesions in the diagnostic workup: from count to qualitative aspects

Beyond mere detection by MRI, CNS localization, and counts of demyelinated lesions, new morphological features might support the diagnostic workup in MS: (1) the presence of a prominent central vein within the majority of MS lesions; (2) the detection of a paramagnetic rim at the edge of a relatively small proportion of lesions; and (3) subpial demyelination. All these radiological findings are strictly related to specific MS-pathological

processes and are not visible on clinical conventional MRI (T2 and T1-weighted MRI contrasts).

Demyelinated MS lesions are centered on small parenchymal veins, a fact clearly described in the earliest pathology studies [13] and recently confirmed in vivo using high-resolution T2*-weighted MRI at 7T and 3T [14–23]. The perivenular nature of MS lesion development directly influences their morphology and brain topography, so that MS lesions are generally ellipsoidal, with a characteristic pattern of distribution that follows the venous vasculature and preferentially involves certain areas of the WM (periventricular and juxtacortical) as well as the edges of the optic nerve, brainstem, and spinal cord (Figure 1). Potentially relevant for the diagnostic workup is that the “central vein sign” has been consistently described as “atypical” in small vessel disease [18, 20, 24–26] and migraine [27], and it may be a useful adjunct to traditional criteria for diagnosing MS in difficult cases [28]. Whether the proportion of perivenular lesions can be used to discriminate demyelinated MS lesions from mimicking lesions in other immunological conditions (e.g. vasculitis and neuromyelitis optica spectrum disorder) should be the matter of further investigation (Figure 1). Using the same imaging approach (high-resolution T2*-weighted sequence), additional information regarding lesion morphology can be obtained. For example, in a proportion of demyelinated MS lesions (~10% of all lesions), a peripheral paramagnetic rim has been initially detected at 7T and, more recently, also at 3T MRI [15, 21, 29–35] [Figure 2A]. Regarding MS-specificity, paramagnetic rims have not been found in vascular lesions [26] and are rare in Susac syndrome [25], though they can be a feature of infectious and neoplastic disorders.

Independently of focal and diffuse WM injury, cortical pathology has been recognized to play a relevant role in the relentless disability accumulation and cognitive impairment of these patients [36–45]. In the context of the diagnostic workup, baseline detection of cortical (mostly leukocortical) lesions in clinically isolated syndrome (CIS) improves the accuracy of diagnosis [46]. Despite this, MRI has been only partially successful in detecting cortical demyelination even through the implementation of several MRI approaches, such as double inversion recovery (DIR) [47], phase-sensitive inversion recovery (PSIR) [48], and high-resolution T2*-weighted sequences [49, 50]. Some of the reasons for low cortical lesion contrast are the background higher T2 relaxation times of the cortex relative to white matter (unfortunately highest in the subpial cortical layers) as well as the partial volume effects of the adjacent cerebrospinal fluid (CSF). Differently from the previously mentioned perivenular lesions, the most frequent (and most difficult to image) subtype of cortical demyelination extensively involve the subpial layers of the cortex (so called “subpial lesions”) and preferentially the depths of sulci. Noteworthy, plaque-like subpial demyelination is typical of MS and is found rarely, if ever, in other inflammatory and neurodegenerative CNS conditions [51]. Strategies to improve subpial lesion detection might consider MRI signal changes deriving from the disruption of the extremely well organized myelo- and cytoarchitecture of the cortex [52].

Take-home message: Novel morphological features of MS-related focal demyelination (central vein sign, paramagnetic rims, subpial demyelination) might help in the diagnostic workup of patients suspected of having MS.

Pathophysiology: from postmortem to in vivo lesion staging

Mechanisms and stages of lesion development [53, 54] are critical aspects of MS pathophysiology. If fully understood, they may point to potential sources of new therapeutic interventions. The permeability of the BBB to intravenous gadolinium is the basis of current radiological staging (new active *vs* chronic lesions). Despite some recent safety concerns that are the subject of several ongoing studies, the judicious use of gadolinium – particularly macrocyclic chelates – is still considered essential in probing BBB permeability [55].

On MRI, newly forming active lesions enhance on T1-weighted images after gadolinium injection, and this enhancement typically lasts between 1 and 8 weeks. Recently, in active MS lesions, two sequential spatiotemporal patterns of enhancement have been identified: centrifugal (inside-out) followed by a centripetal (outside-in) enhancement [56]. Centrifugal enhancement appears to reflect the central vein's BBB opening and the flow of the contrast agent within the parenchyma in which active demyelination is occurring. In a proportion of lesions, after a few days to weeks, the lesion's growth induces diffuse alterations of capillaries' BBB at the lesion edge, which can be recognized on MRI as centripetal enhancement (previously called ring-enhancement) [21, 34, 56]. After enhancement resolves, MS lesions remain visible on T2-weighted scans and are, generally speaking, termed “chronic.” In chronic lesions, permanent axonal loss, resulting from the demyelination process, is commonly represented by different degrees of signal intensity on T1-weighted images [57, 58].

Aside from the status of the BBB (impaired or intact), the presence of ongoing demyelination and the cellular composition of the inflammatory infiltrate are the major discriminants of the pathological lesion staging [53, 54]. Thus, in addition to active (hypercellular/demyelinating) and chronic (hypocellular/demyelinated) lesions, a subset of chronic lesions with a demyelinated/hypocellular core, but a hypercellular edge, has been described in a variable percentage in autopsy cases and thought to contribute to disease progression [53, 54, 59]. These lesions have been called “chronic active” or “slowly expanding,” as macrophages and/or microglia at their margins are found to have engulfed early or late myelin degradation products [53, 54, 59].

Differently from active lesions, in chronic active/slowly expanding lesions, inflammation is not directly associated to frank permeability of the BBB permeability to gadolinium and, as a consequence, this important pathological feature has remained invisible to clinical MRI sequences. It was suggested that lesions with paramagnetic rims, since their first detection at 7T MRI on high-resolution susceptibility imaging [15], might identify in vivo the pathologically described chronic active/slowly expanding lesions. In this context, the paramagnetic source of MRI signal at the lesion edge might be related to the presence of the persistent inflammatory infiltrate (macrophages/microglia) and related paramagnetic species (free radicals and intracellular iron accumulation), but this remains under investigation [15, 21, 29–33, 35] [Figure 2A]. Indeed, the apparent stability of chronic rim lesions over time [31] would seem to indicate that they are not necessarily “slowly expanding.” Back to clinical practice, it might be relevant to know, in each patient, the proportion of lesions with

persistent inflammation at the lesion edge, and to monitor the evolution of these lesions, because potentially they might represent a critical therapeutic target.

A parallel but still fundamental chapter in lesion development is repair – more precisely, the resolution of inflammation and simultaneous remyelination of residual naked axons [60, 61]. MS lesions are prone to remyelinate in a variable percentage across subjects, often incompletely [62–69]. Impaired remyelination contributes directly to neurodegeneration, as naked axons are more susceptible to damage and transection within an inflammatory or toxic environment. Factors sustaining impaired remyelination are a matter of extensive investigation [60, 61, 70], as inducing effective and complete lesion remyelination is the main goal of therapeutic interventions now undergoing clinical testing or in development. Nowadays, the lack of reliable and specific in vivo biomarkers of myelin content changes is a major obstacle to in vivo testing of potentially remyelinating drugs. Initial work on MRI pulse sequences able to map selectively myelin water (the fraction of water between myelin layers) remains promising for this purpose [71–73], though problems with signal-to-noise and cross-site reproducibility remain [73, 74]. Even if less specific, longitudinal magnetization transfer ratio (MTR) assessment has been proposed as a method of tracking lesion demyelination/remyelination [74, 75]. Of note, remyelinated areas within chronic lesions have been seen directly on postmortem 9.4 T MRI [76], suggesting the possibility to detect and monitor these lesions also in vivo.

> Take-home message: There are advantages in redefining radiological lesion staging in order to promote a closer correspondence to histopathology.

Pathophysiology: beyond BBB breakdown, the “hidden” inflammation

Inflammation is widespread in the CNS of MS patients and manifests in ways far beyond the accrual of new lesions, as monitored by serial MRI scans, and impairment of the BBB, as detected by leakage of gadolinium. These “hidden” components of inflammation need to be visualized in MS, particularly in progressive patients who are not eligible for traditional anti-inflammatory/immunomodulatory drugs. In the previous section, the issue of identification of chronic active/slowly expanding lesions in vivo was introduced. In research settings, new contrast agents such as ultrasmall, superparamagnetic iron oxide particles (USPIO) [77–79], as well as complementary imaging techniques, such as translocator protein (TSPO) radioligands in positron emission tomography (PET) studies [80–86], focus on specific biological targets of microglia/macrophage activation in areas with an apparently normal BBB. However, correlations with clinical measures remain to be determined.

Extremely relevant for MS pathogenesis, but overlooked for a long time, is leptomeningeal inflammation. In MS, meningeal inflammation may persist throughout life and spans all clinical disease phenotypes, as demonstrated by the high prevalence and persistence of CSF-specific oligoclonal bands in MS [87]. In the leptomeninges, scattered lymphocytes produce soluble cytokines and myelin-specific immunoglobulins that can affect directly the cortical surface and propagate inflammation within the parenchyma along perivascular spaces [88]. More recently, aggregates of perivascular meningeal lymphocytes, sometimes organizing into tertiary lymphoid follicles, have been seen prevalently in progressive cases and are

thought to be associated with subpial demyelination [88–94]. The radiological correlate of this pathological finding is still elusive; however, foci of perivascular leptomeningeal enhancement have been recently identified on in vivo 3T and 7T postcontrast T2-FLAIR in ~25% of MS patients (~40% of those with primary progressive disease course)[95] [Figure 2B–C]. In two autopsy cases, foci of leptomeningeal enhancement in vivo colocalized with clusters of lymphocytes and macrophages around meningeal vessels and are apposed to subpial cortical demyelination [95] [Figure 2C].

Take-home message: Chronic active/slowly expanding lesions and meningeal inflammation are important aspects of hidden inflammation in MS that need to be visualized in vivo.

Quantitative MRI: what should be moved into clinical practice?

Although non-conventional MRI techniques have contributed to our understanding of the pathophysiology of diffuse tissue injury in MS, their clinical role and pathological substrates have yet to be fully defined. In the meantime, recent trends concentrate attention more on tissue injury/loss in early “sensors” of multifocal brain damage (e.g. thalamus, corpus callosum) and in eloquent brain structures (e.g. pyramidal tracts, visual pathway, hippocampus, spinal cord) as more directly affecting patients' functional outcomes. Highly interconnected to many cortical regions, the thalamus is especially sensitive to overall brain injury, even at earlier stages of the disease and in children with MS, when global tissue loss is not prominent [96–100]. Together with the hippocampus [101–103], thalamic injury seems to highly correlate with cognitive deficits [98, 99]. On the other hand, spinal cord damage parallels accumulation of motor disability [104, 105]. Optimized segmentation techniques have led to more and more reliable volumetric measures of these clinically meaningful structures [106, 107], and introducing them into the clinical practice seems to be the most reasonable approach, so far. Similarly, among the tractography-reconstructed WM fiber bundles [108], efforts should be spent to move into everyday clinical practice the imaging of a few clinically relevant tracts, such as the pyramidal tract and visual pathway – perhaps in conjunction with other imaging modalities such as optical coherence tomography [109–113]. The standardization of non-conventional MRI imaging across centers and over time remains a great challenge, one that is partially being addressed by efforts of international imaging consortia. Of note, clinical trials might be the ideal setting to introduce non-conventional imaging techniques into disease and treatment monitoring as ancillary parts of the study. In this context, longitudinal evaluation of brain and spinal cord volumetric changes, as well as of MTR values within and outside visible lesions, are ongoing in several trials. A separate discussion should be made for the actual and future role of functional MRI (fMRI) in MS [114]. Aside from contributing to our pathophysiological understanding of the reorganization of cortical functional networks following MS-related brain injury, fMRI remains the imaging instrument of choice for testing new potential rehabilitation approaches and eventually symptomatic treatments, for example for fatigue [115] and cognition [116].

Take-home message: Focus more on eloquent brain structures instead of diffuse tissue damage.

Conclusions

In this review article, we aimed to acknowledge and promote recent shifting trends in MS imaging research. Current efforts in ultra-high-field MRI, together with optimization of available and new MRI sequences that can achieve sub-millimeter voxel resolution, are resulting in novel research lines that may better correlate MS-relevant pathological processes to more direct and meaningful imaging findings. A better knowledge of the pathobiology of the disease, together with new instruments to detect and monitor its course, hold promise for a more patient-tailored and effective therapeutic approach.

Acknowledgments

Special thanks to Prof. Andrea Falini (Head of the Department of Neuroradiology, San Raffaele Hospital), Dr. Vittorio Martinelli (Head of Clinical Trials Unit, Division of Neuroscience, San Raffaele Hospital), and Dr. Pascal Sati and Dr. Govind Nair (staff scientists, NINDS, NIH) for valuable advice, assistance with MRI data acquisition/post-processing, and help in figures' preparation. This work was supported in part by the Intramural Research Program of NINDS, NIH.

References

1. Kutzelnigg A, Lassmann H. Pathology of multiple sclerosis and related inflammatory demyelinating diseases. Handb Clin Neurol. 2014; 122:15–58. [PubMed: 24507512]
2. Polman CH, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann Neurol. 2011; 69(2):292–302. [PubMed: 21387374]
3. Filippi M, et al. Insights from magnetic resonance imaging. Handb Clin Neurol. 2014; 122:115–49. [PubMed: 24507516]
4. Filippi M, et al. Association between pathological and MRI findings in multiple sclerosis. Lancet Neurol. 2012; 11(4):349–60. [PubMed: 22441196]
5. Lublin FD, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014; 83(3):278–86. [PubMed: 24871874]
6. Ontaneda D, Fox RJ. Progressive multiple sclerosis. Curr Opin Neurol. 2015; 28(3):237–43. [PubMed: 25887766]
7. Frank JA, et al. Serial contrast-enhanced magnetic resonance imaging in patients with early relapsing-remitting multiple sclerosis: implications for treatment trials. Ann Neurol. 1994; 36(Suppl):S86–90. [PubMed: 8017894]
8. Tauhid S, et al. MRI phenotypes based on cerebral lesions and atrophy in patients with multiple sclerosis. J Neurol Sci. 2014; 346(1–2):250–4. [PubMed: 25220114]
9. Lucchinetti CF, et al. Distinct patterns of multiple sclerosis pathology indicates heterogeneity on pathogenesis. Brain Pathol. 1996; 6(3):259–274. [PubMed: 8864283]
10. Lucchinetti C, et al. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol. 2000; 47(6):707–17. [PubMed: 10852536]
11. Konig FB, et al. Persistence of immunopathological and radiological traits in multiple sclerosis. Arch Neurol. 2008; 65(11):1527–32. [PubMed: 19001173]
12. Metz I, et al. Pathologic heterogeneity persists in early active multiple sclerosis lesions. Ann Neurol. 2014; 75(5):728–38. [PubMed: 24771535]
13. Charcot JM. Histologie de la sclerose en plaques. Gaz des Hop (Paris). 1868; 41:554–566.
14. Tan IL, et al. MR venography of multiple sclerosis. AJNR Am J Neuroradiol. 2000; 21(6):1039–42. [PubMed: 10871010]
15. Hammond KE, et al. Quantitative in vivo magnetic resonance imaging of multiple sclerosis at 7 Tesla with sensitivity to iron. Ann Neurol. 2008; 64(6):707–13. [PubMed: 19107998]
16. Tallantyre EC, et al. Demonstrating the perivascular distribution of MS lesions in vivo with 7-Tesla MRI. Neurology. 2008; 70(22):2076–8. [PubMed: 18505982]

17. Sati P, et al. FLAIR*: a combined MR contrast technique for visualizing white matter lesions and parenchymal veins. Radiology. 2012; 265(3):926–32. [PubMed: 23074257]
18. Tallantyre EC, et al. Ultra-high-field imaging distinguishes MS lesions from asymptomatic white matter lesions. Neurology. 2011; 76(6):534–9. [PubMed: 21300968]
19. Gaitan MI, et al. Multiple sclerosis shrinks intralesional, and enlarges extralesional, brain parenchymal veins. Neurology. 2013; 80(2):145–51. [PubMed: 23255828]
20. Kau T, et al. The “central vein sign”: is there a place for susceptibility weighted imaging in possible multiple sclerosis? Eur Radiol. 2013; 23(7):1956–62. [PubMed: 23436147]
21. Absinta M, et al. Seven-tesla phase imaging of acute multiple sclerosis lesions: A new window into the inflammatory process. Ann Neurol. 2013; 74(5):669–78. [PubMed: 23813441]
22. Muller K, et al. Detailing intra-lesional venous lumen shrinking in multiple sclerosis investigated by sFLAIR MRI at 7-T. J Neurol. 2014; 261(10):2032–6. [PubMed: 25119839]
23. Dal-Bianco A, et al. Veins in plaques of multiple sclerosis patients - a longitudinal magnetic resonance imaging study at 7 Tesla. Eur Radiol. 2015; 25(10):2913–20. [PubMed: 25903703]
24. Lummel N, et al. Presence of a central vein within white matter lesions on susceptibility weighted imaging: a specific finding for multiple sclerosis? Neuroradiology. 2011; 53(5):311–7. [PubMed: 20585764]
25. Wuerfel J, et al. Lesion morphology at 7 Tesla MRI differentiates Susac syndrome from multiple sclerosis. Mult Scler. 2012; 18(11):1592–9. [PubMed: 22711711]
26. Kilsdonk ID, et al. Improved differentiation between MS and vascular brain lesions using FLAIR* at 7 Tesla. Eur Radiol. 2014; 24(4):841–9. [PubMed: 24317461]
27. Solomon, A., et al. Annals of Clinical and Translational Neurology. 2015. “Central vessel sign” on 3T FLAIR* MRI for the differentiation of multiple sclerosis from migraine. in press
28. George I, et al. Clinical 3-tesla FLAIR* MRI improves diagnostic accuracy in multiple sclerosis. Mult Scler. Jan 14.2016
29. Pitt D, et al. Imaging cortical lesions in multiple sclerosis with ultra-high-field magnetic resonance imaging. Arch Neurol. 2010; 67(7):812–8. [PubMed: 20625086]
30. Bagnato F, et al. Tracking iron in multiple sclerosis: a combined imaging and histopathological study at 7 Tesla. Brain. 2011; 134(Pt 12):3602–15. [PubMed: 22171355]
31. Bian W, et al. A serial in vivo 7T magnetic resonance phase imaging study of white matter lesions in multiple sclerosis. Mult Scler. 2012
32. Yao B, et al. Chronic multiple sclerosis lesions: characterization with high-field-strength MR imaging. Radiology. 2012; 262(1):206–15. [PubMed: 22084205]
33. Hagemeier J, et al. Iron deposition in multiple sclerosis lesions measured by susceptibility-weighted imaging filtered phase: a case control study. J Magn Reson Imaging. 2012; 36(1):73–83. [PubMed: 22407571]
34. Gaitan MI, et al. Initial investigation of the blood-brain barrier in MS lesions at 7 tesla. Mult Scler. 2013; 19(8):1068–73. [PubMed: 23246799]
35. Mehta V, et al. Iron is a sensitive biomarker for inflammation in multiple sclerosis lesions. PLoS One. 2013; 8(3):e57573. [PubMed: 23516409]
36. Kutzelnigg A, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain. 2005; 128(Pt 11):2705–12. [PubMed: 16230320]
37. Roosendaal SD, et al. In vivo MR imaging of hippocampal lesions in multiple sclerosis. J Magn Reson Imaging. 2008; 27(4):726–31. [PubMed: 18302199]
38. Roosendaal SD, et al. Accumulation of cortical lesions in MS: relation with cognitive impairment. Mult Scler. 2009; 15(6):708–14. [PubMed: 19435749]
39. Calabrese M, et al. Cortical lesions in primary progressive multiple sclerosis: a 2-year longitudinal MR study. Neurology. 2009; 72(15):1330–6. [PubMed: 19365054]
40. Calabrese M, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. Arch Neurol. 2009; 66(9):1144–50. [PubMed: 19752305]
41. Calabrese M, et al. Imaging distribution and frequency of cortical lesions in patients with multiple sclerosis. Neurology. 2010; 75(14):1234–40. [PubMed: 20739644]

42. Calabrese M, et al. A 3-year magnetic resonance imaging study of cortical lesions in relapse-onset multiple sclerosis. Ann Neurol. 2010; 67(3):376–83. [PubMed: 20373349]
43. Calabrese M, Filippi M, Gallo P. Cortical lesions in multiple sclerosis. Nat Rev Neurol. 2010; 6(8): 438–44. [PubMed: 20625376]
44. Calabrese M, et al. Cortical lesion load associates with progression of disability in multiple sclerosis. Brain. 2012; 135(Pt 10):2952–61. [PubMed: 23065788]
45. Calabrese M, et al. Exploring the origins of grey matter damage in multiple sclerosis. Nat Rev Neurosci. 2015; 16(3):147–58. [PubMed: 25697158]
46. Filippi M, et al. Intracortical lesions: relevance for new MRI diagnostic criteria for multiple sclerosis. Neurology. 2010; 75(22):1988–94. [PubMed: 21115953]
47. Geurts JJ, et al. Cortical lesions in multiple sclerosis: combined postmortem MR imaging and histopathology. AJNR Am J Neuroradiol. 2005; 26(3):572–7. [PubMed: 15760868]
48. Sethi V, et al. Improved detection of cortical MS lesions with phase-sensitive inversion recovery MRI. J Neurol Neurosurg Psychiatry. 2012; 83(9):877–82. [PubMed: 22807559]
49. Mainero C, et al. In vivo imaging of cortical pathology in multiple sclerosis using ultra-high field MRI. Neurology. 2009; 73(12):941–8. [PubMed: 19641168]
50. Nielsen AS, et al. Contribution of cortical lesion subtypes at 7T MRI to physical and cognitive performance in MS. Neurology. 2013; 81(7):641–9. [PubMed: 23864311]
51. Fischer MT, et al. Disease-specific molecular events in cortical multiple sclerosis lesions. Brain. 2013; 136(Pt 6):1799–815. [PubMed: 23687122]
52. Mainero C, et al. A gradient in cortical pathology in multiple sclerosis by in vivo quantitative 7 T imaging. Brain. 2015; 138(Pt 4):932–45. [PubMed: 25681411]
53. van der Valk P, De Groot CJ. Staging of multiple sclerosis (MS) lesions: pathology of the time frame of MS. Neuropathol Appl Neurobiol. 2000; 26(1):2–10. [PubMed: 10736062]
54. Lassmann H. Review: the architecture of inflammatory demyelinating lesions: implications for studies on pathogenesis. Neuropathol Appl Neurobiol. 2011; 37(7):698–710. [PubMed: 21696413]
55. Malayeri AA, et al. National Institutes of Health Perspective on Reports of Gadolinium Deposition in the Brain. J Am Coll Radiol. 2016
56. Gaitan MI, et al. Evolution of the blood-brain barrier in newly forming multiple sclerosis lesions. Ann Neurol. 2011; 70(1):22–9. [PubMed: 21710622]
57. van Walderveen MA, et al. Histopathologic correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis. Neurology. 1998; 50(5):1282–8. [PubMed: 9595975]
58. van Waesberghe JH, et al. Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability. Ann Neurol. 1999; 46(5):747–54. [PubMed: 10553992]
59. Lassmann H, van Horssen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. Nat Rev Neurol. 2012; 8(11):647–56. [PubMed: 23007702]
60. Chari DM. Remyelination in multiple sclerosis. Int Rev Neurobiol. 2007; 79:589–620. [PubMed: 17531860]
61. Franklin RJ, Gallo V. The translational biology of remyelination: Past, present, and future. Glia. 2014; 62:1905–1915. [PubMed: 24446279]
62. Prineas JW, et al. Multiple sclerosis: remyelination of nascent lesions. Ann Neurol. 1993; 33(2): 137–51. [PubMed: 8434875]
63. Raine CS, Wu E. Multiple sclerosis: remyelination in acute lesions. J Neuropathol Exp Neurol. 1993; 52(3):199–204. [PubMed: 7684075]
64. Patrikios P, et al. Remyelination is extensive in a subset of multiple sclerosis patients. Brain. 2006; 129(Pt 12):3165–72. [PubMed: 16921173]
65. Albert M, et al. Extensive cortical remyelination in patients with chronic multiple sclerosis. Brain Pathol. 2007; 17(2):129–38. [PubMed: 17388943]
66. Goldschmidt T, et al. Remyelination capacity of the MS brain decreases with disease chronicity. Neurology. 2009; 72(22):1914–21. [PubMed: 19487649]
67. Bramow S, et al. Demyelination versus remyelination in progressive multiple sclerosis. Brain. 2010; 133(10):2983–98. [PubMed: 20855416]

68. Chang A, et al. Cortical remyelination: a new target for repair therapies in multiple sclerosis. Ann Neurol. 2012; 72(6):918–26. [PubMed: 23076662]
69. Cui QL, et al. Oligodendrocyte progenitor cell susceptibility to injury in multiple sclerosis. Am J Pathol. 2013; 183(2):516–25. [PubMed: 23746653]
70. Kotter MR, Stadelmann C, Hartung HP. Enhancing remyelination in disease--can we wrap it up? Brain. 2011; 134(Pt 7):1882–900. [PubMed: 21507994]
71. Laule C, et al. Myelin water imaging in multiple sclerosis: quantitative correlations with histopathology. Mult Scler. 2006; 12(6):747–53. [PubMed: 17263002]
72. Sati P, et al. Micro-compartment specific T2* relaxation in the brain. Neuroimage. 2013; 77:268–78. [PubMed: 23528924]
73. Alonso-Ortiz E, Levesque IR, Pike GB. MRI-based myelin water imaging: A technical review. Magn Reson Med. 2014; 73(1):70–81. [PubMed: 24604728]
74. Levesque IR, et al. Reproducibility of quantitative magnetization-transfer imaging parameters from repeated measurements. Magn Reson Med. 2010; 64(2):391–400. [PubMed: 20665783]
75. Chen JT, et al. Magnetization transfer ratio evolution with demyelination and remyelination in multiple sclerosis lesions. Ann Neurol. 2008; 63(2):254–62. [PubMed: 18257039]
76. Schmierer K, Parkes HG, So PW. Direct visualization of remyelination in multiple sclerosis using T2-weighted high-field MRI. Neurology. 2009; 72(5):472. [PubMed: 19188581]
77. Vellinga MM, et al. Pluriformity of inflammation in multiple sclerosis shown by ultra-small iron oxide particle enhancement. Brain. 2008; 131(Pt 3):800–7. [PubMed: 18245785]
78. Tourdias T, et al. Assessment of disease activity in multiple sclerosis phenotypes with combined gadolinium- and superparamagnetic iron oxide-enhanced MR imaging. Radiology. 2012; 264(1): 225–33. [PubMed: 22723563]
79. Maarouf A, et al. Ultra-small superparamagnetic iron oxide enhancement is associated with higher loss of brain tissue structure in clinically isolated syndrome. Mult Scler. Oct 19.2015
80. Banati RB, et al. The peripheral benzodiazepine binding site in the brain in multiple sclerosis: quantitative in vivo imaging of microglia as a measure of disease activity. Brain. 2000; 123(Pt 11): 2321–37. [PubMed: 11050032]
81. Cosenza-Nashat M, et al. Expression of the translocator protein of 18 kDa by microglia, macrophages and astrocytes based on immunohistochemical localization in abnormal human brain. Neuropathol Appl Neurobiol. 2009; 35(3):306–28. [PubMed: 19077109]
82. Oh U, et al. Translocator protein PET imaging for glial activation in multiple sclerosis. J Neuroimmune Pharmacol. 2011; 6(3):354–61. [PubMed: 20872081]
83. Politis M, Su P, Piccini P. Imaging of microglia in patients with neurodegenerative disorders. Front Pharmacol. 2012; 3:96. [PubMed: 22661951]
84. Politis M, et al. Increased PK11195 PET binding in the cortex of patients with MS correlates with disability. Neurology. 2012; 79(6):523–30. [PubMed: 22764258]
85. Ratchford JN, et al. Decreased microglial activation in MS patients treated with glatiramer acetate. J Neurol. 2012; 259(6):1199–205. [PubMed: 22160466]
86. Takano A, et al. In vivo TSPO imaging in patients with multiple sclerosis: a brain PET study with [18F]FEDAA1106. EJNMMI Res. 2013; 3(1):30. [PubMed: 23618062]
87. Petzold A. Intrathecal oligoclonal IgG synthesis in multiple sclerosis. J Neuroimmunol. 2013; 262(1–2):1–10. [PubMed: 23890808]
88. Lucchinetti CF, et al. Inflammatory cortical demyelination in early multiple sclerosis. N Engl J Med. 2011; 365(23):2188–97. [PubMed: 22150037]
89. Magliozzi R, et al. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. Brain. 2007; 130(Pt 4):1089–104. [PubMed: 17438020]
90. Magliozzi R, et al. A Gradient of neuronal loss and meningeal inflammation in multiple sclerosis. Ann Neurol. 2010; 68(4):477–93. [PubMed: 20976767]
91. Howell OW, et al. Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis. Brain. 2011; 134(Pt 9):2755–71. [PubMed: 21840891]

92. Choi SR, et al. Meningeal inflammation plays a role in the pathology of primary progressive multiple sclerosis. Brain. 2012; 135(Pt 10):2925–37. [PubMed: 22907116]

93. Kuerten S, et al. Tertiary lymphoid organ development coincides with determinant spreading of the myelin-specific T cell response. Acta Neuropathol. 2012; 124(6):861–73. [PubMed: 22842876]

94. Magliozzi R, et al. B-cell enrichment and Epstein-Barr virus infection in inflammatory cortical lesions in secondary progressive multiple sclerosis. J Neuropathol Exp Neurol. 2013; 72(1):29–41. [PubMed: 23242282]

95. Absinta M, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. Neurology. 2015; 85(1):18–28. [PubMed: 25888557]

96. Mesaros S, et al. Evidence of thalamic gray matter loss in pediatric multiple sclerosis. Neurology. 2008; 70(13 Pt 2):1107–12. [PubMed: 18272867]

97. Henry RG, et al. Connecting white matter injury and thalamic atrophy in clinically isolated syndromes. J Neurol Sci. 2009; 282(1–2):61–6. [PubMed: 19394969]

98. Minagar A, et al. The thalamus and multiple sclerosis: modern views on pathologic, imaging, and clinical aspects. Neurology. 2013; 80(2):210–9. [PubMed: 23296131]

99. Kipp M, et al. Thalamus pathology in multiple sclerosis: from biology to clinical application. Cell Mol Life Sci. 2015; 72(6):1127–47. [PubMed: 25417212]

100. Bisecco A, et al. Connectivity-based parcellation of the thalamus in multiple sclerosis and its implications for cognitive impairment: A multicenter study. Hum Brain Mapp. 2015; 36(7):2809–25. [PubMed: 25873194]

101. Sicotte NL, et al. Regional hippocampal atrophy in multiple sclerosis. Brain. 2008; 131(Pt 4): 1134–41. [PubMed: 18375977]

102. Longoni G, et al. Deficits in memory and visuospatial learning correlate with regional hippocampal atrophy in MS. Brain Struct Funct. 2015; 220(1):435–44. [PubMed: 24189776]

103. Sacco R, et al. Cognitive impairment and memory disorders in relapsing-remitting multiple sclerosis: the role of white matter, gray matter and hippocampus. J Neurol. 2015

104. Kearney H, Miller DH, Ciccarelli O. Spinal cord MRI in multiple sclerosis-diagnostic, prognostic and clinical value. Nat Rev Neurol. 2015; 11(6):327–338. [PubMed: 26009002]

105. Gass A, et al. MRI monitoring of pathological changes in the spinal cord in patients with multiple sclerosis. Lancet Neurol. 2015; 14(4):443–54. [PubMed: 25748099]

106. Horsfield MA, et al. Rapid semi-automatic segmentation of the spinal cord from magnetic resonance images: Application in multiple sclerosis. Neuroimage. 2010; 50(2):446–55. [PubMed: 20060481]

107. Liu W, et al. In vivo imaging of spinal cord atrophy in neuroinflammatory diseases. Ann Neurol. 2014; 76(3):370–8. [PubMed: 25042583]

108. Ciccarelli O, et al. Diffusion-based tractography in neurological disorders: concepts, applications, and future developments. Lancet Neurol. 2008; 7(8):715–27. [PubMed: 18635020]

109. Gordon-Lipkin E, et al. Retinal nerve fiber layer is associated with brain atrophy in multiple sclerosis. Neurology. 2007; 69(16):1603–9. [PubMed: 17938370]

110. Siger M, et al. Optical coherence tomography in multiple sclerosis: thickness of the retinal nerve fiber layer as a potential measure of axonal loss and brain atrophy. J Neurol. 2008; 255(10): 1555–60. [PubMed: 18825432]

111. Petzold A, et al. Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurol. 2010; 9(9):921–32. [PubMed: 20723847]

112. Dorr J, et al. Association of retinal and macular damage with brain atrophy in multiple sclerosis. PLoS One. 2011; 6(4):e18132. [PubMed: 21494659]

113. Saidha S, et al. Optical coherence tomography reflects brain atrophy in MS: A four year study. Ann Neurol. 2015; 78(5):801–13. [PubMed: 26190464]

114. Filippi M, Rocca MA. Present and future of fMRI in multiple sclerosis. Expert Rev Neurother. 2013; 13(12 Suppl):27–31. [PubMed: 24289839]

115. Mainero C, et al. Enhanced brain motor activity in patients with MS after a single dose of 3,4-diaminopyridine. Neurology. 2004; 62(11):2044–50. [PubMed: 15184612]

116. Filippi M, et al. Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR imaging measures--an explorative study. Radiology. 2012; 262(3):932–40. [PubMed: 22357892]

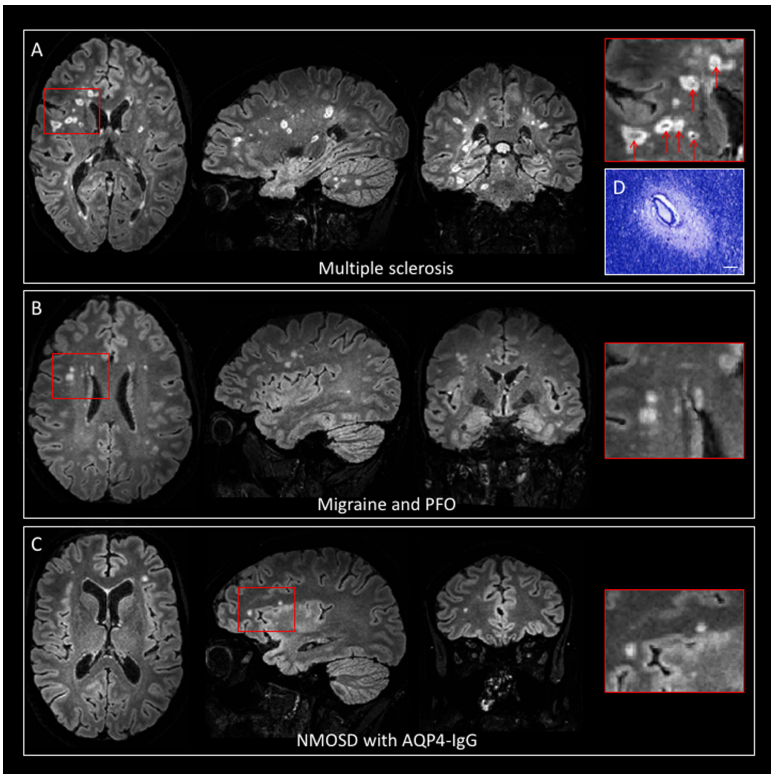

Figure 1. Vasculoscentric *vs* non-vasculocentric lesion appearance

Precontrast 3T FLAIR* images [magnified views in red boxes, for sequence details see Sati et al., Radiology 2012] in three different neurological conditions showing discrete white matter lesions:

(A) 33-year-old woman with relapsing-remitting MS;

(B) 53-year-old woman with migraine and patent foramen ovale (PFO);

(C) 54-year-old woman with neuromyelitis optica spectrum disorder (NMOSD) with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG).

A prominent central vein is clearly discernable in the majority of demyelinated MS lesions in vivo (red arrows, A), whereas MS-mimicking lesions in microembolic/ischemic conditions (B) and NMOSD (C) do not present this morphological feature.

(D) Pathological insert showing the vasculocentric development of a demyelinated MS lesion in a 59-year-old man with progressive MS (Luxol fast blue-periodic acid Schiff staining [LFB-PAS], scale bar 100 μm).

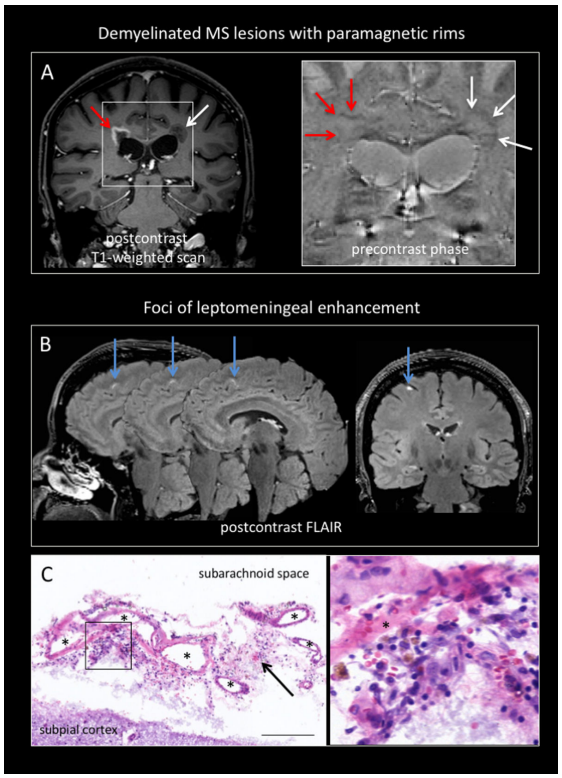

Figure 2. MS-related "hidden" inflammation

(A) Two periventricular lesions with paramagnetic rims on precontrast 3T phase images in a 31-year-old woman with relapsing-remitting MS. The rim on phase images reflects the presence of paramagnetic substances, (possibly inflammation-related) at the lesion edge. Lesion 1. Active lesion with peripheral leakage of gadolinium (centripetal pattern) and paramagnetic rim (red arrows);
Lesion 2. Chronic lesion with paramagnetic rim (white arrows).
(B) Multiple foci of leptomeningeal enhancement (cyan arrows) on postcontrast FLAIR images in a 42-year-old woman with relapsing-remitting MS.
(C) Perivascular inflammatory infiltrate in the leptomeninges (black arrows and magnified box) where leptomeningeal enhancement was found in vivo [10 μm-thick Hematoxylin & Eosin (H&E) representative section; asterisks indicate meningeal venules; scale bar 200 μm]. From Absinta et al., Neurology 2015, Jul 7;85(1):18–28, doi:10.1212/WNL.0000000000001587 with permission.