Published in final edited form as:

J Neuroimmunol. 2017 March 15; 304: 72–80. doi:10.1016/j.jneuroim.2016.09.015.

Imag(in)ing Multiple Sclerosis: Time to Take Better Pictures

Daniel S. Reich, MD, PhD

Abstract

Magnetic resonance imaging (MRI) has led to the identification of widespread brain abnormalities in multiple sclerosis (MS) that extend far beyond the classic white matter lesion. These findings have generated the idea that MS should be understood as a disease of the whole brain, not just the white matter. While it is no doubt the case that many different pathways are ultimately involved in the destruction of brain tissue that occurs in MS, the implications of the accumulated evidence for understanding disease pathophysiology – and hence the overall significance of these imaging findings – are doubtful. Here, I argue that the principled use of imaging can, in fact, address questions about the genesis of these whole-brain abnormalities, rather than simply describe them.

Introduction

Multiple sclerosis (MS) is the commonest nontraumatic cause of chronic disability in young adults, afflicting about 0.1% of Americans. It causes lifelong disability, and after a time that disability often starts to accumulate relentlessly – a phase of the disease that is called, somewhat unfortunately, “progressive MS.” Under the microscope, the brain in MS exhibits inflammation, demyelination, and neurodegeneration. Although at the time of this writing there are 12 approved medications in the United States, and more in various stages of development, and although those medications reduce symptoms and appear to variably delay accumulation of disability, treatment remains expensive and only partially effective, and it often needs to be changed.

One hundred years ago, the only way to study the biology of the disease was as Dawson did: examining the brain at autopsy (1). Working in Edinburgh, Dawson provided some of the best pathological descriptions of the disease and identified features of MS plaques, or lesions, that are still far from understood. Today, of course, we can study the effects of the disease in living people through the window of magnetic resonance imaging (MRI), and MRI of the brain in MS shows us much the same thing that Dawson saw 100 years ago: focal lesions, most prominently in the cerebral white matter, and the consequent accelerated brain atrophy. These are the hallmarks of the disease, and they’re what’s used to make the diagnosis (2).

The earliest MRI scans of MS were obtained in London around 1980 (3). The demonstration that MRI can “see” white matter lesions in the MS brain must have been quite dramatic.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Early cross-sectional and longitudinal MRI studies quickly followed, to the point where today there are 10 or more papers each week that are retrieved through a PubMed search for “MRI and multiple sclerosis.” These early studies identified critical features of MS lesions. Studying those lesions, researchers learned a great deal about when they appear, how they change over time, what accompanies them (notably breakdown of the blood-brain barrier), how they correlate with neurological symptoms during relapse, and how they are affected by various therapies. Importantly, this knowledge could only have been gleaned from imaging: cross-sectional pathology studies could never have yielded that wealth of information in typical cases. With this technology in hand, it must have seemed, to some, that the disease would soon be solved.

However, even early on, people began to realize that the presence, number, and even volume of these lesions – while tremendously valuable for making the diagnosis and assessing response to therapy in clinical trials – was not telling the whole story. Consider clinical relapses, for example. Serial studies at the NIH established that new lesions appear many times more frequently than new clinical symptoms, and these lesions persist following resolution of the symptoms (4). Interestingly, a focal lesion in a clinically eloquent location, such as the posterior limb of the internal capsule, can be entirely asymptomatic, whereas an acute infarct in much the same place can hardly fail to send someone to the hospital (Figure 1A). Even more perplexingly, it is not uncommon to evaluate an MS patient with a high lesion load but symptoms no more severe than a numb toe (Figure 1B). Indeed, in cross-sectional studies of any reasonable size, the lesion number and volume can explain at most about 30%, and usually far less, of the variance in clinical disability (5,6). This is certainly disappointing in a disease where it is so clear that the signature pathological hallmark – the white matter lesion – can be detected so efficiently.

Imaging research takes a detour

The emergence of the so-called clinical-radiological paradox was roughly contemporaneous with the development of a few key MRI techniques sensitive to something other than longitudinal and transverse magnetic relaxation. These techniques came with more than just sensitivity: the signal could be quantified and thereby more easily compared in a standardized fashion. Quantification opened up a whole new area of study in MRI applied to clinical problems, such as MS, and it came at a time when conventional imaging approaches seemed to have reached their limit.

One major line of research emerged from studying the diffusion of water in brain tissue, which can be accomplished thanks in no small part to work done at the NIH in the late 1980s and early 1990s (7,8). Diffusion tensor imaging (DTI), capable of producing extraordinary images of white matter fibers from in vivo scans lasting only a few minutes, has become very popular: PubMed lists 1718 publications from 2014 alone.

Interestingly enough, the same year that DTI was first reported in fixed brains of cats, just a few hundred feet away at the NIH, Henry McFarland, Joseph Frank, and Nicholas Patronas were producing outstanding images of MS on a human MRI scanner (Figure 2A). The standard pulse sequences – producing images “weighted” to proton density and the T1 and

T2 relaxation time constants – are for the most part the workhorses used in clinical radiology today. But in the research world, there was a hunger to do something different, which led to investigations into not only diffusion MRI but also magnetization-transfer weighting and proton spectroscopy.

Beginning around the same time, there was a massive proliferation of the application of image processing tools to MRI data that was largely made necessary by the development of functional MRI techniques. Analyzing fMRI data requires extensive image processing and statistical modeling, which contributed greatly to the proliferation of image processing tools, along with greater computational power, new approaches to image analysis, phased-array radiofrequency coils, and 3D gradient-echo sequences (Figure 2B). Interestingly, when studied with a 3D T1-weighted gradient-echo scan, lesions can have a great deal of internal structure, even when the scan was obtained on a 1.5-tesla system with a quadrature head coil. These details must reflect the underlying biology, but they didn't make much of an impression on the literature. Instead, what people were doing with images like these was measuring brain volume and trying to distinguish between white matter and gray matter – a simplified view of the brain that recalls anatomical descriptions from prior centuries.

It is therefore worth stepping back and listing the most important insights about MS from MRI studies of the last 20 years, what I call the “post-lesion era.” In my judgment, these insights are the following: (1) the brain atrophies at a remarkable rate over the course of the disease; (2) MRI, as currently implemented, is not pathologically specific, or at least not usefully so; and (3) the accepted clinical phenotypes of MS are not separable by MRI.

Large studies have shown that the brain atrophies at a rate of about 0.5% per year in MS, about twice as fast as in healthy people (9). This process is illustrated in Supplementary Video 1, which was made from about 100 MRI scans of an individual with MS over a 20-year period. Whether atrophy is evidence of a primary neurodegenerative process or is secondary to inflammatory destruction of the neuropil is still a matter of debate (10), but there is no question that on some level it represents the complete and irreversible loss of brain tissue – exactly what early treatment with disease modifying therapies seeks to prevent. The current effort to improve measurement of atrophy, whether over the whole brain or specifically in white matter, gray matter, or thalamus, is important, but what's really needed are careful experiments – clinical trials, long-term natural history studies – to understand its causes in vivo. Doing so will require much better imaging, particularly of spinal cord and brainstem disease, than is available today.

The second major insight derived from research over the past 20 years is that the pathologies that occur in MS – inflammation, demyelination, and neuroaxonal loss – do not have simple MRI correlates. As mentioned above, the MRI signal can be sensitized to various relaxation properties of tissue subjected to strong magnetic fields, as well as to other properties such as diffusion. Water-bound protons give by far the strongest signal due to their abundance in biological tissues, but MRI systems can also be set up to be sensitive to protons bound to other molecules or to various other nuclei. Additionally, the local environment of protons can also affect relaxation properties, as can exogenously administered contrast agents. Combinations of these approaches – the details of which are beyond the scope of this article

– have been proposed to be biologically specific, and some of the claims are based on comparison with histology. However, these markers are either indirect (for example, imaging protons in water molecules trapped between myelin bilayers rather than protons in the myelin itself), so heavily correlated with one another as to preclude straightforward interpretation, or diluted due to spatial sensitivity (meaning that various pathologies occurring in the same place will contribute to the measurement). Even abnormal permeability of the blood-brain barrier does not signify the presence of specific cell populations and cytokines, and in some instances – for example, immune reconstitution in progressive multifocal encephalopathy – it may be salutary rather than deleterious. Thus, the lack of simple MRI-pathology correlation, while certainly disappointing, should not come as a surprise.

Despite the poor specificity of MRI for particular pathological processes, study after study has demonstrated its remarkable sensitivity for tissue abnormalities. The failure to distinguish between clinically relapsing and progressive MS, the third major insight from the last 20 years of imaging research, is surely important – particularly since focal lesion formation is well known to be the basis of true relapses, which by definition are absent in primary progressive MS. But although people with primary progressive MS have fewer lesions on average (11), the overlap is great, and on a case-by-case basis assignment of phenotype based on MRI is impossible; an example is provided in Figure 3. Yet our phenotype classification (12) and inclusion criteria for large-scale clinical trials remain fundamentally unchanged, despite compelling evidence that MRI-based classification may be more useful for predicting treatment response. The best example of this is the OLYMPUS trial in primary-progressive MS (13), which overall was a failure: on average, patients did not improve when treated with rituximab. But the subgroup that looked more like relapse-onset by MRI – younger people who developed new contrast-enhancing lesions during the trial – seemed to respond at least partially.

These results – while important – provide some understanding of the disease process. At the very least, they constrain our ideas about what is going on in MS, though mechanistically they only provide limited insight. But a look back at the bulk of MS imaging research over the past 20 years suggests a deeper problem: that we have more or less stopped looking at the images we make and trying to make them better. We have replaced images with dots on scatter plots and numbers in tables. We have substituted population studies for in-depth studies of individuals. This is remarkable in a disease that is among the most diverse neurological disorders known, in which a person's brain MRI is as uniquely recognizable as his or her fingerprint or face. We have often taken the convenient path, on the one hand by studying processes that play out over days to weeks, such as lesion development, with serial imaging every few months, and on the other hand by imaging annual changes, such as brain atrophy in progressive MS, that can barely be detected in that time frame in individuals.

Roads no longer worth taking

As a field, it is time to refocus our efforts to truly image the disease as it plays out in individuals. To do so, we need to let go of four dearly held assumptions: (1) that MS brains

should be averaged together; (2) that 1 mm^3 voxels are “high resolution”; (3) that pathology is always the gold standard; and (4) that MS-related changes should fit convenient schedules.

The first assumption to be purged is that MS brain scans should be merged to perform “group analyses.” This type of analysis is fundamental to advanced image-processing techniques like statistical parametric mapping, voxel-based morphometry (14), and the popular tract-based spatial statistics approach to analyzing DTI data (15). All of these approaches share the underlying assumption that MS plays out the same way in different people. Yet we know it doesn’t: most of the time, the variance is much more interesting than the mean.

There are also substantial technical hurdles to coregistering brains affected by diseases such as MS, hurdles that are often swept under the rug. Figure 4 shows what happened when my colleagues and I tried repeatedly to match the brains of three people with MS to an atlas that consists of the average of 152 healthy brains – the so-called Montreal Neurological Institute (MNI) template. The MS cases in the bottom two rows have substantial atrophy and many focal lesions. None of the registration approaches really seems to work, and some fail terribly. The basic problem here is fundamental: when tissue is lost, as often happens in MS, there’s really no way to figure out from the images which parts of two people’s brains correspond. In other words, you can’t register something to nothing.

The second concept that needs to be abandoned is the somewhat complacent idea that 1 mm^3 isotropic voxels are “high resolution.” If we place a 1 mm^3 voxel in a portion of the body of the corpus callosum that harbors large axons of about 5 microns in diameter (16), such a voxel should contain about 40,000 axons (17). But if we image the same location with $0.2 \times 0.2 \times 1\text{ mm}$ voxels, there would be about 1600 axons. Technically, this is possible: Figure 5 shows such an image from a healthy volunteer taken on a 7-tesla scanner. While 1600 axons per voxel is still a lot, it is meaningfully better than 40,000 if one is interested in assessing the structure of this tissue.

Thirdly, we need to abandon the idea – admittedly one that is often foisted on images by our biologist colleagues – that insights into biology can’t be gleaned from noninvasive macroscopic imaging. In fact, MRI can actually *help* us do pathology. Supplementary Video 2 shows a postmortem scan of part of the intact brain of a person with MS, again taken on a 7-tesla scanner, in this case with 150 micron isotropic voxels. There is a huge range of pathology that can be seen by scrolling through these slices. On the other hand, when brains are cut after autopsy into 1 cm thick slices, as is done routinely, there’s a big sampling problem: only findings that are present on the surface and that can be seen or felt can be sampled. Of course, MRI cannot replace pathology, but it can help a great deal by sampling much larger swaths of tissue and by doing so frequently and while the patient is still alive. And it can also be used to guide the pathological sampling, as we have recently described (18).

Finally, we must stop assuming that MS-related changes over time fit neatly into convenient schedules. The various disease-related processes in MS play out with very different time courses. An individual lesion develops and forms over a period of a few months, and in

some cases changes dramatically over a few days. On the other hand, atrophy can be very slow – 0.5% per year, on average, but with a wide range (9) – a rate that is comparable to the measurement error. Thus, to detect real atrophy in a typical MS case, several years of scans may be required.

New paths to forge

To move forward, I propose five areas of focus to advance the field of imaging in MS: (1) make better, more detailed images; (2) image the spatiotemporal dynamics; (3) perform very long-term studies; (4) define in detail the radiological-pathological correlation in animal models; and (5) study disease onset. My group at NINDS is pursuing some of these, and I will provide examples in passing.

Figure 6 juxtaposes the first published MRI scan of MS, from 1980, with a 7-tesla scan from NIH. Clearly the field has made a lot of progress in its ability to image details such as small lesions and small veins. But this 7T image isn't good enough. We need to dive down further so that we can really take pictures on the level of detail that is relevant to the disease. What might we see if we do that? We might be able to see remyelinated "shadow plaques" directly, as has been demonstrated by postmortem imaging (19). We might be able to see inflammation in the leptomeninges, a small portion of which can be visualized with T2-weighted FLAIR MRI scans performed at least 10 minutes after gadolinium contrast injection in about a third of cases of progressive MS (20). We might be able to characterize the perivenular topography of MS plaques in far greater detail than we have done previously using an advanced segmented echo-planar imaging readout scheme (21). Such visualization might be diagnostically useful (22), or potentially related to perivascular inflammatory cuff formation (23), but perhaps with improved detection we might even see the neovascularization that can support smoldering inflammation or even nascent repair at the lesion edge (24,25).

The second area of growth is to study the dynamics of tissue damage, rather than its mere presence or absence. At pathology, a variety of lesion types can be seen in MS (26,27), but how these change over time can really only be inferred by imaging. In 2011, we showed that new white matter lesions, which mostly form in early stages of the disease, can change their dynamic patterns of contrast enhancement in a matter of days (28). This reflects a shift in the locus of blood-brain-barrier opening from the lesion center to its periphery, and I believe this finding gives insight into the ways in which inflammatory demyelinating lesions form in the brain. We've been pursuing this finding in subsequent studies at 7-tesla MRI (29,30). Figure 7 shows a lesion where contrast enhancement begins at the lesion periphery. On high-resolution T2*-weighted imaging before contrast injection, there is a very clear rim on both the phase image, and usually on the magnitude image, that colocalizes with the part of the lesion where the contrast material leaks out of small capillaries. One month later, the contrast enhancement and rim have both resolved, indicating not only that the rim is an endogenous marker of blood-brain barrier opening, but also telling us something about the biology. Such rims may be formed by the presence of paramagnetic species such as iron, some serum proteins, and free radicals, and we believe that their presence at the lesion edge may signify part of the brain's physiologic response to acute inflammation – perhaps an

attempt to contain the damage and prevent the new lesion from growing forever. This is just a hypothesis, and it needs to be investigated at the tissue level and animal models, but without dynamic imaging we would never have generated it.

Third, studies should focus more on how the disease plays out in individuals over really long epochs. Cross-sectional study of a spectrum of cases at different disease stages does not really substitute for long-term longitudinal follow-up over periods on the order of 20 years or more, the time span over which MS plays out. A few such imaging-based studies have been published (31–33), but more are necessary. This will require the development of statistical methods, such as normalization, that can utilize old data and account for changes in acquisition parameters (34). In work done several years ago, we investigated enlargement of the cerebral ventricles in MS over many years – a proxy for cerebral atrophy – in patients studied at the NINDS Neuroimmunology Branch. Using a mixed-effects approach to model not only the rate of ventricular enlargement but also the effects of changing acquisition parameters across 1331 scans over up to 11 years per patient (there were >100 separate T1-weighted imaging protocols in this dataset), we found that in order to accurately predict the long-term rate of ventricular enlargement, 5 to 6 years of data were required. Thus, short-term studies, even studies as long as 2 or 3 years, can't really tell us very much about how the disease changes over time.

The fourth imperative is to vastly improve the images we make of inflammatory demyelination in animal models in order to better link the observations to those we can make in MS. Of course, in vivo imaging in small animals is far from trivial. There are small-bore, high-field MRI systems to image animals, but the structures to be imaged are correspondingly small, and as such the resolution is often insufficient to look at the relevant level of detail in all cases. A simple example derives from work we are doing at NIH using a primate model of MS, experimental autoimmune encephalomyelitis in the common marmoset. Figure 8 shows images from a single animal. In the top row, the image on the left was obtained after formalin fixation of the brain, and a lesion in the white matter is clearly visible (circle). In the center, the same type of scan was performed in vivo, demonstrating a dark dot in the center of the lesion that derives from deoxyhemoglobin within the lesion's central vein. The deoxyhemoglobin is washed away because blood is replaced by saline at the end of the experiment, so the vein is not so clear in the postmortem scan despite its higher resolution. The corresponding pathological section is shown on the right, stained with hematoxylin and eosin, and indeed demonstrates the central vein, which is shown in detail in the middle row using a variety of pathological techniques to demonstrate the perivascular inflammatory reaction and associated demyelination. But of course the major advantage of studying an animal model is that animals can be assessed before the disease is induced and at various time points thereafter. This time series is presented in the bottom row, where images from baseline to the end of the experiment show how this particular perivenular lesion appears and evolves over time (35,36).

Finally, imaging may be the best way to study the earliest detectable events in the disease. There's currently a major trend in the field to address the problem of progressive MS (37). Given the major morbidity associated with progression, this focus is laudable; if successful, it would immeasurably help many people with MS who are confined to a wheelchair or who

are headed in that direction. Considerable money and effort are now being thrown at this problem, but of course what remains unknown is whether progression can be pharmacologically halted, let alone reversed. Indeed, studies repeatedly show that the seeds of disease progression are planted very early on: brain atrophy can be detected in populations with clinically isolated syndromes (38,39) and even in people with asymptomatic brain lesions suggestive of MS, the so-called “radiologically isolated syndrome” (40). But almost nothing is known about how the disease really develops in these very early stages, or even when and where it starts. All we have are speculations.

In an ongoing collaboration between our group at NINDS and Philip De Jager’s group at Harvard Medical School, we are currently pursuing a study, known as Genes and Environment in Multiple Sclerosis* (NCT01353547, NCT01617395), which will hopefully make it possible to investigate true disease onset as opposed to just the first reported symptoms. In this study, we are exploring whether the progress in identifying MS susceptibility genes (41,42) and environmental risk factors will allow the identification of people at risk while they are still entirely healthy. As MS is relatively rare even in “high-risk” groups such as first-degree relatives with multiple risk alleles and environmental exposures, large international studies will probably be required, and as such careful consideration of the imaging methods is critical. But the potential value is illustrated in Figure 9, which shows the evolution from health to MS in a man who had a normal MRI scan as a healthy volunteer in a research protocol 14 years before presenting with clinically isolated syndrome. The absence of ventricular enlargement in the follow-up scan is both striking and consistent with the hypothesis that population-level atrophy in radiologically and clinically isolated syndromes is mostly due to subclinical inflammation rather than primary neurodegeneration.

To conclude: MS is a multifocal disease that plays out differently in different people. These differences are as important as the commonalities, and, as such, making progress in MS research will require us to take better pictures in the context of hypothesis-driven research studies, and then to examine those pictures with great care. Thirty-five years of MRI-based research clearly demonstrate that imaging, with its unique ability to track and localize the dynamics of the disease with ever-greater precision, is going to play a critical role in solving the puzzle of this disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The ideas presented here in no small measure derive from conversations with trainees, colleagues, and mentors, notably Irene Cortese, Henry McFarland, Steven Jacobson, Peter Calabresi, Pascal Sati, and Govind Nair. I thank them as well as the many participants in research studies at the NIH Neuroimmunology Branch and Johns Hopkins MS Center from whom I’ve learned a great deal. My work is supported by the Intramural Research Program at NINDS.

*<http://www.facebook.com/pages/Genes-and-Environment-in-Multiple-Sclerosis-GEMS-Research-Study/200900853288242>

References

1. Dawson, JW. The Histology of Disseminated Sclerosis. In: Bruce, AN., editor. Trans Roy Soc Edin. Vol. 50. 1916. p. 517-740.
2. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology*. 2011 Feb; 69(2): 292–302. [PubMed: 21387374]
3. Young IR, Hall AS, Pallis CA, Legg NJ, Bydder GM, Steiner RE. Nuclear magnetic resonance imaging of the brain in multiple sclerosis. *Lancet*. 1981 Nov 14; 2(8255):1063–6. [PubMed: 6118521]
4. Harris JO, Frank JA, Patronas N, McFarlin DE, McFarland HF. Serial gadolinium-enhanced magnetic resonance imaging scans in patients with early, relapsing-remitting multiple sclerosis: implications for clinical trials and natural history. *Annals of Neurology*. 1991 May; 29(5):548–55. [PubMed: 1859184]
5. Barkhof F. The clinico-radiological paradox in multiple sclerosis revisited. *Curr Opin Neurol*. 2002 Jun 1; 15(3):239–45. [PubMed: 12045719]
6. Goodin DS. Magnetic resonance imaging as a surrogate outcome measure of disability in multiple sclerosis: have we been overly harsh in our assessment? *Annals of Neurology*. 2006 Apr; 59(4): 597–605. [PubMed: 16566022]
7. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys J*. 1994; 66(1):259–67. [PubMed: 8130344]
8. van Zijl, P., Davis, D., Moonen, CTW. Diffusion spectroscopy in living systems. In: Gillies, RJ., editor. *NMR in Physiology and Biomedicine*. 1. San Diego: Academic Press; 1994. p. 185-98.
9. De Stefano, N., Giorgio, A., Battaglini, M., Rovaris, M., Sormani, MP., Barkhof, F., et al. *Neurology*. Vol. 74. Lippincott Williams & Wilkins; 2010 Jun 8. Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes; p. 1868-76.
10. Stys PK, Zamponi GW, van Minnen J, Geurts JGG. Will the real multiple sclerosis please stand up? *Nat Rev Neurosci*. 2012 Jul; 13(7):507–14. [PubMed: 22714021]
11. Thompson AJ, Kermode AG, Wicks D, MacManus DG, Kendall BE, Kingsley DP, et al. Major differences in the dynamics of primary and secondary progressive multiple sclerosis. *Annals of Neurology*. 1991; 29(1):53–62. [PubMed: 1996879]
12. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014 Jul 15; 83(3):278–86. [PubMed: 24871874]
13. Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Annals of Neurology*. 2009 Oct; 66(4):460–71. [PubMed: 19847908]
14. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *NeuroImage*. 2000 Jun 1; 11(6 Pt 1):805–21. [PubMed: 10860804]
15. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage*. 2006 Jul 15; 31(4):1487–505. [PubMed: 16624579]
16. Aboitiz F, Scheibel AB, Fisher RS, Zaidel E. Fiber composition of the human corpus callosum. *Brain Res*. 1992 Dec 11; 598(1–2):143–53. [PubMed: 1486477]
17. Alexander DC, Hubbard PL, Hall MG, Moore EA, Ptito M, Parker GJM, et al. Orientationally invariant indices of axon diameter and density from diffusion MRI. *NeuroImage*. 2010 Oct 1; 52(4):1374–89. [PubMed: 20580932]
18. Absinta M, Nair G, Filippi M, Ray-Chaudhury A, Reyes-Mantilla MI, Pardo CA, et al. Postmortem magnetic resonance imaging to guide the pathologic cut: individualized, 3-dimensionally printed cutting boxes for fixed brains. *J Neuropathol Exp Neurol*. 2014 Aug; 73(8):780–8. [PubMed: 25007244]
19. Schmierer K, Parkes HG, So P-W. Direct visualization of remyelination in multiple sclerosis using T2-weighted high-field MRI. *Neurology*. 2009 Feb 3. 72(5):472. [PubMed: 19188581]

20. Absinta M, Vuolo L, Rao A, Nair G, Sati P, Cortese ICM, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. *Neurology*. 2015 Jul 7; 85(1):18–28. [PubMed: 25888557]
21. Sati P, George IC, Shea CD, Gaitán MI, Reich DS. FLAIR*: a combined MR contrast technique for visualizing white matter lesions and parenchymal veins. *Radiology*. 2012 Dec; 265(3):926–32. [PubMed: 23074257]
22. Mistry N, Dixon J, Tallantyre E, Tench C, Abdel-Fahim R, Jaspan T, et al. Central veins in brain lesions visualized with high-field magnetic resonance imaging: a pathologically specific diagnostic biomarker for inflammatory demyelination in the brain. *JAMA Neurol American Medical Association*. 2013 May; 70(5):623–8.
23. Gaitán MI, Sati P, Nair G, Reich DS. Multiple sclerosis shrinks intralesional, and enlarges extralesional, brain parenchymal veins. *Neurology*. 2013 Jan 8; 80(2):145–51. [PubMed: 23255828]
24. Proescholdt MA, Jacobson S, Tresser N, Oldfield EH, Merrill MJ. Vascular endothelial growth factor is expressed in multiple sclerosis plaques and can induce inflammatory lesions in experimental allergic encephalomyelitis rats. *J Neuropathol Exp Neurol*. 2002 Oct; 61(10):914–25. [PubMed: 12387457]
25. Girolamo F, Coppola C, Ribatti D, Trojano M. Angiogenesis in multiple sclerosis and experimental autoimmune encephalomyelitis. *Acta Neuropathol Commun*. 2014 Jul 22.2(1):84. [PubMed: 25047180]
26. Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Annals of Neurology*. 2000 Jun; 47(6):707–17. [PubMed: 10852536]
27. Frischer JM, Weigand SD, Guo Y, Kale N, Parisi JE, Pirko I, et al. Clinical and pathological insights into the dynamic nature of the white matter multiple sclerosis plaque. *Annals of Neurology*. 2015 Aug 1. n/a–n/a.
28. Gaitán, MI., Shea, CD., Evangelou, IE., Stone, RD., Fenton, KM., Bielekova, B., et al. *Annals of Neurology*. Vol. 70. Wiley Subscription Services, Inc A Wiley Company; 2011 Jul. Evolution of the blood-brain barrier in newly forming multiple sclerosis lesions; p. 22-9.
29. Gaitán MI, Sati P, Inati SJ, Reich DS. Initial investigation of the blood-brain barrier in MS lesions at 7 tesla. *Mult Scler*. 2013 Jul; 19(8):1068–73. [PubMed: 23246799]
30. Absinta M, Sati P, Gaitán MI, Maggi P, Cortese ICM, Filippi M, et al. Seven-tesla phase imaging of acute multiple sclerosis lesions: a new window into the inflammatory process. *Annals of Neurology*. 2013 Nov; 74(5):669–78. [PubMed: 23813441]
31. Fisher E, Lee J-C, Nakamura K, Rudick RA. Gray matter atrophy in multiple sclerosis: a longitudinal study. *Annals of Neurology*. 2008 Sep; 64(3):255–65. [PubMed: 18661561]
32. Fisniku LK, Brex PA, Altmann DR, Miszkil KA, Benton CE, Lanyon R, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain*. 2008 Mar; 131(Pt 3):808–17. [PubMed: 18234696]
33. Bermel RA, You X, Foulds P, Hyde R, Simon JH, Fisher E, et al. Predictors of long-term outcome in multiple sclerosis patients treated with interferon beta. *Annals of Neurology*. 2013 Jan; 73(1): 95–103. [PubMed: 23378325]
34. Shinohara RT, Sweeney EM, Goldsmith J, Shiee N, Mateen FJ, Calabresi PA, et al. Statistical normalization techniques for magnetic resonance imaging. *NeuroImage: Clinical*. 2014; 6:9–19. [PubMed: 25379412]
35. Gaitán MI, Maggi P, Wohler J, Leibovitch E, Sati P, Calandri IL, et al. Perivenular brain lesions in a primate multiple sclerosis model at 7-tesla magnetic resonance imaging. *Mult Scler*. 2014 Jan; 20(1):64–71. [PubMed: 23773983]
36. Maggi P, Macri SMC, Gaitán MI, Leibovitch E, Wholer JE, Knight HL, et al. The formation of inflammatory demyelinated lesions in cerebral white matter. *Annals of Neurology*. 2014 Oct; 76(4):594–608. [PubMed: 25088017]
37. Fox RJ, Thompson A, Baker D, Baneke P, Brown D, Browne P, et al. Setting a research agenda for progressive multiple sclerosis: The International Collaborative on Progressive MS. *Mult Scler*. 2012 Nov; 18(11):1534–40. [PubMed: 22917690]

38. Brex PA, Jenkins R, Fox NC, Crum WR, O’Riordan JI, Plant GT, et al. Detection of ventricular enlargement in patients at the earliest clinical stage of MS. *Neurology*. 2000 Apr 25; 54(8):1689–91. [PubMed: 10762518]
39. Dalton CM, Brex PA, Jenkins R, Fox NC, Miszkiel KA, Crum WR, et al. Progressive ventricular enlargement in patients with clinically isolated syndromes is associated with the early development of multiple sclerosis. *J Neurol Neurosurg Psychiatr*. 2002 Aug; 73(2):141–7. [PubMed: 12122170]
40. Azevedo CJ, Overton E, Khadka S, Buckley J, Liu S, Sampat M, et al. Early CNS neurodegeneration in radiologically isolated syndrome. *Neurology: Neuroimmunology & Neuroinflammation*. 2015 Jun; 2(3):e102–2. [PubMed: 25884012]
41. Hafler DA, Compston A, Sawcer S, Lander ES, Daly MJ, et al. International Multiple Sclerosis Genetics Consortium. Risk alleles for multiple sclerosis identified by a genomewide study. *N Engl J Med*. 2007 Aug 30; 357(9):851–62. [PubMed: 17660530]
42. Sawcer S, Hellenthal G, Pirinen M, Spencer CCA, Patsopoulos NA, Moutsianas L, et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature*. 2011 Aug 11; 476(7359):214–9. [PubMed: 21833088]

Highlights

- Research with advanced MRI has identified that MS is a disease of the whole brain.
- This research has sought to establish surrogate markers for diffuse tissue damage.
- It is time to renew efforts to use imaging to study MS pathophysiology.

Figure 1.

A: Left, axial T2-weighted fluid-attenuation inversion recovery (FLAIR) image from a 33-year-old woman with MS, showing a focal lesion in the posterior limb of the left internal capsule. Right, axial diffusion-weighted image showing an acute lacunar infarct in a similar location. B: Axial FLAIR image from a 36-year-old man with relapsing-remitting MS, showing extensive involvement of the white matter.

Figure 2.

A: Axial MRI scans through the centrum semiovale in a 40-year-old woman with relapsing-remitting MS, obtained in 1994. Top-left: proton density-weighted; bottom-left: T2-weighted; top-right: T1-weighted; bottom-right: T1-weighted after intravenous administration of gadolinium-based contrast material. The arrows point to a lesion that enhances following contrast administration, meaning that it is bright on the post-contrast T1-weighted image. It is invisible on the pre-contrast T1-weighted image. B: Axial 3D T1-weighted scan from the same individual 8 years later. Note the degree to which lesions (arrows) are visible as hypointense foci on this type of T1-weighted image relative to the 2D spin-echo image in panel A (top-right). Note also the inhomogeneity of the signal within each of the lesions, suggesting differential sensitivity to intralesional pathological processes.

Figure 3. Sagittal T2-weighted MRI scans of the cervical spinal cord in individuals with primary-progressive (A, 51-year-old man) and relapsing-remitting MS (B, 41-year-old man). C: Axial T2-weighted FLAIR MRI from the relapsing-remitting MS case whose cervical cord is shown in B. A preponderance of spinal cord lesions and paucity of cerebral lesions are thought to be typical of primary-progressive MS, but this is not the case here.

Figure 4.

One slice from five different registration methods for three subjects (one subject on each row). The Montreal Neurological Institute template, which is the registration target, is at the top left. From Eloyan A, Shou H, Shinohara RT, Sweeney EM, Nebel MB, et al. (2014) Health Effects of Lesion Localization in Multiple Sclerosis: Spatial Registration and Confounding Adjustment. PLoS ONE 9(9): e107263. doi:10.1371/journal.pone.0107263

Figure 5.
Sagittal T2*-weighted gradient-echo MRI scan of the corpus callosum in a healthy volunteer.

Figure 6.

A: The first published MRI scan of a person with MS (Young, I. R., Hall, A. S., Pallis, C. A., Legg, N. J., Bydder, G. M., & Steiner, R. E. (1981). Nuclear magnetic resonance imaging of the brain in multiple sclerosis. *Lancet*, 2(8255), 1063–1066. [http://doi.org/10.1016/S0140-6736\(81\)91273-3](http://doi.org/10.1016/S0140-6736(81)91273-3)). The scan has T1-weighting, and arrows point to focal lesions that are hypointense relative to background white matter. B: A 7-tesla T2*-weighted MRI scan of an MS case showing focal hyperintense lesions with central hypointense veins and, in some cases, peripheral hypointense rims.

Figure 7.

7-tesla MRI of the brain of a 48-year-old woman with secondary-progressive MS. In A, the lesion demonstrates contrast-enhancement on the gadolinium-enhanced T1-weighted (T1w) image. On T2*-weighted pre-gadolinium imaging, the lesion shows a clear hypointense rim on both magnitude and phase reconstructions. The lesion's central vein is also clearly seen as a hypointense line running through the middle of the lesion. One month later (B), the lesion no longer enhances with contrast, and the rim (but not the central vein) is no longer apparent. Adapted from Gaitán, M. I., Sati, P., Inati, S. J., & Reich, D. S. (2013). Initial investigation of the blood-brain barrier in MS lesions at 7 tesla. *Multiple Sclerosis* (Houndmills, Basingstoke, England), 19(8), 1068–1073. <http://doi.org/10.1177/1352458512471093>

Figure 8.

Top row: Left, T2*-weighted 7-tesla MRI of the formalin-fixed brain of a marmoset with experimental autoimmune encephalomyelitis (EAE). The circle highlights a focal white matter lesion. Center, corresponding in-vivo MRI, which depicts the lesion's central vein as a focal hypointensity. Right, whole-mount hematoxylin-and-eosin (H&E)-stained section at the same level. Middle row, close-up images of the lesion circled in the top row as seen on H&E staining and immunohistochemistry for CNPase (a myelin marker), Iba-1 (a microglial marker), and CD3 (a T cell marker); details in Maggi, P., Macri, S. M. C., Gaitán, M. I., Leibovitch, E., Wholer, J. E., Knight, H. L., et al. (2014). The formation of inflammatory demyelinated lesions in cerebral white matter. *Annals of Neurology*, 76(4), 594–608. <http://doi.org/10.1002/ana.24242>. Bottom row, evolution of EAE in the same marmoset from day 0 (pre-immunization) to day 134 (the terminal MRI scan prior to sacrifice).

Figure 9.

A: Axial T2-weighted FLAIR scan in a 29-year-old healthy man who was taking part in a clinical research protocol at the NIH. B: Axial T2-FLAIR (left) and post-contrast T1-weighted (right) scans 14 years later after presentation with clinically isolated syndrome, showing interval development of several non-enhancing lesions (open arrows) and a contrast-enhancing lesion in the left corona radiata.