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Imag(in)ing multiple sclerosis: Time to take better pictures

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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.

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1. 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 14 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 (Dawson, 1916). 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 being 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 (Polman et al., 2011).

The earliest MRI scans of MS were obtained in London around 1980 (Young et al., 1981). The demonstration that MRI can "see" white matter lesions in the MS brain must have been quite dramatic. 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 lesions 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 National Institutes of Health (NIH) established that new lesions appear many times more frequently than new clinical symptoms, and these lesions persist following resolution of the symptoms (Harris et al., 1991). 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 (Fig. 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 (Fig. 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 (Barkhof, 2002; Goodin, 2006). 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.

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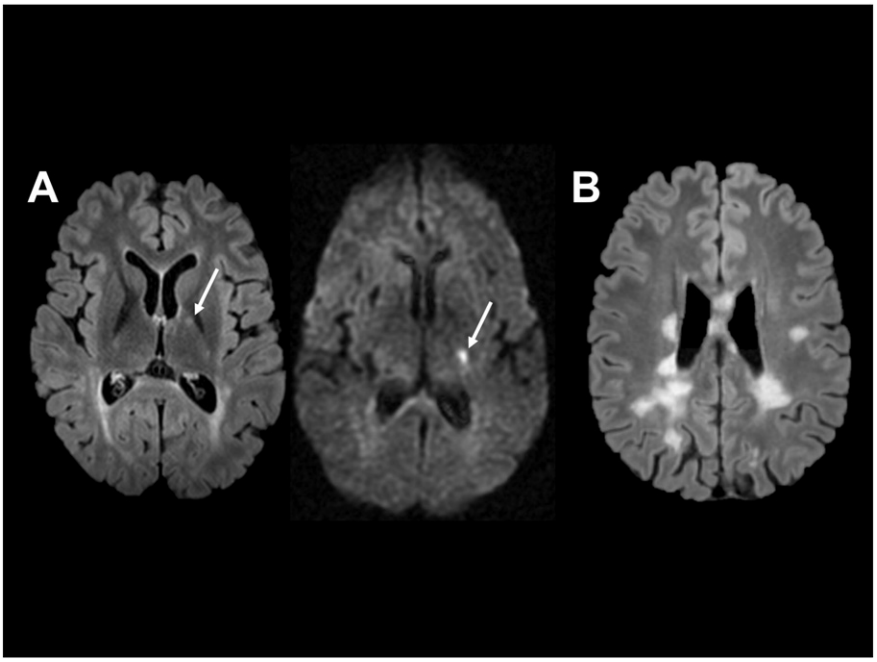

Fig. 1. A: Left, axial T2-weighted fluid-attenuation inversion recovery (FLAIR) image from a 33-year-old woman with MS, showing a focal lesion in the posterior limb of the left internal capsule. Right, axial diffusion-weighted image showing an acute lacunar infarct in a similar location. B: Axial FLAIR image from a 36-year-old man with relapsing-remitting MS, showing extensive involvement of the white matter.

2. 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 (Basser et al., 1994; van Zijl et al., 1994). Diffusion tensor imaging (DTI), capable of producing extraordinary images of white matter fibers from in vivo

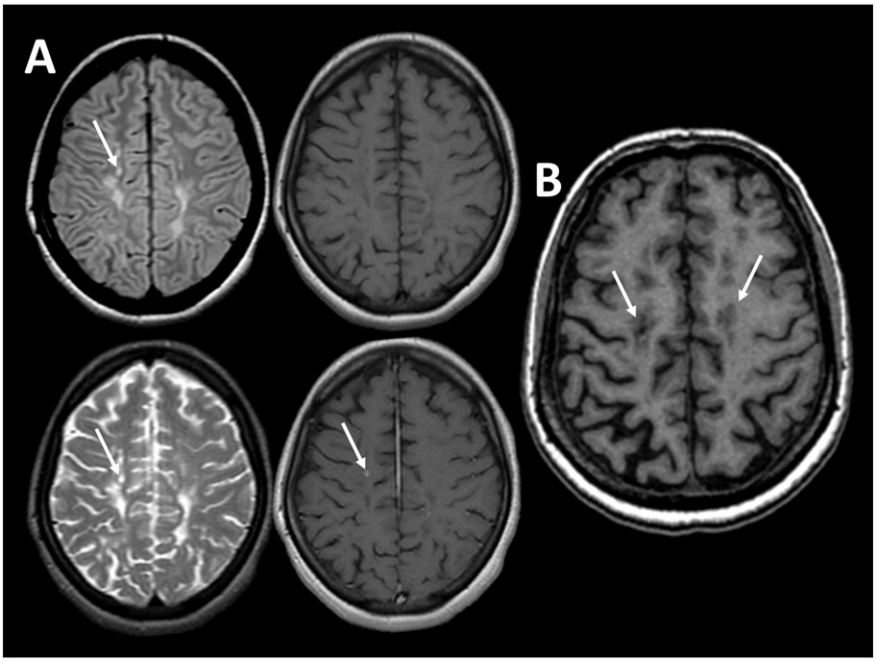

Fig. 2. A: Axial MRI scans through the centrum semiovale in a 40-year-old woman with relapsing-remitting MS, obtained in 1994. Top-left: proton density-weighted; bottom-left: T2-weighted; top-right: T1-weighted; bottom-right: T1-weighted after intravenous administration of gadolinium-based contrast material. 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.