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What Can Medical Imaging Tell Us About Multiple Sclerosis?*

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Abstract

Multiple sclerosis (MS) is a progressive neurodegenerative disease that induces complex patterns of anatomical, biochemical and pathophysiological changes in the human nervous system. Identifying these changes helps clinicians and researchers to distinguish MS from other diseases with similar symptoms, and tracking them over time is necessary in order to monitor the efficacy of treatments and assess patients' changing needs. For these purposes, clinicians and researchers rely on two medical imaging modalities: magnetic resonance imaging (MRI) and positron emission tomography (PET). The most common protocols for these two technologies have complementary roles, with T1-weighted and T2-weighted MRI revealing structural changes, such as lesions and demyelination, and PET detecting local changes in energy consumption, and thus of brain and nervous system activity. However, more experimental approaches to both MRI and PET show potential for expanding the capabilities of both. PET in particular has untapped versatility due to its ability to detect signals from a wide variety of radiotracers, each of which helps to track concentrations of a particular kind of disease-relevant molecule. Furthermore, the utility of PET for MS has increased in recent years due to improvements in and growing adoption of entire-body PET scanners. In this review, we summarize how clinicians currently use imaging to diagnose and monitor MS. We then survey experimental imaging protocols and the evidence for and against their applicability to MS.

Keywords

Multiple sclerosis, medical imaging, magnetic resonance imaging, positron emission tomography, radiotracers.

Contents

Introduction

This review is an expansion of a presentation given at the 2024 Brain Health Alliance Spring Symposium. The original purpose of the presentation was to introduce non-specialists, including patients and their care-givers, to key concepts in imaging relevant to MS diagnosis, monitoring, and research. This article covers the same topics with the same intent but in more detail.

Review Methodology

We initially set out to answer a series of questions that a patient or care-giver is likely to have when learning about the applicability of medical imaging to MS:

- Why use medical imaging at all?
- What kinds of medical imaging are available?
- Are they safe?
- Are the conclusions drawn from them reliable?
- What is the current state of the art?
- What improvements might we see over the next few years?

To answer each question, we searched for scholarly articles, both primary research articles and other literature reviews, published within the past ten years that partially or fully addressed these questions. We then compared and summarized the reported results, highlighting concordances and caveats.

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MRI: structural and functional imaging

MRI is an imaging modality that uses magnetic fields. Different procedures use this same technology to capture different kinds of information (illustrated in Figure 1). T1-weighted and T2-weighted structural MRI detect the shape and density of tissue (Mikulis and Roberts 2007). Diffusion tensor MRI (DT-MRI) detects the density and orientation of white matter (myelinated axons) (Andersen et al. 2018). Functional MRI (fMRI) measures blood flow and oxygenation change, typically at 1-2 samples per second, usually as proxies for brain activity (Rocca et al. 2022). Magnetic Resonance Spectroscopy (MRS) estimates concentrations of metabolites, including neurotransmitters GABA and glutamate (Mikulis and Roberts 2007).

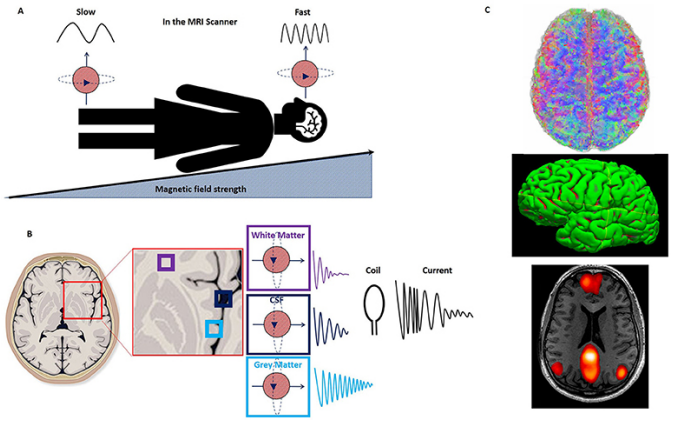

Figure 1: A. The MRI machine generates a magnetic field with varying strength over the length of the person's body. Greater field strengths impart faster spins to protons, mainly those in hydrogen nuclei. B. When we relax the magnetic field, the protons release the energy they gained from it as smaller electromagnetic waves that we can detect with a metal coil. Different tissues constrain the movements of hydrogen protons in different ways, influencing the amount of energy they absorb and release. C. Top: Diffusion tensor imaging is an MRI procedure that allows us to trace the directions of tracts of white matter. Middle: T1- and T2-weighted structural MRI enable us to measure the volume and shape of tissue. Bottom: Functional MRI measures the volume and oxygenation level of blood in the brain, which can serve as a proxy for brain activity. Image source: (Broadhouse 2019), distributed under the Creative Commons Attribution License

MRI does not involve exposure to ionizing radiation but does expose patients and technicians to strong electromagnetic fields (EMF) (Keevil et al. 2022). In the US, MRI centers must comply with Food and Drug Administration (FDA) regulations that limit the intensity of EMF exposure (Delfino 2015), which have also become *de facto* standards in the European Union, where efforts to harmonize the regulations in different member countries continue (Certaines and Cathelineau 2001). The most important contraindication for MRI is metal in the body, because strong magnetic fields can heat metal to dangerous temperatures (Keevil et al. 2022; Certaines and Cathelineau 2001).

Structual MRI has become one of the most common ways of diagnosing MS, but several other conditions that cause lesions in the brain and spinal cord look similar in MRI images (Geraldes et al. 2018). The authors of (Geraldes et al. 2018) propose the MIMICS acronym to help radiologists remember to look for key features indicative of one or more

Table 1: Some MS mimics and their differentiating features, summarized from (Geraldes et al. 2018). Columns: M1 = meningeal enhancement (of contrast at edge of meninges), I1 = indistinct border or increasing lesion size, M2 = macrobleeds or microbleeds, I2 = cortical or lacunar infarcts (areas of dead tissue), C = cavities, complete ring enhancement, or calcifications, S = symmetrical lesions, lesions that spare U-fibres, siderosis, or spinal cord extensive lesions

Condition	M1	I1	M2	I2	C	S
infection, other inflammatory, neoplasm	o	o	x	x	x	x
neuromyelitis optica spectrum disorders	x	o	x	x	o	o
cerebrovascular disease and aging	x	x	o	o	x	o
migraine	x	x	x	o	x	o
leukodystrophies, mitochondrial disease	x	o	x	x	o	o
metabolic disorder	x	x	x	x	x	o

of these other diagnoses (Table 1).

MRI can help distinguish between relapsing-remitting MS (RRMS) and primary progressive MS (PPMS) (Siger 2022). In the brains and spinal cords of RRMS patients, T2-weighted MRI shows more focal lesions and acute inflammatory lesions with contrast enhancement (Siger 2022). In PPMS patients, MRI reveals more features of chronic inflammation, including slowly evolving/expanding lesions (SELs), leptomeningeal enhancement (LME), and brain and spinal cord atrophy (Siger 2022). Diffuse spinal cord abnormalities are also more common in PPMS (Siger 2022). PPMS patients tend to have more cortical lesions, which correlate with greater cognitive deficits However, focal lesions

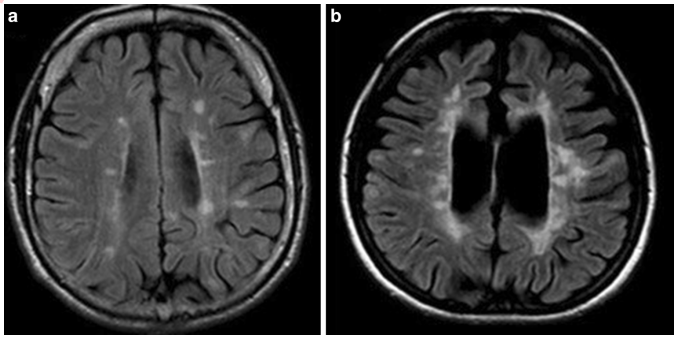

Figure 2: The above images show axial plane brain MRI scans of two atypical PPMS patients who show multiple focal lesions in periventricular, deep and juxtacortical white matter more common in RRMS in addition to brain atrophy. Image source: (Siger 2022), distributed under Creative Commons Attribution 4.0 International License

can also occur in RRMS patients as in Figure 2 (Siger 2022).

Chronic, low-intensity regions in T1-weighted images ("black holes") in the brain indicate severe demyelination and nerve damage (Siger 2022). Increases in size and number of black holes indicate progression in PPMS and transition from RRMS to secondary progressive MS (SPMS) (Siger 2022). Using axial fluid attenuated inversion recovery (FLAIR) to invert the brightness of some features, including the black holes so that they show up as bright white dots can make them easier to see, as in

the bottom row of 3.

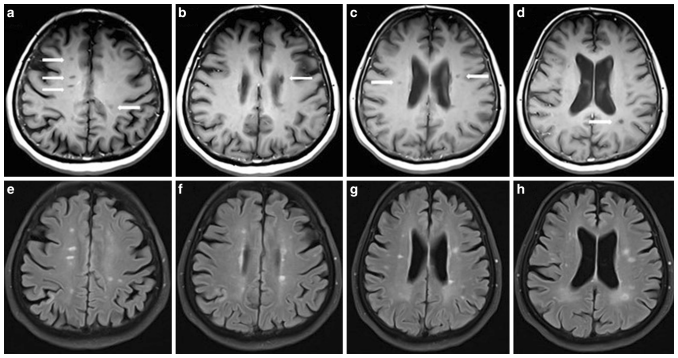

Figure 3: Examples of black holes indicated by white arrows in four PPMS patients. Top row: Axial T1-weighted spin-echo images. Bottom row: Axial fluid attenuated inversion recovery (FLAIR) images with corresponding hyperintense lesions in the same locations. Image source: (Siger 2022), distributed under Creative Commons Attribution 4.0 International License

PET Safety considerations

PET requires the injection of tracers that emit ionizing radiation (Devine and Mawlawi 2010). Researchers have thoroughly studied how much radiation each organ of the body receives from a dose of a given size (Devine and Mawlawi 2010). The cancer risk associated with a single dose is proportional to the amount used (Devine and Mawlawi 2010). The body clears the tracer in a matter of hours (Devine and Mawlawi 2010). In the US and Europe, in addition to the usual standards for safety and efficacy that apply to all pharmaceuticals, radiotracers must meet requirements for radiation safety (Herscovitch 2022; Ballinger and Koziorowski 2017). A common guiding principle known as "As Low As Reasonably Achievable" (ALARA) dictates that the radiologist should use the smallest dose of tracer that provides the imaging contrast needed to achieve the objective of the imaging procedure (Susselman and Center n.d.; Musolino et al. 2008).

In clinical settings in the US, a specialist known as a Certified Nuclear Medicine Technologist (CNMT) takes responsibility for the key safety considerations of PET imaging (Neal 2020). A CNMT holds a certification from the Nuclear Medicine Technology Certification Board (https://www.nmtcb.org/). Their responsibilities typically include working directly with the patient, discussing the safety and appropriateness of a scan, working directly with clinicians to evaluate suitability of imaging procedures, calibrating, inspecting, and operating scanners, administering radiopharmaceuticals and tracers, monitoring the patient's wellbeing during the procedure, and assessing the technical quality of imaging data (Neal 2020; Mann et al. 2017).

FDG-PET: a well-established measure of brain activity

PET is a versatile imaging technology that introduces radioactive molecules (radiotracers) into the body and tracks how they distribute themselves (Paula Faria et al. 2014). $[^{18}F]$Fluorodeoxyglucose PET (FDG-PET) detects the rate of glucose consumption in the brain, showing regions of lower activity (Paula Faria et al. 2014). Using FDG-PET to detect regions of decreased brain activity indicative of neurodegeneration is common to diagnosis and monitoring of MS, Alzheimer's, Parkinson's, and other conditions (Minoshima et al. 2022). By showing different patterns of energy usage in the brain, FDG-PET makes visible differences in pathology among a wide variety of neurodegenerative diseases (Figure 4).

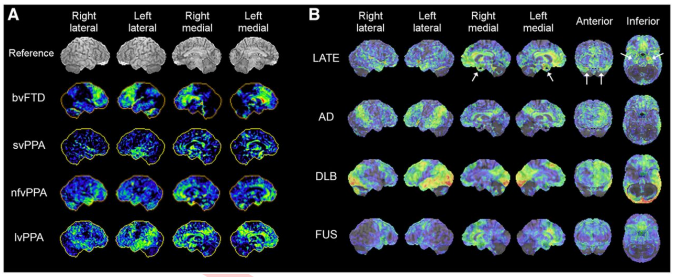

Figure 4: Example z-scores of FDG-PET images from patients with different neurodegenerative diseases relative to healthy controls; A. top to bottom: frontotemporal dementia behavioral variant (bvFTD), semantic variant primary progressive aphasia (svPPA), nonfluent variant primary progressive aphasia (nfvPPA), logopenic variant primary progressive aphasia (lvPPA); B. Images on this side are superimposed on the reference MRI image. top to bottom: limbic-predominant age-related TDP-43 encephalopathy (LATE), Alzheimer's disease (AD), dementia with Lewy bodies (DLB), fused in sarcoma (FUS). Image source from (Minoshima et al. 2022), used in accordance with the Journal of Nuclear Medicine's policy regarding non-commercial reuse of excerpted material: https://jnm.snmjournals.org/page/permissions

State of the art: PET for myelin detection and entire-body PET

The past decade has seen new technologies move from the research phase to clinical practice, including entire-body PET scans and amyloid-binding radiotracers.

All radiotracers that bind to beta-amyloid proteins also bind to white matter, even without beta-amyloid (Morbelli et al. 2019). Sites of lower brightness in amyloid PET match black holes in T1-weighted MRI and white matter lesions in T2-weighted MRI (Morbelli et al. 2019). Even though three beta amyloid-binding radiotracers have received FDA approval (Rabinovici et al. 2023), researchers and clinicians still disagree on how to optimize and standardize imaging protocols for measuring myelination (Morbelli et al. 2019). Consequently, Procedures for identifying regions of interest and uptake cutoffs also vary widely between studies, making comparison of results difficult (Morbelli et al. 2019).

FDG-PET is useful for measuring activity not only in the brain but in the spine, organs, and peripheral nervous system (Surti et al. 2020). Earlier approaches to scanning the entire patient involved moving the scanner bed (Surti et al. 2020), but recent advances in sensor technology have made possible a field of view large enough to cover a typical adult body without movement (Surti et al. 2020). This leads to less motion noise and improved sensitivity (Surti et al. 2020), which in turn allows measurement of tracer uptake and clearance dynamics and use of less radiotracer (Surti et al. 2020).

Research frontier: PET for detecting inflammation

Because inflammation, possibly due to autoimmune response to the body's own myelin, is a key feature of MS pathology (Haase and Linker 2021), mapping inflammation in the brain and body could yield vital insights. The first method that researchers have attempted is to use FDG-PET to measure increased metabolic activity in regions of high inflammation (Paula Faria et al. 2014). In animal studies, this approach has worked well in the spinal cord but not in the brain (Paula Faria et al. 2014). This may be due to the higher basal level of activity in the non-inflamed brain (Paula Faria et al. 2014). Additionally, even when imaging does show clear changes in metabolic activity, interpretation is not straightforward: A study with 12 human MS patients found that lesions could be either hyper-metabolic when acute or hypo-metabolic when chronic (Paula Faria et al. 2014).

An alternate approach is to find radiotracers that bind to proteins indicative of inflamed tissue. Activated microglia, macrophages, and astrocytes increase expression of 18-kD translocator protein (TSPO) receptors (Weijden et al. 2021). $[^{11}C]$PK11195 is the first widely studied TSPO-binding tracer (Weijden et al. 2021). Other, more specific experimental tracers can distinguish activation of microglia from activation of astrocytes (Weijden et al. 2021), which provides additional diagnostic value, as microglial activation can promote tissue survival (Weijden et al. 2021).

From a meta-analysis of 156 case-control human studies, including 20 on MS, we see that TSPO-PET holds some promise for differential diagnosis (Picker et al. 2023). "Widespread cGM [cortical gray matter] increases [in TSPO signal] were only present in AD and other neurodegenerative disorders" (Picker et al. 2023). "Cortico-limbic increases were most prominent for AD [Alzheimer's disease], MCI [mild cognitive impairment], other neurodegenerative disorders, mood disorders, and multiple sclerosis" (Picker et al. 2023). "Thalamic involvement was observed for AD, other neurodegenerative disorders, chronic pain and functional disorders, and multiple sclerosis" (Picker et al. 2023). From the quotes above, we can see that TSPO-PET can identify localized inflammation and thereby help distinguish patients with neurological diseases from healthy individuals, but the overlap in biomarkers among different neurodegenerative diseases may complicate distinguishing among them.

However, after the initial diagnosis, TSPO-PET has shown clearer utility for tracking the course of the disease. Widespread uptake correlates with age, disease duration and progression, and disability (Weijden et al. 2021), and SPMS patients show higher uptake than do RRMS patients (Weijden et al. 2021). Higher TSPO tracer uptake correlates with higher MRI contrast, another sign of inflammation so that the two forms of imaging can serve to confirm each other (Weijden et al. 2021), but TSPO-PET can also distinguish chronically inflamed lesions from non-inflamed lesions even in cases where they look similar in MRI images (Figure 5) (Airas et al. 2015).

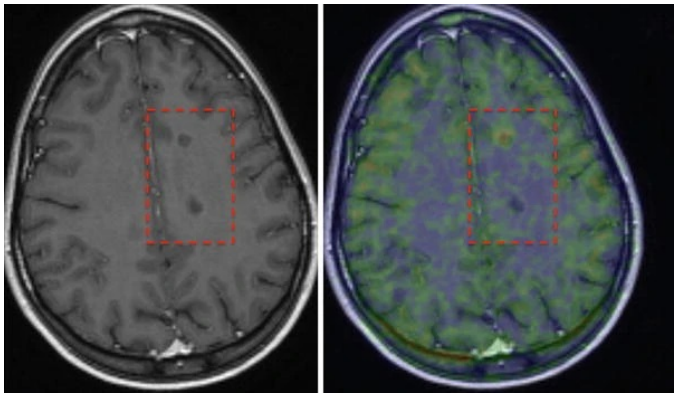

Figure 5: Left: A T1-weighted MRI image shows two similar-looking black holes outlined by a broken red line. Right: TSPO-PET shows high uptake in the chronically active lesion above and low uptake in the chronically inactive lesion below. Image source: (Airas et al. 2015), distributed under the Creative Commons CC BY license

Conclusion

PET and MRI are two imaging modalities, each with multiple imaging protocols that capture different features. T1- and T2-weighted and diffusion tensor MRI tell us about the structure of the brain and body, including myelination of nerves. FDG-PET and functional MRI can measure local brain activity. PET using FDA-approved beta amyloid-binding radiotracers can detect differences in myelination, and researchers are testing ways of using PET to measure inflammation. Meanwhile, biochemists are currently working to expand the library of tracers. These different approaches all provide different kinds of evidence that help distinguish MS from other conditions and track the location and severity of damage to the nervous system. Imaging will continue to play an important role in the diagnosis and monitoring of MS in the future, and new approaches will enable a more nuanced understanding of the condition.

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