# What can imaging technologies tell us about multiple sclerosis in 2024?

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# Why image?

Humans are not spherical, well-mixed compartments of chemicals.

from https://en.wikipedia.org/wiki/File:SphericalCow2.gif, created by Ingrid Kallick, in the public domain

# Uses of neuroimaging in the study, diagnosis, and treatment of multiple sclerosis (MS)

**Differential diagnosis** distinguishing MS from other conditions

**Tracking progression** Are things getting worse?

- Where in the peripheral nervous system has demyelination occurred?
- Where in the brain has neurodegeneration occurred?
- How severe is the damage?
- Can we predict where damage will occur next?

**Measuring effectiveness of treatments** Are thing getting better?

- Is damage slowing? Stopping? Reversing?
- Can we track the underlying biochemical factors?

# Magnetic resonance imaging (MRI)

- A category of imaging methods that make use of magnetic fields that induce vibrations in molecules
- T1-weighted and T2-weighted structural MRI detect density and shape of tissue.
- diffusion tensor MRI (DT-MRI) can detect the density and orientation of white matter (myelinated axons).
- Functional MRI (fMRI) measures changes in blood flow and blood oxygenation over at  1 second time resolution.
- Magnetic Resonance Spectroscopy (MRS) can estimate the concentrations of various metabolites, including the neurotransmitters GABA and glutamate.

# Positron emission tomography (PET)

- A versatile imaging technology that tracks how molecules containing radioactive atoms (radiotracers) distribute themselves through the body.
- [$^{18}$F]Fluorodeoxyglucose PET (FDG-PET), the oldest and most well-established PET technique, can detect the rate of glucose consumption in the brain, showing regions of heightened or diminished activity.
- Radiotracers that bind to $\beta$-Amyloid proteins, which play a role in neurodegeneration in other diseases, have received FDA approval.
- Other tracers can locate sites of increased inflammation.

Source: Athreya et al. 2020. *Brainiacs Journal*

# Differential diagnosis: features not typical of MS

- 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 |

Source: Geraldes et al. 2018. *Nature Reviews Neurology*

# Identifying MS subtypes

- MRI can help distinguish from primary progressive MS (PPMS), relapsing-remitting MS (RRMS).
- RRMS: T2-weighted MRI shows more focal lesions and acute inflammatory lesions with contrast enhancement.
- PPMS: more MRI features of chronic inflammation, including slowly evolving/expanding lesions (SELs), leptomeningeal enhancement (LME), and brain and spinal cord atrophy.
- Both show lesions in the periventricular areas and deep white matter.

# However...

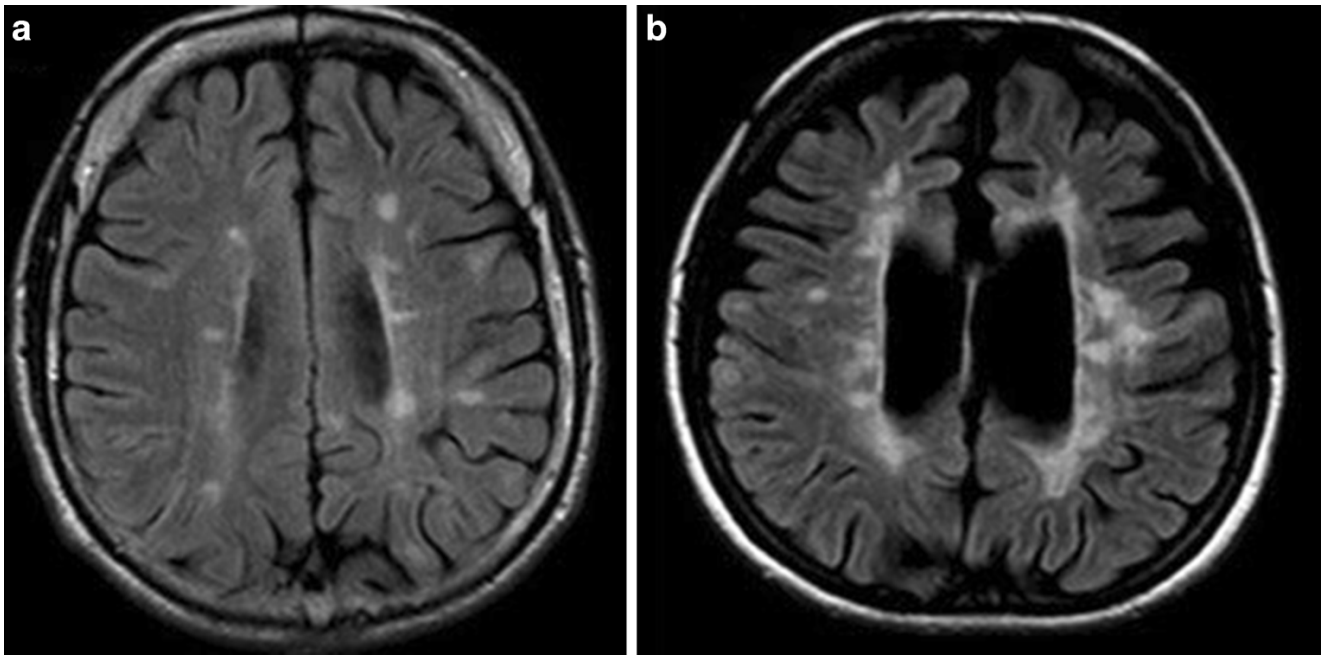


Figure: Looks can be deceiveing. The above images show axial plane brain MRI scans of two atypical PPMS patients who show multiple focal lesions in periventricular, deep and juxtacortical white matter more common in RRMS in addition to brain atrophy.

Source: Siger, 2022, *Clinical Neuroradiology*

# More identifying features of progressive phases

- Diffuse spinal cord abnormalities are more common in PPMS.
- PPMS patients tend to have more cortical lesions, which correlate with greater cognitive deficits.
- Chronic low-intensity regions in T1-weighted images ("black holes") in the brain indicate severe demyelination and nerve damage.
- Increases in size and number of black holes indicate progression in PPMS and transition from relapsing-remitting to secondary progression in secondary progressive MS (SPMS).

Source: Siger, 2022, *Clinical Neuroradiology*

# Find the Black Holes

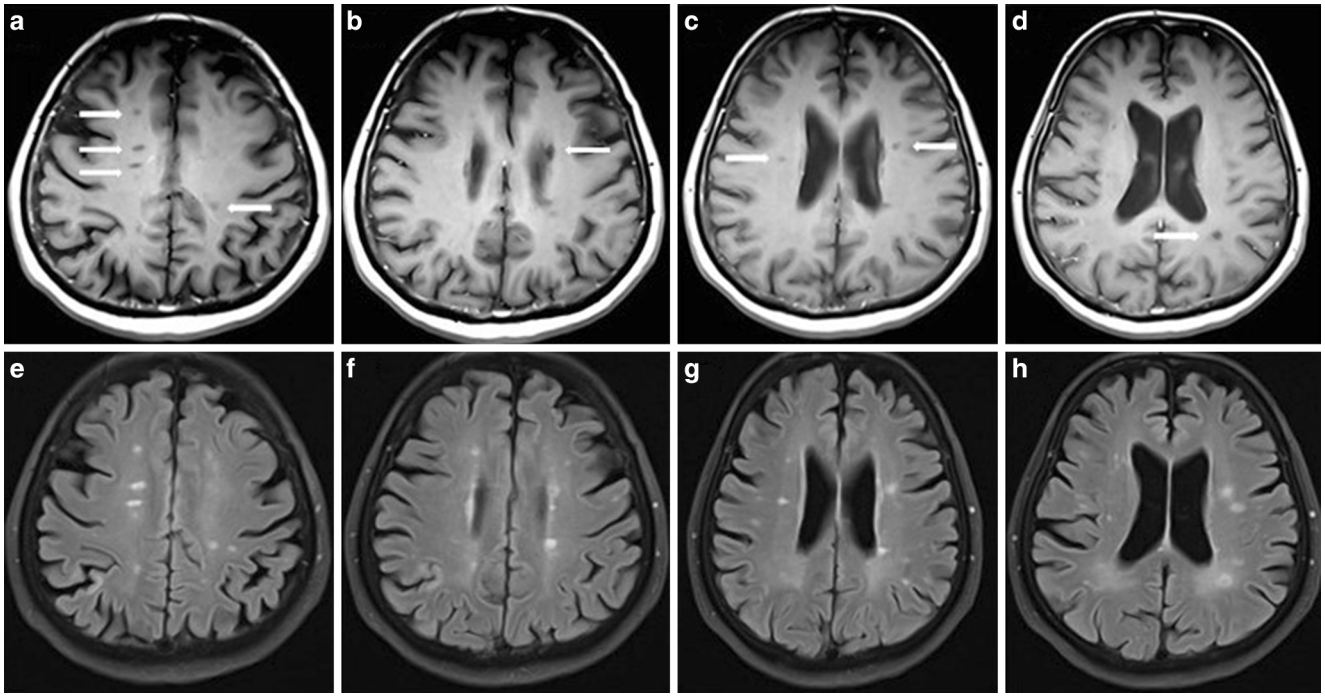


Figure: Examples of black holes indicated by white arrows in four PPMS patients. Top row: Axial T1-weighted spin-echo images. Bottom row: Axial fluid attenuated inversion recovery (FLAIR) images with corresponding hyperintense lesions in the same locations.

Source: Siger, 2022, *Clinical Neuroradiology*

# Measuring metabolic activity

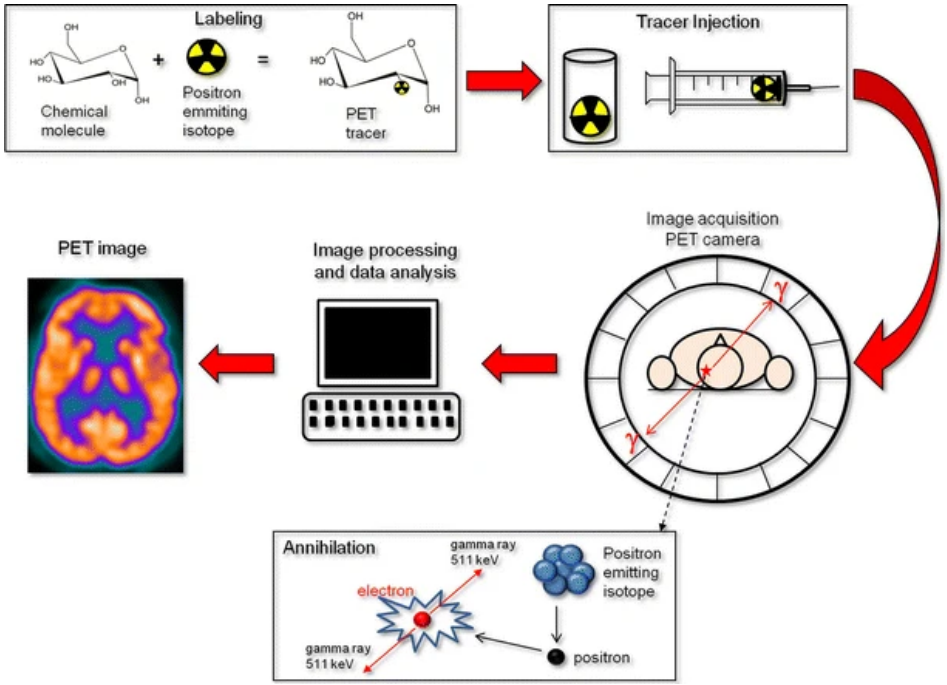


Figure: A general outline of the PET imaging process.

- 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.

Source: Faria et al., 2014, *Journal of Neuroimmune Pharmacology*

# Measuring metabolic activity-for inflammation!

- Researchers have attempted to use FDG-PET to measure increased metabolic activity in regions of high inflammation.
- In animal studies, this approach worked well in the spinal cord but not in the brain.
- This may be due to the higher basal level of activity in the non-inflamed brain.
- A study with 12 human MS patients found that lesions could be either hyper-metabolic when acute or hypo-metabolic when chronic.

Source: Faria et al., 2014, *Journal of Neuroimmune Pharmacology*

# Amyloid PET imaging for myelin detection

- All radiotracers that bind to $\beta$-amyloid also bind to white matter, even in the absence of $\beta$-amyloid.
- In coregistered images, sites of decreased brightness in amyloid PET corresponded to black holes in T1-weighted MR and white matter lesions in T2-weighted MR.
- [$^{11}$C]Pittsburgh compound-B preferentially binds to normal white matter and sites of remyelination versus lesions.
- However, its half-life is too short for widespread clinical use.
- Uptake levels of fluorine-based amyloid radiotracers such as [$^{18}$F]Florabetapir also correlate with myelination.
- No one has yet fully optimized imaging protocols for measuring myelination.
- Procedures for identifying regions of interest or uptake cutoffs also vary widely between studies.

Source: Morbelli et al., 2018, *European Journal of Nuclear Medicine and Molecular Imaging*

# Neuro-inflammation

- Activated microglia, macrophages, and astrocytes increase expression of 18-kD translocator protein (TSPO) receptors.
- [$^{11}$C]PK11195 is the first widely-used TSPO-binding radiotracer.
- Newer tracers have higher affinity, but that affinity varies depending on which variant of the TSPO gene a patient has.
- Higher TSPO tracer uptake and higher MRI contrast correlate, supporting belief that both are markers of inflammation.
- In MS patients, widespread increase in TSPO uptake correlates with increased age, duration, progression, and clinical disability.
- SPMS patients showed higher uptake than did RRMS patients.
- Acetate-like radiotracers provide a way to study the monocarboxylate transporter signalling specific to activated astrocytes.
- Microglia can also upregulate adenosine signalling in order to attenuate inflammation and increase tissue survival, a process we can detect with adenosine 2A receptor-specific radiotracers.

Source: Weijden et al., 2020, *PET and SPECT in Neurology*

# Conclusion

- PET and MRI are complementary technologies.
- T1-weighted, T2-weighted, and diffusion-tensor MRI tell us about the structure of the brain and peripheral nervous system, helping to find lesions and demyelination.
- PET, in conjunction with a growing library of radiotracers, can tell us about the distribution of different kinds of molecules in the brain.
- This includes the deposition of amyloid plaques, another clue to the presence of lesions and demyelination.
- fMRI tells us about oxygen consumption in the brain.
- FDG-PET tells us about glucose consumption by the brain.
- Both can help track brain atrophy.
- Both PET and MRI spectroscopy can tell us about metabolites that can indicate inflammation.
- These techniques can help with both differential diagnosis and tracking of disease progression.

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