neuro

Institut-Hôpital
neurologique de Montréal

Montreal Neurological
Institute-Hospital

Mapping brain myelin content using quantitative MRI

Christine Tardif, PhD

Assistant Professor, McGill University

Associate Director, MR Unit, McConnell Brain Imaging Centre

Co-Director, Quebec Bio-Imaging Network

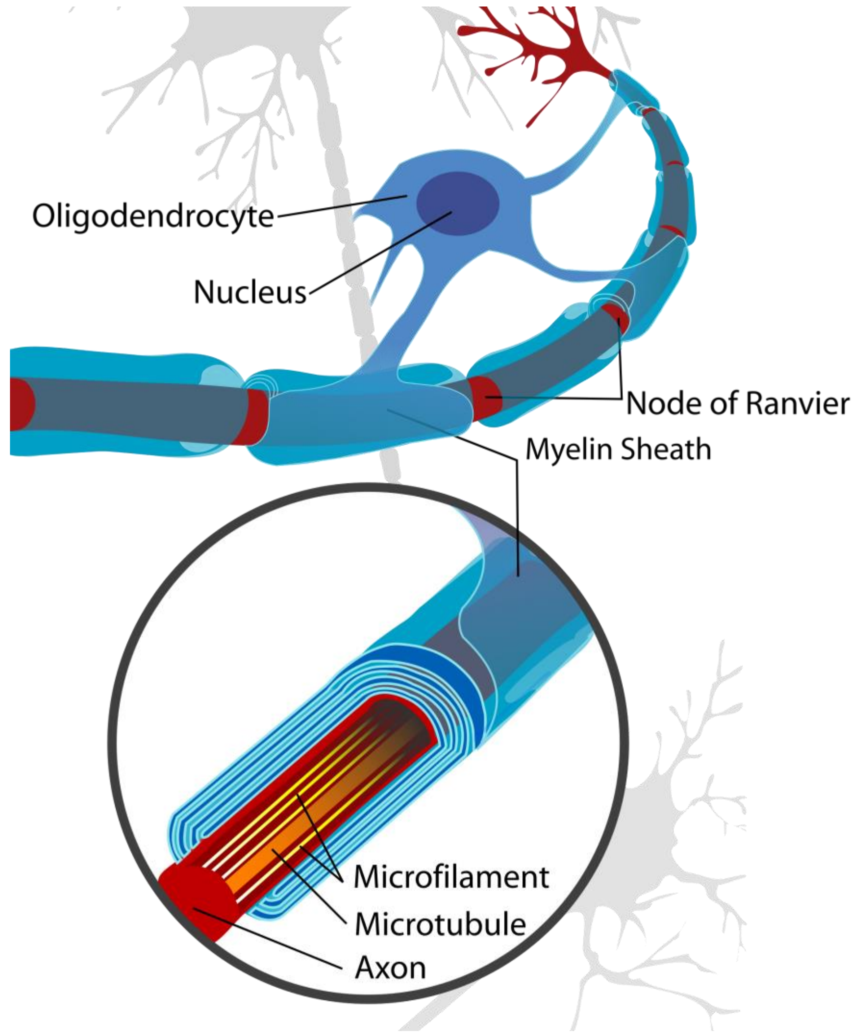
McGill

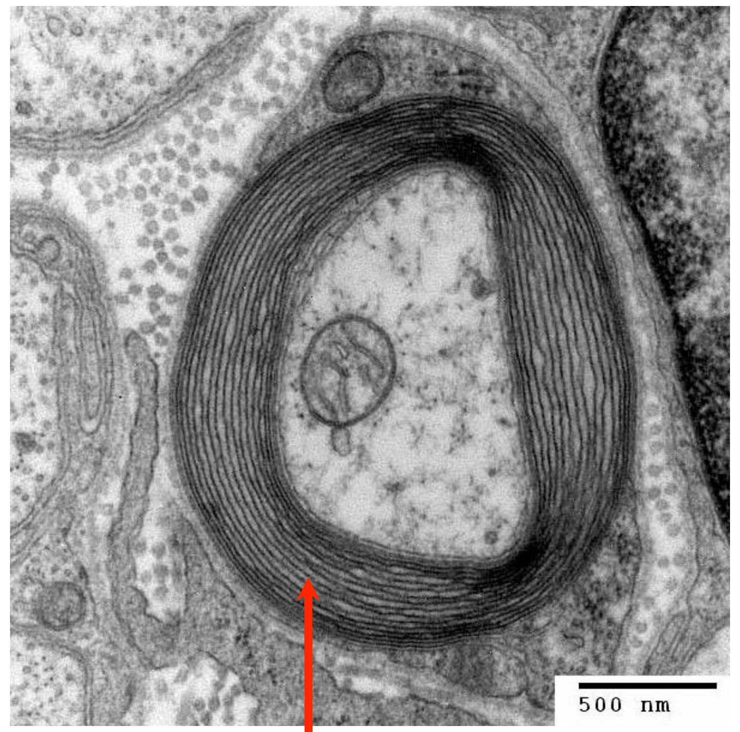
Department of **Biomedical Engineering**

Department of **Neurology & Neurosurgery**

Myelin is a major source of contrast in cerebral MRI

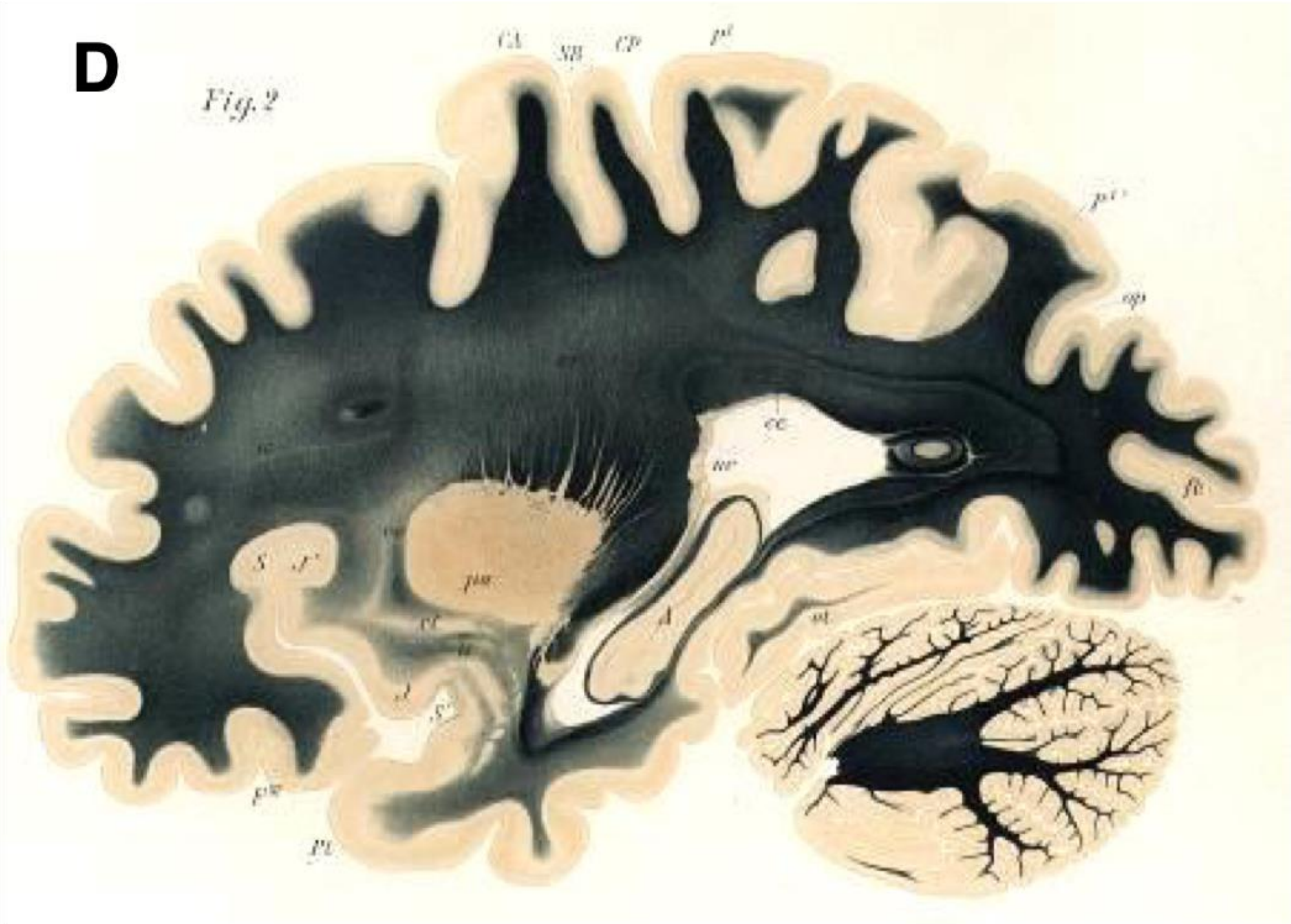
Myelin is a lipid-rich bi-layer that is wrapped around axons.





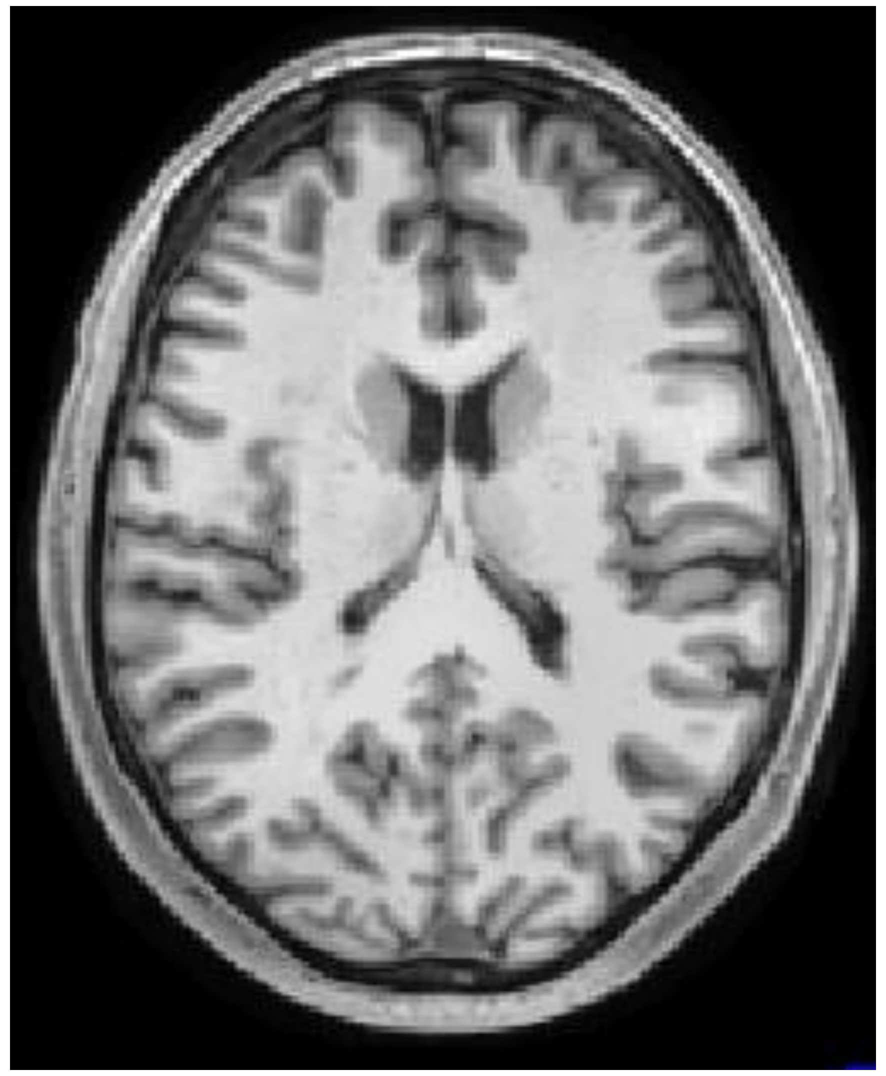
Myelin sheath

The white matter is very myelinated.



Myelination at 2 years of age
Flechsig, 1920

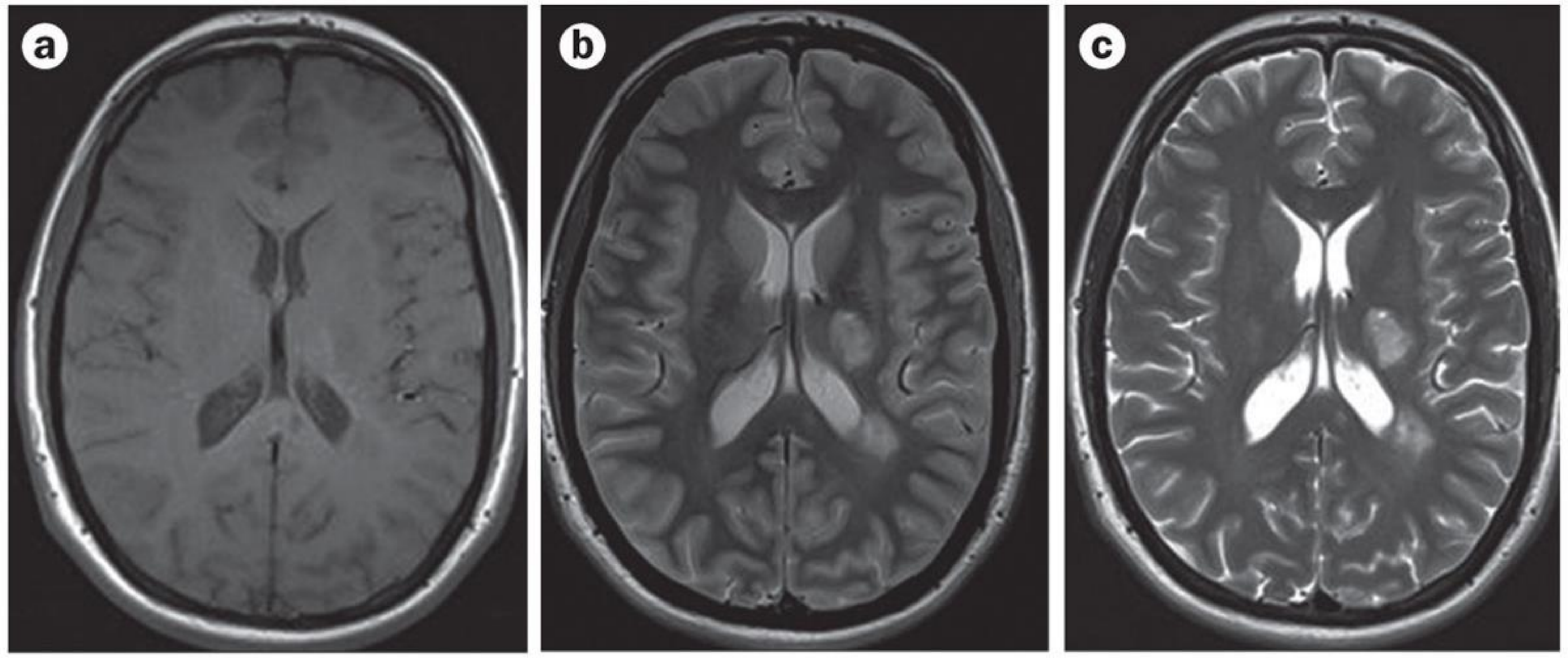
Strong contrast between white and grey matter in MRI



T1-weighted image

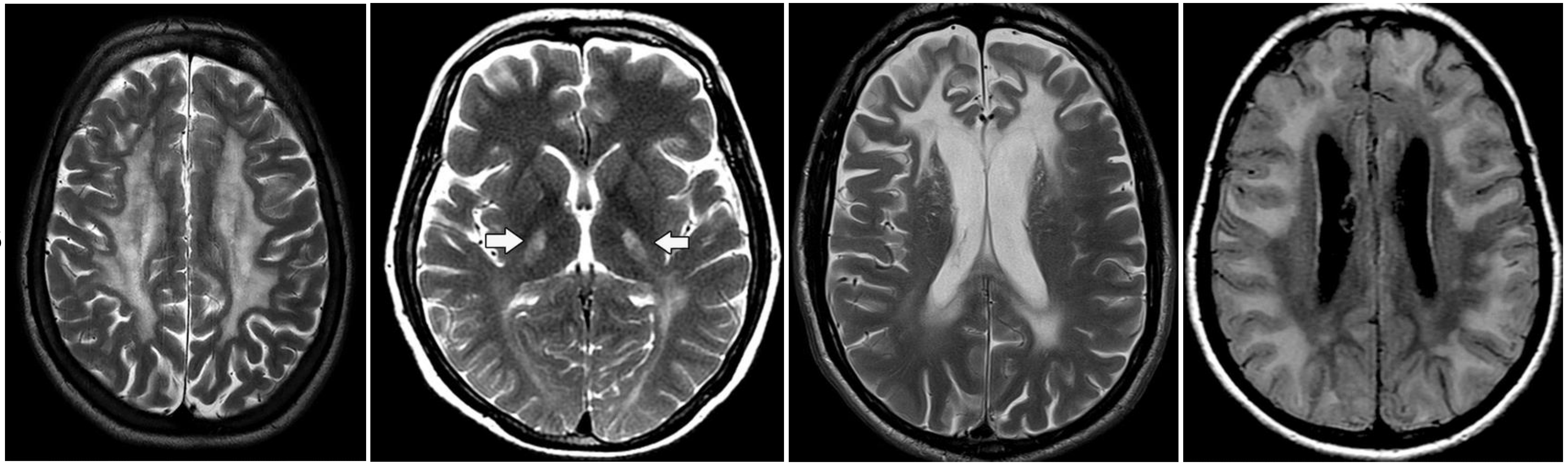
MRI is used in the clinic to diagnose demyelinating disorders

Multiple sclerosis



Rovira et al., Nature Rev Neurol 2015

Leukodystrophies



Resende et al., RadioGraphics 2019

Why use quantitative MRI to map cerebral myelin?

- To remove methodological biases
- To improve specificity: conventional “weighted” imaging is not specific to myelin
- To quantitatively monitor disease progression and response to treatment
- To strengthen the relationship between MRI biomarkers and disability

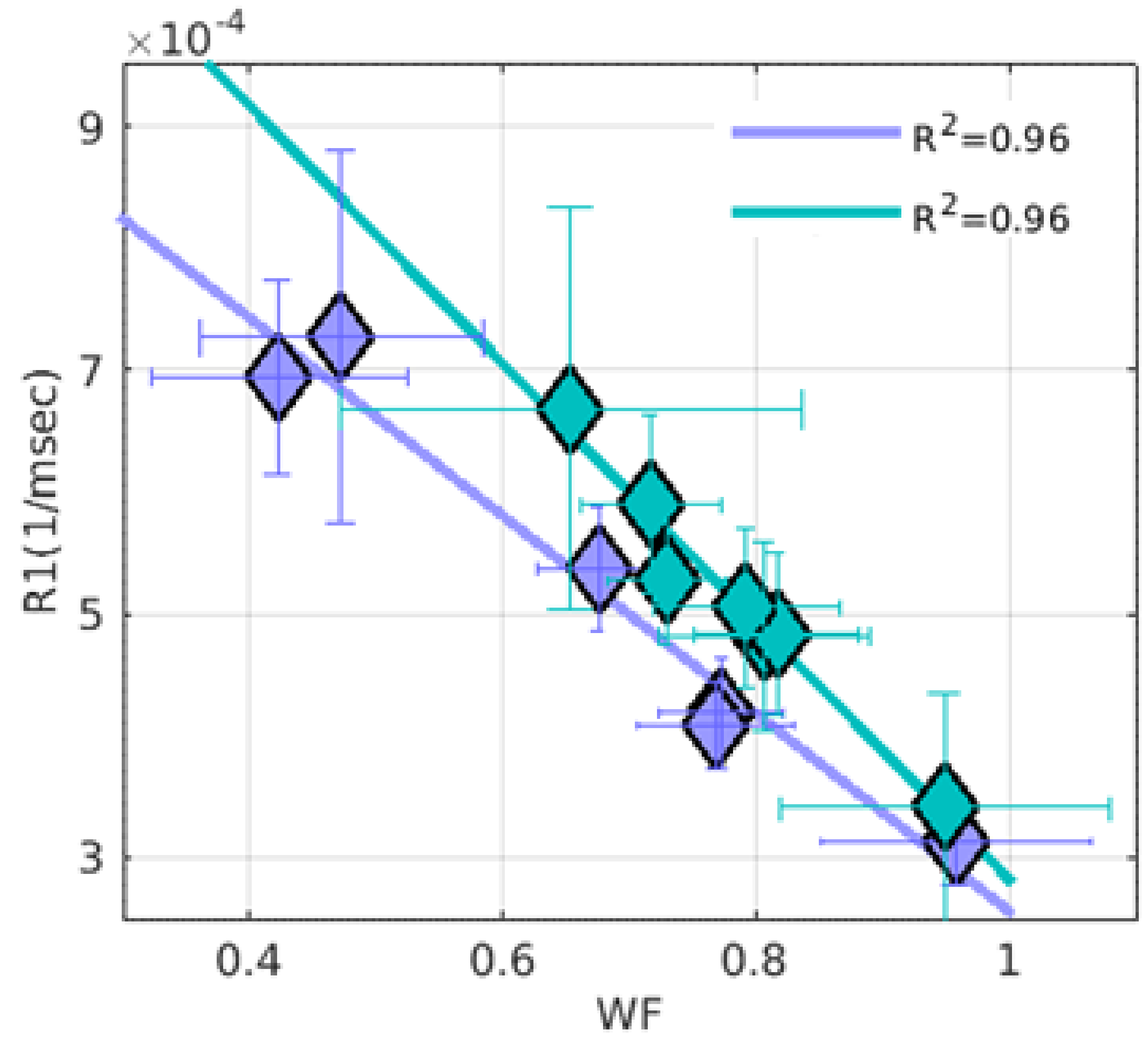
Many myelin mapping techniques to choose from

1. T1 relaxometry
2. Magnetization transfer (MT) imaging
3. Inhomogeneous MT
4. Myelin water imaging

T1 relaxation - sensitive but not specific to myelin

T1 relaxation is more efficient for lipids than proteins

- cholesterol (Koenig, MRM 1991)
- sphingomyelin and galactocerebroside (Kucharczyk et al., Radiology 1994)



(water fraction)

2 different phospholipids:

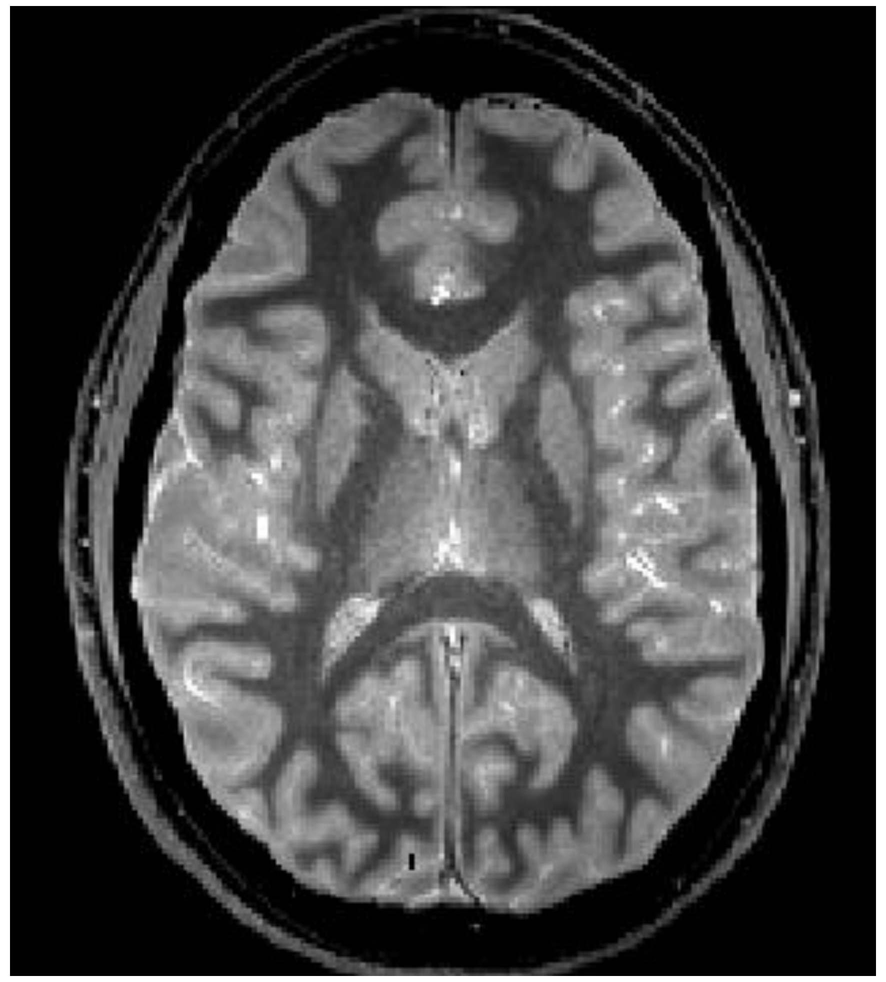
PC Phosphatidylcholine

PS Phosphatidylserine

Shtangel & Mezer, ISMRM 2018

T1 is also sensitive to water content, iron concentration, oxygenation, ...

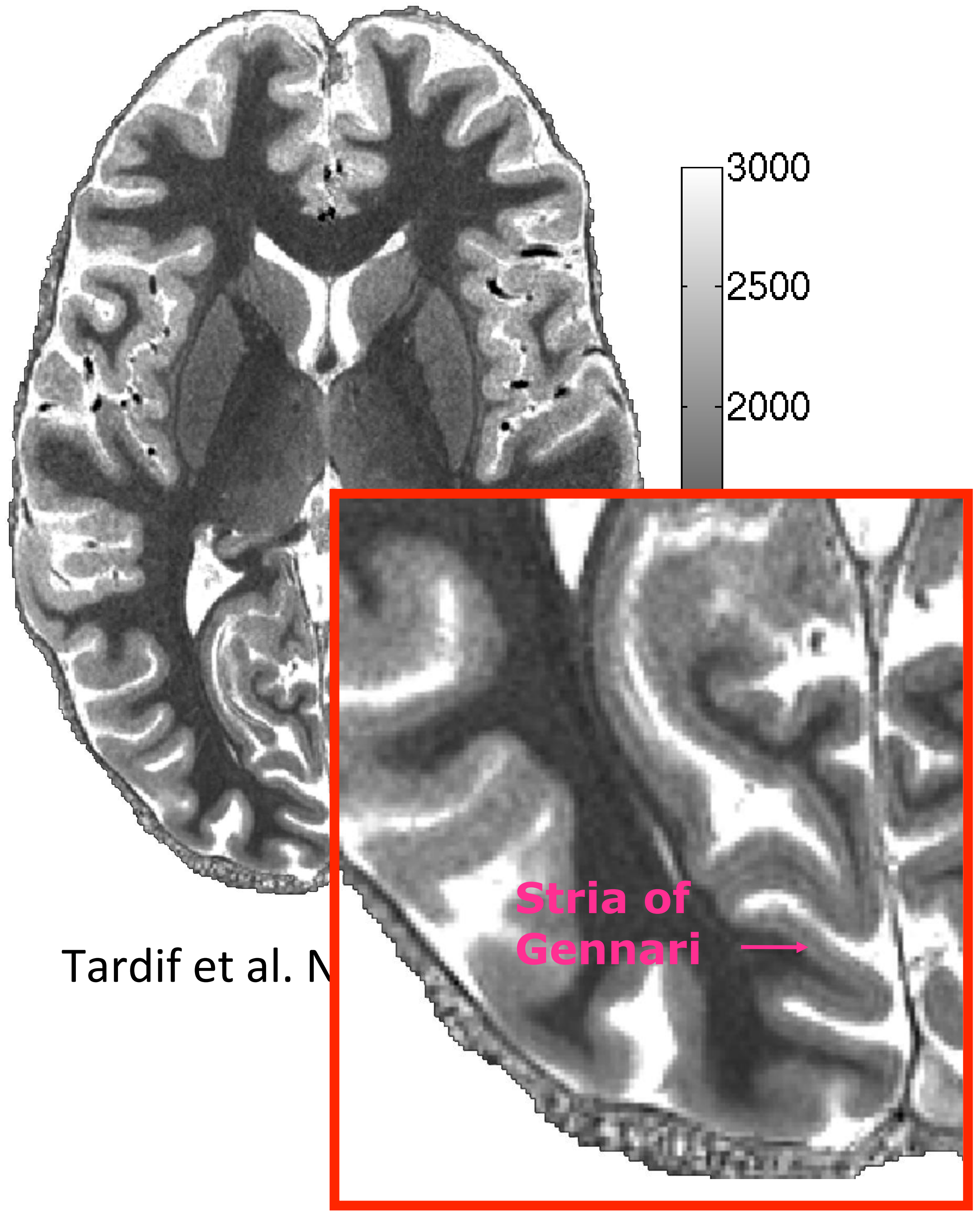
T1 map
[500, 2200] msec



PD map
[0.3, 1.3]

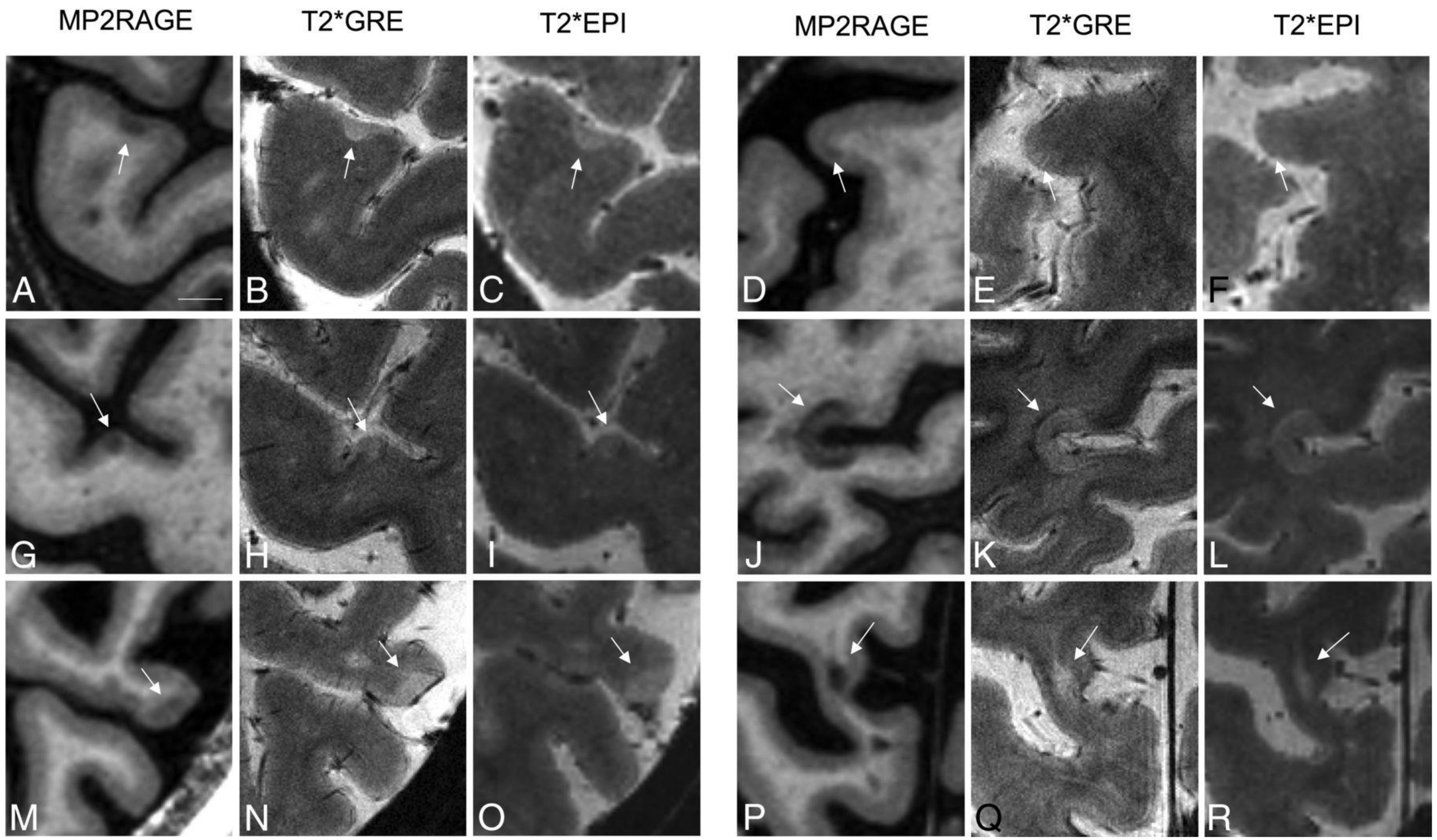
T1 relaxometry - an efficient and widely available technique

0.5mm isotropic MP2RAGE T1 map



Tardif et al. N

Improved detection of cortical lesions in multiple sclerosis

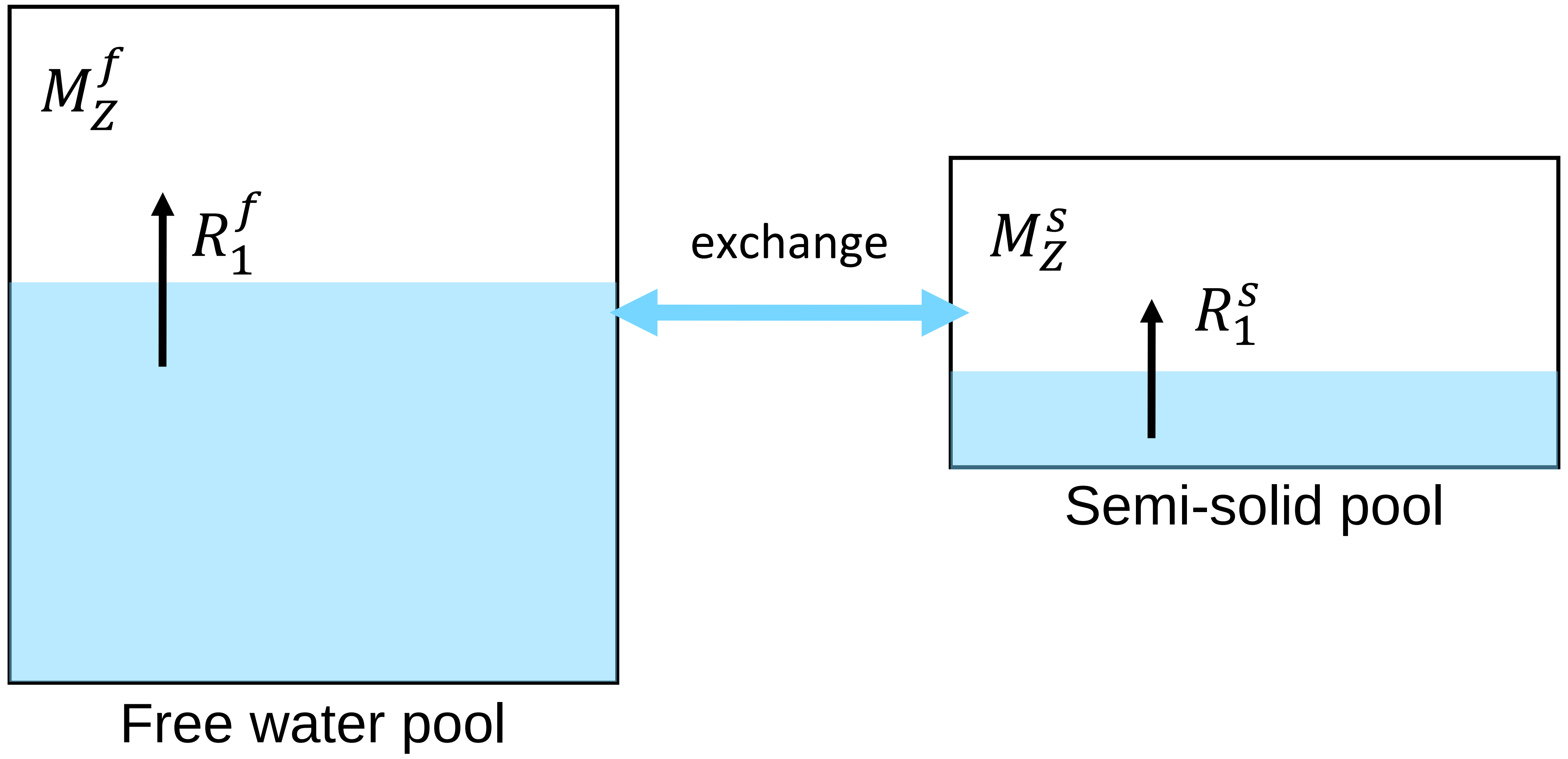


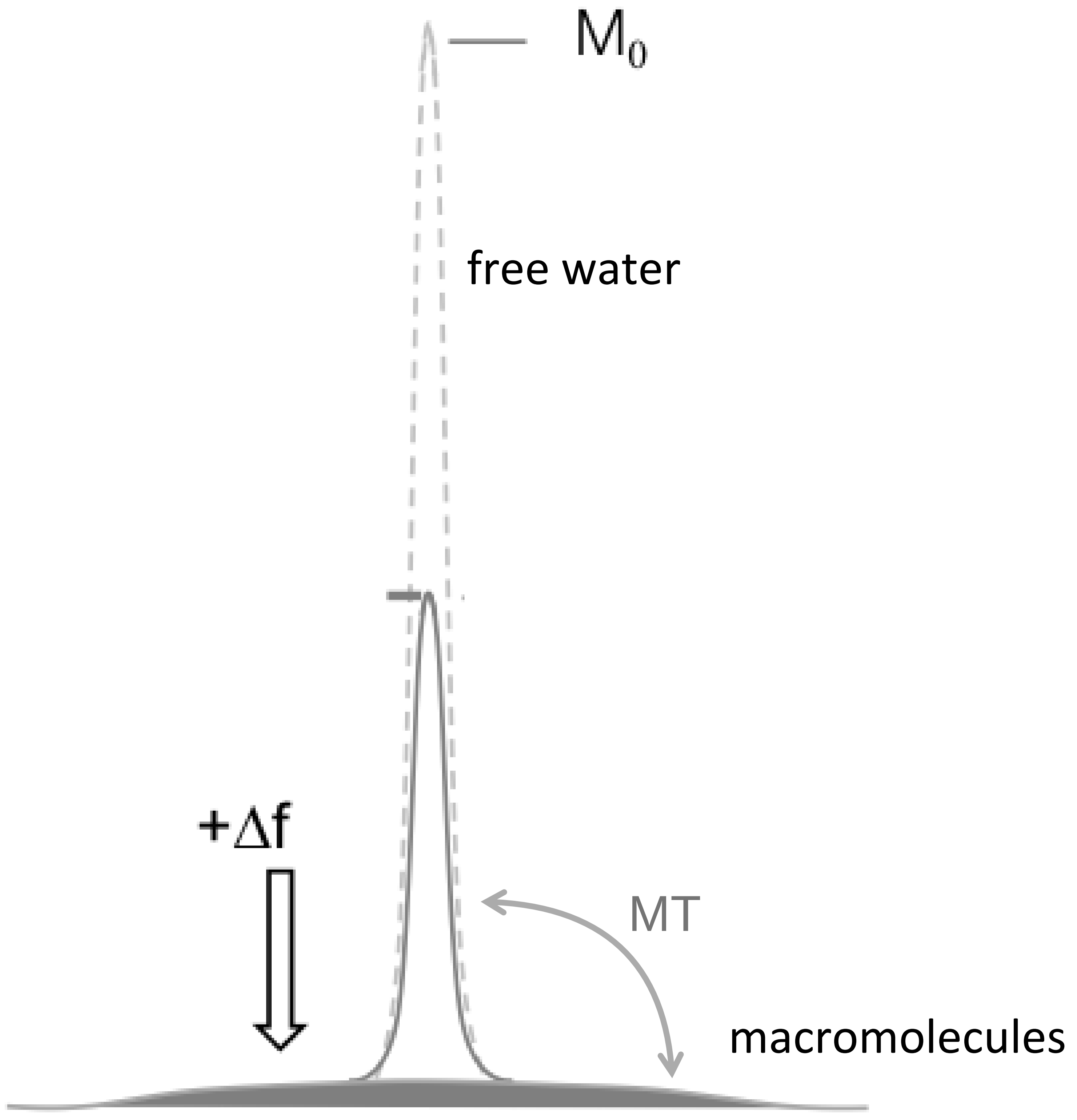
Beck et al., AJNR 2018

Magnetization transfer imaging - to indirectly image macromolecules

2 pool model:

- Protons in semi-solid pool have a short T2 (~10us), too short for direct observation using a clinical MRI scanner
- Apply RF pulse off resonance to selectively saturate the bound pool
- MT between pools will result in a decrease in the free water magnetization





Henkelman et al., NMR in Biomed 2001
Sled, NeuroImage 2018

neuro

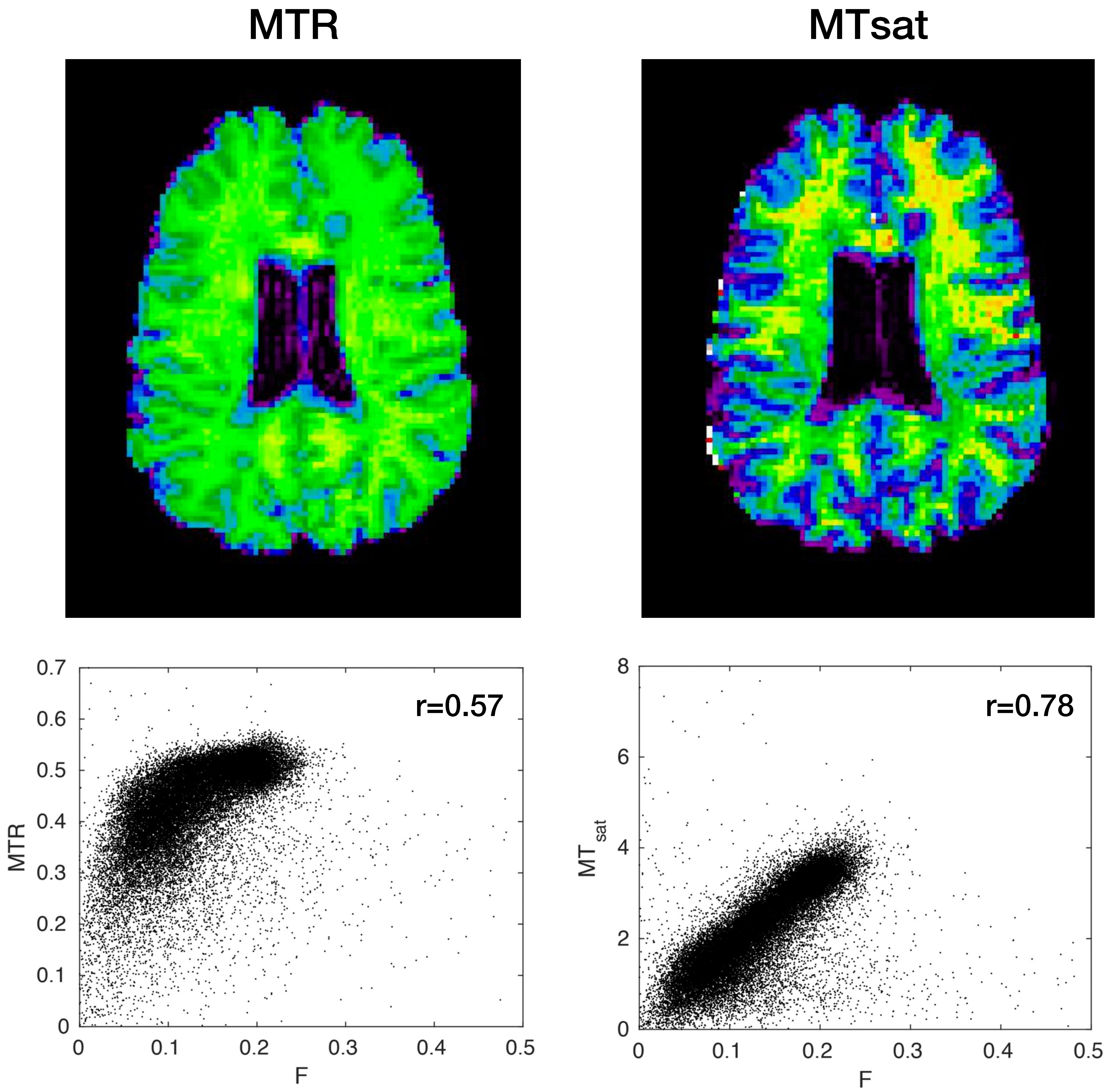
Magnetization transfer saturation (MTsat) - a good compromise

- The MT ratio (MTR) is a semi-quantitative technique because it depends on the acquisition parameters chosen.

$$MTR = \frac{S_0 - S_{MT}}{S_0}$$

- MT saturation (MTsat): corrected for B1 non-uniformity and counteracting T1 effects.

(Helms et al. MRM 2008)

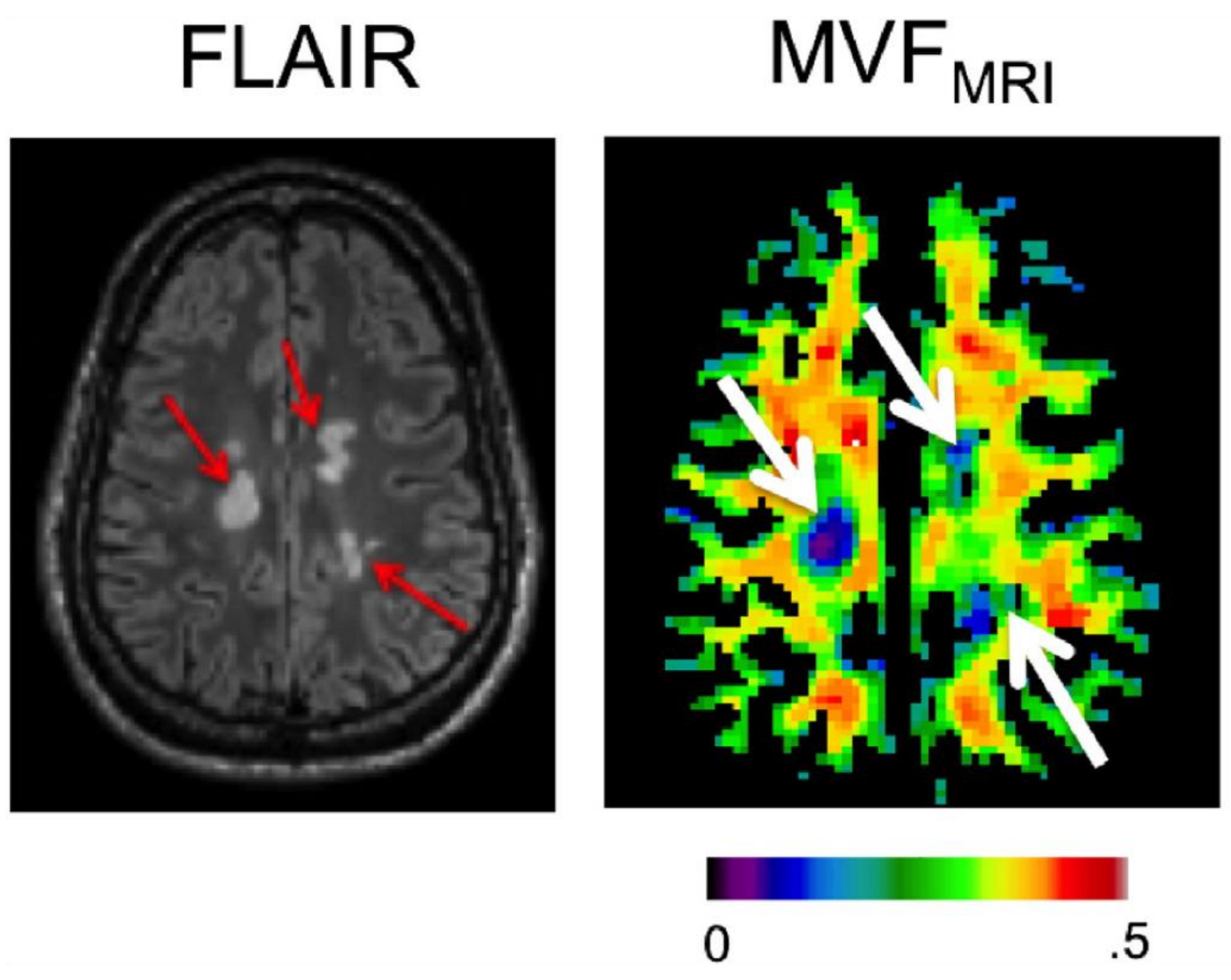


(bound pool fraction)

Campbell et al. NeuroImage 2018

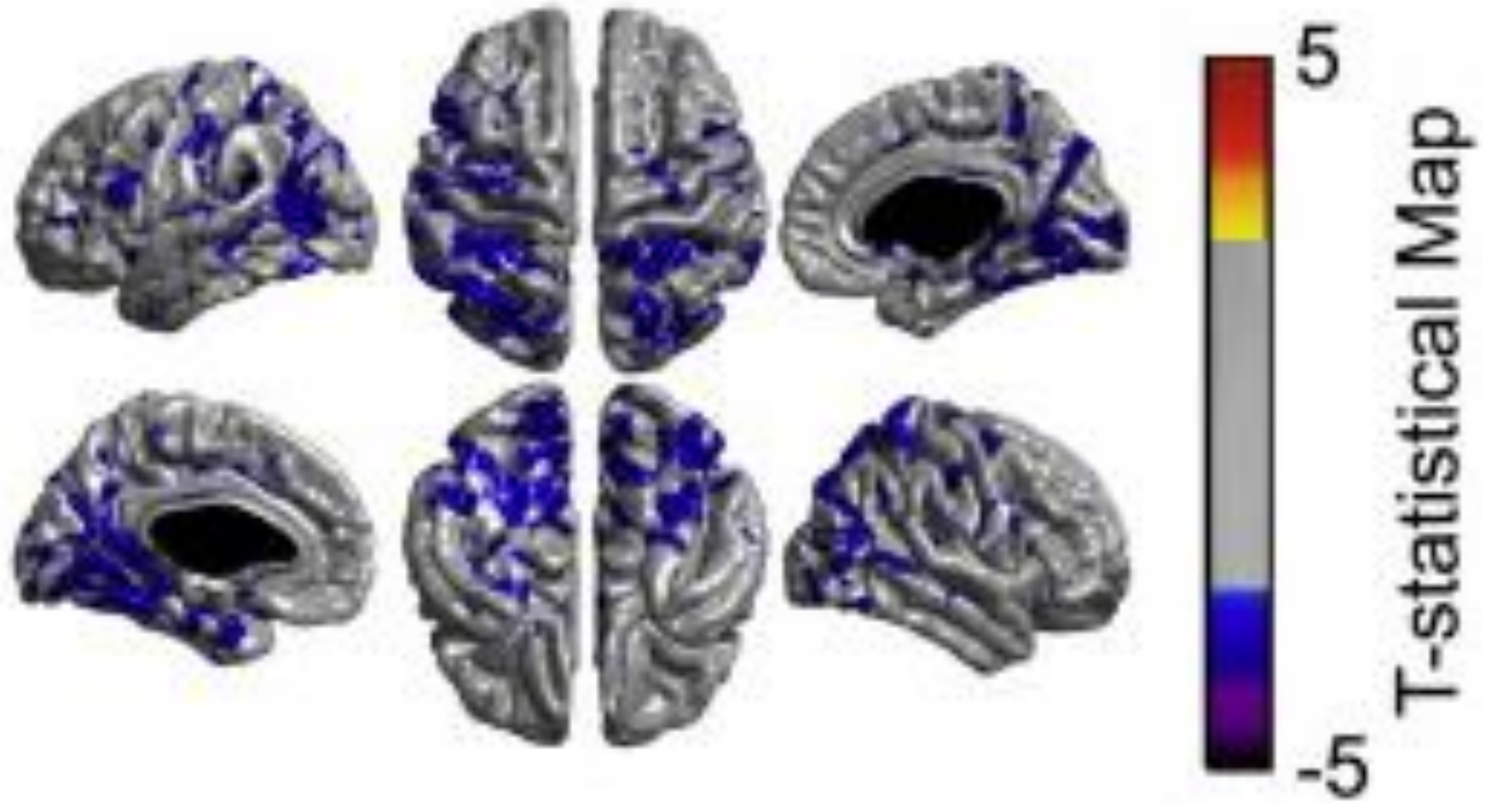
MT imaging is widely used to study MS and other myelin-related disorders

WM MS lesions



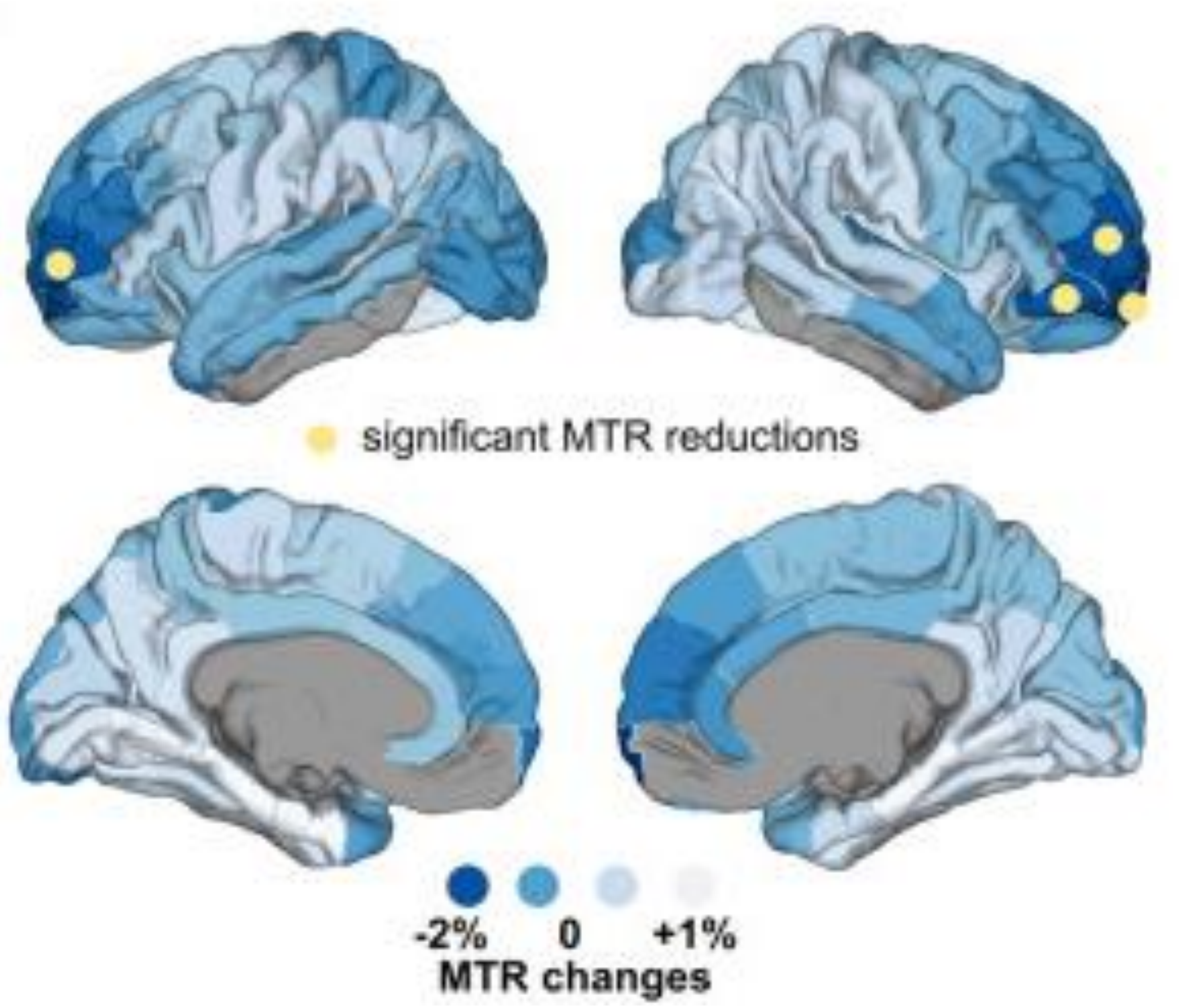
Stikov, Campbell et al. NeuroImage 2015

Cortical MS pathology



Rudko et al. NeuroImage: Clinical 2016

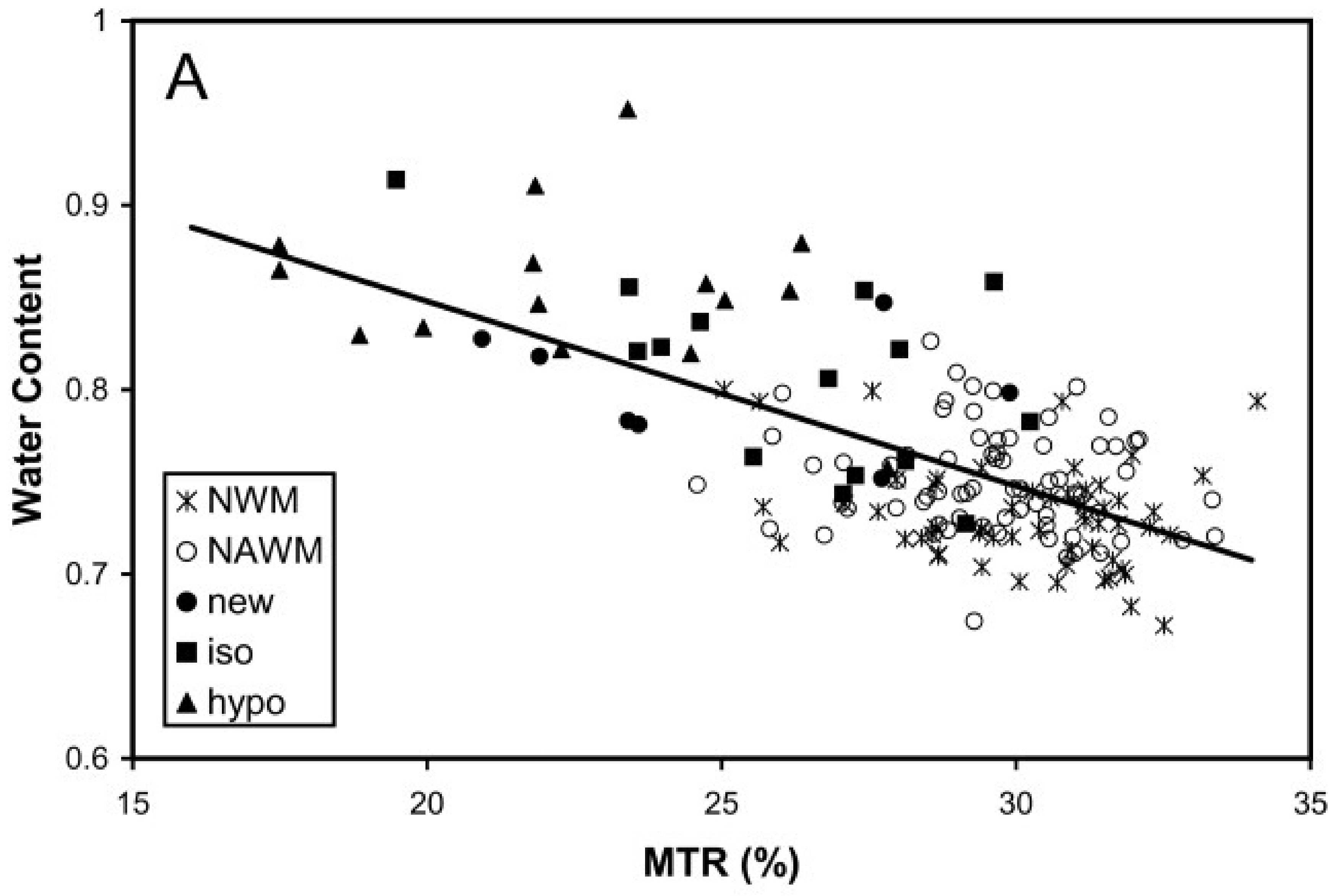
Cortical pathology in schizophrenia



Wei et al. Schizophrenia Research 2018

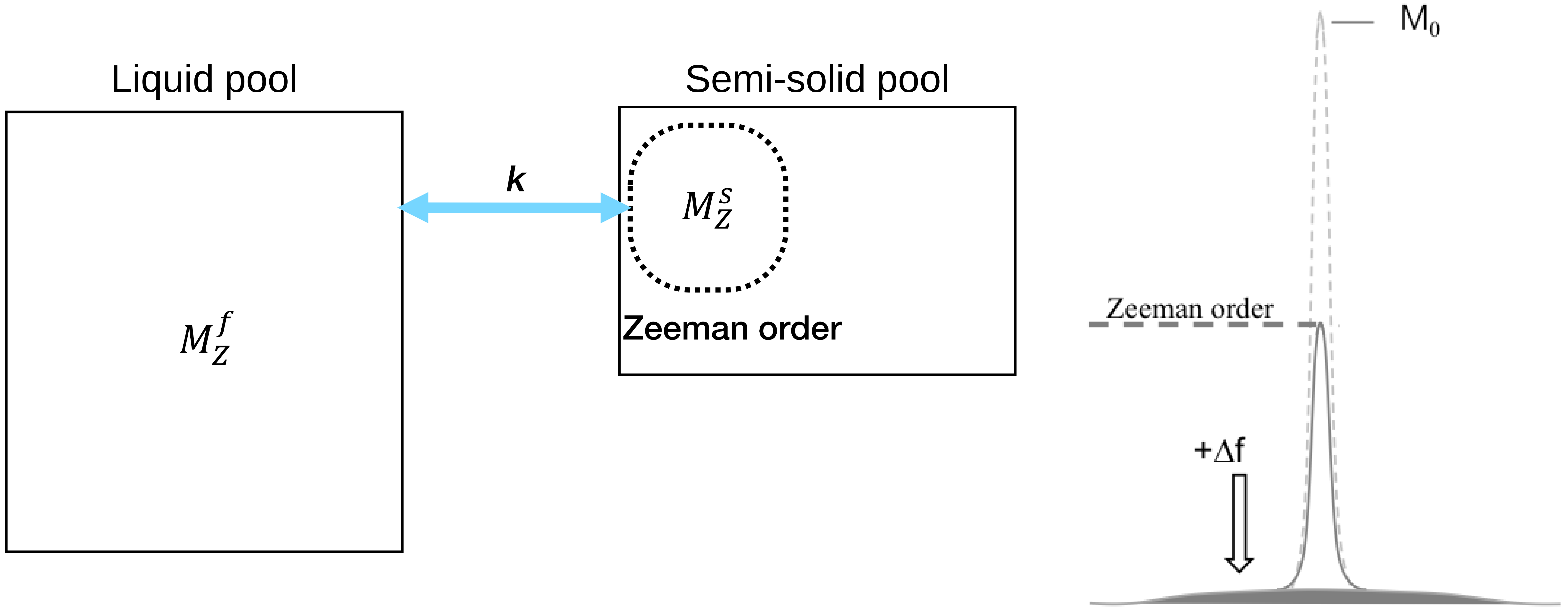
T1 and MT are not specific to myelin

- Many macromolecules contribute to T1 and MT
- T1 and MTR are a function of tissue water content
- T1 is also sensitive to other tissue features, such as iron content

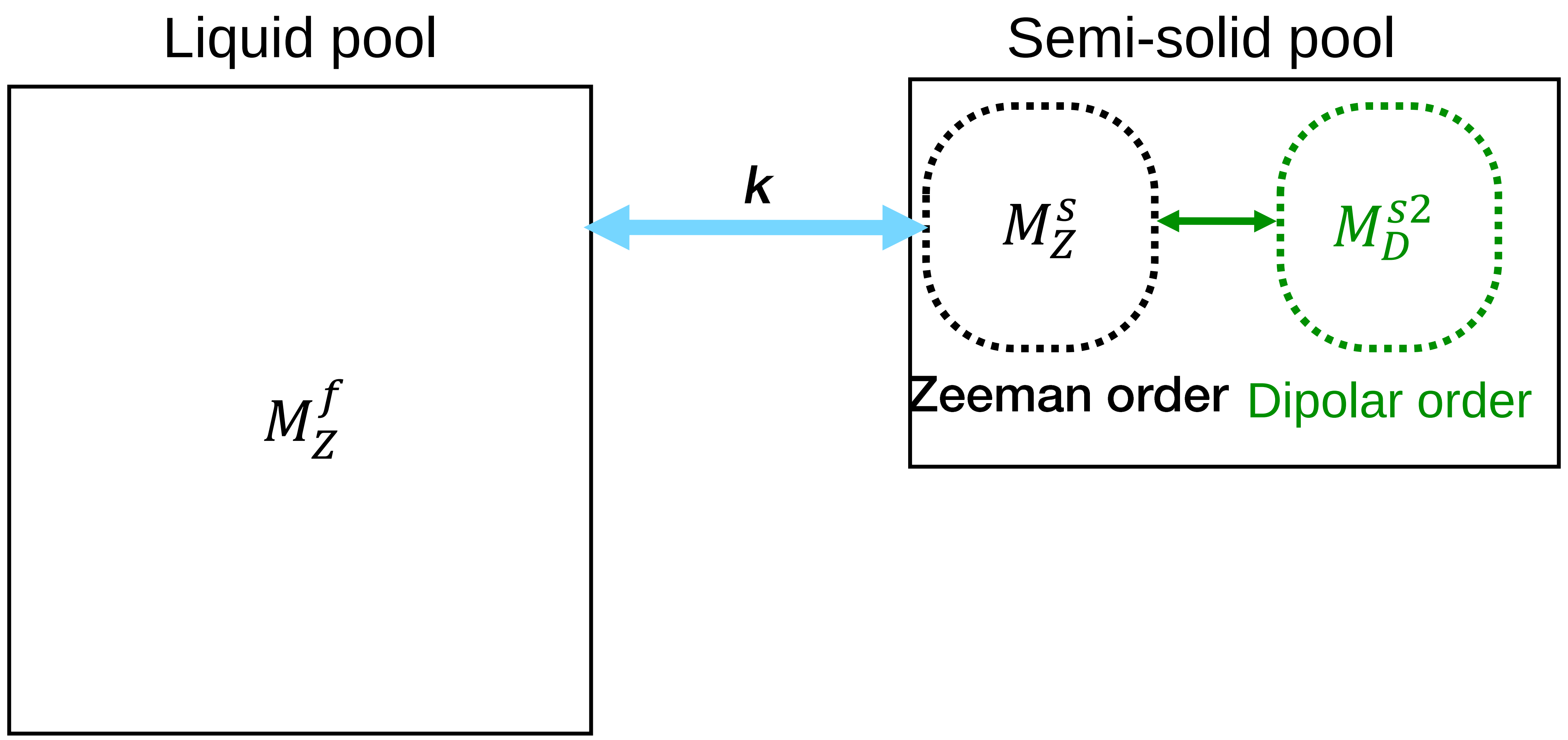


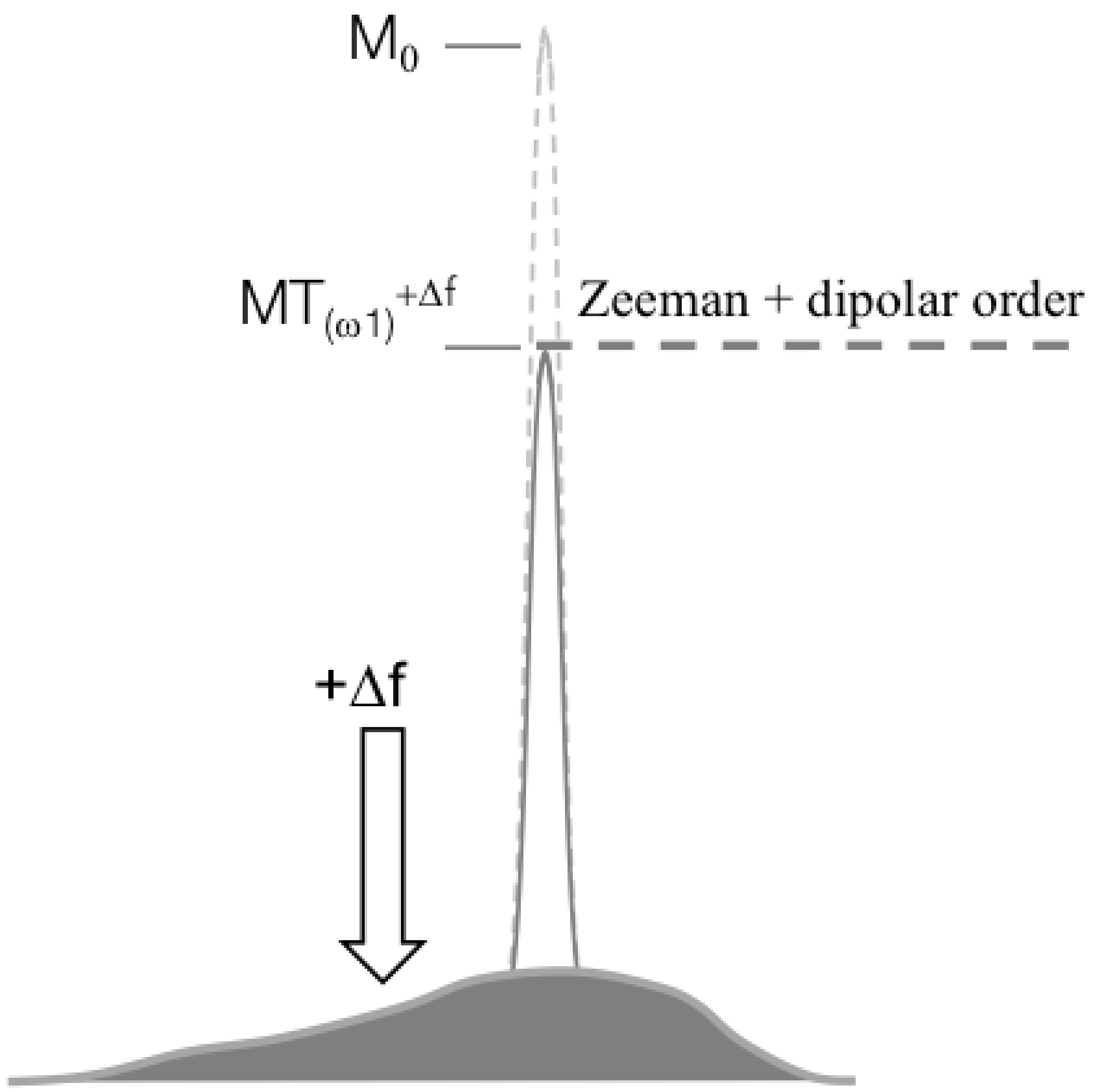
Vavasour et al. JMRI 2011

inhomogeneous MT - the dipolar reservoir



inhomogeneous MT - the dipolar reservoir

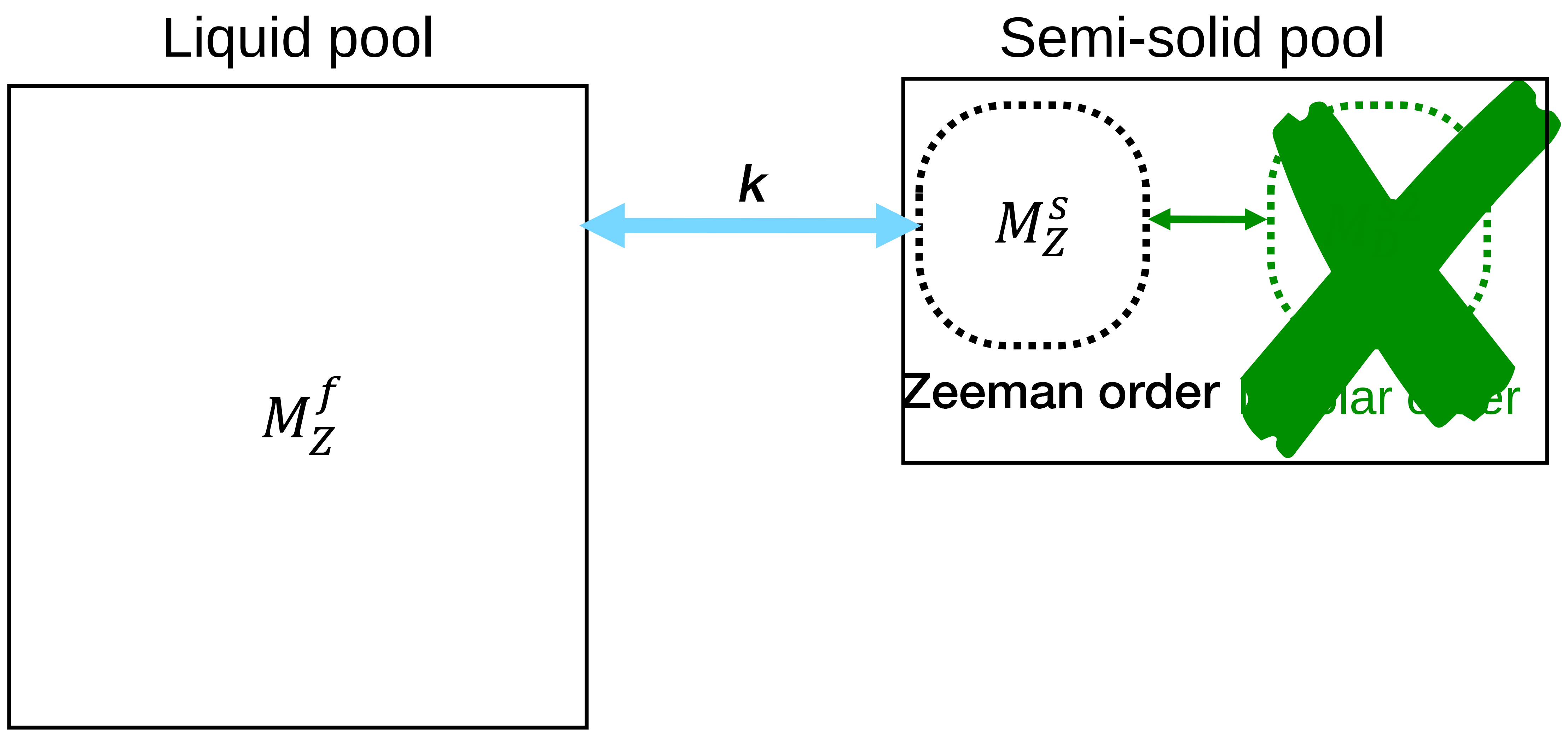


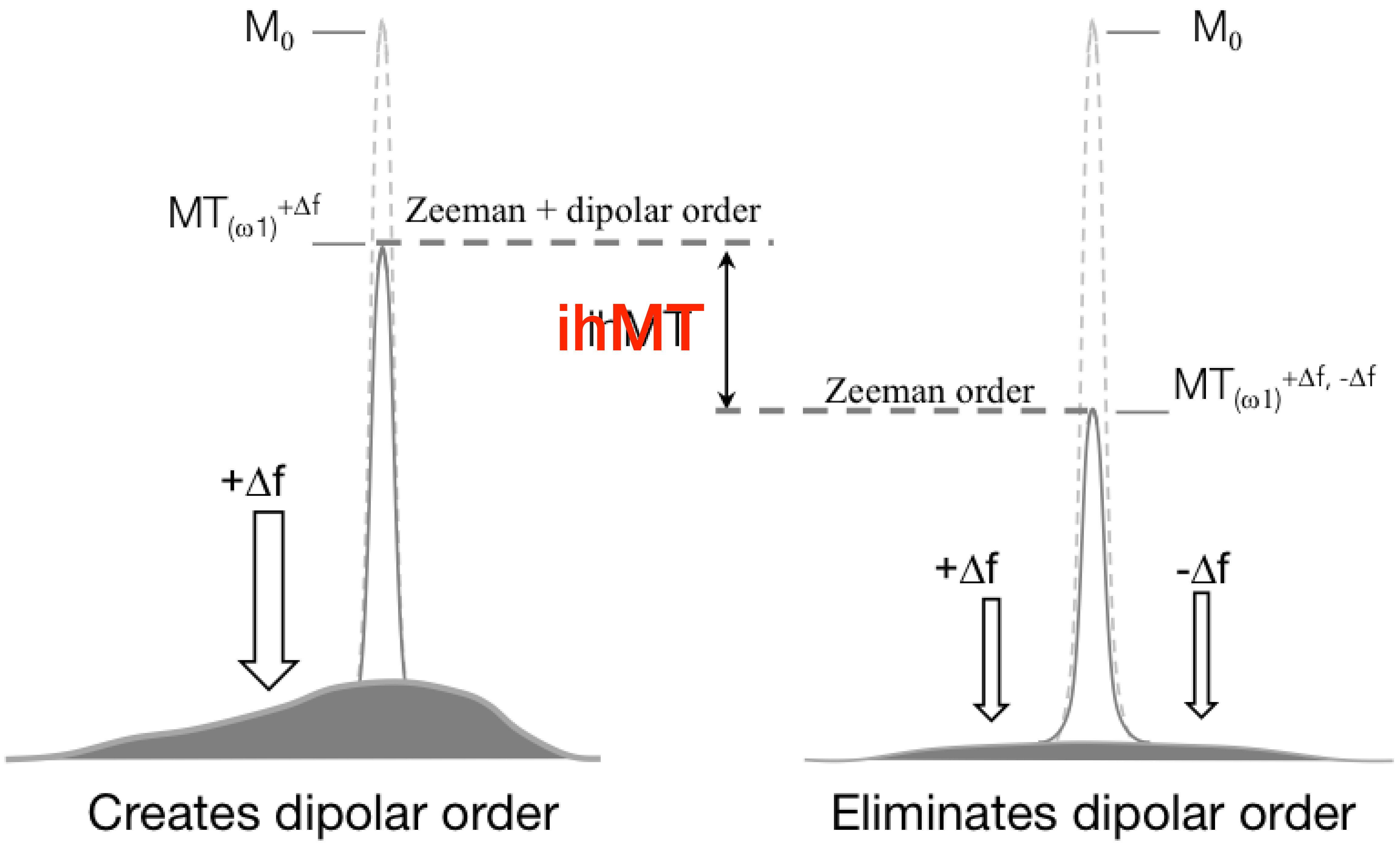


Creates dipolar order

Morrison, Stanisz & Henkelman, J Magn Reson, B 1995
Morrison & Henkelman, MRM 1995
Provotorov, Sov. Phys. JETP 1962
Duhamel, ISMRM 2019

inhomogeneous MT - the dipolar reservoir





Morrison, Stanisz & Henkelman, J Magn Reson, B 1995
Morrison & Henkelman, MRM 1995
Provotorov, Sov. Phys. JETP 1962
Duhamel, ISMRM 2019

ihMTR and ihMTsat

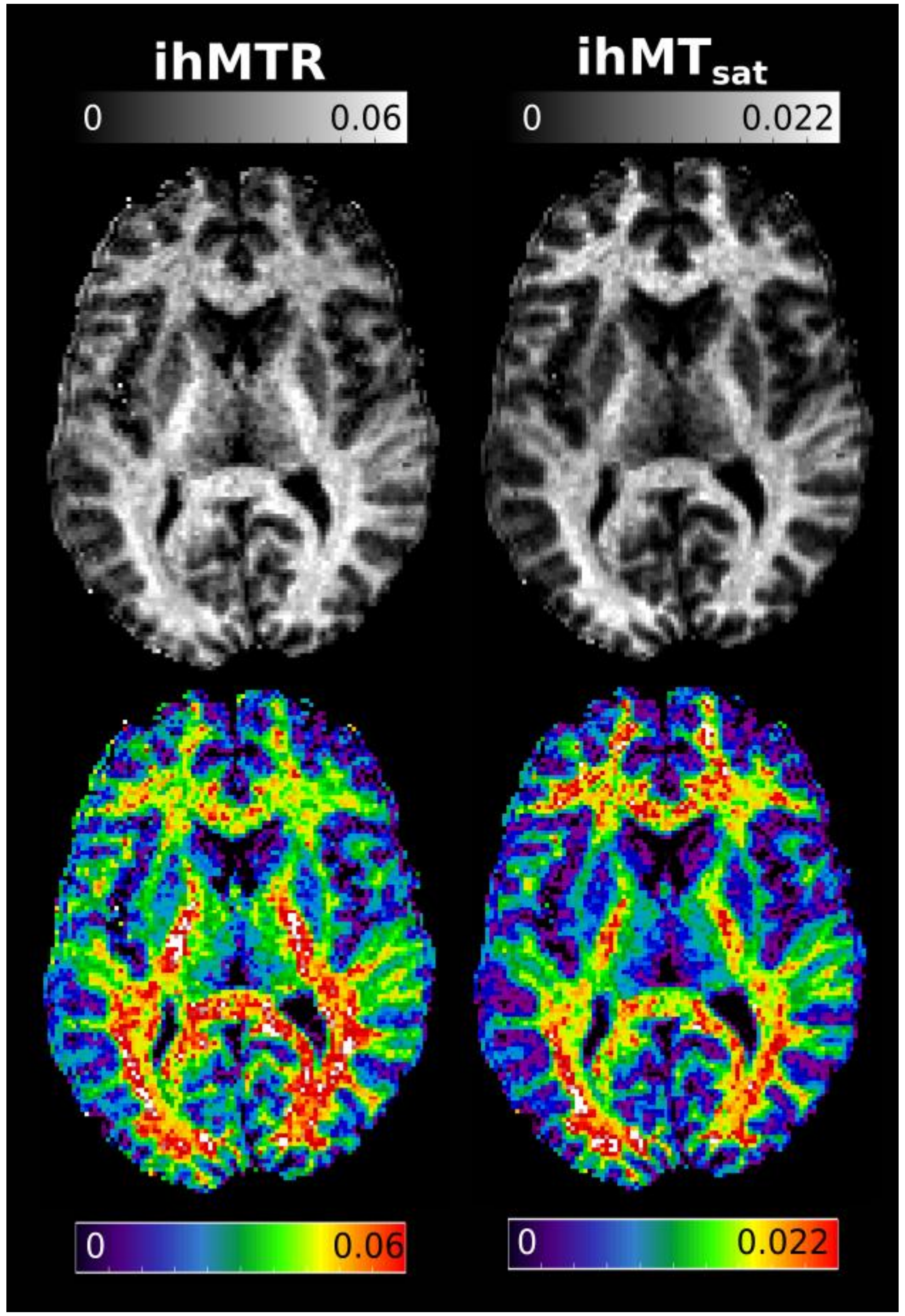
Must acquire a minimum of 3 images to calculate ihMTR:

- single frequency saturation
- dual frequency saturation
- no saturation

$$ihMT = MT^{+\Delta f} + MT^{-\Delta f} + MT^{+\Delta f,-\Delta f} + MT^{-\Delta f,+\Delta f}$$

$$ihMTR = \frac{ihMT}{S_0}$$

Similarly to MTsat, we can calculate ihMTsat to remove confounding T1 effects



Rowley et al. ISMRM 2020

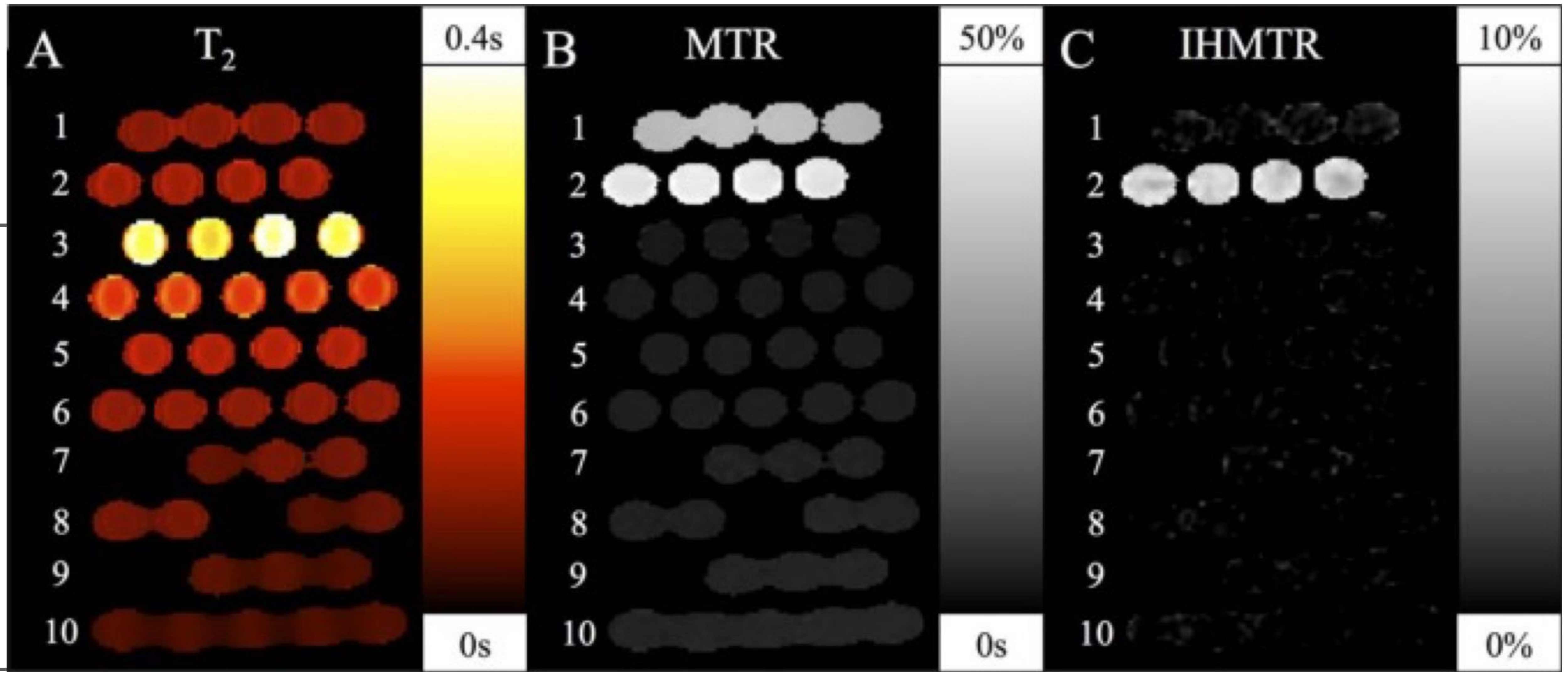
ihMT - more specific to lipid-rich lamellar structures

lamellar structure containing long chains of methylene protons

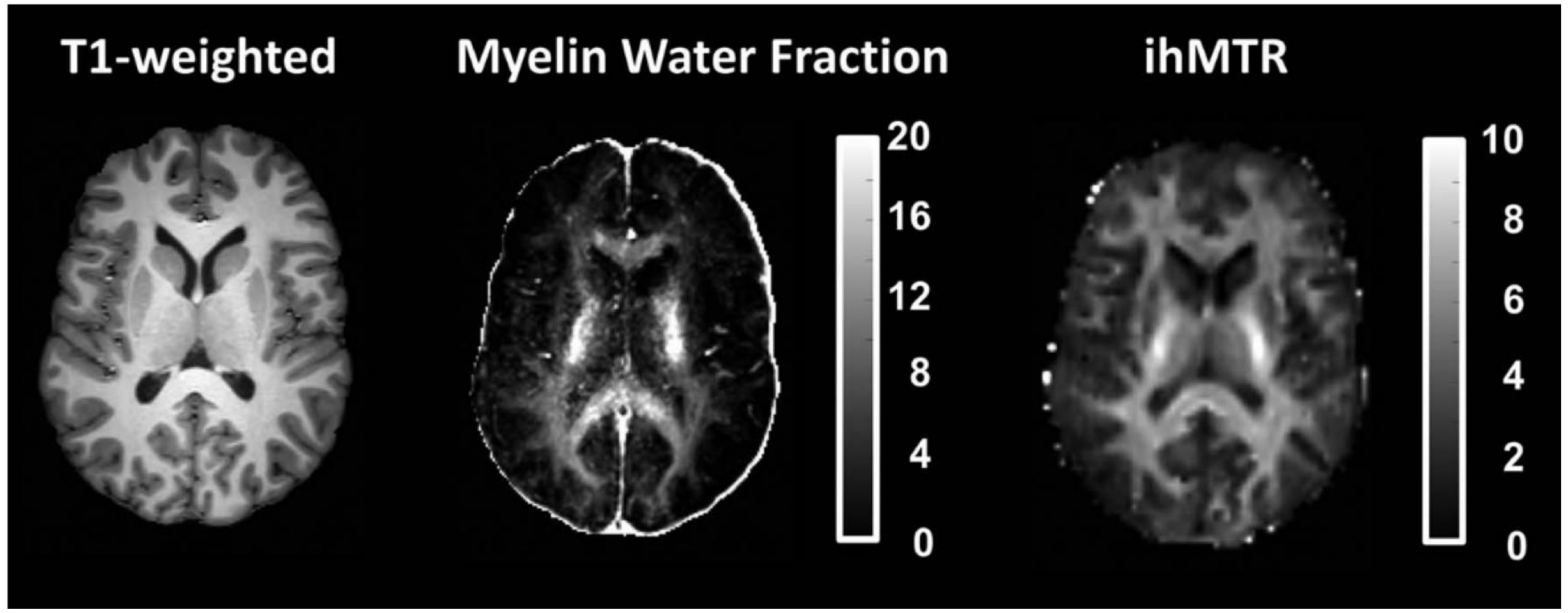
egg white protein

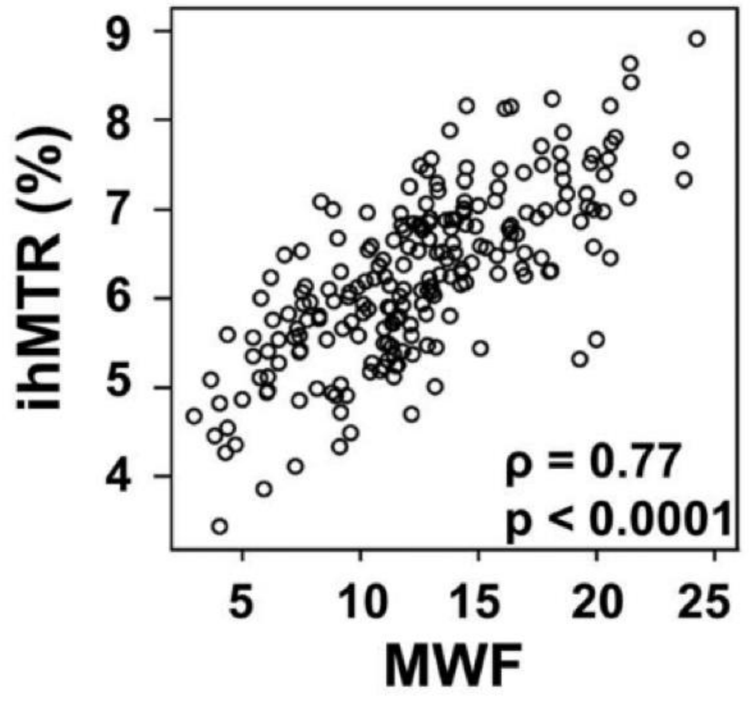
hair conditioner

solutions with increasing concentrations of MnCl



Varma et al. MRM 2015

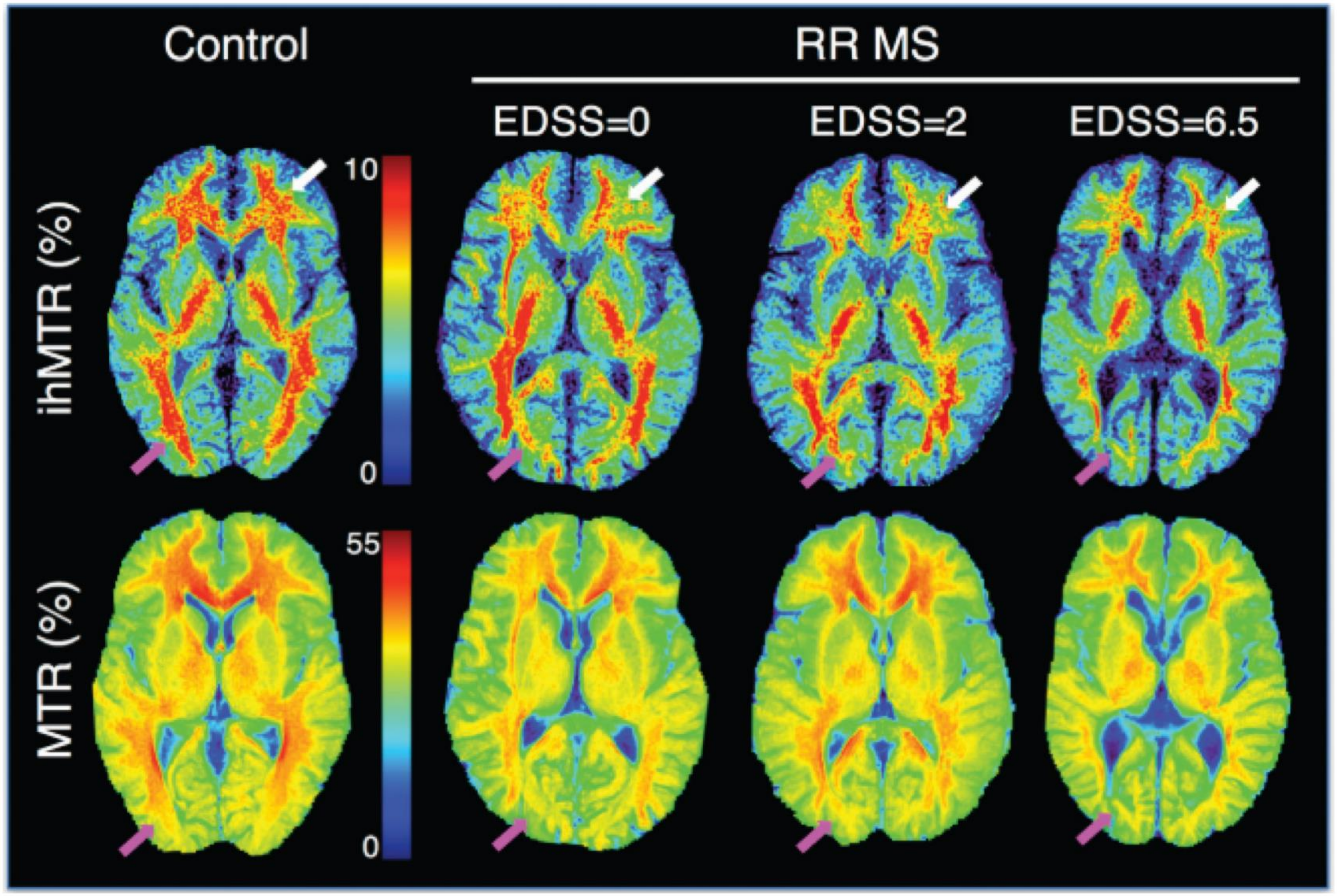


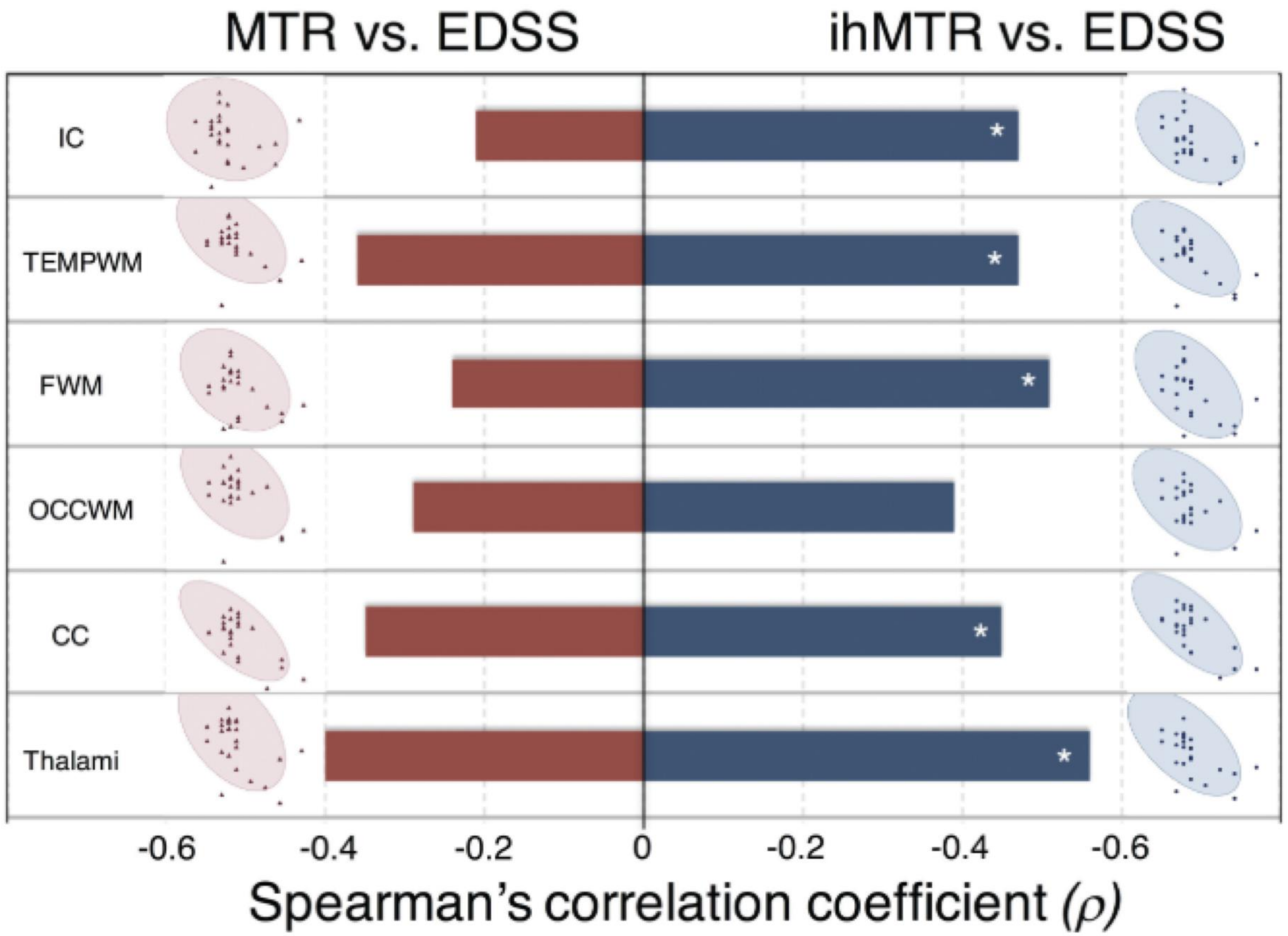


Ercan et al. MRM 2018

Inhomogeneous MT in multiple sclerosis (MS)

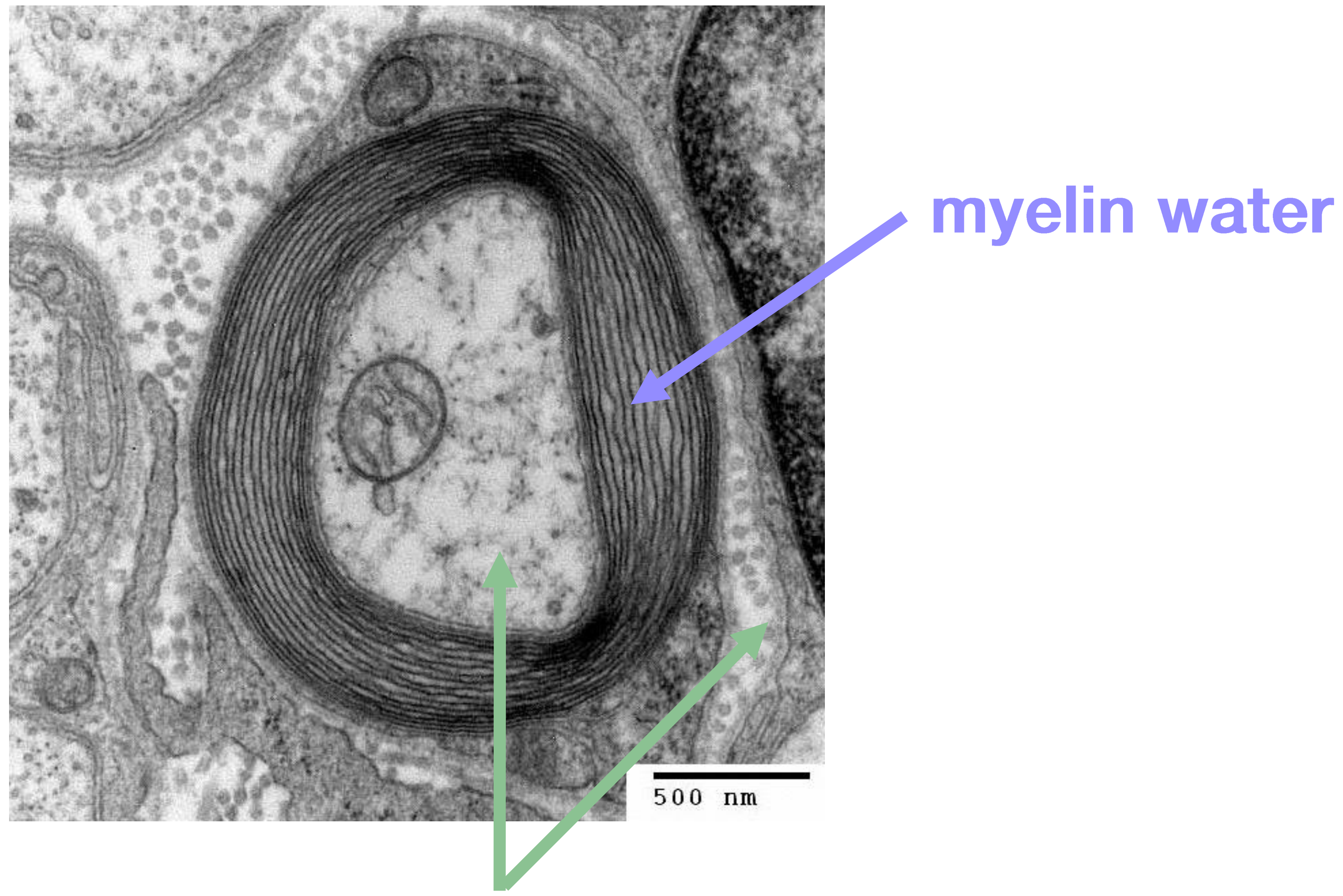
Relapsing remitting (RR) MS patients





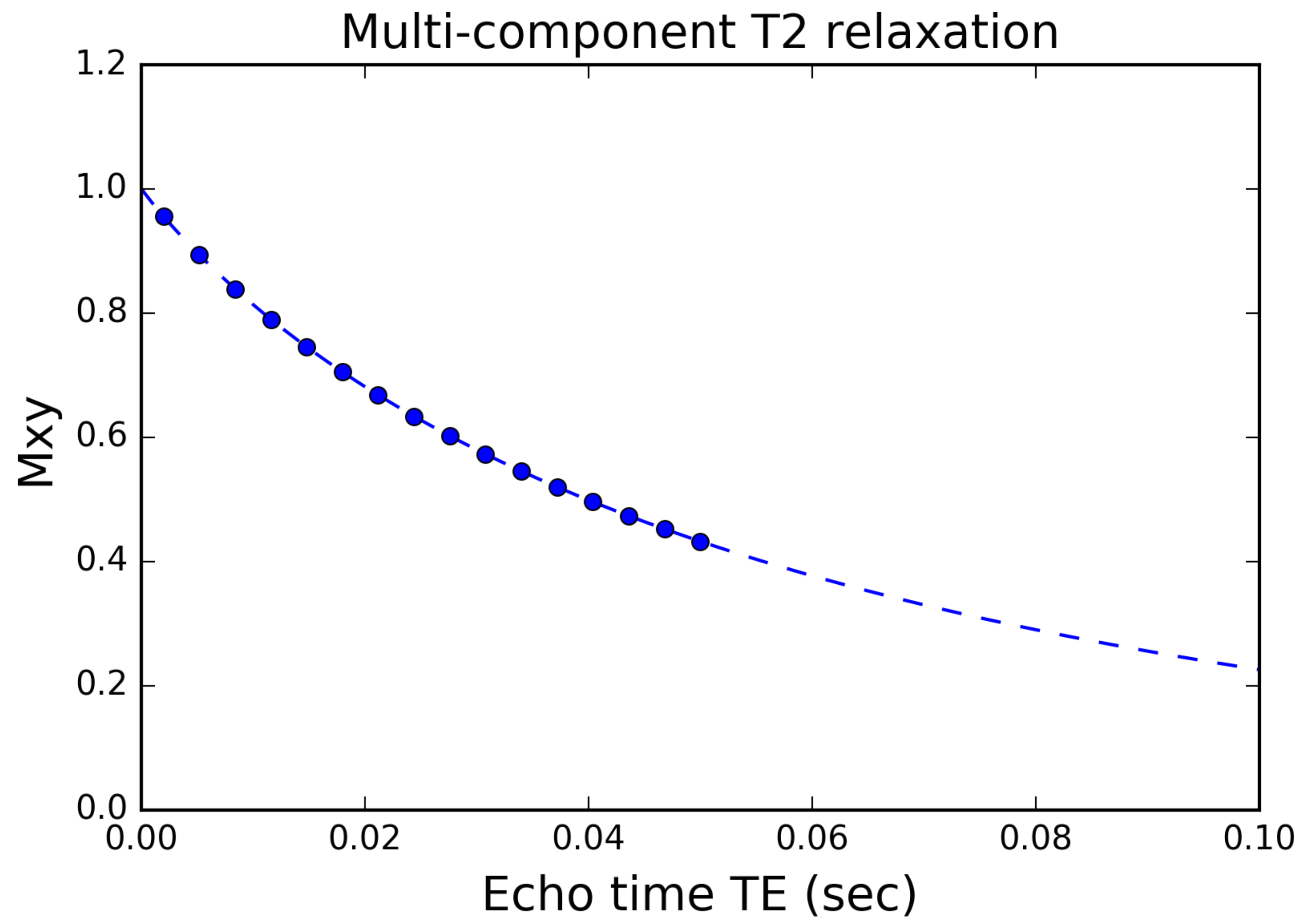
Obberghen et al. AJNR 2017

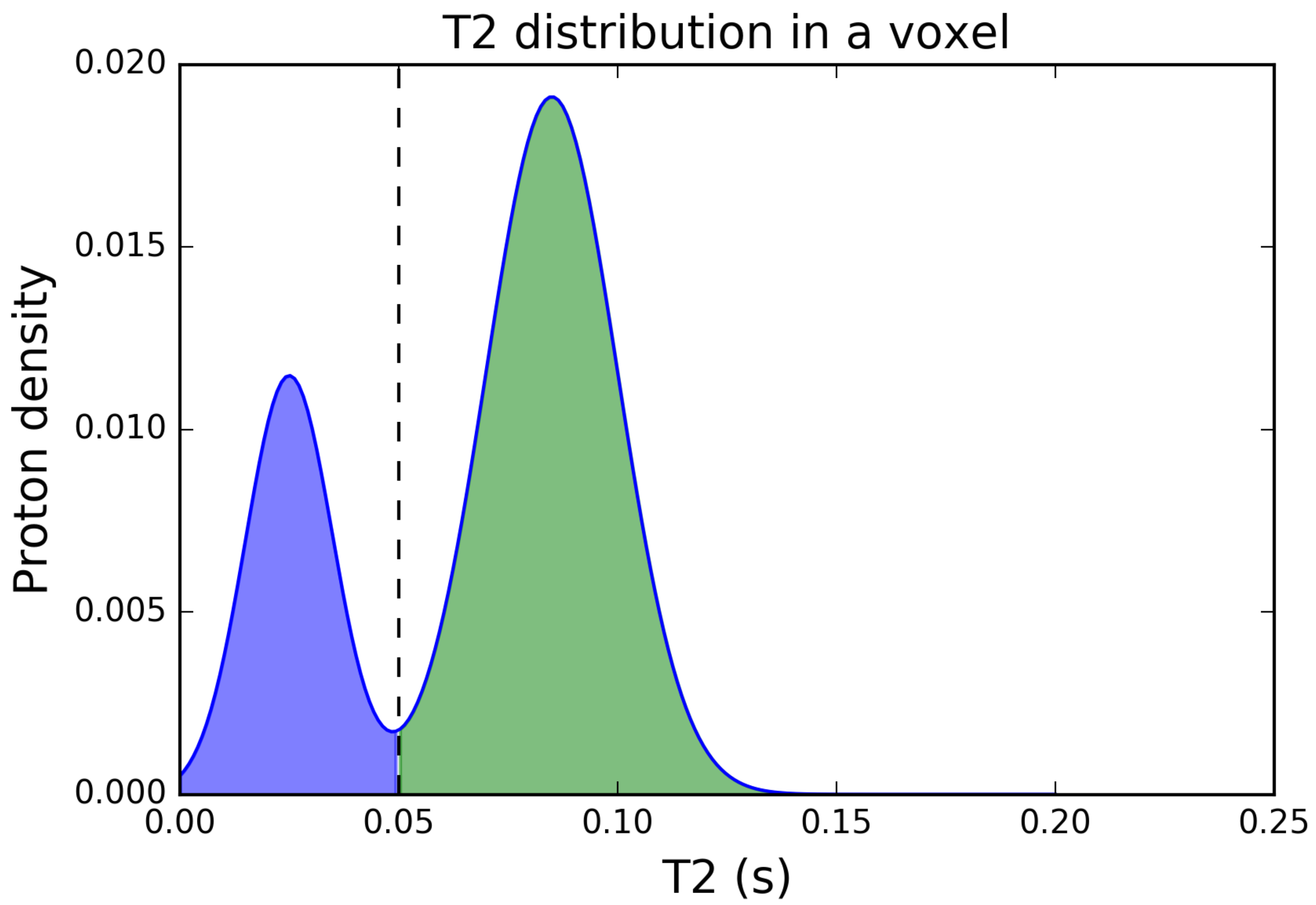
Myelin water imaging - looking at different microstructural compartments



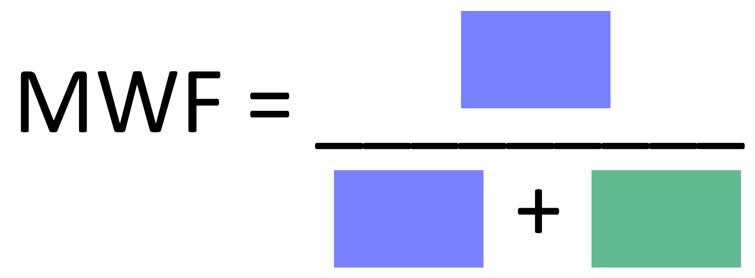
Total signal in a voxel is the sum over the different compartments:

$$y_i = \sum_{j=1}^{M} s_j e^{-t_i/T_{2,j}}, \quad i = 1, 2, \ldots, N.$$



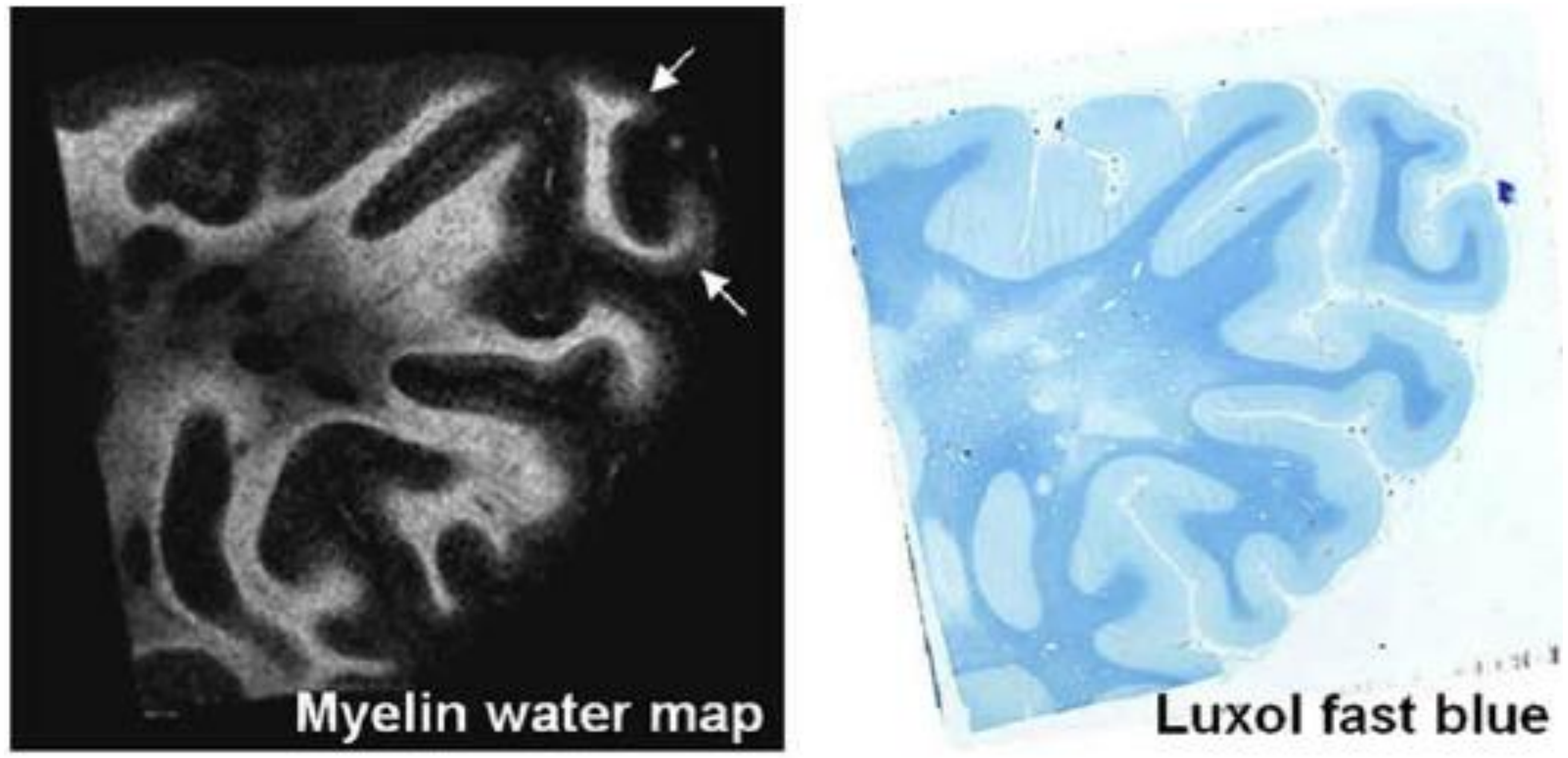


Myelin water fraction

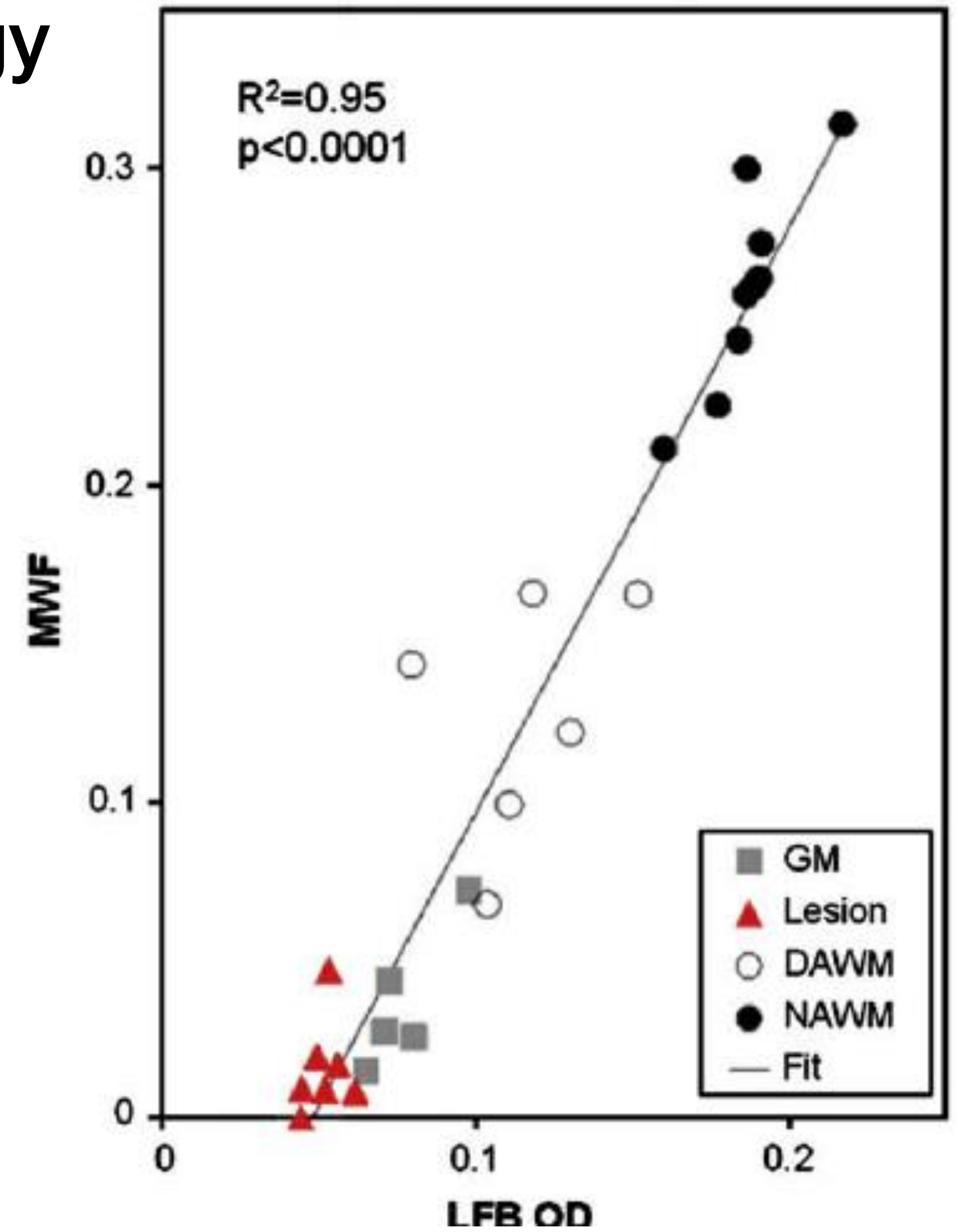


Myelin water imaging - a more specific biomarker

Validation in postmortem MS tissue using histology



Laule et al, NeuroImage 2008



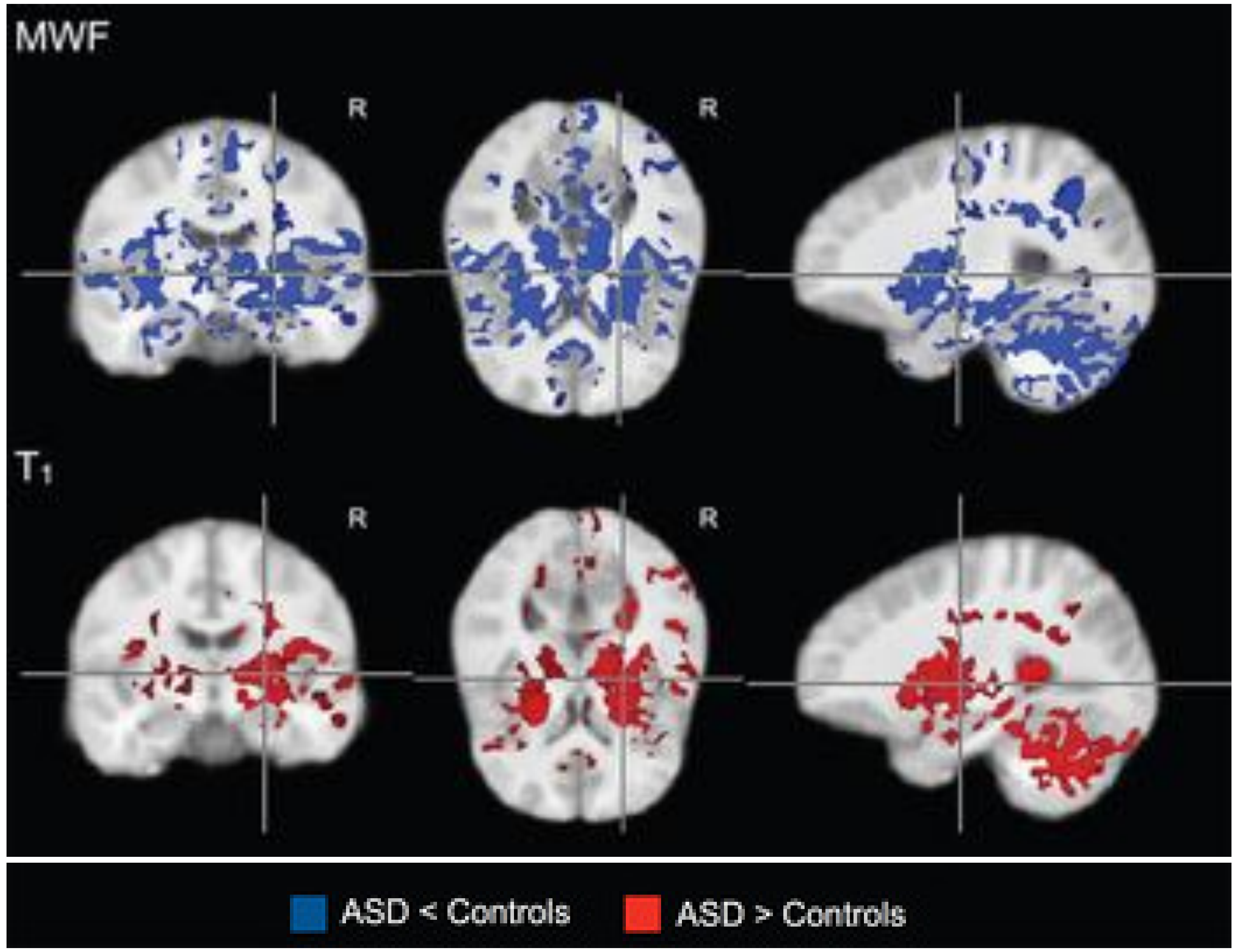
Limitations:

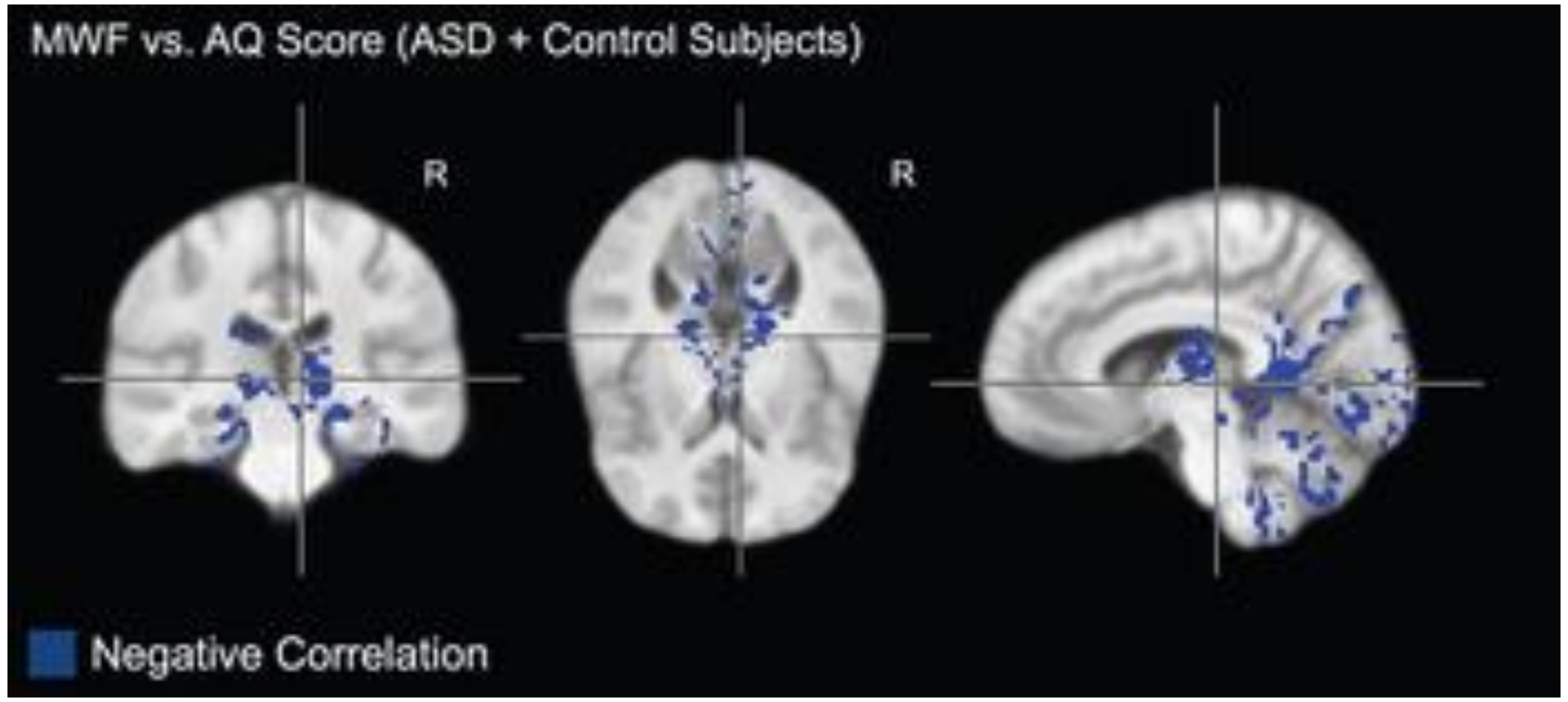
- low efficiency
- custom sequences
- complex fitting

Alonso-Ortiz et al. MRM 2015
MacKay & Laule, Brain Plasticity 2016
Lee et al., JMRI 2020

MWF is associated with social disabilities in autism spectrum disorder (ASD)

Whole brain MWF measured using McDESPOT





Deoni et al., Psychological Med 2015

Summary

- There are many quantitative myelin mapping techniques available
- They are widely used to study healthy myelinatination as well as de- and dys-myelinating disorders
- Myelin water imaging and inhomogeneous MT are more specific biomarkers

Future directions:

- Improve efficiency of MWI and ihMT
- Multi-modal imaging to gain information about myelin ultrastructure (eg. g-ratio)
- Tract-specific myelin metrics

Acknowledgements

Daniel Andrews
Sarah McGillivray
Christopher Rowley
Sajjad Feizollah
Mark Nelson
Tim Wu
Ilana Leppert

Ilana Leppert
Marius Tuznik
Mike Ferreira
Marcus Couch
Jennifer Campbell
Prof. David Rudko
Prof. Rick Hoge