Studying central nervous system (CNS) diseases with advanced MRI

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Staff Scientist
Translational Neuroradiology Section

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PI: Daniel S. Reich, MD, PhD

Mission statement:

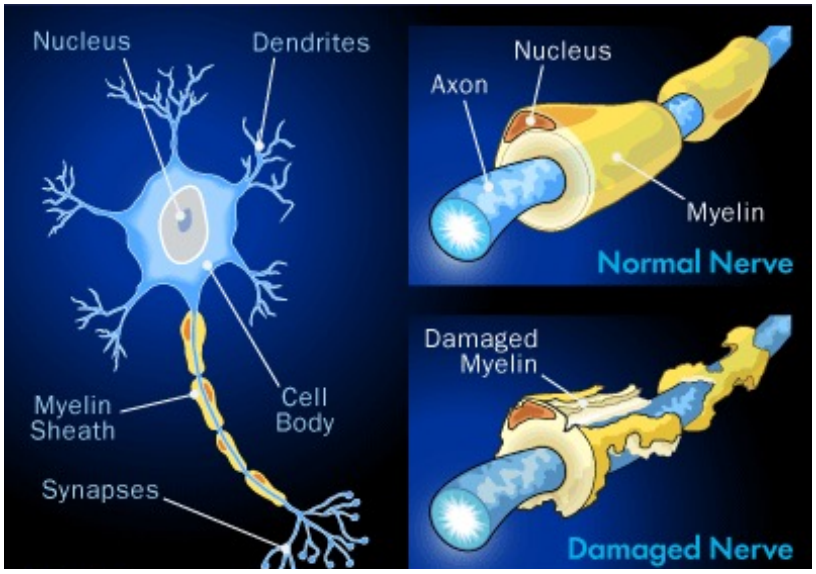
"Our research focuses on the use of **advanced MRI** techniques to **understand the sources of disability** in MS and on ways of adapting those techniques for use in **research trials** and **routine patient care**."

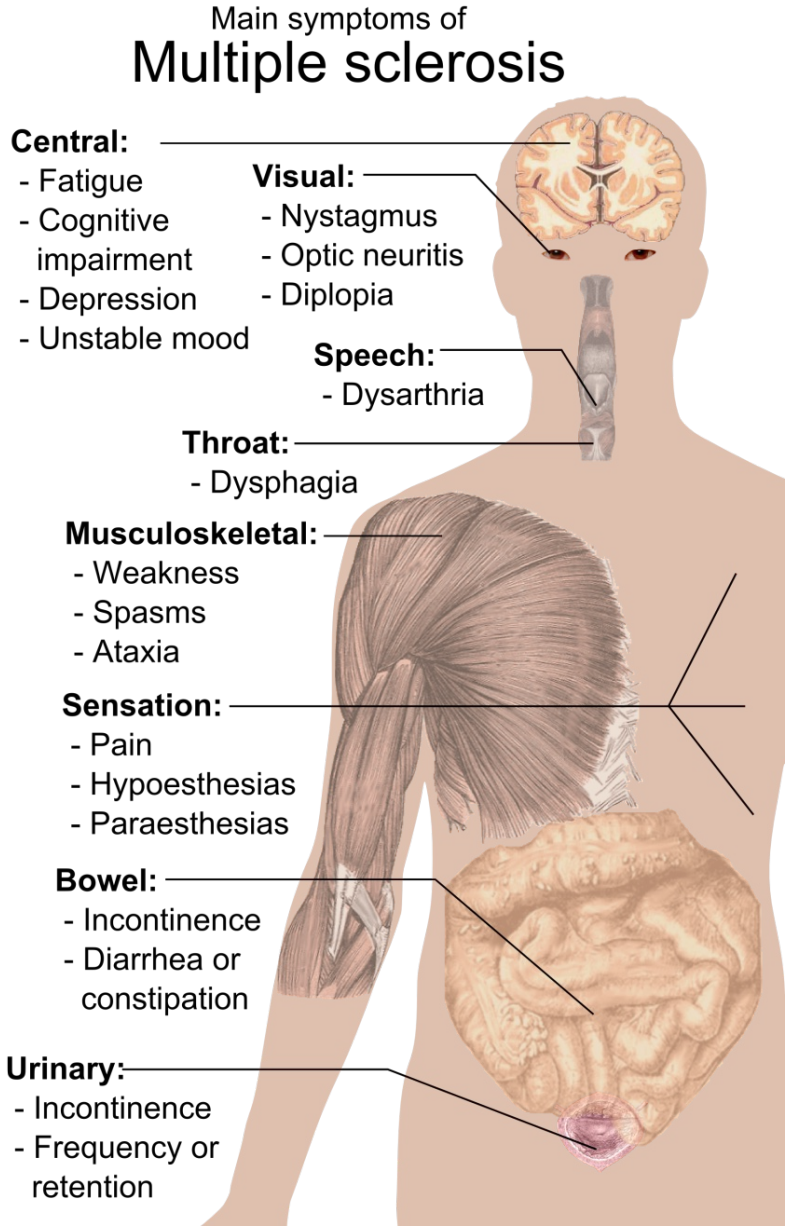
MS: a disabling disease of the central nervous system

Prevalence:
400,000 in the US

Origin:
Still unknown

Pathology:
- Inflammation
- Demyelination
- Axonal loss
- Neuronal loss

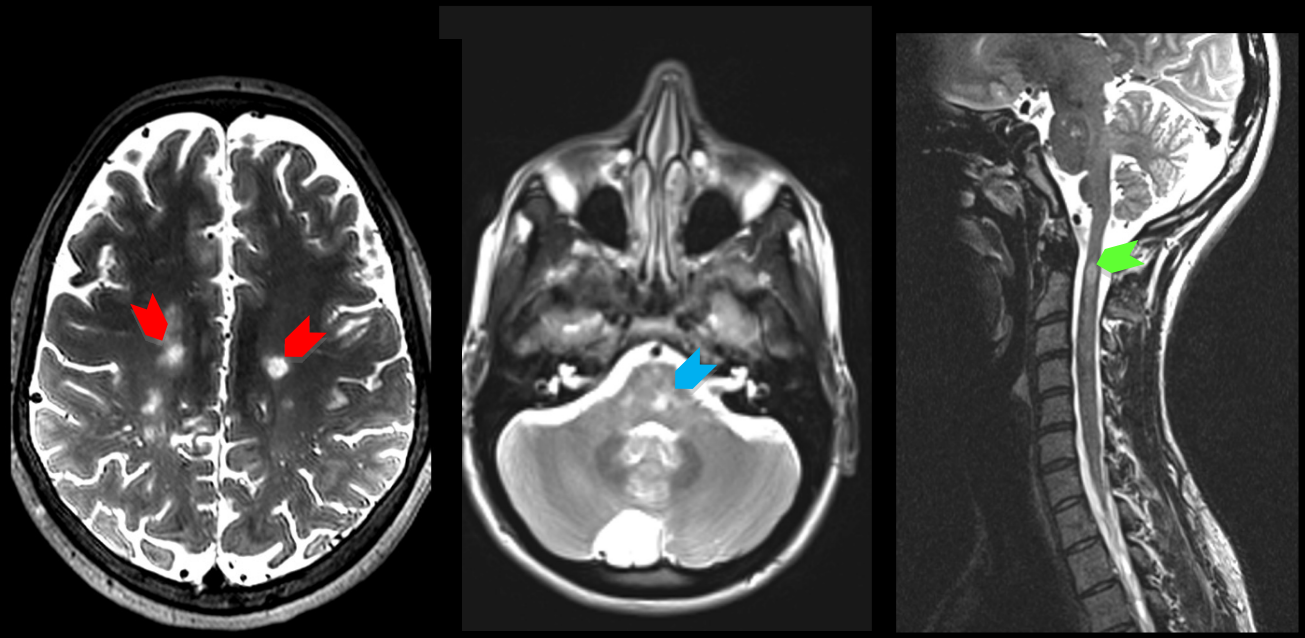


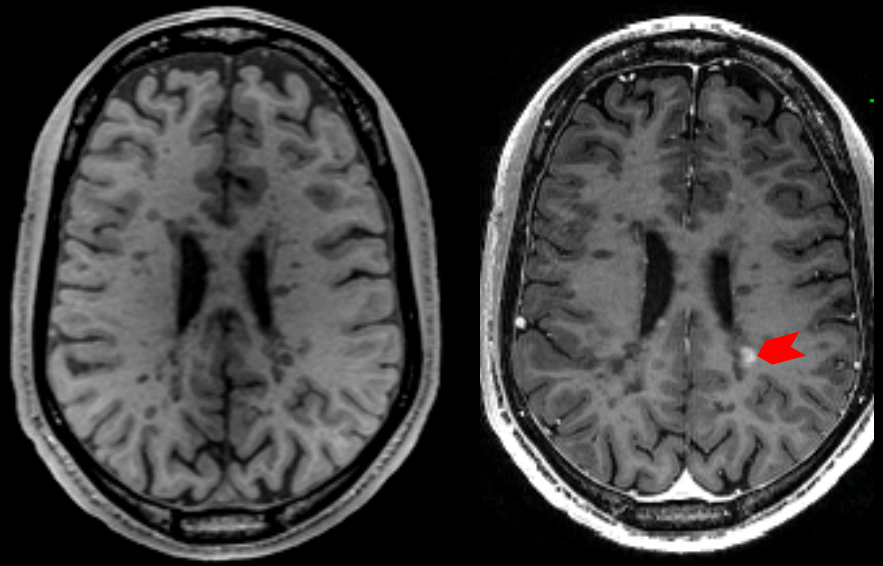


Many disease-modifying treatments exist **but no cure yet…**

MRI and MS

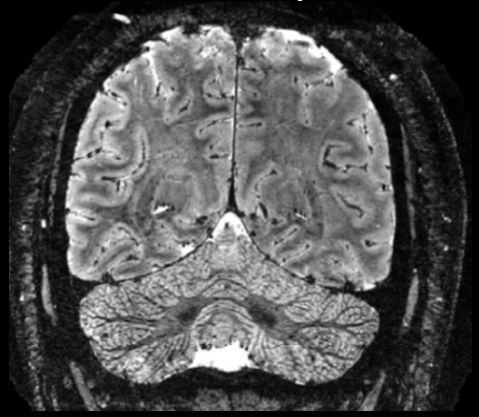
Clinical MRI is routinely used for **diagnosing** and **monitoring** the disease





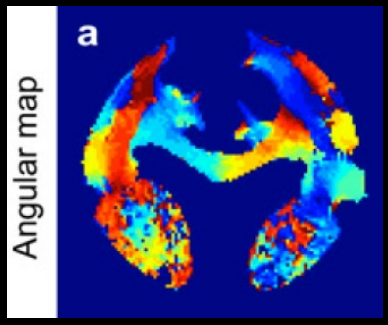
Advanced MRI sequences/techniques

Anatomy



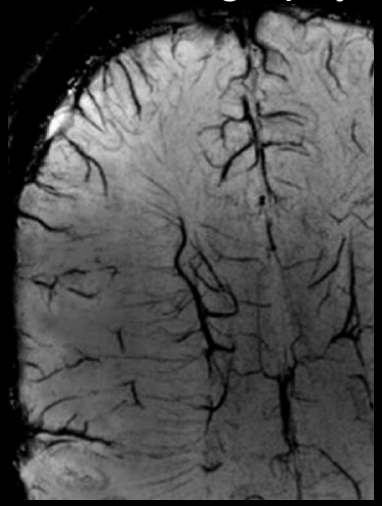
Duyn, Magn Reson Imaging (2010)

White matter fiber orientation



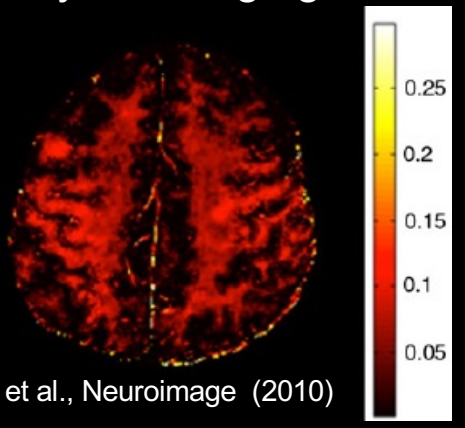
Lee et al., Neuroimage (2011)

Venography



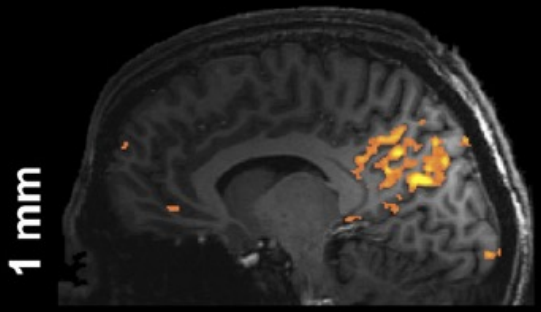
Barnes and Haacke,
Magn Reson Imaging Clin N Am. (2011)

Myelin imaging



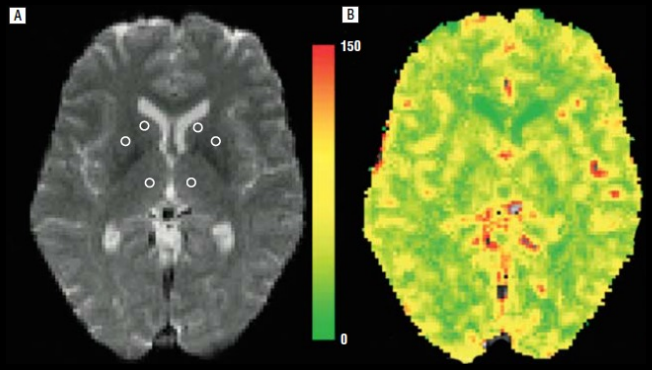
Hwang et al., Neuroimage (2010)

Functional MRI (fMRI)



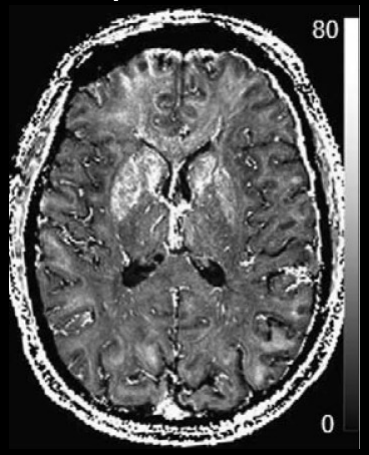
De Martino et al., Neuroimage (2011)

Perfusion (CBF, CBV)



Inglese et al., Arch Neur (2008)

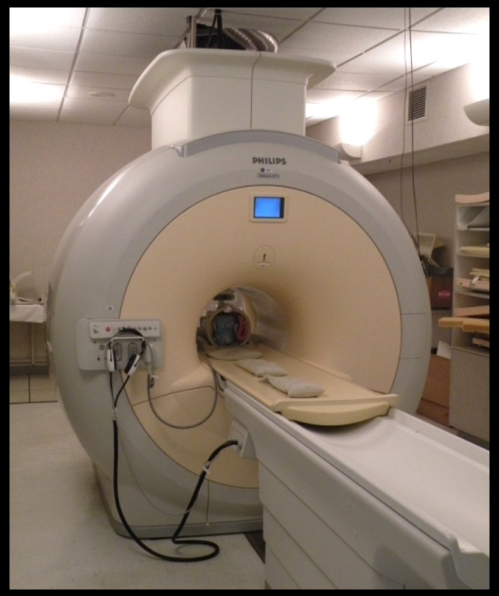
Iron quantification



Yao et al., Neuroimage (2008)

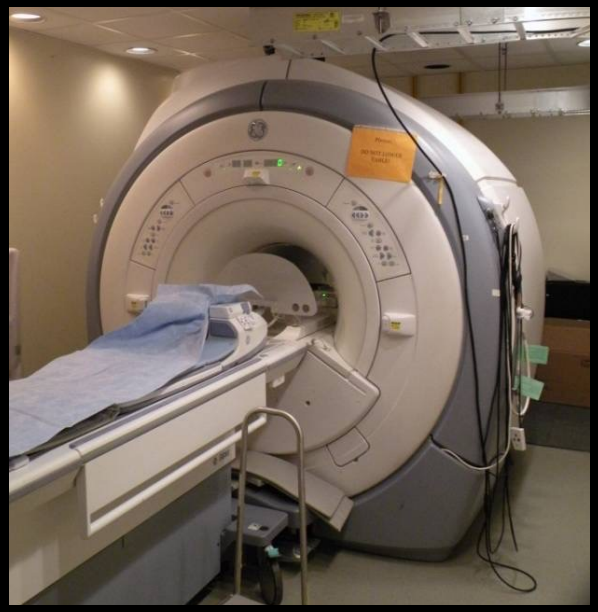
Advanced MRI scanner: ultra-high-field (≥7T)

1.5 T MRI



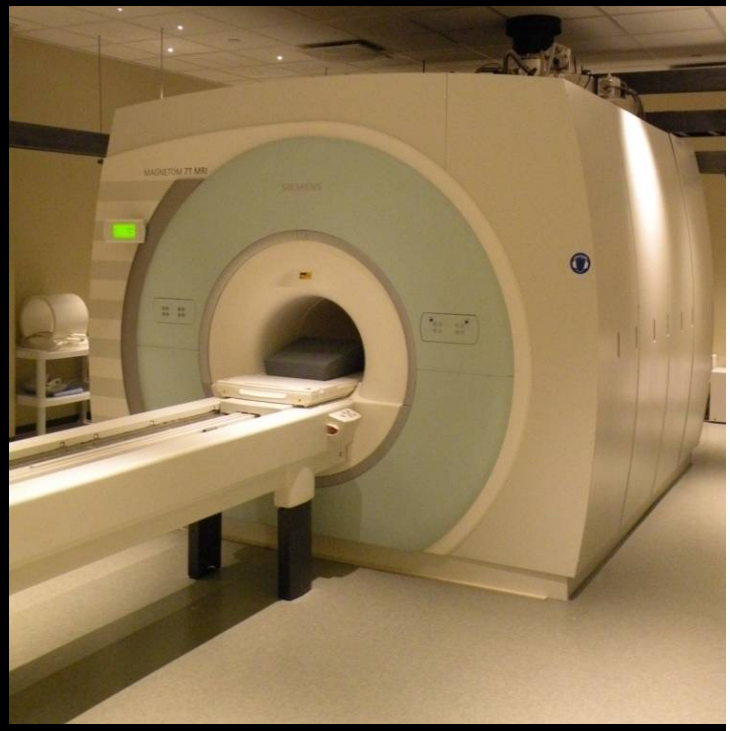
> 4,500 systems (US)

3.0 T MRI



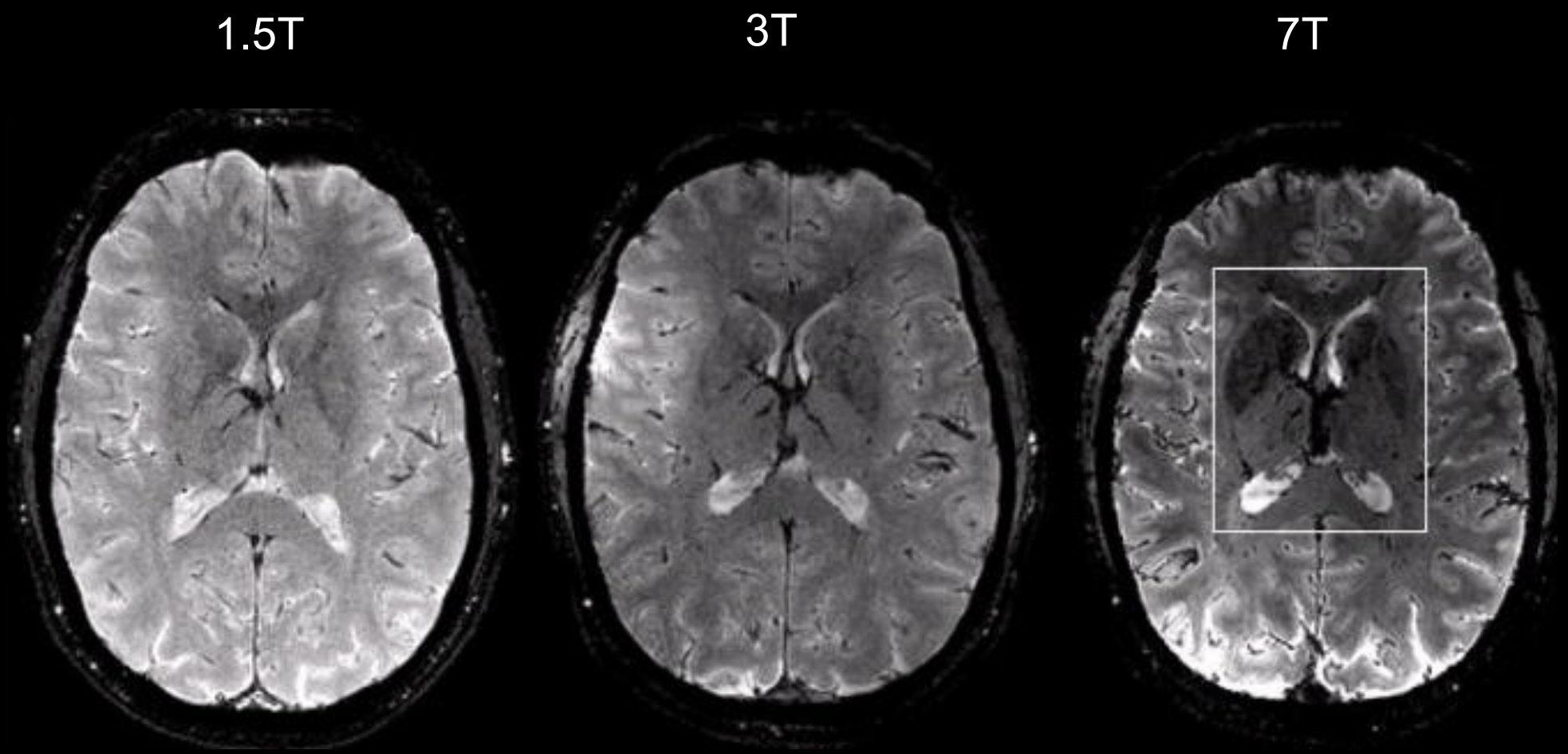
> 550 systems (US)

7.0 T MRI



25 UHF systems (US)

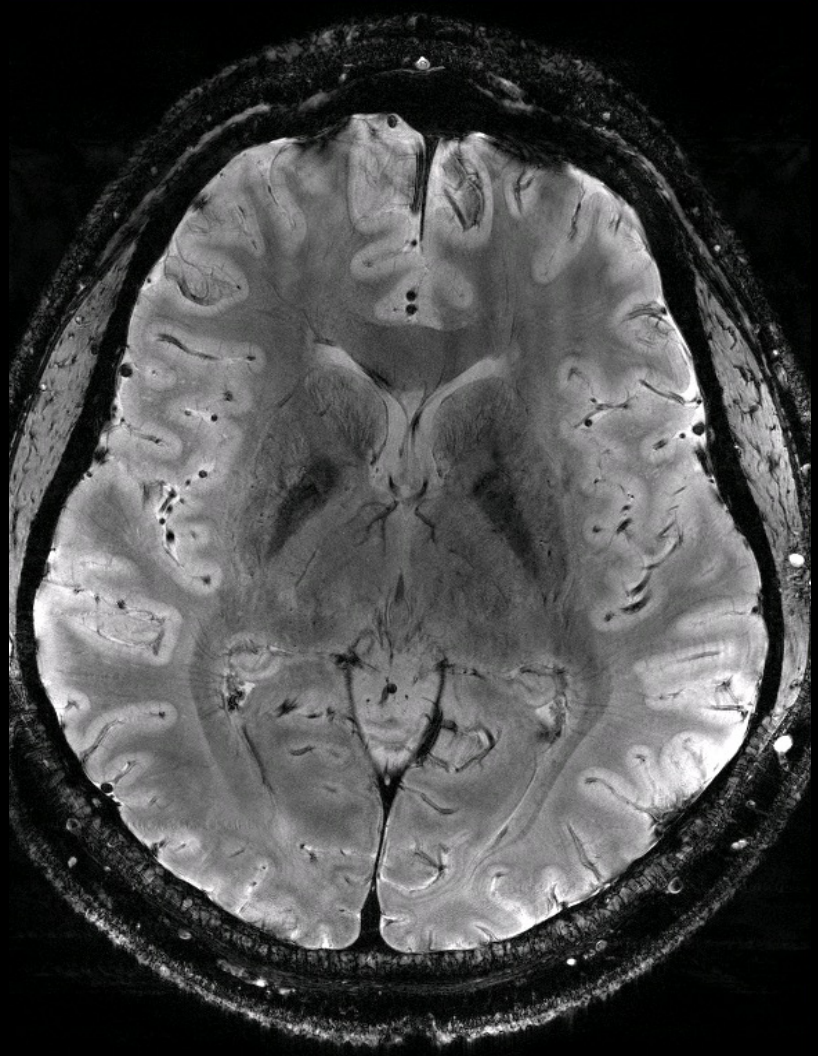
Advantages of UHF MRI

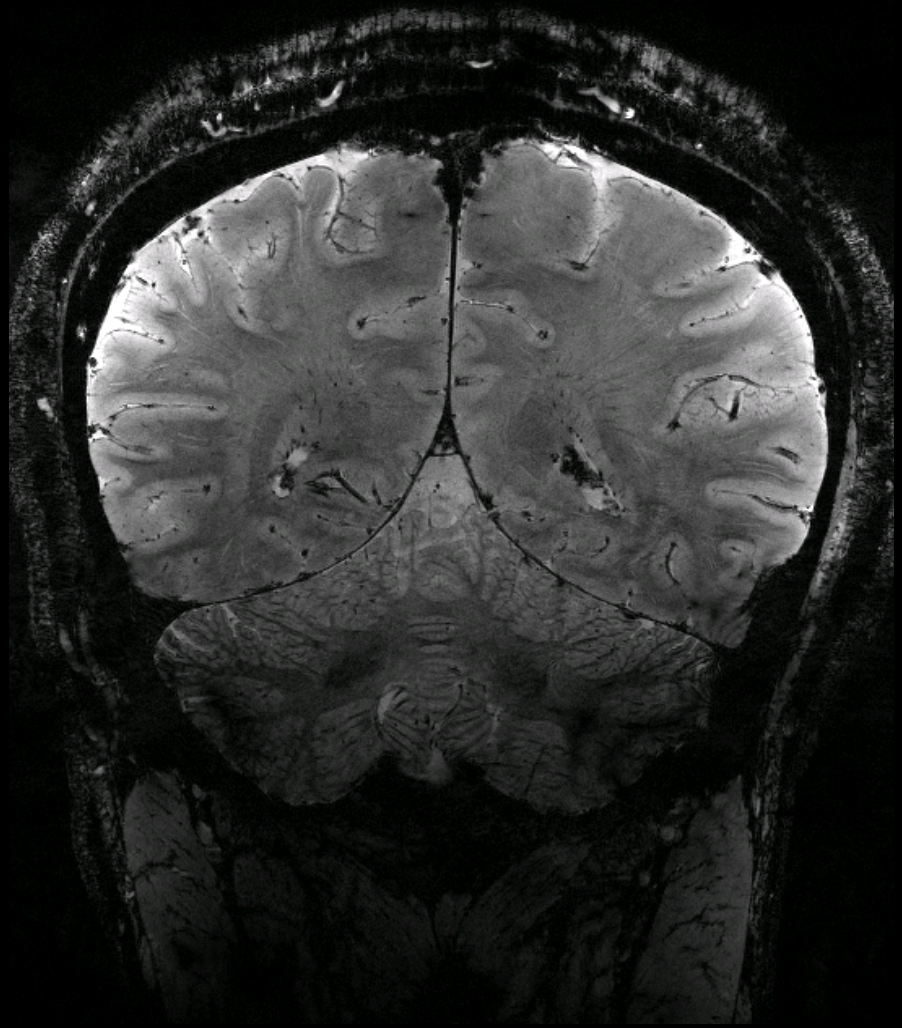


Increase in both signal (SNR) & contrast (CNR)

Yao et al., Neuroimage, 2009

Advantages of UHF MRI

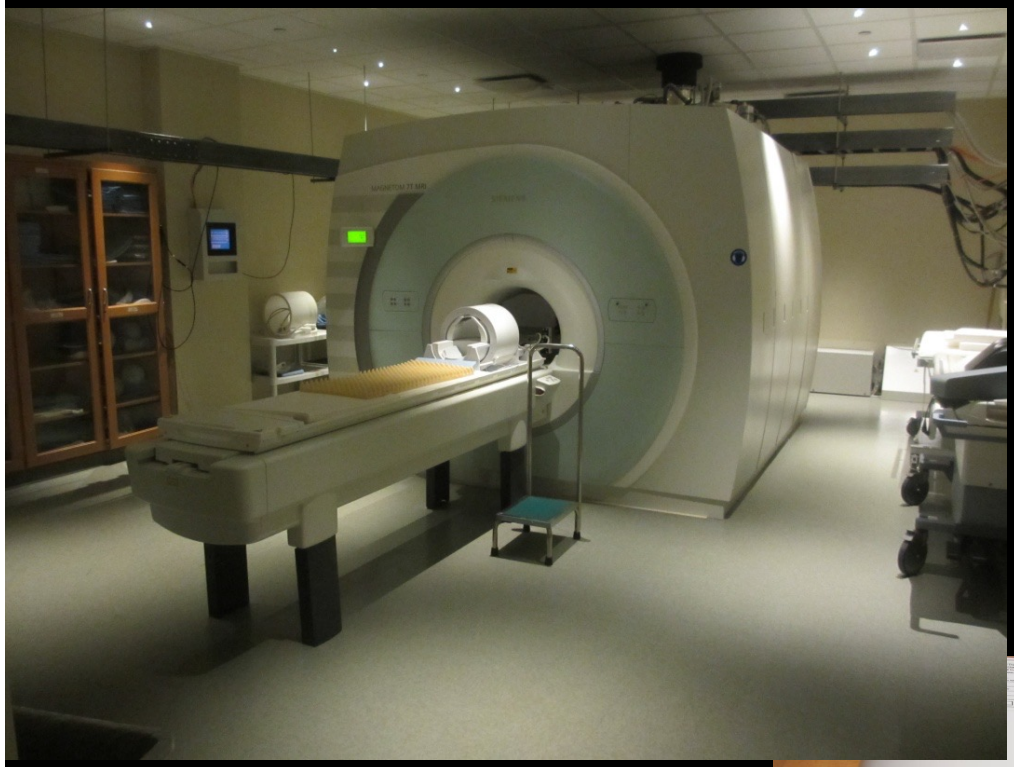




Increase in image resolution

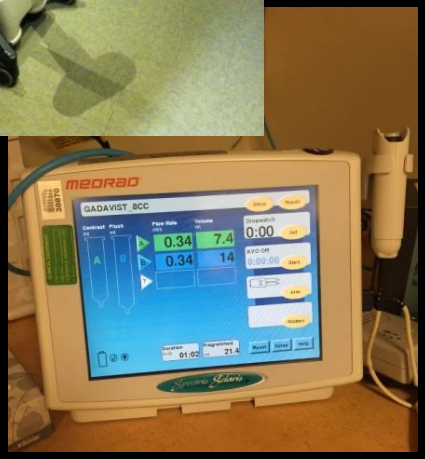
T2*w 2D Gradient Echo (GRE)
0.25 x 0.25 x 1 mm

7T MRI at NIH (FMRIF)



Actively-shielded 7T
Siemens scanner

32-channel RX head coil



power injector (Medrad)

7T MS imaging at FMRIF

- **since 2011** (installation of 7T magnetom), **350+** MRIs performed on **115** subjects (2/3 MS and 1/3 healthy volunteers);
- Currently, **1-3 MS subjects per week** (include all types of disabilities);
- Patients undergo a 3T MRI first and are thoroughly screened for 7T;
- 7T MRI is **well tolerated** by patients
  (only one event of extreme vertigo);
- 7T MRI is **brain only** and can be performed with or without Gadolinium-based **contrast agent** (magnevist ->gadavist).

Why using 7T MRI for MS?

I. To better detect *in vivo* MS pathology

II. To better diagnose MS by MRI

III. To find new imaging markers of MS disease activity

IV. To conduct translational pre-clinical MS research

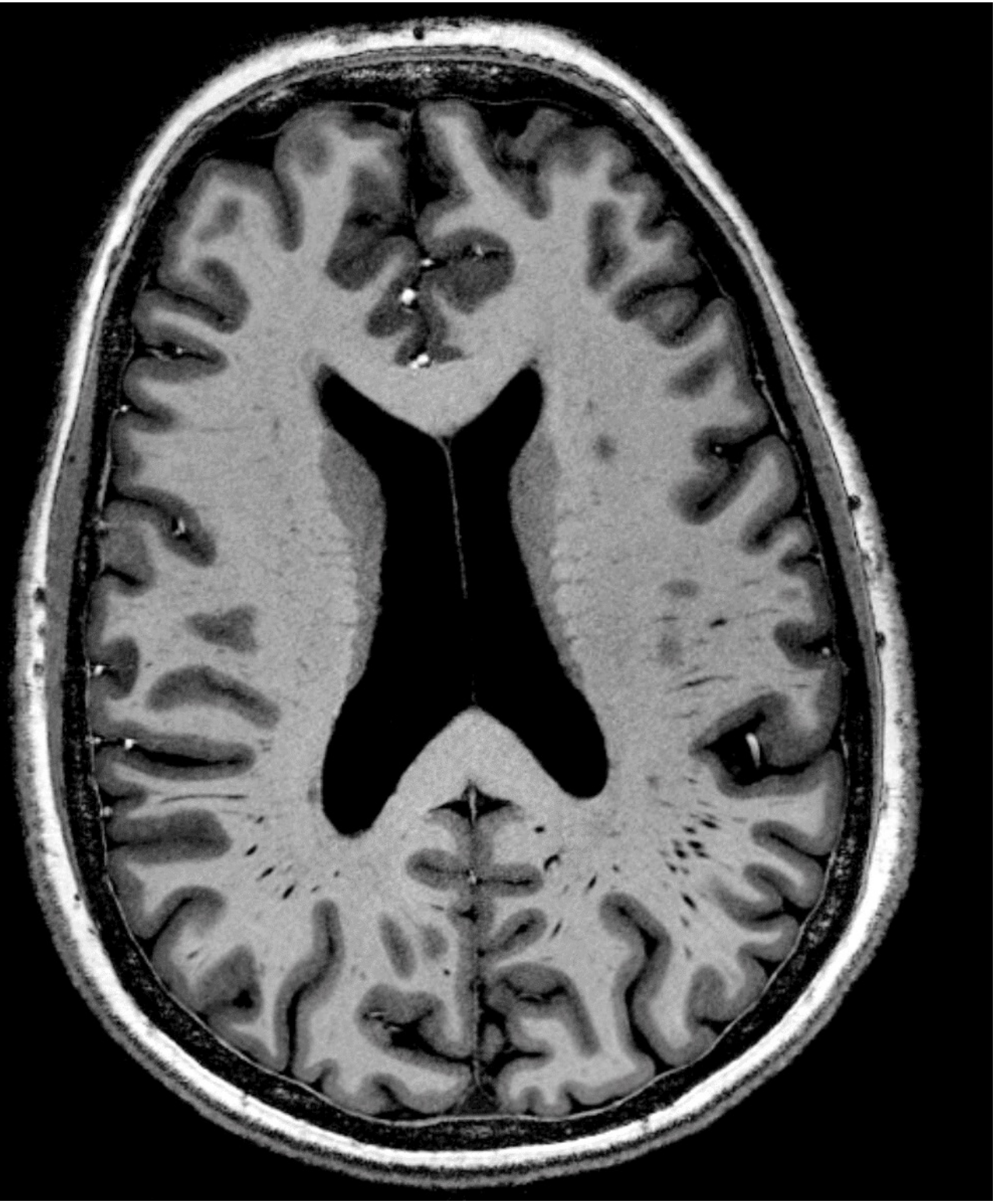
I. To better detect *in vivo* MS pathology

The MRIcroscope

Healthy subject

T1w MP2RAGE

350 um isotropic

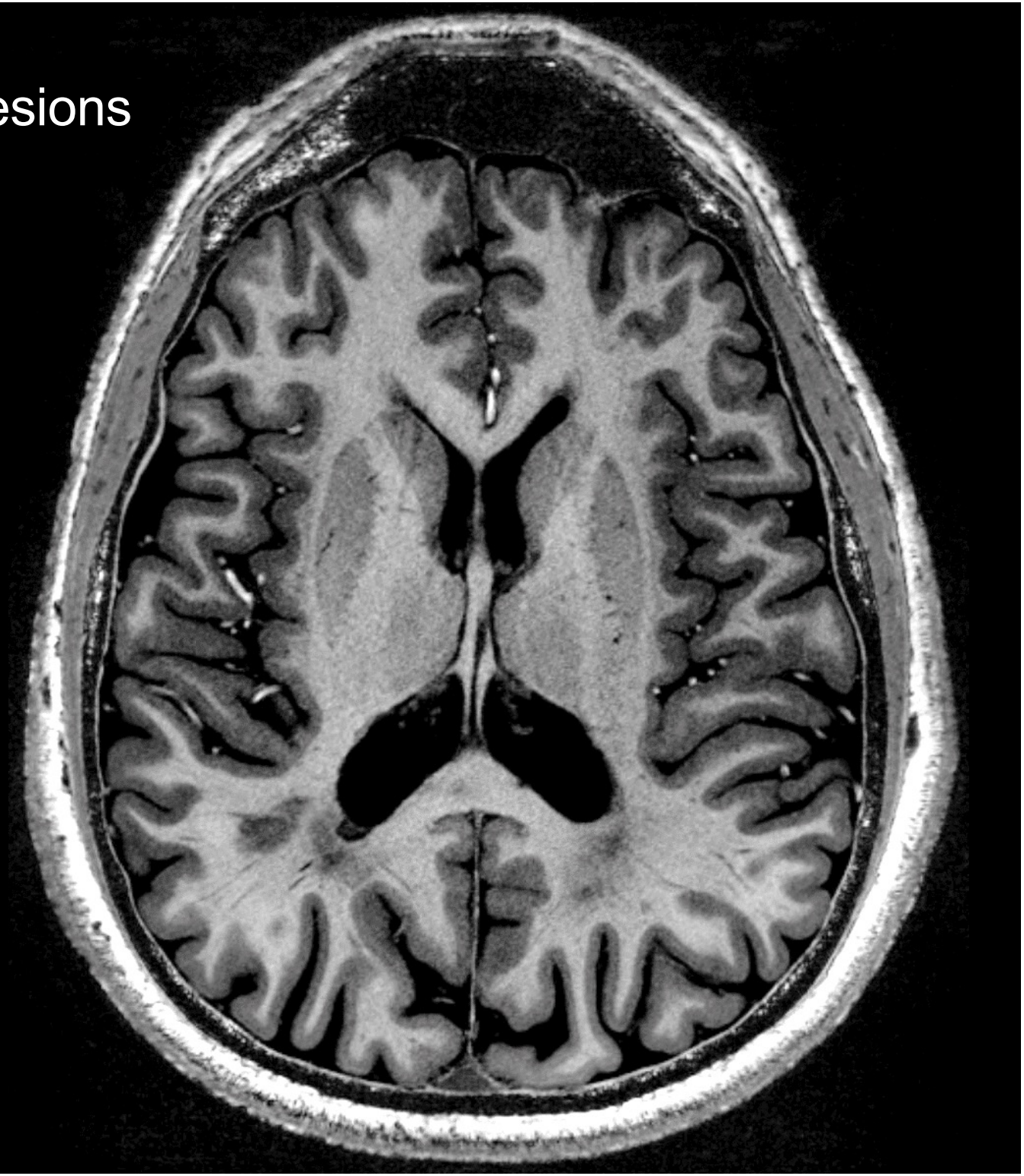


MRIcroscopy of MS lesions

MS subject

T1w MP2RAGE

350 um isotropic

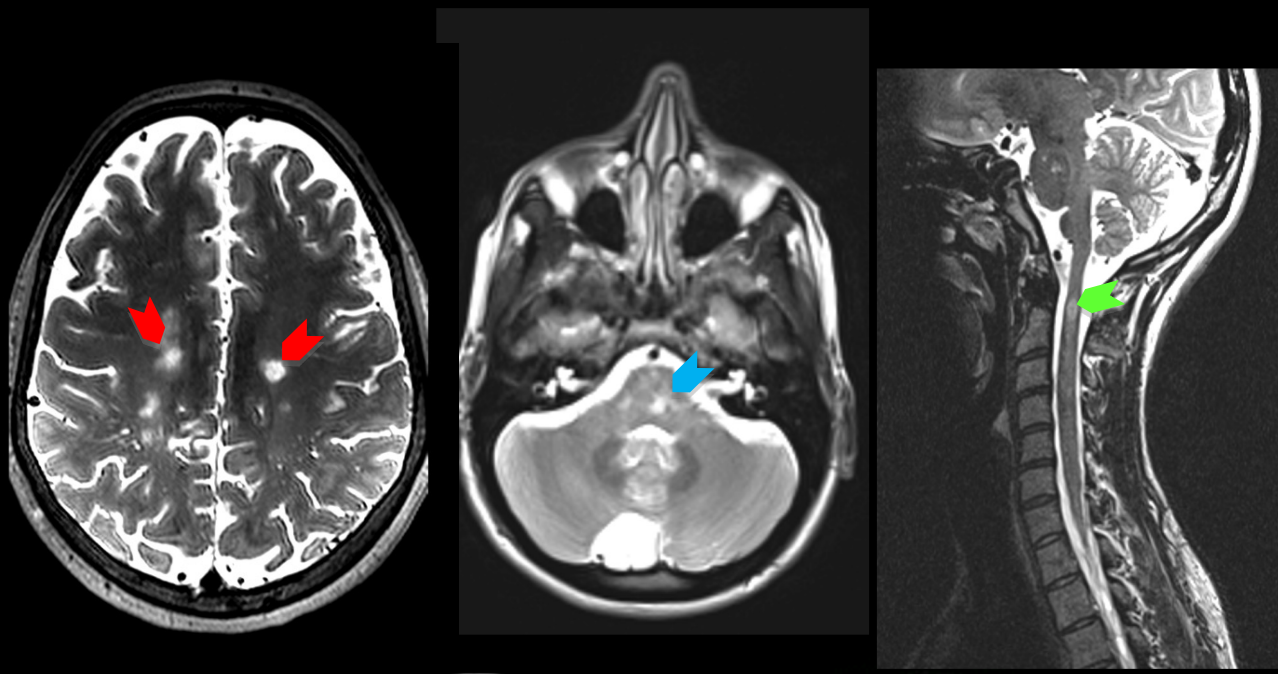


II. To better diagnose MS by MRI

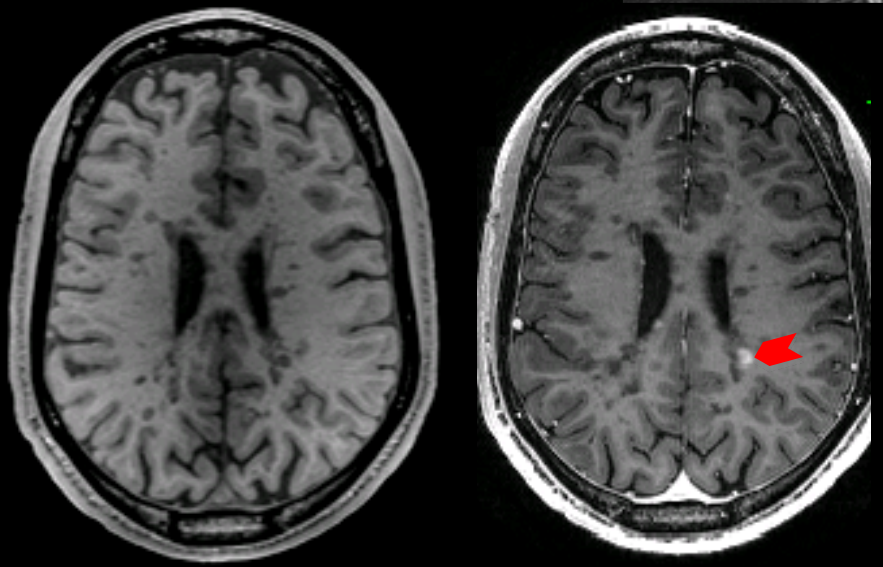
Diagnosing MS with MRI

2010 McDonald criteria

- **Dissemination in space (DIS)**
  One or more T2 lesions in two or more characteristic locations (periventricular, juxtacortical, infratentorial, spinal cord)



- **Dissemination in time (DIT)**
  New T2 lesion and/or gadolinium-enhancing lesion (s)

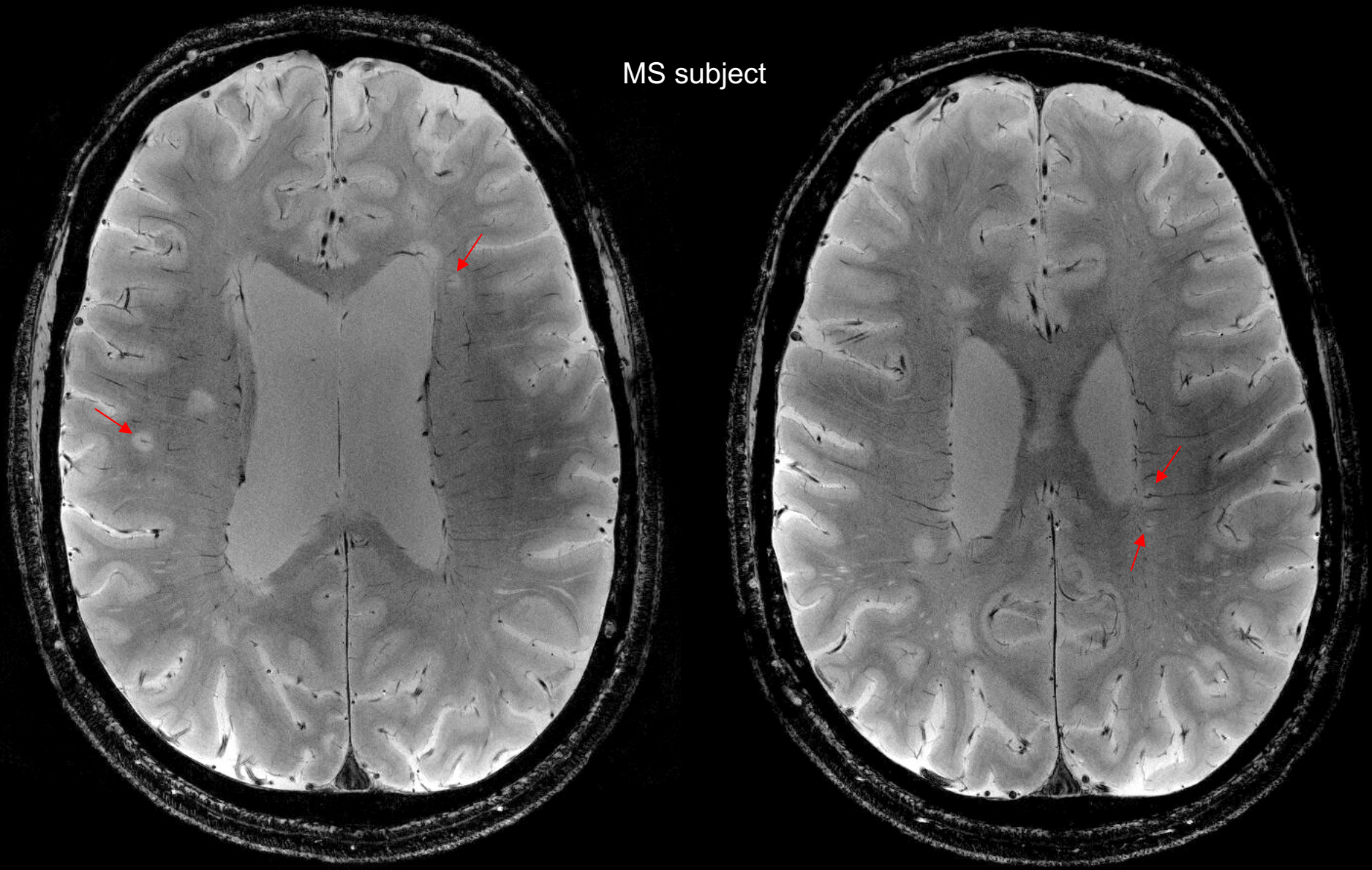


Misdiagnosis of MS is common

- Sensitivity and specificity of McDonald criteria are imperfect (80-90%)
- McDonald criteria require first to rule out other disorders that can mimic MS *(migraine, fibromyalgia, small vessel ischemic cerebrovascular disease, neuromyelitis optica spectrum disorders,…)*
- Misdiagnosis of MS is common (5%-35%)
- Misdiagnosis expose patients to unnecessary disease modifying therapies (DMTs) (harmful side effects), psychosocially suffering, and have economic consequences to healthcare system (5% of 400,000 of US patients => 1 billion USD/year for DMTs)

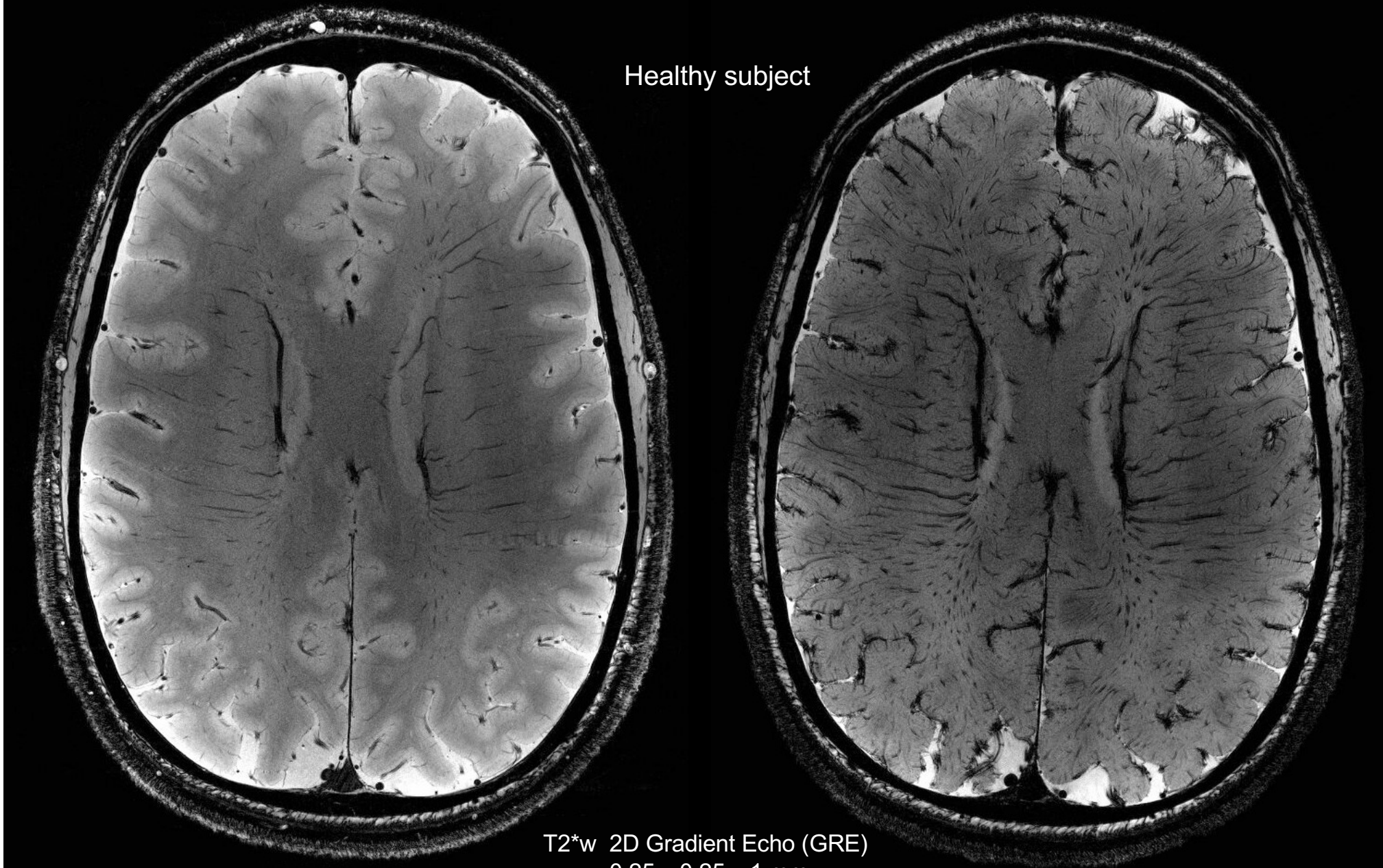
Solomon & Weinshenker, Curr Neurol Neurosci Rep (2013) 13:403
Solomon et al., Neurology (2012) 78:1986-91

Central vein in MS lesion



T2*w 2D Gradient Echo (GRE)
0.25 x 0.25 x 1 mm

Coincidence due to the high density of cerebral vessels ?



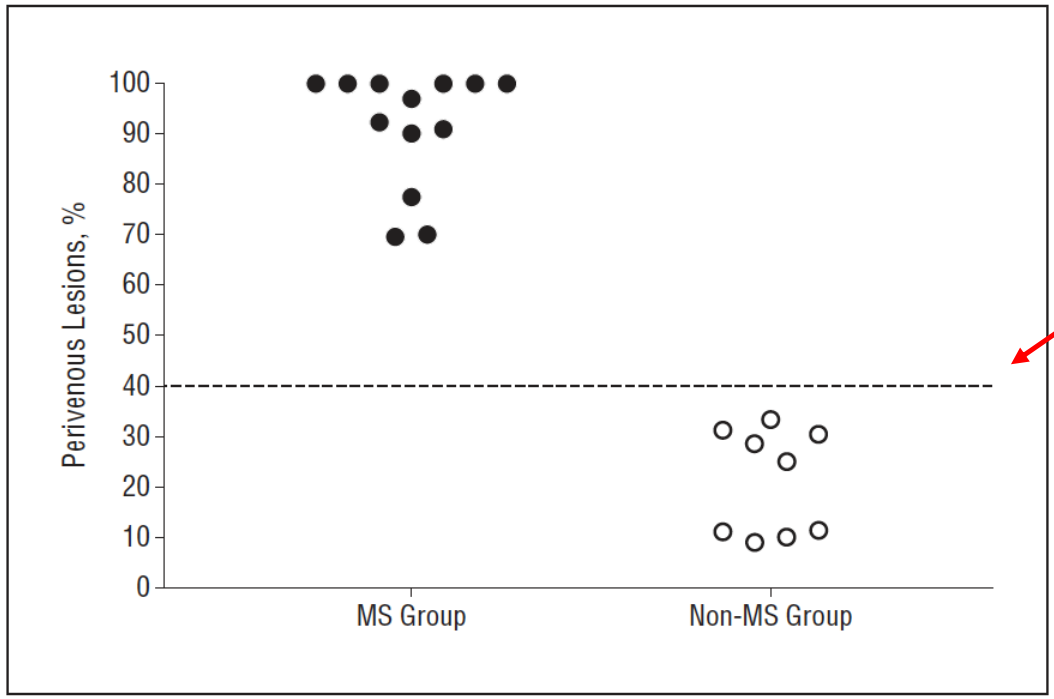
ORIGINAL CONTRIBUTION

Central Veins in Brain Lesions Visualized With High-Field Magnetic Resonance Imaging

A Pathologically Specific Diagnostic Biomarker for Inflammatory Demyelination in the Brain

Niraj Mistry, MA; Jennifer Dixon, PhD; Emma Tallantyre, PhD; Christopher Tench, PhD; Rasha Abdel-Fahim, MBBCh; Tim Jaspan, FRCR; Paul S. Morgan, PhD; Peter Morris, PhD; Nikos Evangelou, FRCP

22 patients (13 MS and 9 other diseases)

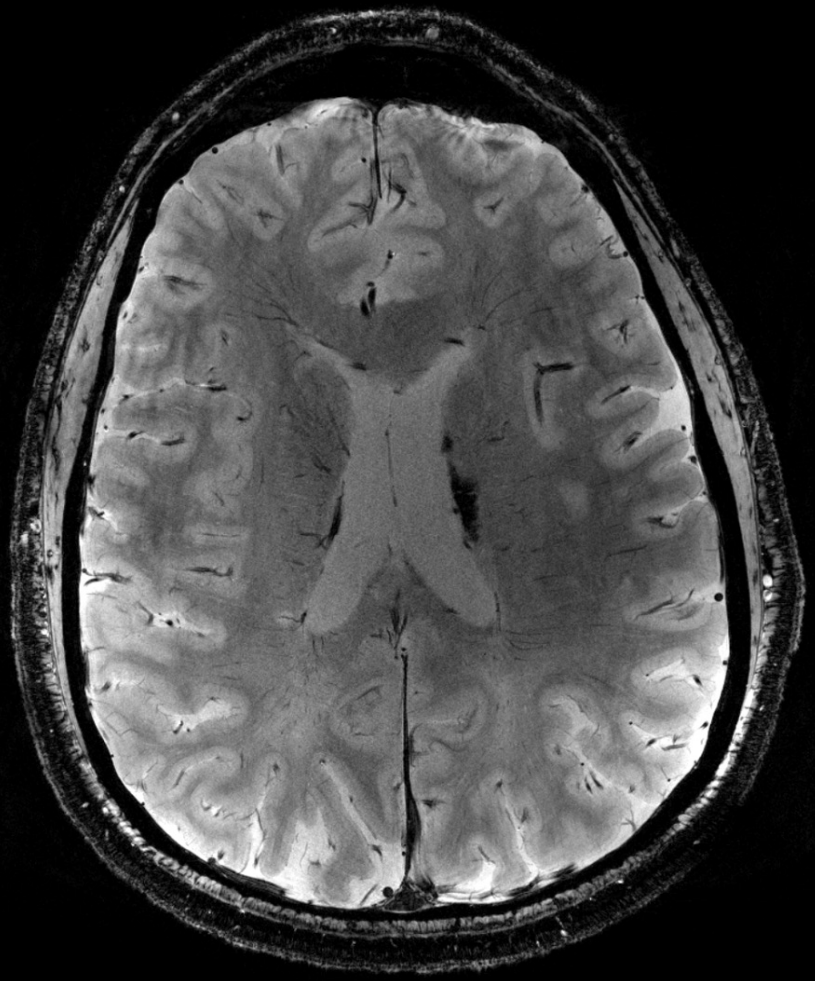


40% rule ?

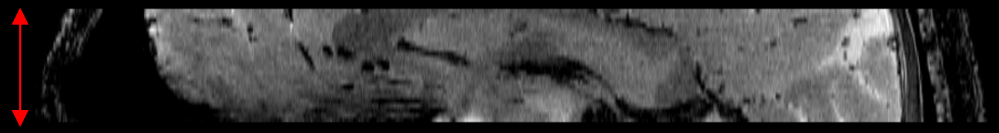
Central vein (CV) in MS: a new criterion for diagnosing MS ?

- Lower proportion of CV reported in other diseases: Neuromyelitis optica , Systemic autoimmune diseases , Cerebral small vessel disease, Migraine, …
- Definition of CV criterion: 40% rule? Six-lesion rule? Combined DIT-DIS & CV?
- Clinical validation needed: multi-center imaging study with (300+) subjects at first clinical/radiological presentation (not yet diagnosed)

Limitations of conventional T2* imaging



T2*w 2D Gradient Echo (GRE)
0.25 x 0.25 x 1 mm



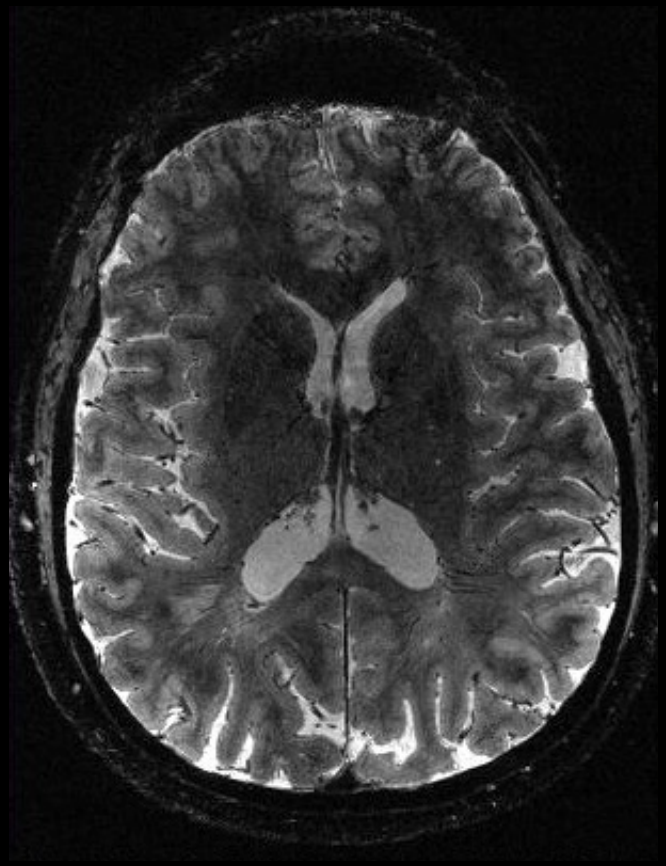
2.5 cm per slab (25 slices)
9 min per slab

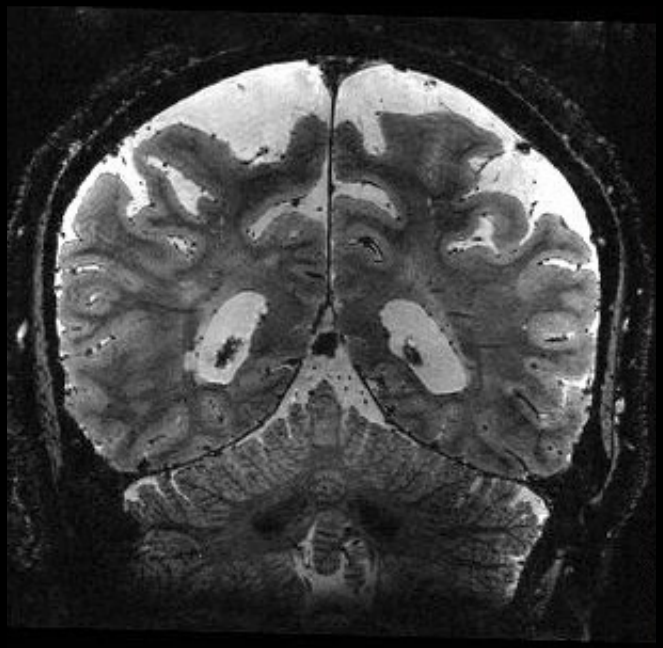
Whole brain would take > 45 min !

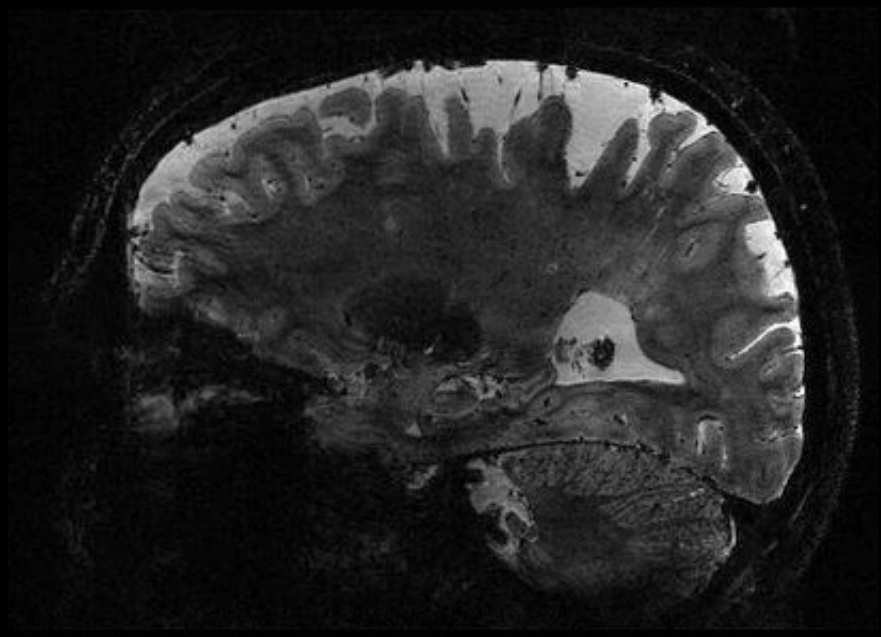
Rapid high-resolution T2*w imaging @ 7T

T2*w 3D multishot EPI
(NIH sequence)
500 um isotropic

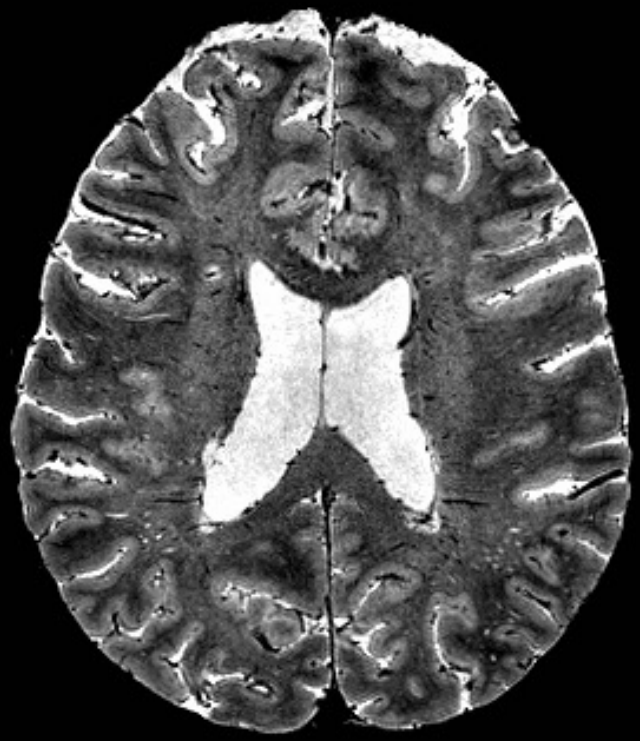
Whole brain in less than 8 min!



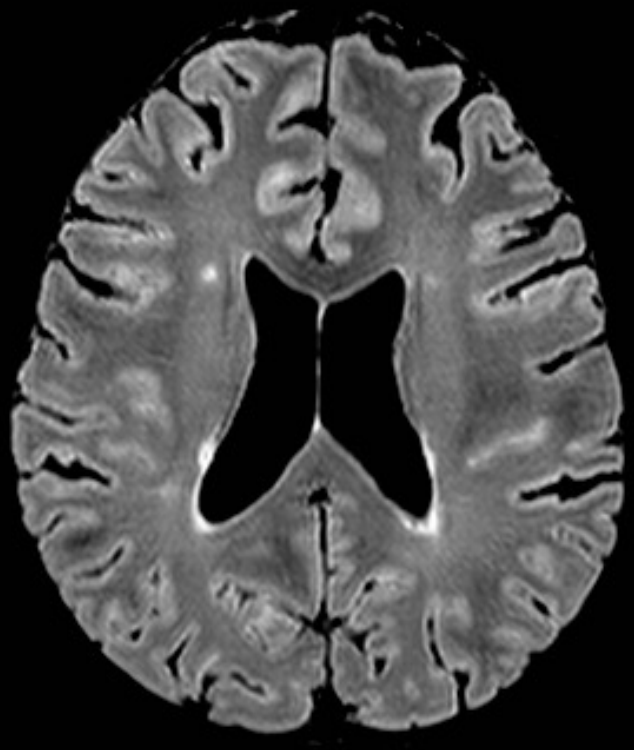




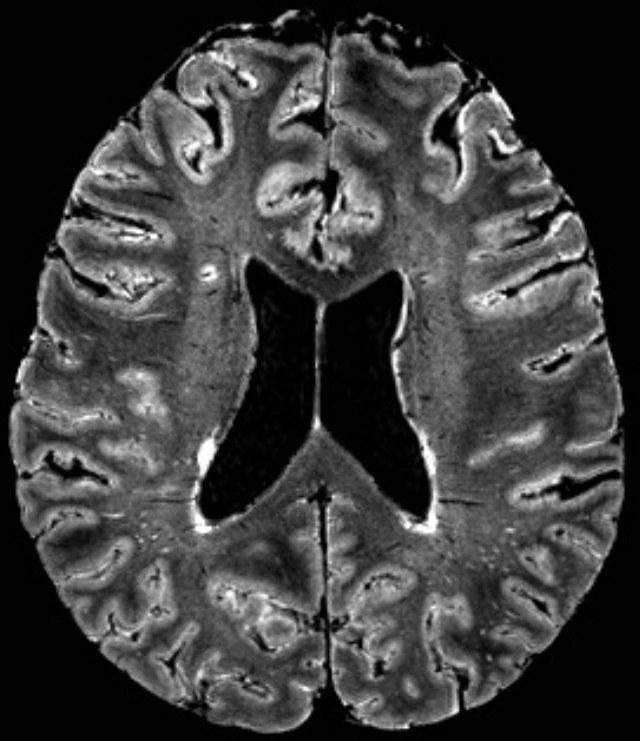
A new combined MR contrast: FLAIR*



T2* 3D EPI (NIH)
0.5 mm iso



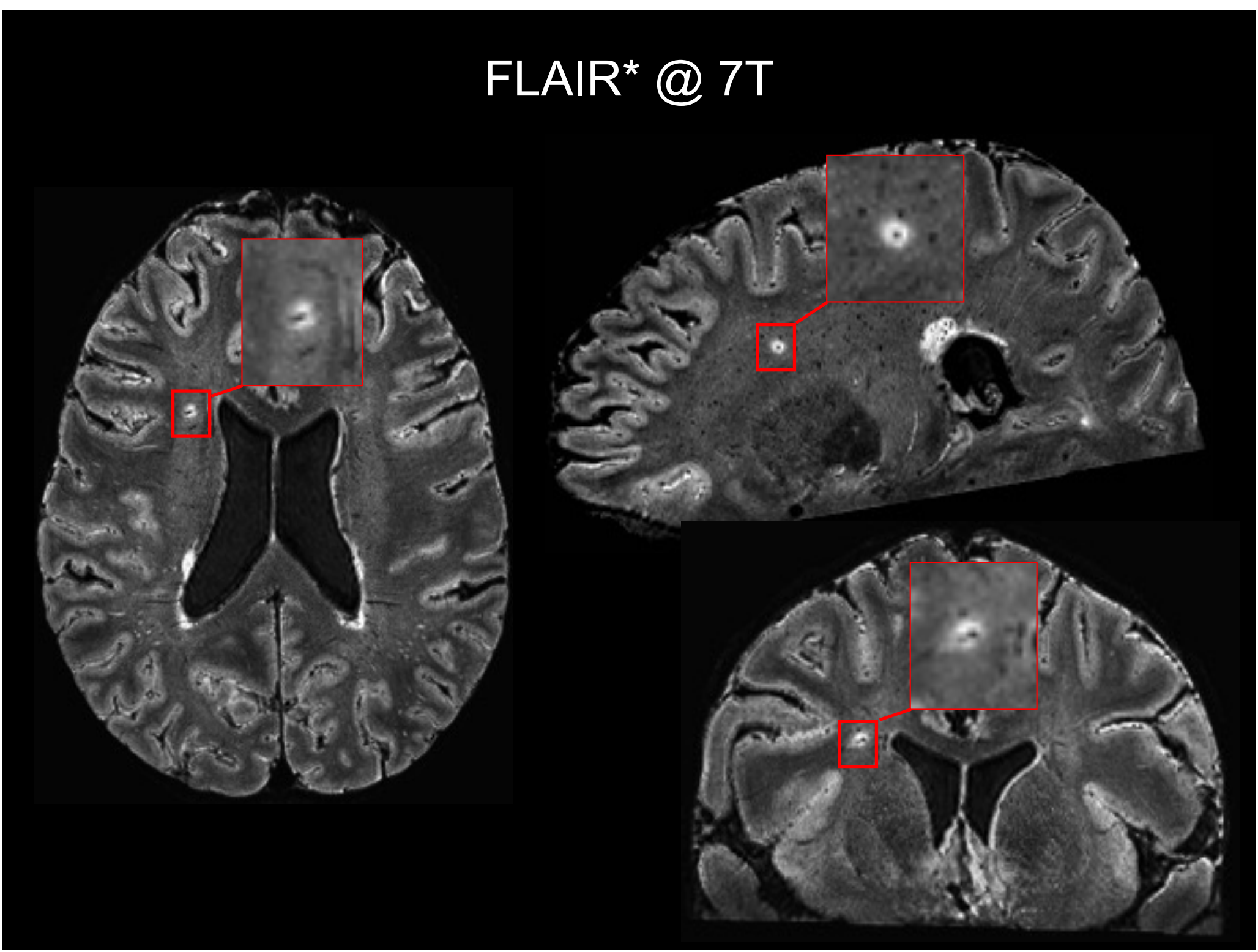
FLAIR
0.8 mm iso



FLAIR* (NIH)
0.5 mm iso

Sati et al., Radiology (2012) 265(3):926-32
Sati et al., Multiple Sclerosis (2014) 20(11):1464-70

FLAIR* @ 7T



ORIGINAL RESEARCH ■ TECHNICAL DEVELOPMENTS

FLAIR*: A Combined MR Contrast Technique for Visualizing White Matter Lesions and Parenchymal Veins[1]

Pascal Sati, PhD
Ilena C. George, BA
Colin D. Shea, MS
María I. Gaitán, MD
Daniel S. Reich, MD, PhD

Radiology

J Neurol (2014) 261:1356–1364
DOI 10.1007/s00415-014-7351-6

ORIGINAL COMMUNICATION

Morphological features of MS lesions on FLAIR* at 7 T and their relation to patient characteristics

Iris D. Kilsdon
Wolter L. de
Jeroen J. J. G

Eur Radiol (2014) 24:841–849
DOI 10.1007/s00330-013-3080-y

NEURO

Improved differentiation between MS and vascular brain lesions using FLAIR* at 7 Tesla

Iris D. Kilsdon
Marcus C. de
Peter R. Luijte

ANNALS of Clinical and Translational Neurology
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ANA American Neurological Association

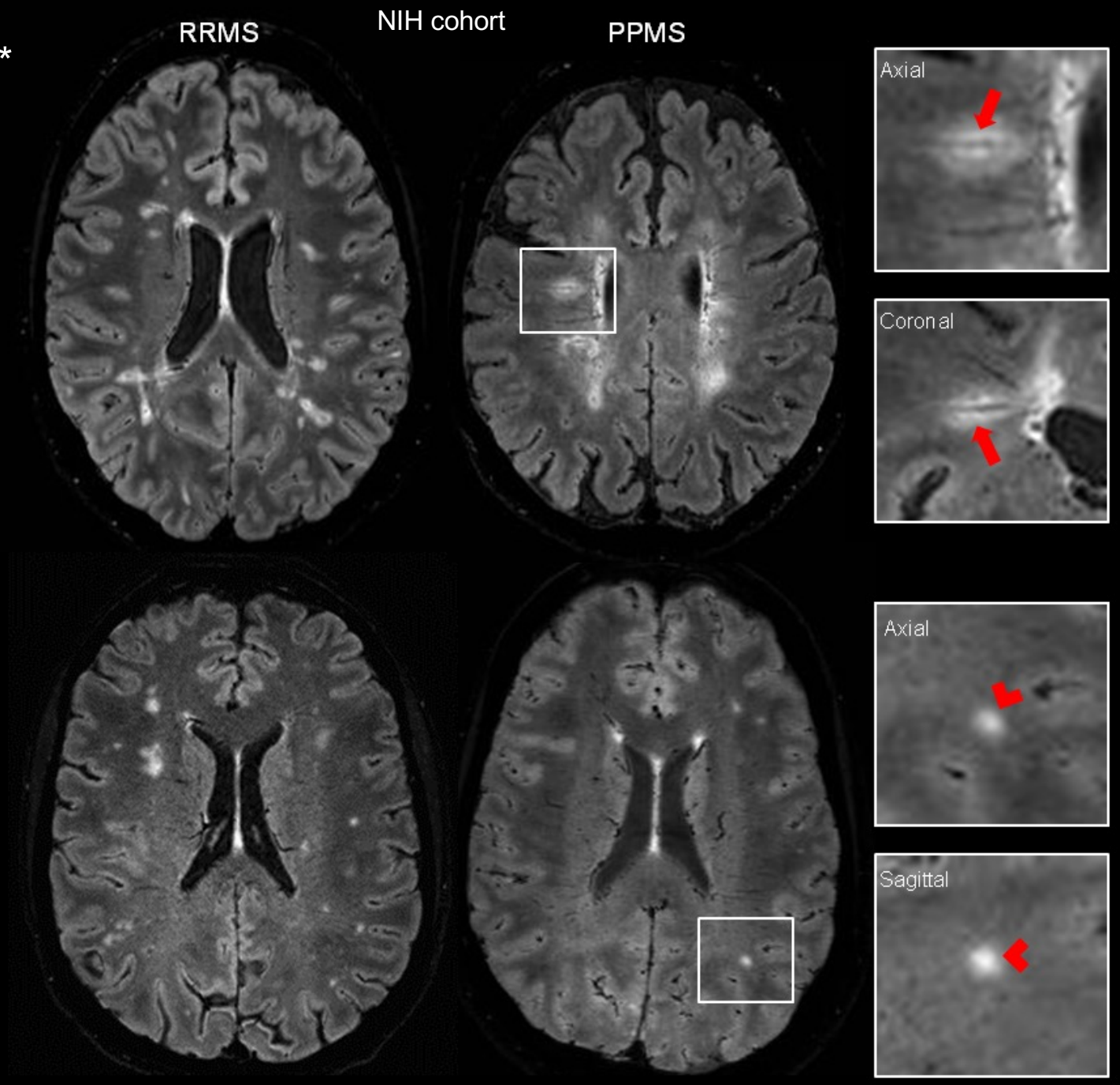
RESEARCH PAPER

"Central vessel sign" on 3T FLAIR* MRI for the differentiation of multiple sclerosis from migraine

Andrew J. Solomon[1], Matthew K. Schindler[2], Diantha B. Howard[3], Richard Watts[4], Pascal Sati[2], Joshua P. Nickerson[4] & Daniel S. Reich[2]

[1]Department of Neurological Sciences, University of Vermont College of Medicine, Burlington, Vermont
[2]Translational Neuroradiology Unit, Division of Neuroimmunology and Neurovirology, National Institute of Neurological Disorders and Stroke, Bethesda, Maryland
[3]Vermont Center for Clinical and Translational Science, Burlington, Vermont
[4]Department of Radiology, University of Vermont College of Medicine, Burlington, Vermont

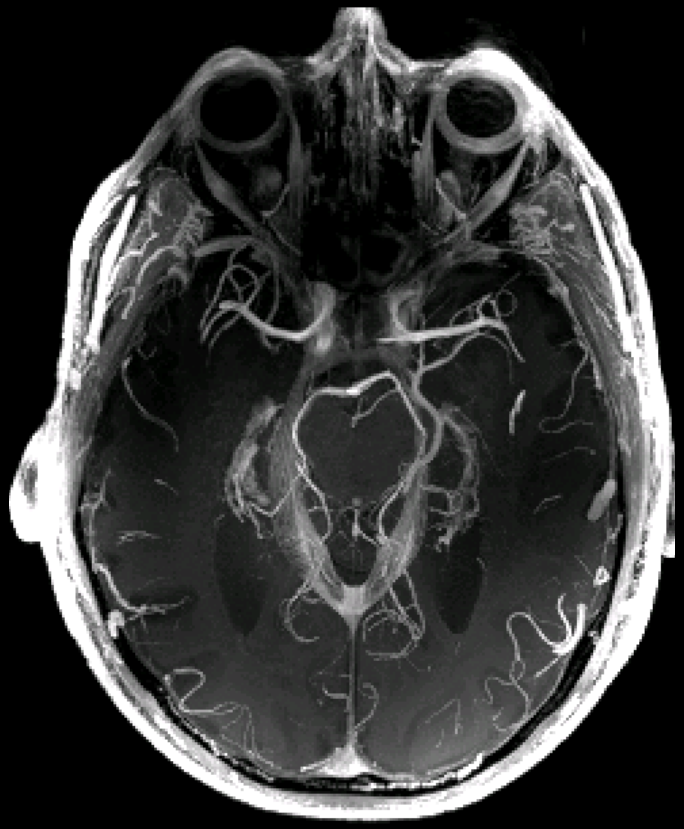
Multi-center 3T FLAIR* imaging

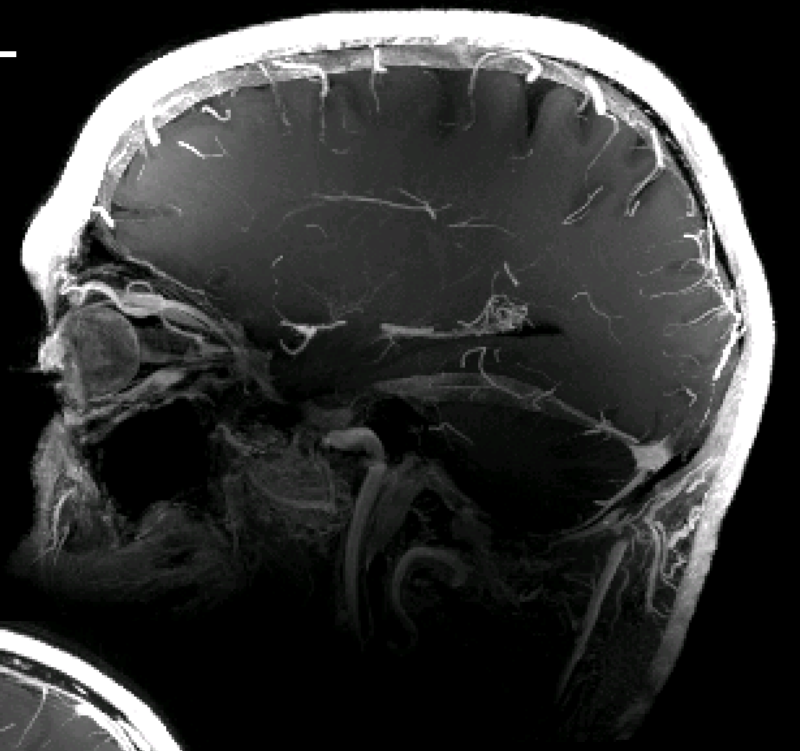


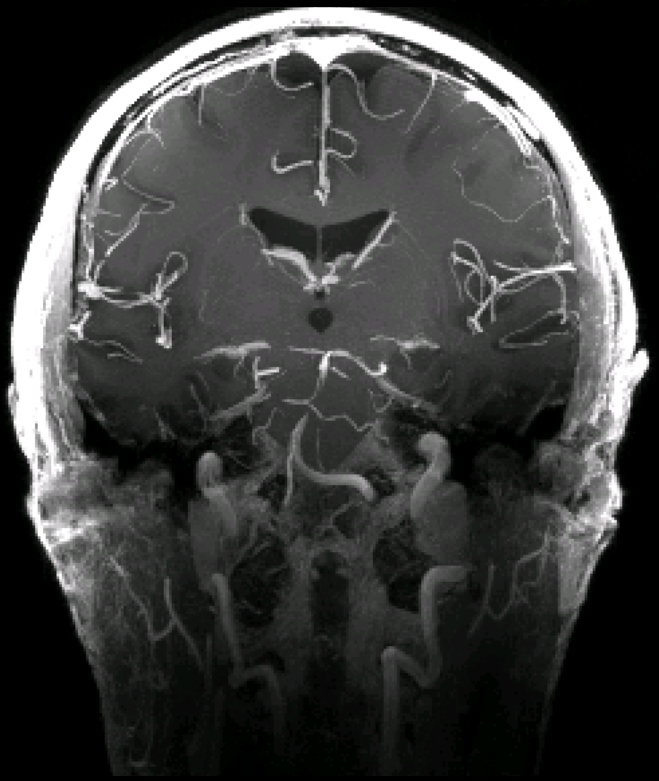
II. To find new imaging markers of MS disease activity

inflammation, demyelination/remyelination, axonal damage,…

Gadolinium-based contrast agent @ 7T







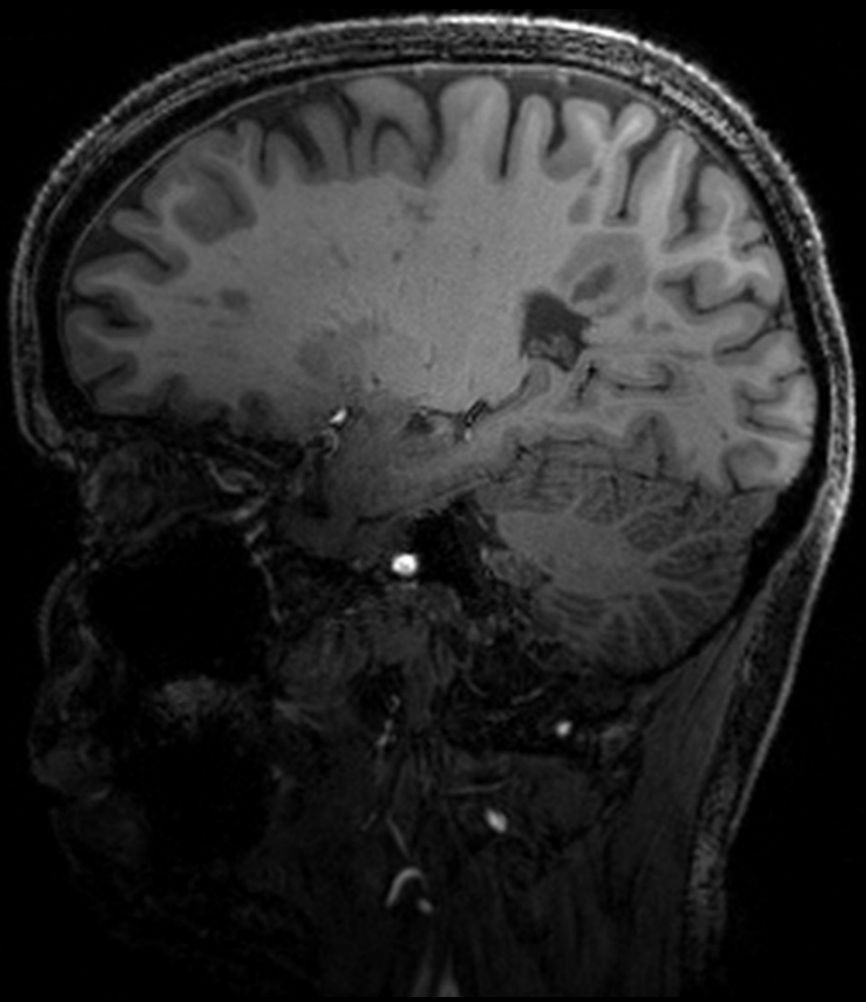
T1w 3D MPRAGE
voxel size = 0.7 mm isotropic
Single dose of Gadavist (0.1 mL/kg)
Maximum Intensity Projection

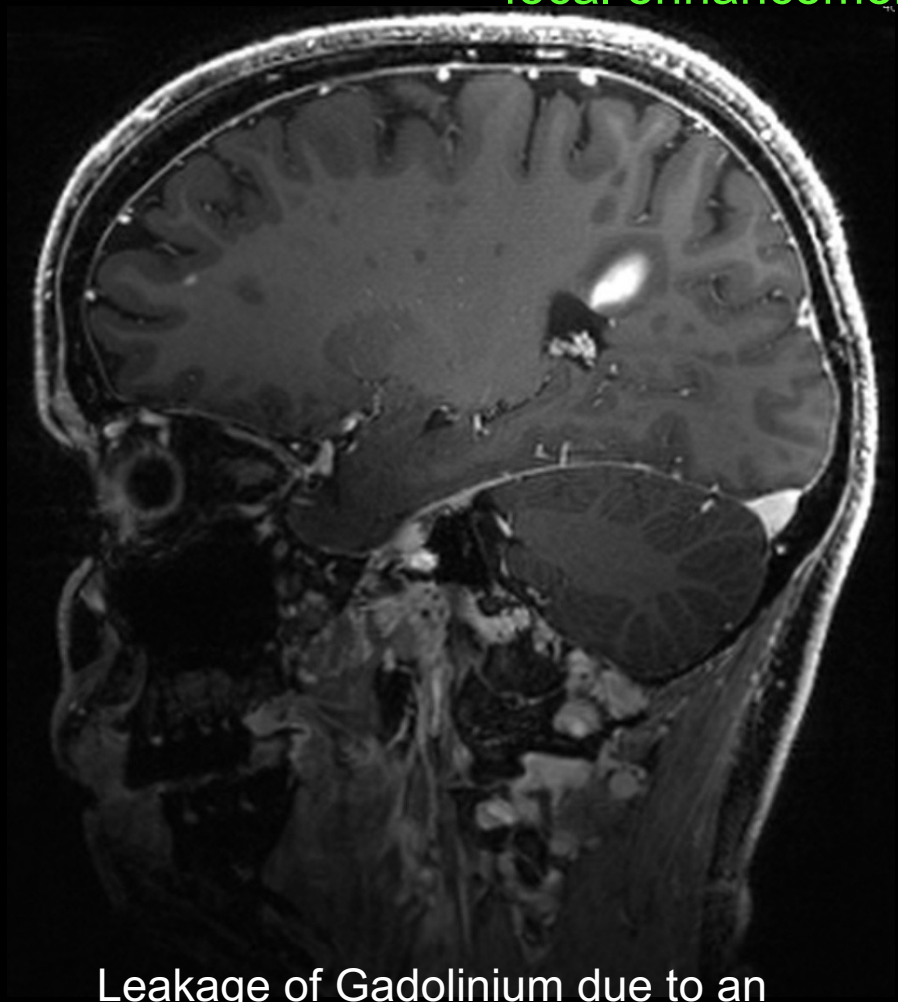
Active MS lesions

pre-injection

5 min post-injection

focal enhancement





Leakage of Gadolinium due to an open blood-brain-barrier

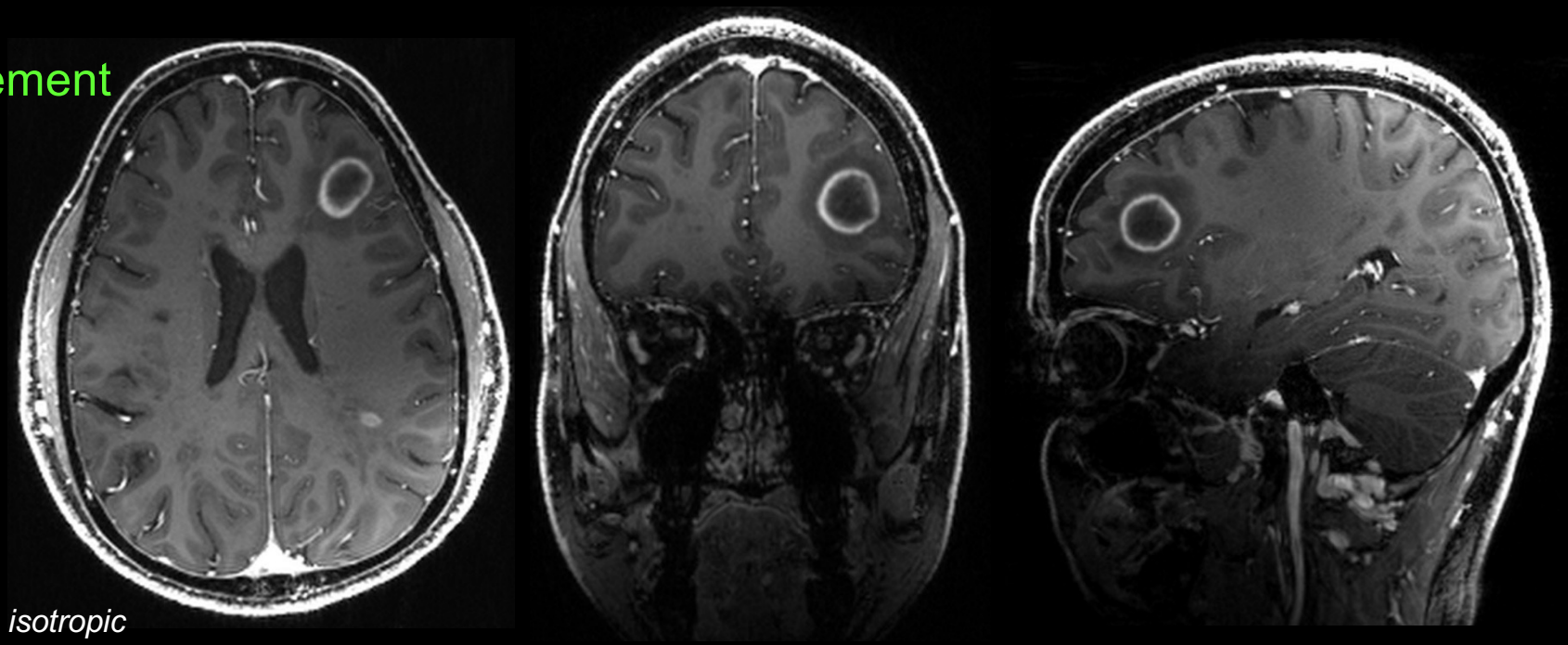
T1w 3D MPRAGE

voxel size = 0.7 mm isotropic

Single dose of Gadavist (0.1 mL/kg)

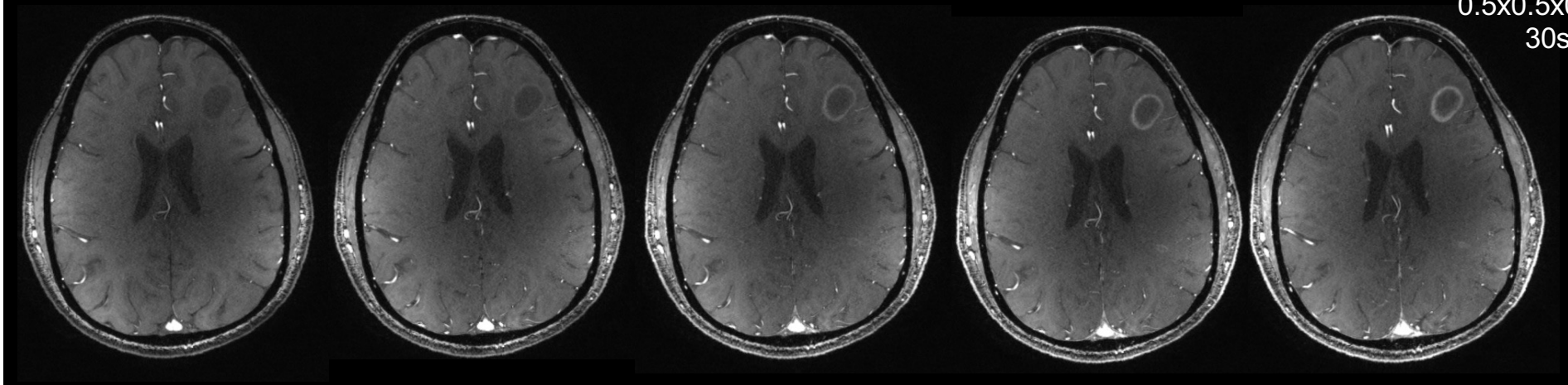
Active MS lesions

ring enhancement



T1w 3D MPRAGE
voxel size = 0.7 mm isotropic
Single dose of Gadavist (0.1 mL/kg)

Dynamic Contrast Enhancement (DCE - 3D FLASH)
0.5x0.5x0.8 mm^3
30s/volume

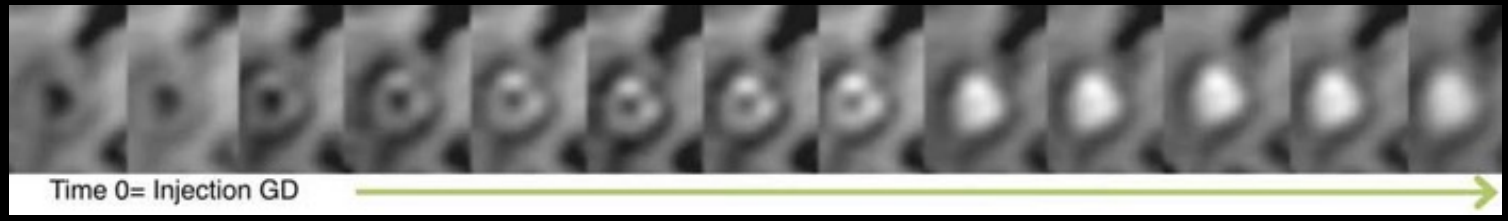


time

MS lesion development according to DCE patterns

Day 1
Centrifugal DCE pattern

Day 5
Centripetal DCE pattern



Day 25
Centripetal DCE pattern

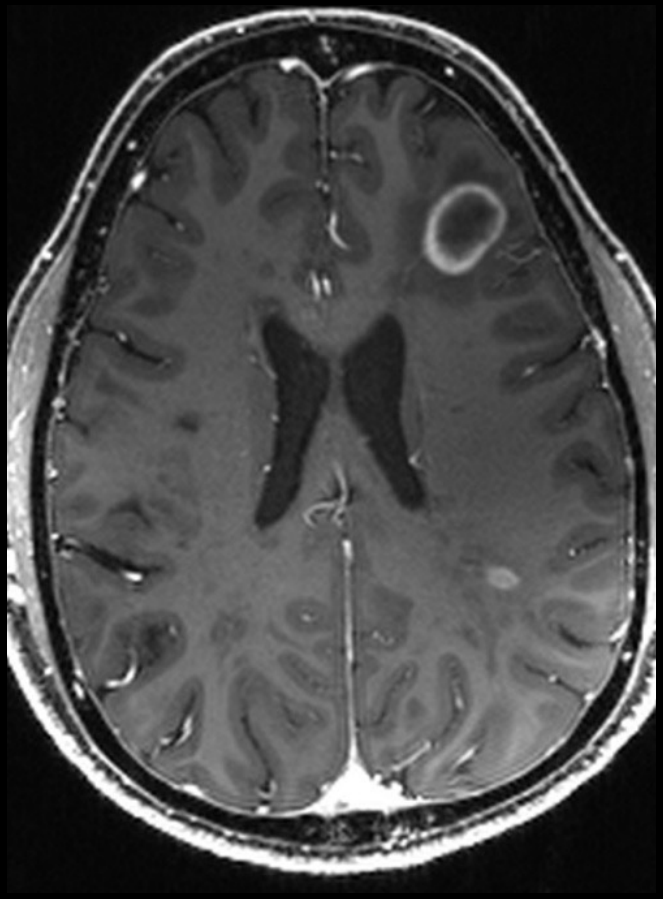
Gaitan et al., Ann Neurol 2011

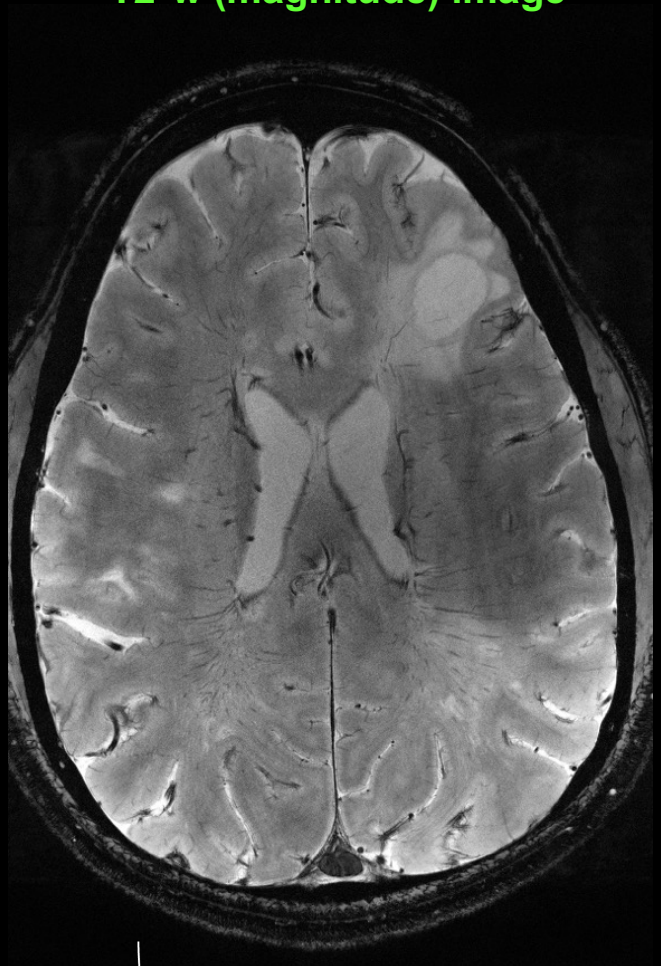
Gaitan et al., Mult Scler 2013

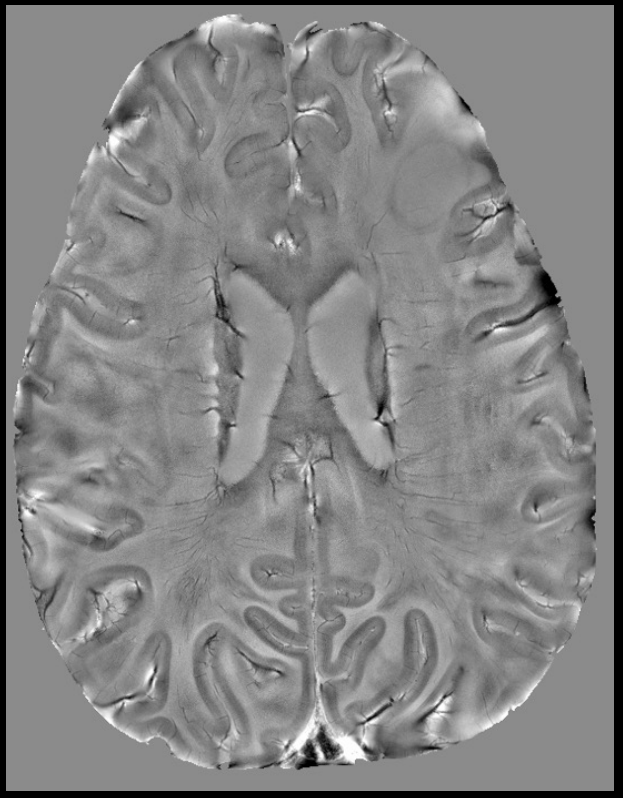
Ring-enhancing MS lesions

T2*w (magnitude) image

Phase image







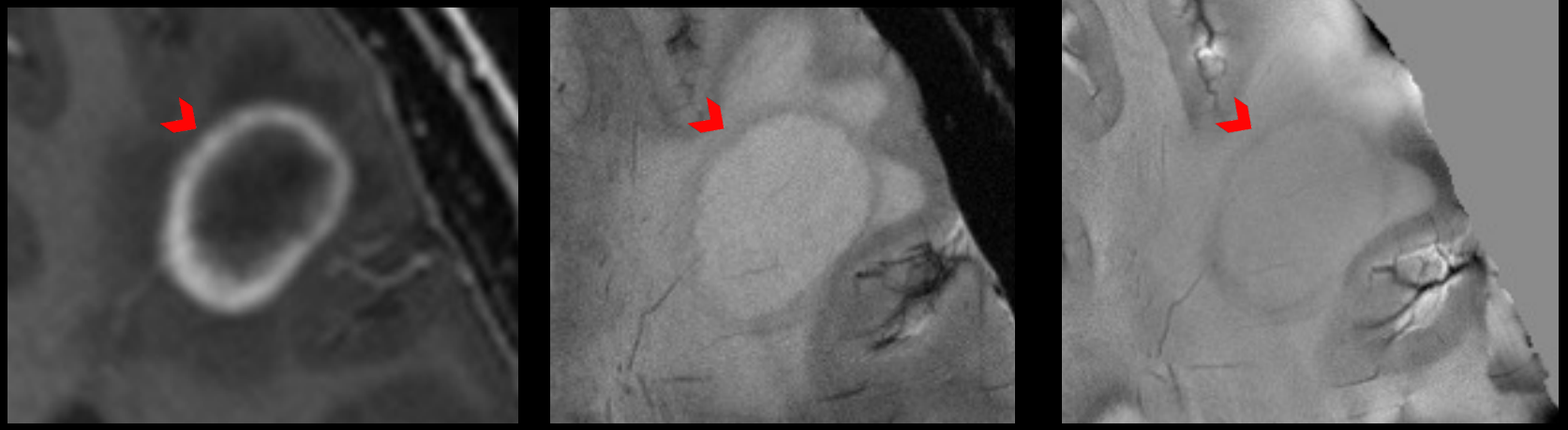
T1w MPRAGE
0.7 mm isotropic

T2*w 2D Gradient Echo (GRE)
0.25 x 0.25 x 1 mm

Ring-enhancing MS lesions

Without Gad (endogenous contrast)

With Gad



T1w MPRAGE | T2*w (magnitude) | Phase

ORIGINAL ARTICLE

Seven-Tesla Phase Imaging of Acute Multiple Sclerosis Lesions: A New Window into the Inflammatory Process

Martina Absinta, MD,[1,2] Pascal Sati, PhD,[1] María I. Gaitán, MD,[1] Pietro Maggi, MD,[1,3] Irene C. M. Cortese, MD,[1] Massimo Filippi, MD,[2] and Daniel S. Reich, MD, PhD[1]

Objective: In multiple sclerosis (MS), accurate, in vivo characterization of dynamic inflammatory pathological changes occurring in newly forming lesions could have major implications for understanding disease pathogenesis and mechanisms of tissue destruction. Here, we investigated the potential of ultrahigh-field magnetic resonance imaging (MRI; 7T), particularly phase imaging combined with dynamic contrast enhancement, to provide new insights in acute MS lesions.

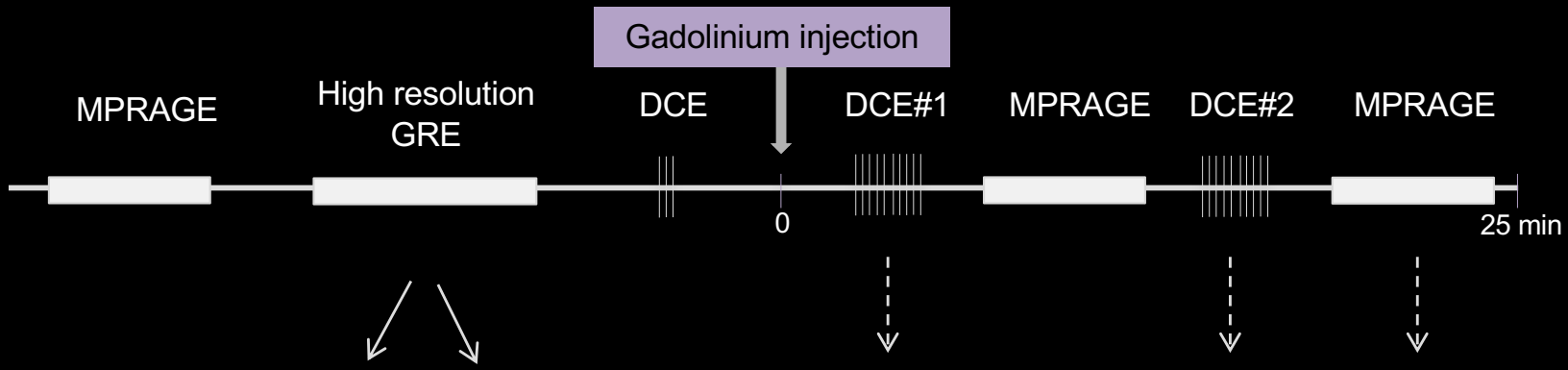
Methods: Sixteen active MS patients were studied at 7T. Noncontrast, high-resolution T2* magnitude and phase scans, T1 scans before/after gadolinium contrast injection, and dynamic contrast-enhanced (DCE) T1 scans were acquired. T2*/phase features and DCE pattern were determined for acute and chronic lesions. When possible, 1-year follow-up 7T MRI was performed.

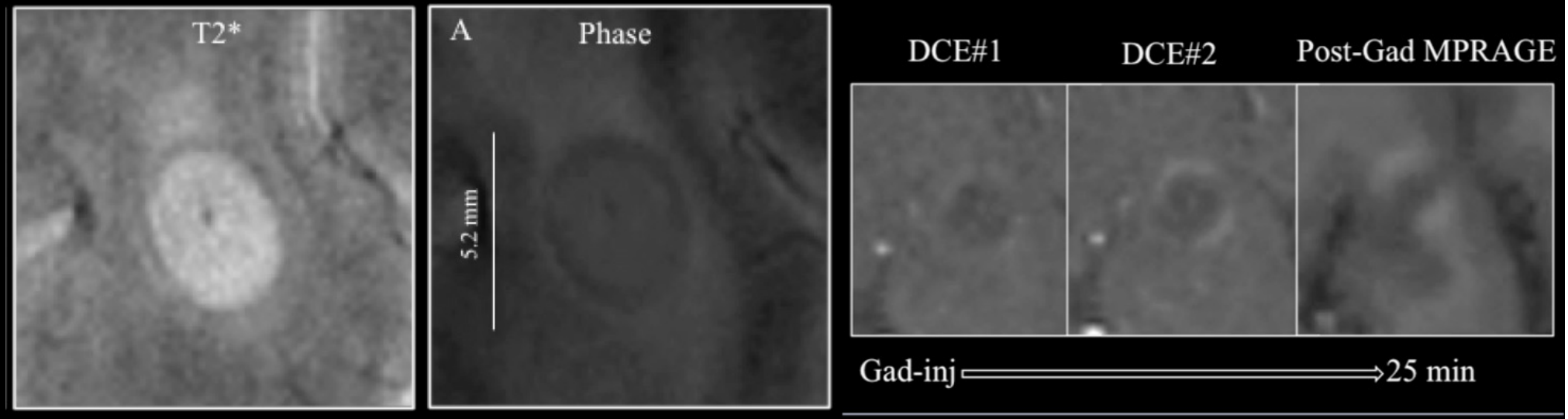
Results: Of 49 contrast-enhancing lesions, 44 could be analyzed. Centrifugal DCE lesions appeared isointense or hypointense on phase images, whereas centripetal DCE lesions showed thin, hypointense phase rims that clearly colocalized with the initial site of contrast enhancement. This pattern generally disappeared once enhancement resolved. Conversely, in 43 chronic lesions also selected for the presence of hypointense phase rims, the findings were stable over time, and the rims were typically thicker and darker. These considerations suggest different underlying pathological processes in the 2 lesion types.

Interpretation: Ultrahigh-field MRI and, especially, phase contrast, are highly sensitive to tissue changes in acute MS lesions, which differ from the patterns seen in chronic lesions. In acute lesions, the hypointense phase rim reflects the expanding inflammatory edge and may directly correspond to inflammatory byproducts and sequelae of blood–brain barrier opening.

ANN NEUROL 2013;74:669–678

16 patients scanned, 44 enhancing lesions analyzed





New finding: phase rim co-localizes with ring-enhancement in active MS lesions

Persistent 7-tesla phase rim predicts poor outcome in new multiple sclerosis patient lesions

Martina Absinta,[1,2] Pascal Sati,[1] Matthew Schindler,[1] Emily C. Leibovitch,[1] Joan Ohayon,[1] Tianxia Wu,[1] Alessandro Meani,[2] Massimo Filippi,[2] Steven Jacobson,[1] Irene C.M. Cortese,[1] and Daniel S. Reich[1]

[1]Division of Neuroimmunology and Neurovirology, National Institute of Neurological Disorders and Stroke (NINDS), NIH, Bethesda, Maryland, USA. [2]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy.

BACKGROUND. In some active multiple sclerosis (MS) lesions, a strong immune reaction at the lesion edge may contain growth and thereby isolate the lesion from the surrounding parenchyma. Our previous studies suggest that this process involves opening of the blood-brain barrier in capillaries at the lesion edge, seen on MRI as centripetal contrast enhancement and a colocalized phase rim. We hypothesized that using these features to characterize early lesion evolution will allow in vivo tracking of tissue degeneration and/or repair, thus improving the evaluation of potential therapies for chronic active lesions.

METHODS. Centripetally and centrifugally enhancing lesions were studied in 17 patients with MS using 7-tesla MRI. High-resolution, susceptibility-weighted, T1-weighted (before/after gadolinium), and dynamic contrast–enhanced scans were acquired at baseline and months 1, 3, 6, and 12. For each lesion, time evolution of the phase rim, lesion volume, and T1 hypointensity were assessed. In autopsies of 3 progressive MS cases, the histopathology of the phase rim was determined.

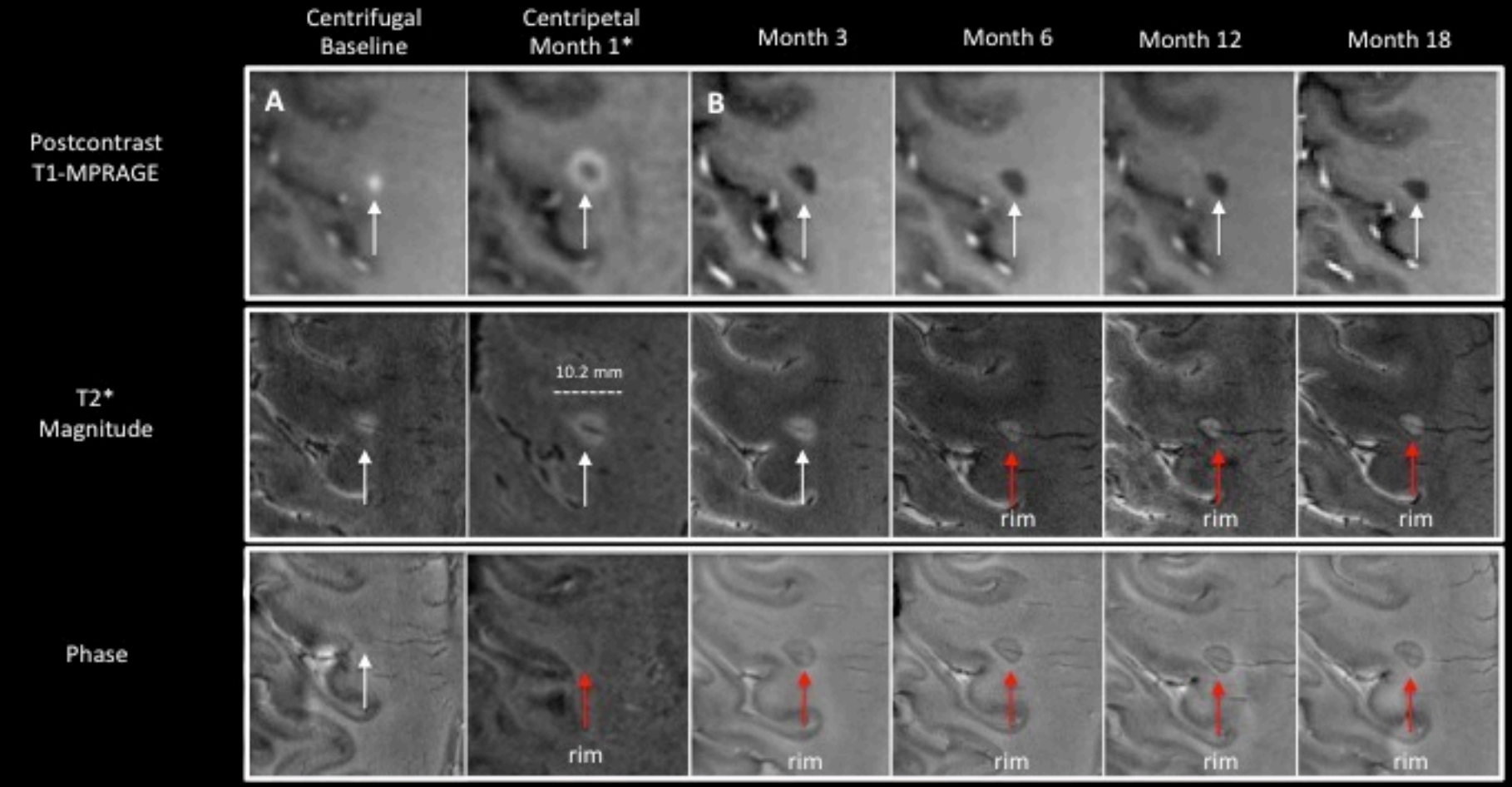
RESULTS. In centripetal lesions, a phase rim colocalized with initial contrast enhancement. In 12 of 22, this phase rim persisted after enhancement resolved. Compared with centripetal lesions with transient rim, those with persistent rim had less volume shrinkage and became more T1 hypointense between months 3 and 12. No centrifugal lesions developed phase rims at any time point. Pathologically, persistent rims corresponded to an iron-laden inflammatory myeloid cell population at the edge of chronic demyelinated lesions.

CONCLUSION. In early lesion evolution, a persistent phase rim in lesions that shrink least and become more T1 hypointense over time suggests that the rim might mark failure of early lesion repair and/or irreversible tissue damage. In later stages of MS, phase rim lesions continue to smolder, exerting detrimental effects on affected brain tissue.

TRIAL REGISTRATION. NCT00001248.

FUNDING. The Intramural Research Program of NINDS supported this study.

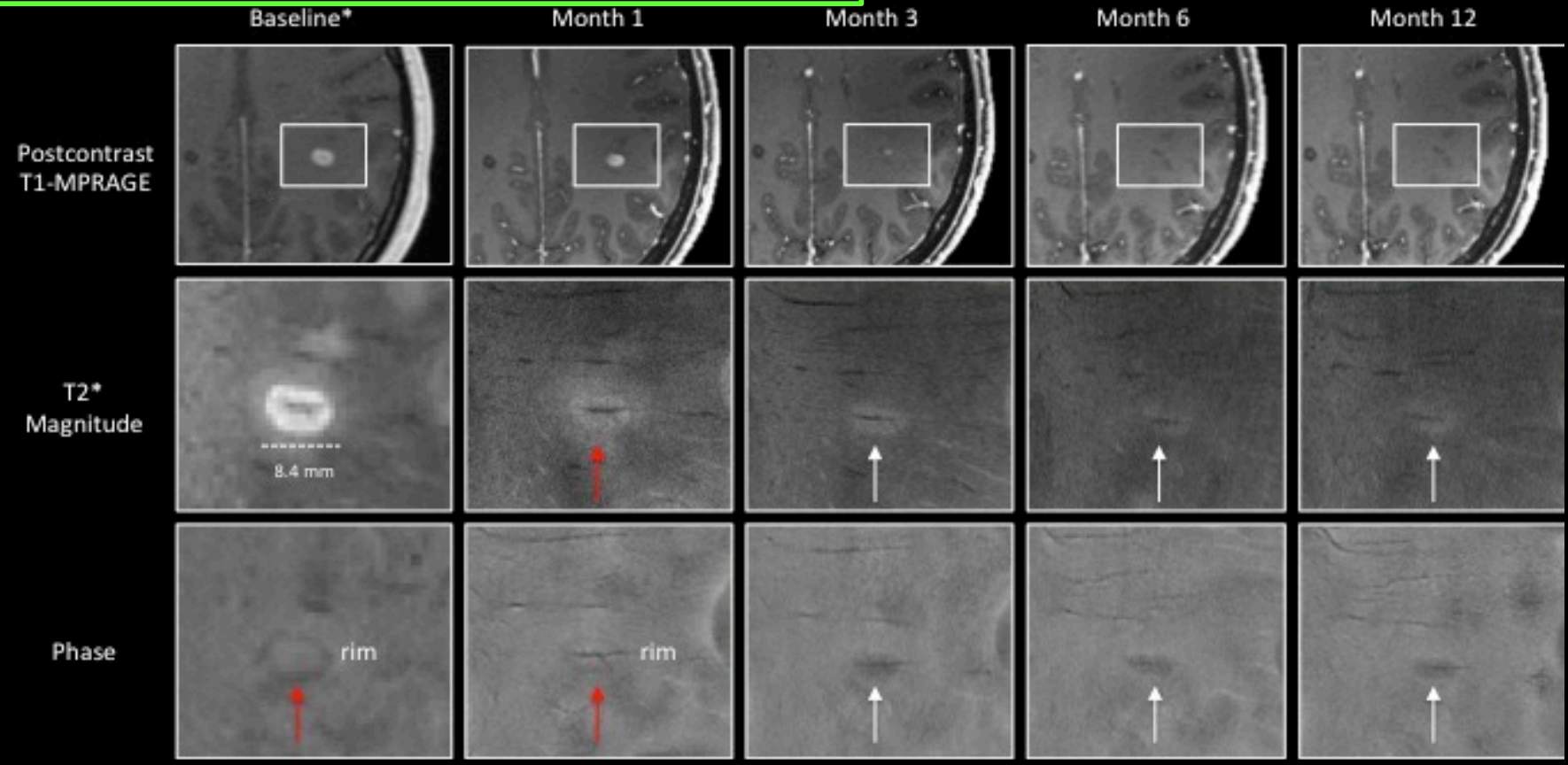
Persistent phase rim after enhancement resolution



Persistent rim visible on both T2*/phase, increase in lesion intensity and stable lesion size

Chronic inflammation ?

Transient phase rim after enhancement resolution



Transient rim only visible on phase, reduction in lesion intensity and size

Repair ?

- **Our hypothesis:** Phase rim is a marker of acute inflammation (open BBB) & chronic inflammation (closed BBB)

- Ongoing confirmatory study: USPIO in phase rim lesions (Dr. Matthew Schindler)

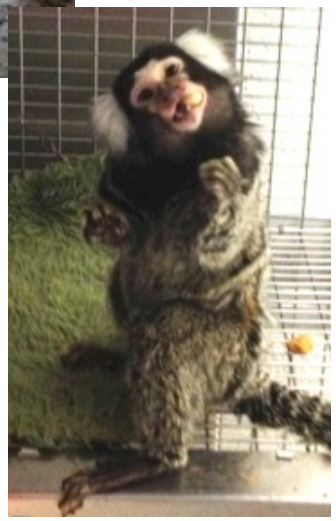
  Compare Gad and USPIO enhancement in phase rim lesions. Non-gad enhancing lesions with phase rim should uptake USPIO through blood-derived macrophages.

- Ongoing intervention study: Steroids in phase rim lesions (Dr. Martina Absinta)

  Asses the effects of steroids on phase rim lesions. Steroids could prevent the phase rim to become persistent and allow a better outcome for the MS lesion (reduction in intensity and size),

IV. To conduct translational pre-clinical MS research

Common Marmoset (*Callithrix jacchus*)

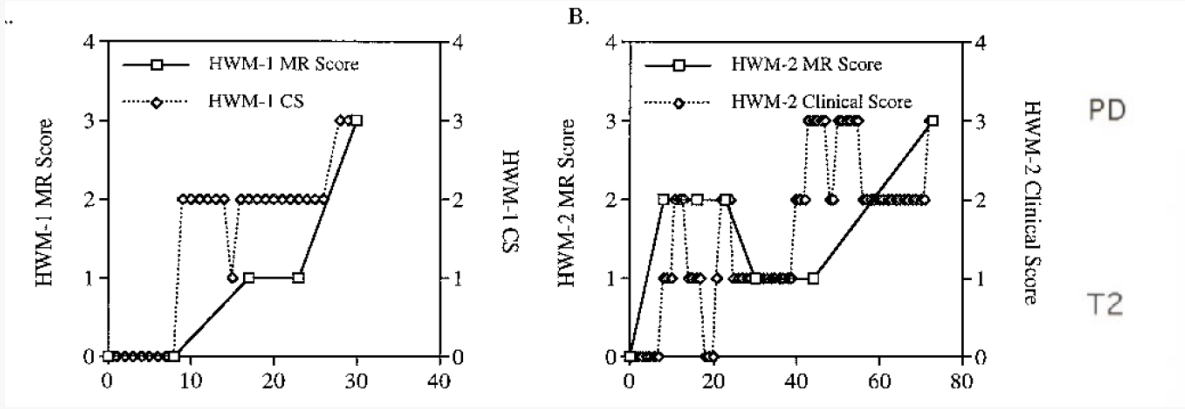


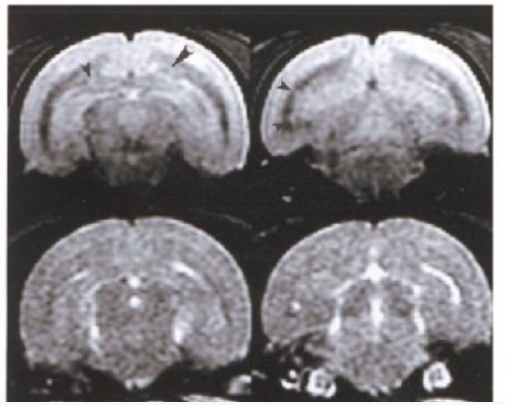
- Small New World monkey (northeastern Brazil)
- Highly active, playful, and eye contact communication
- High fecundity: 2+ offsprings; every 6 months
- Easy to handle as a laboratory animal
- Useful model for neuroscience, stem cell research, reproductive biology, regenerative medicine, drug toxicology, **immunity and autoimmune diseases**

Experimental autoimmune encephalomyelitis in marmoset

EAE induction: human white matter homogenate + Freund's complete adjuvant. *Massacesi et al., Ann Neurol. 1995*

Clinical presentation: Aggressive course with severe neurological signs or chronic relapsing-remitting course, mild neurological signs, and complete recovery from initial attack. *Jordan EK et al., AJNR Am J Neuroradiol. 1999*

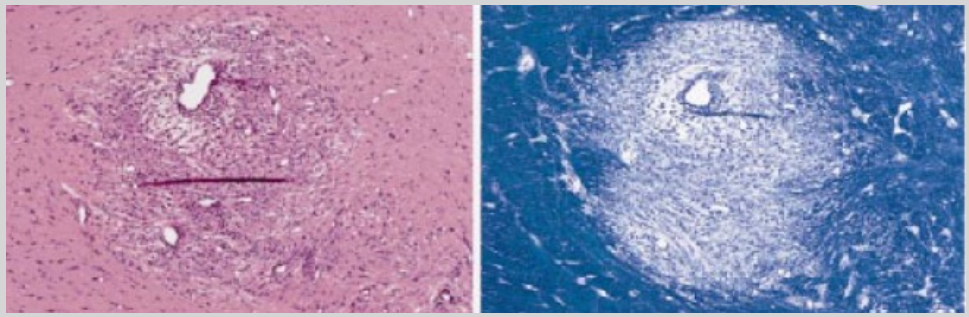




1.5T human MRI (NIH)

Pathology: scattered perivascular inflammatory infiltrates surrounded by large concentric areas of demyelination and associated with intense macrophage infiltration and mild astrogliosis. *Jordan EK et al., AJNR Am J Neuroradiol. 1999*

H&E
Dense perivascular mononuclear infiltration



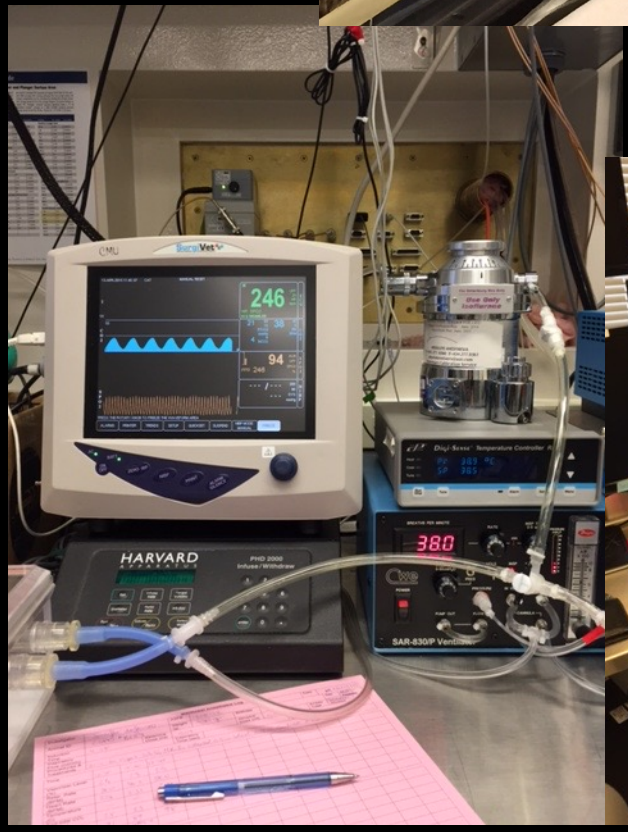
LFB
Demyelination

Ultra-high-field (7 Tesla) MRI of marmoset brain

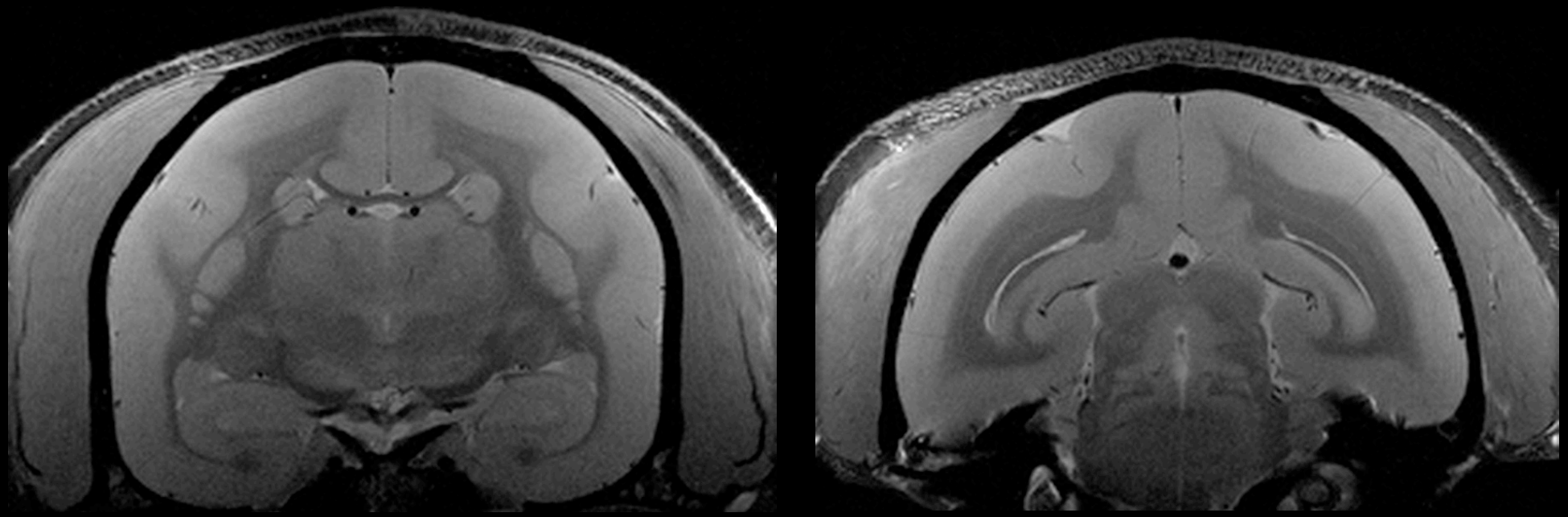
5 & 8-channel RX head coils

7T Bruker

Dr. Afonso Silva laboratory

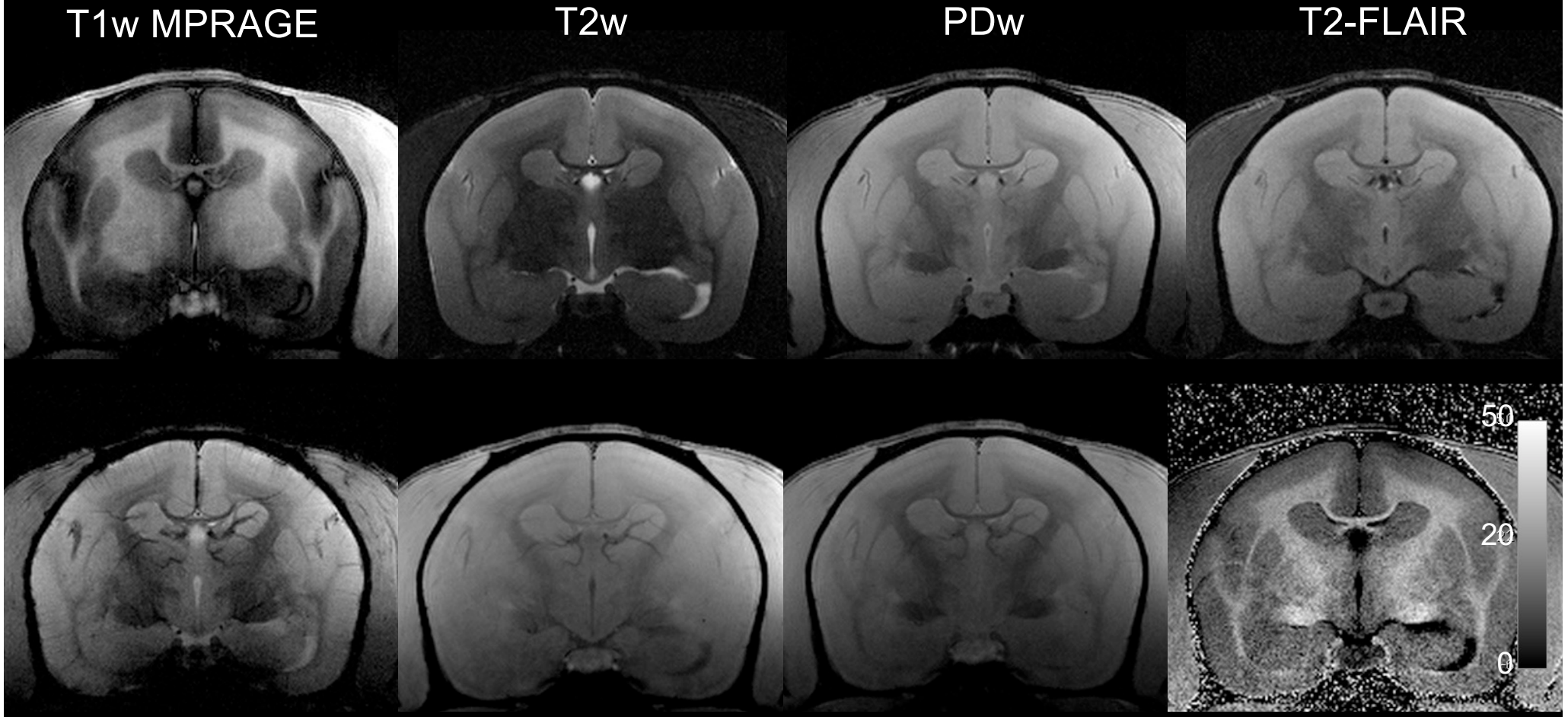


High-resolution MRI



Proton-density contrast
(125 μm in-plane resolution)

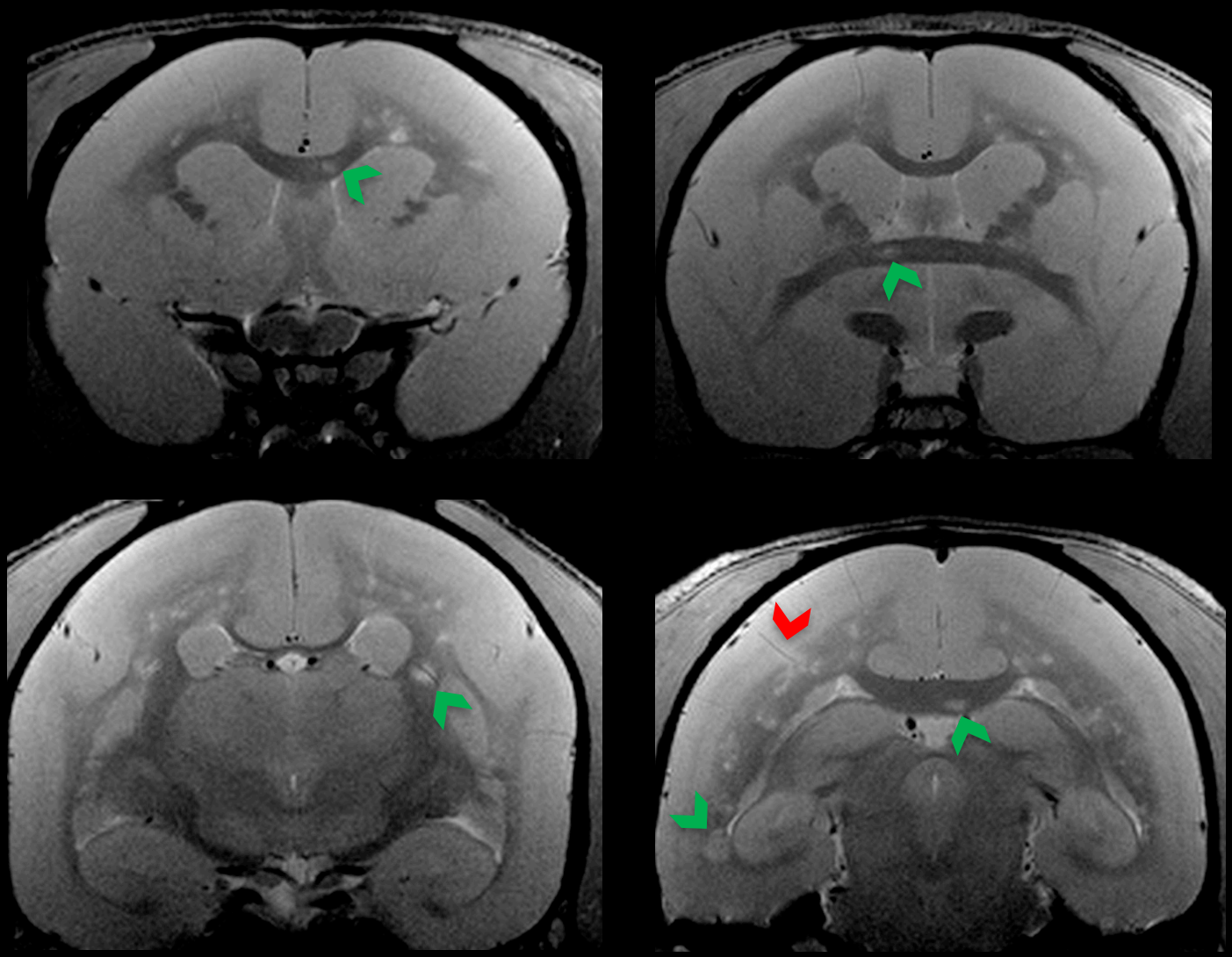
Multi-contrast MRI



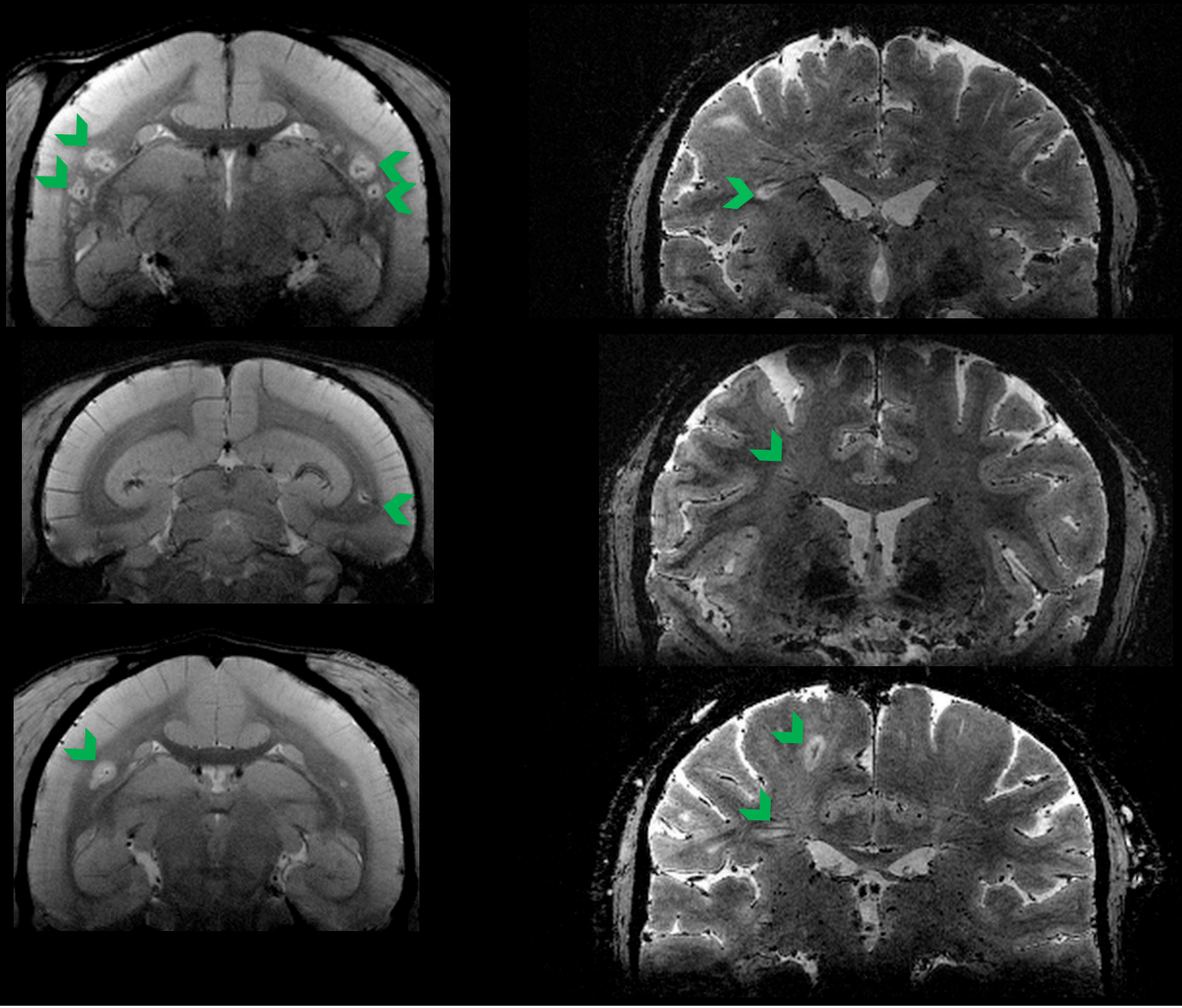
Voxel size =150 μm x 150 μm x 1 mm

Total scan time = 60 min

MRI of marmoset EAE brain lesions



Central vein in EAE and MS lesions



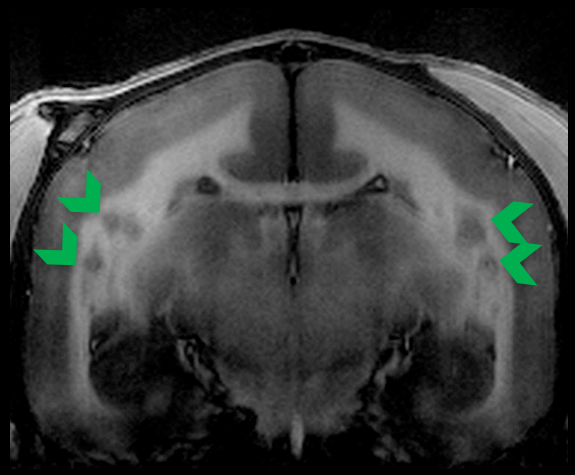
Acute lesions in EAE and MS

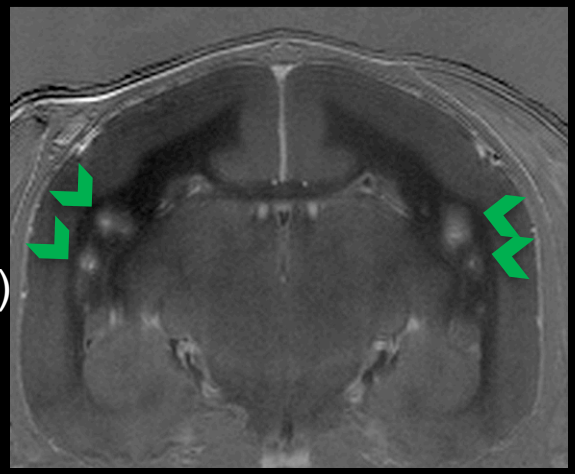
(injection of gadobutrol contrast agent)

pre-injection

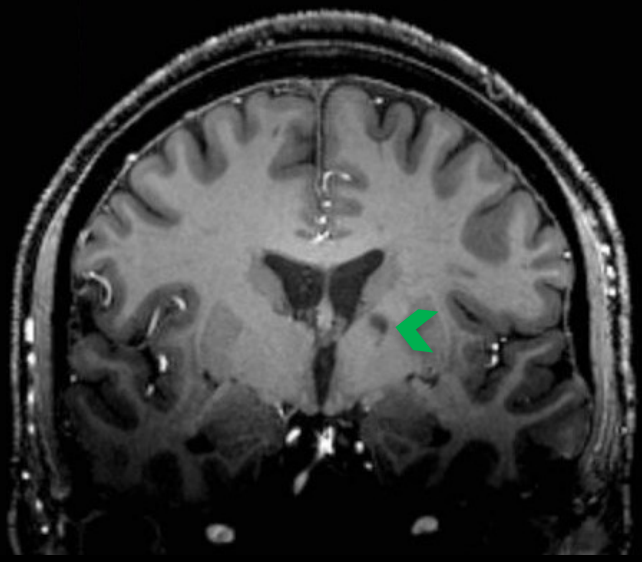
post-injection

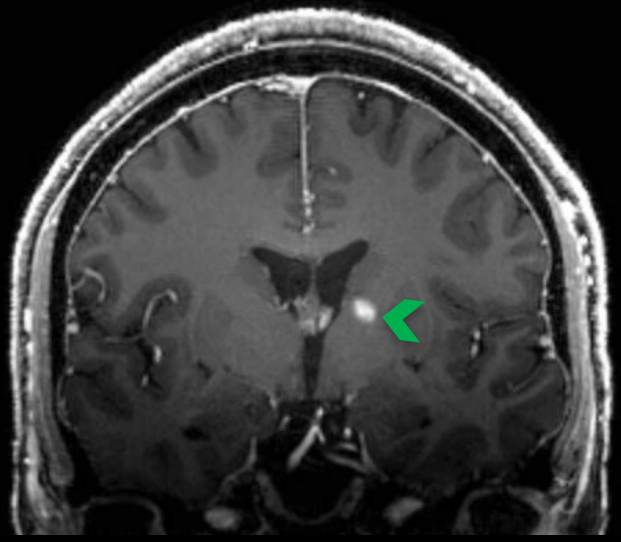
(difference image)





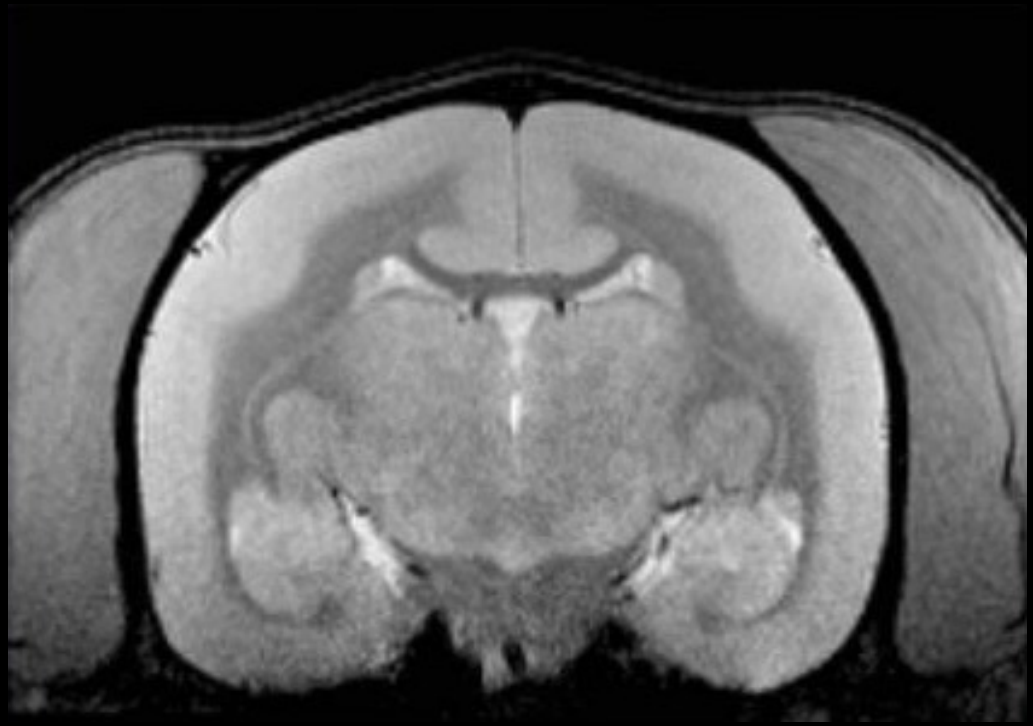
Triple-dose (0.3 mL/kg)





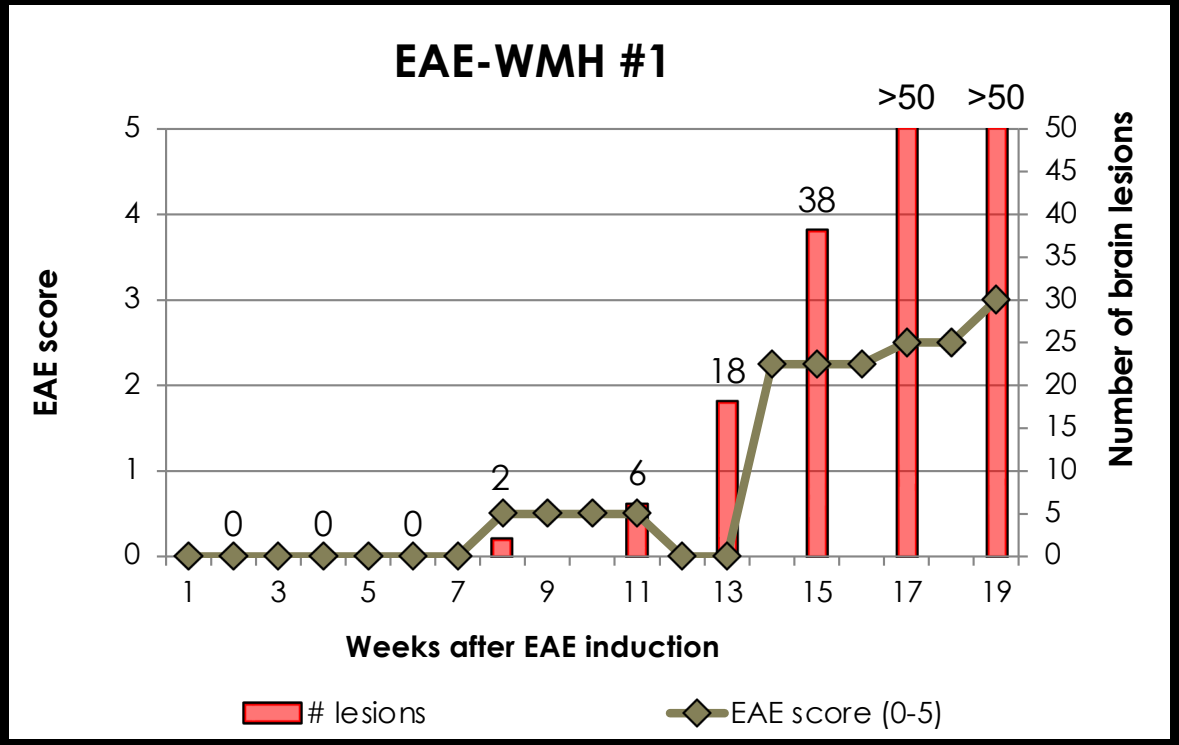
single-dose (0.1 mL/kg)

Serial MRI of marmoset EAE



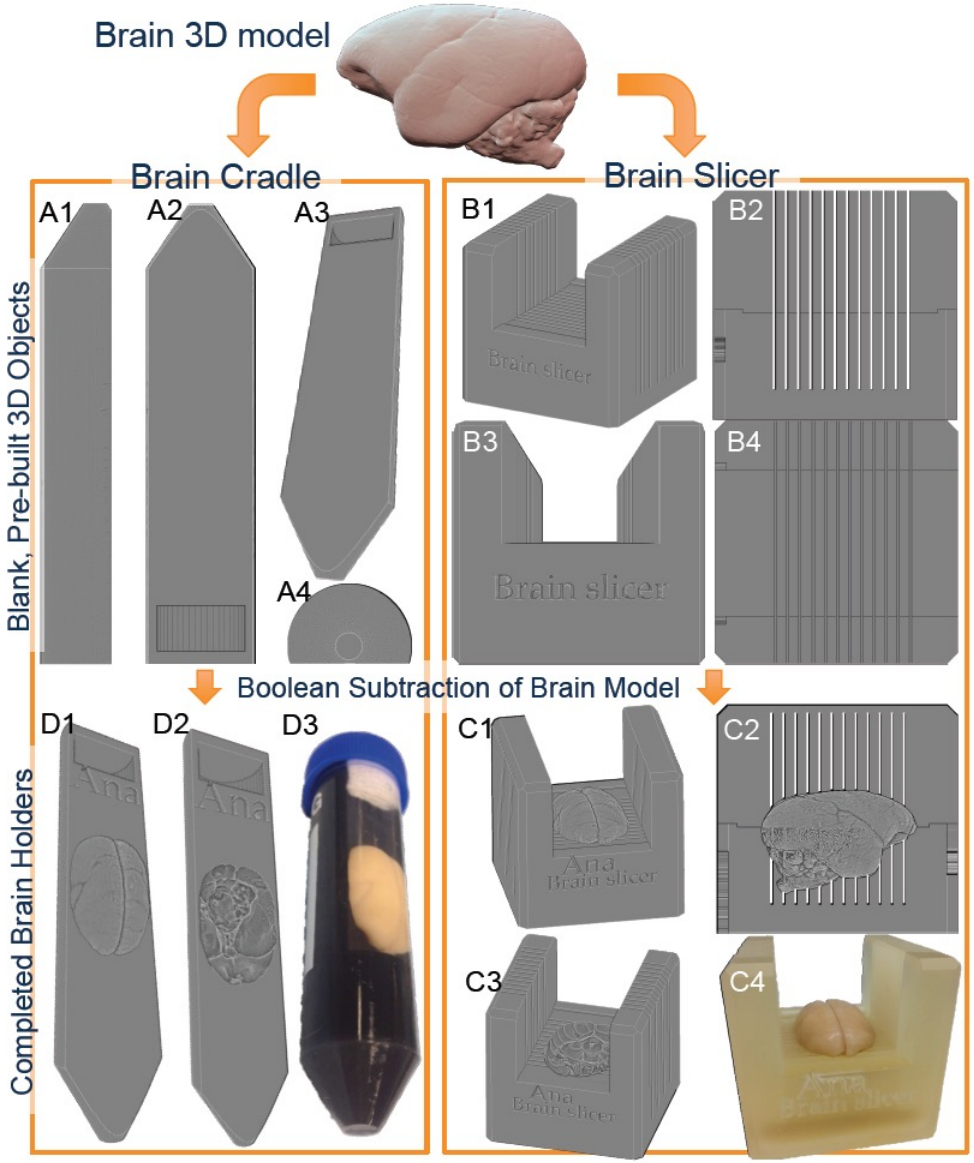
From baseline (healthy) until termination (severe disease)

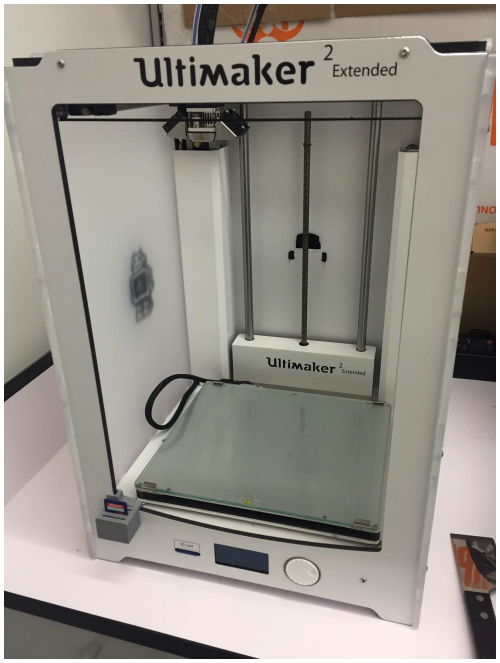
MRI as an outcome for marmoset EAE studies



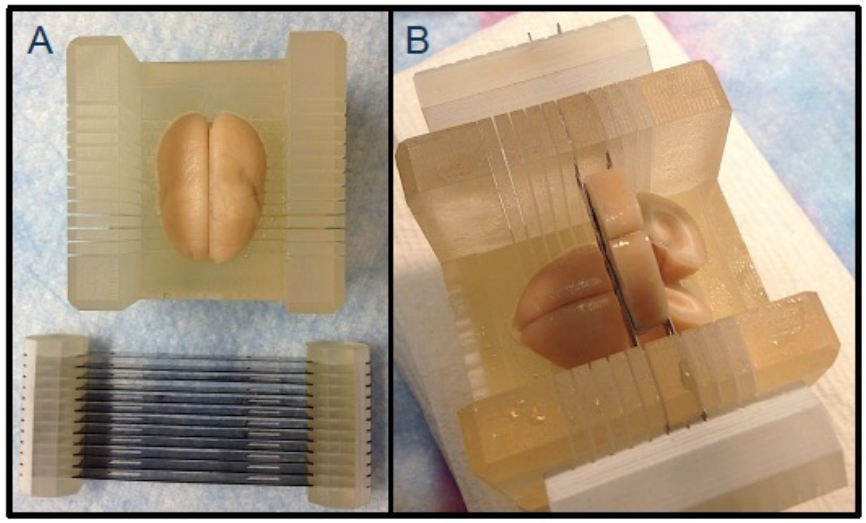
Lesion load, lesion volume, enhancing lesions,…

3D-printed brain holder and slicer



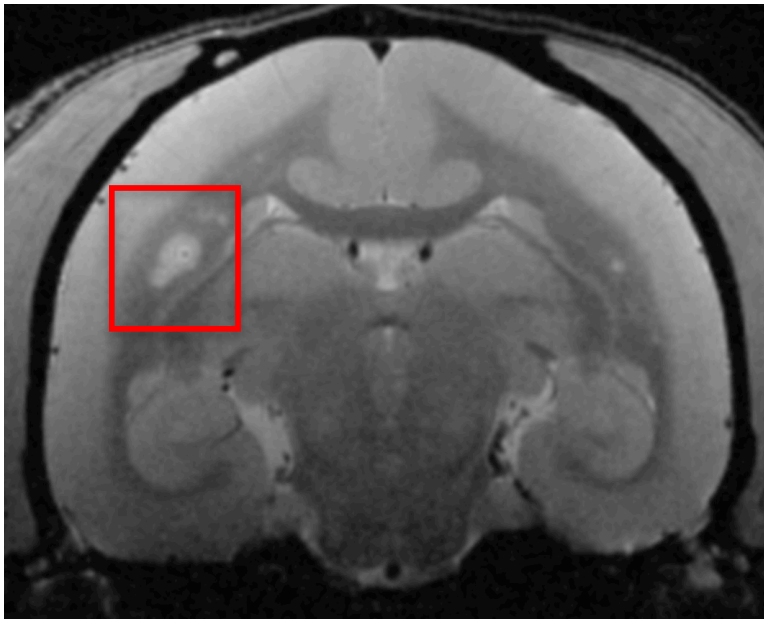


Nick Luciano (postbac)

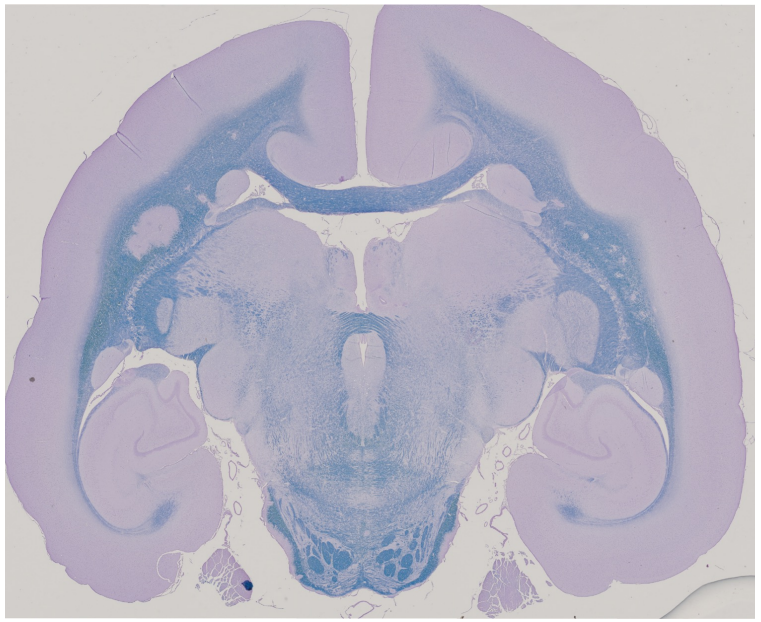


Guy *et al*., Journal of Neuroscience Methods. 2016

in vivo MRI

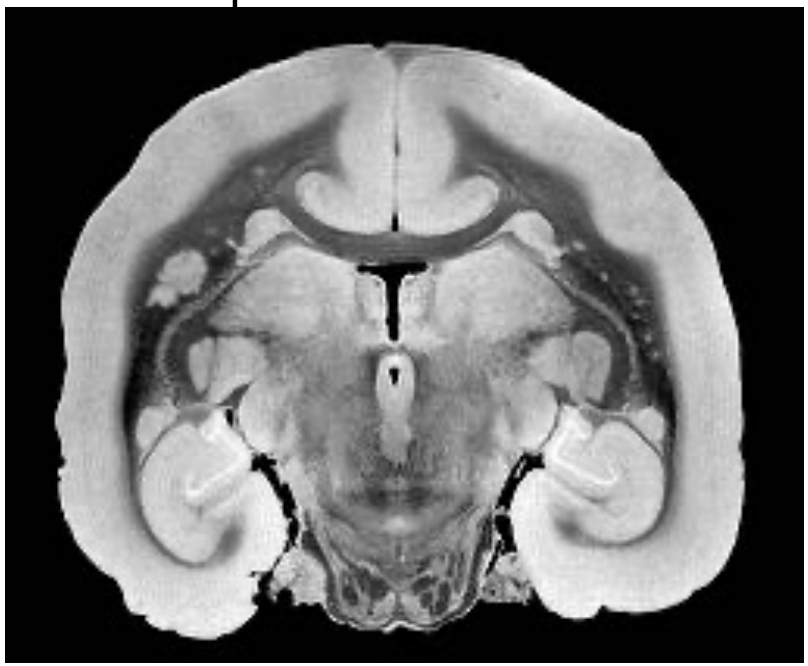


Histopathology



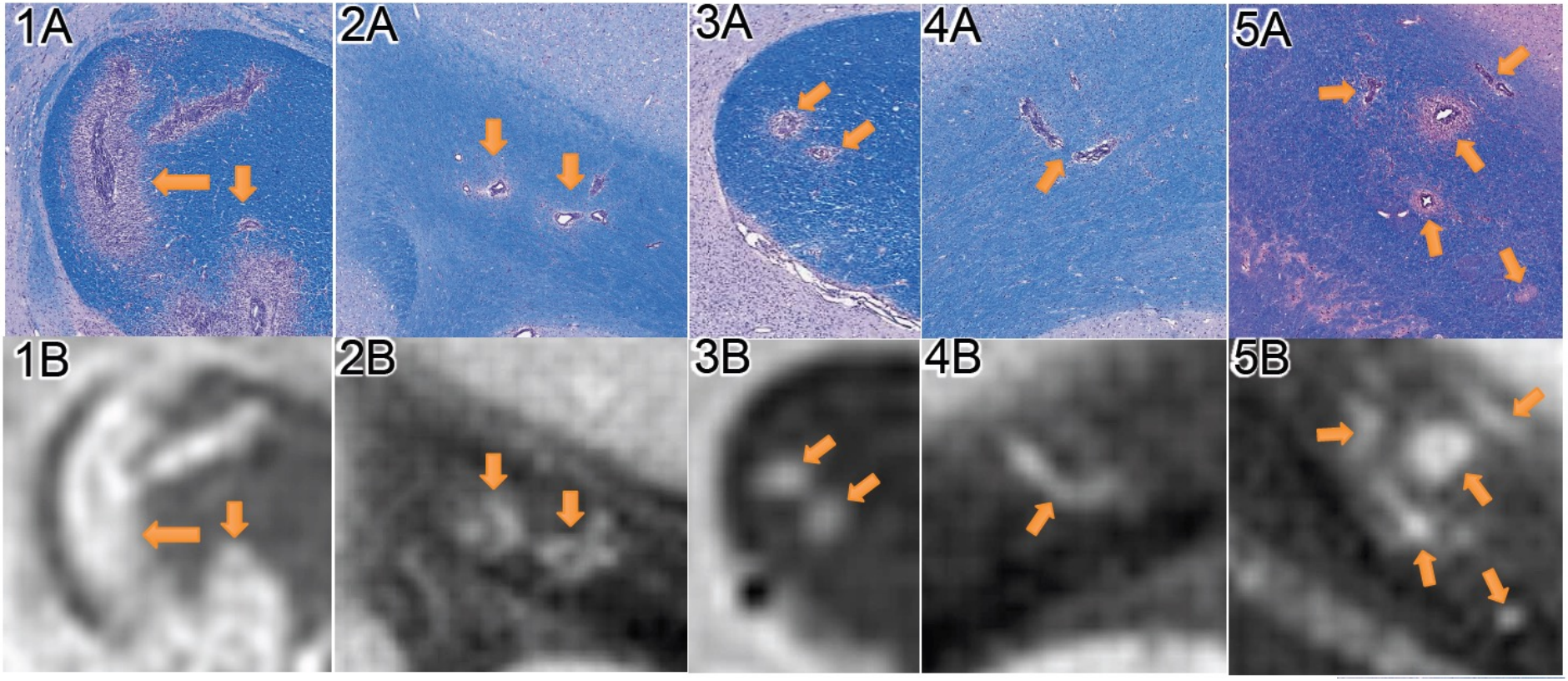
(Dr. Seung Kwon Ha)

postmortem MRI



Absinta *et al*., Journal Neuropathol Exp Neurol. 2014
Guv *et al*.. Journal of Neuroscience Methods. 2016

Method for validation of novel MRI markers



Guy *et al*., Journal of Neuroscience Methods. 2016

Method for unraveling the lesion formation process

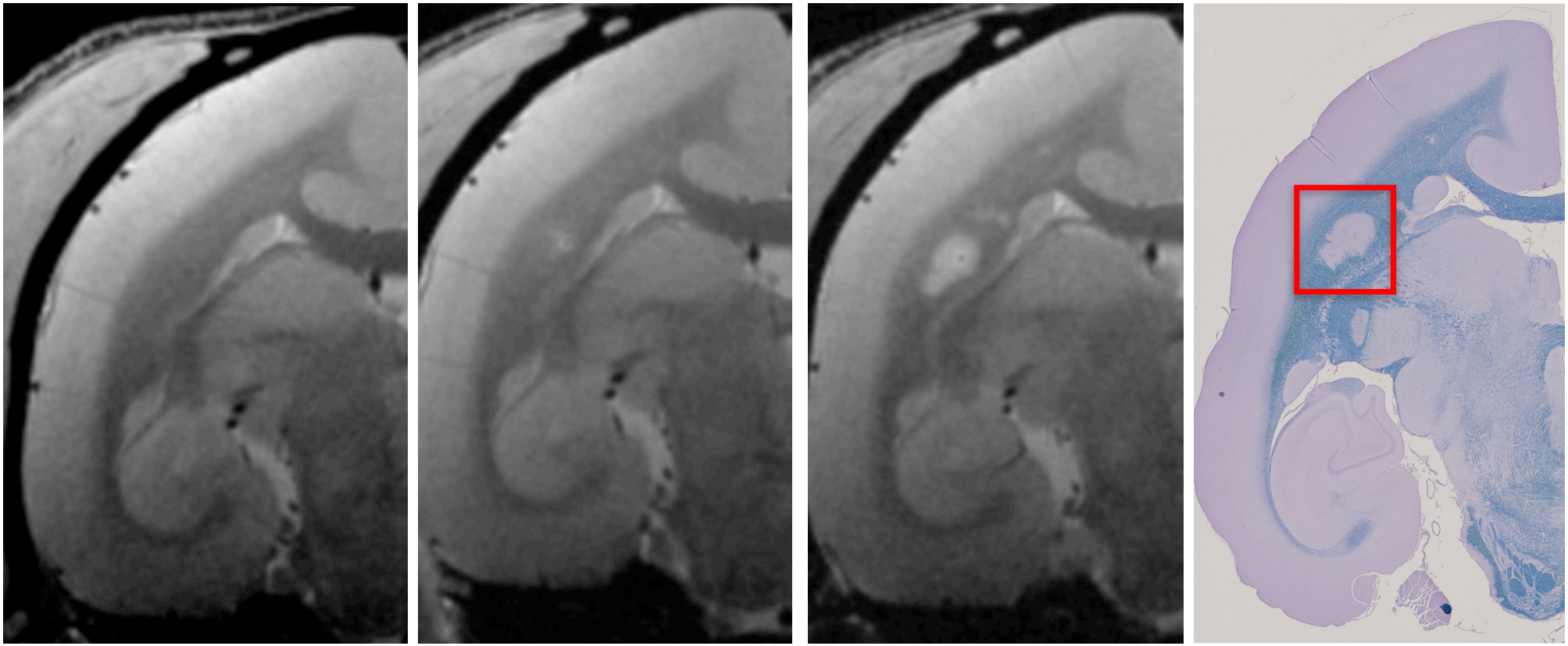
" Back in time" strategy

2 weeks before terminal MRI

1 week before terminal MRI

Terminal MRI

Histopathology



$t_{lesion} = -1$

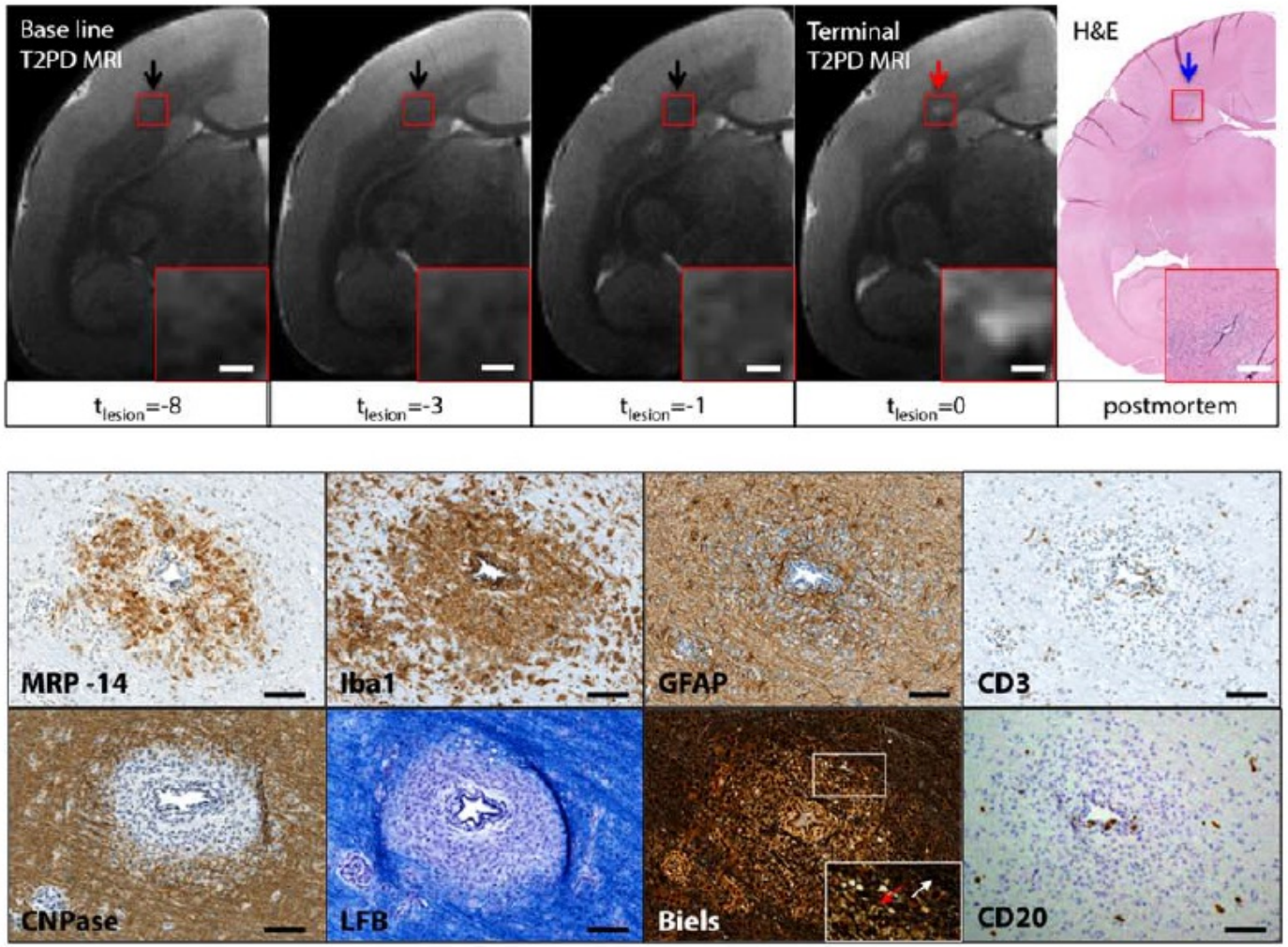
$t_{lesion} = 0$

$t_{lesion} = +1$

Lesion age can be determined based on serial MRI

Maggi P *et al*. Ann Neurol. 2014

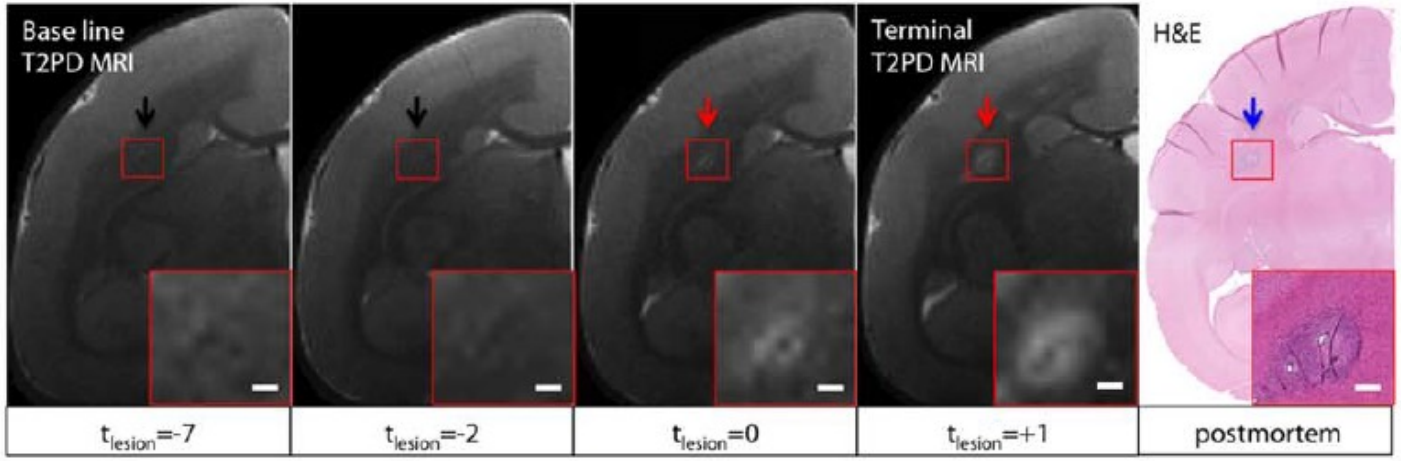
Acute lesions (< 1 week old)

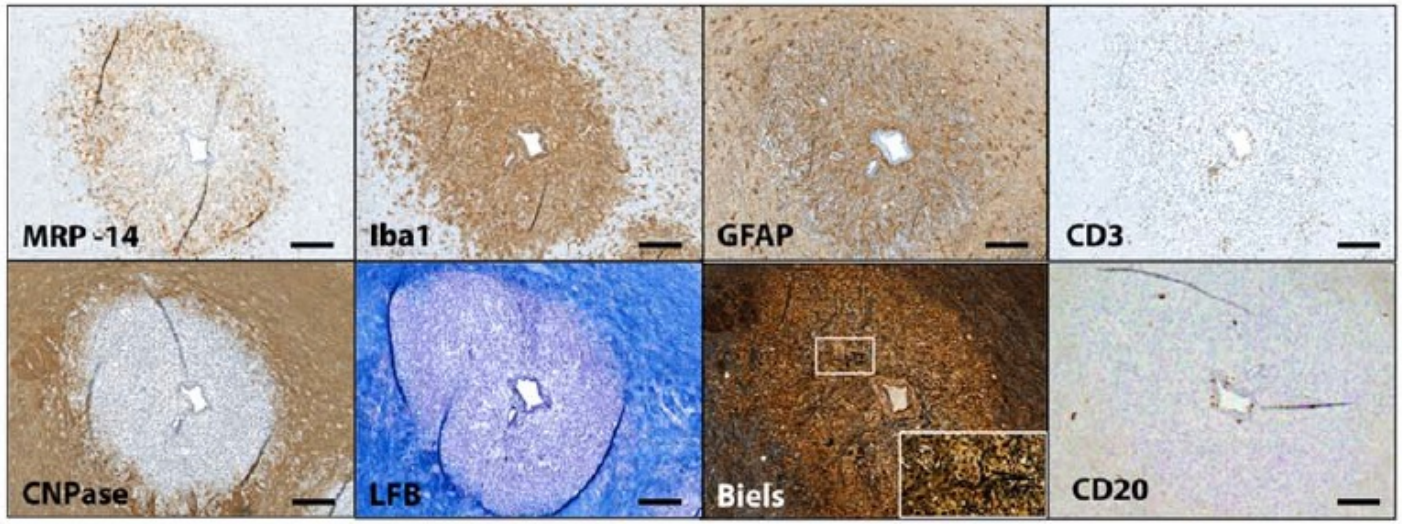


Pathological signature:

- **Perivascular cuff:** lymphocytes, activated microglia and macrophages
- **Parenchyma:** blood-derived macrophages, demyelination and axonal disruptions

Subacute lesions (1-5 week old)

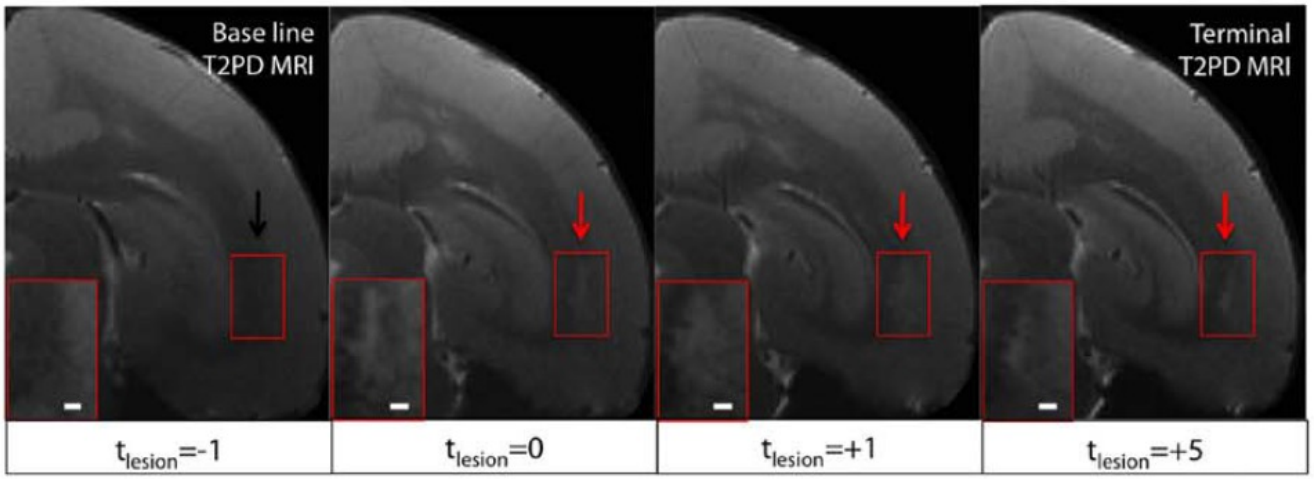


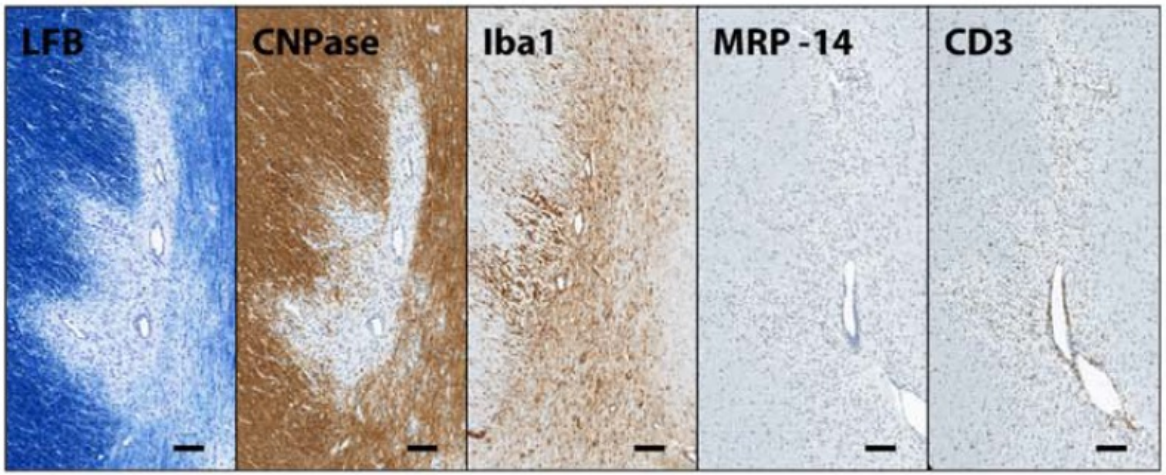


Pathological signature:

- Blood-derived macrophages are present **at the lesion edge.**
- Lesion is **expanding** (demyelination and axonal disruptions)

Late subacute lesions (>5 week old)

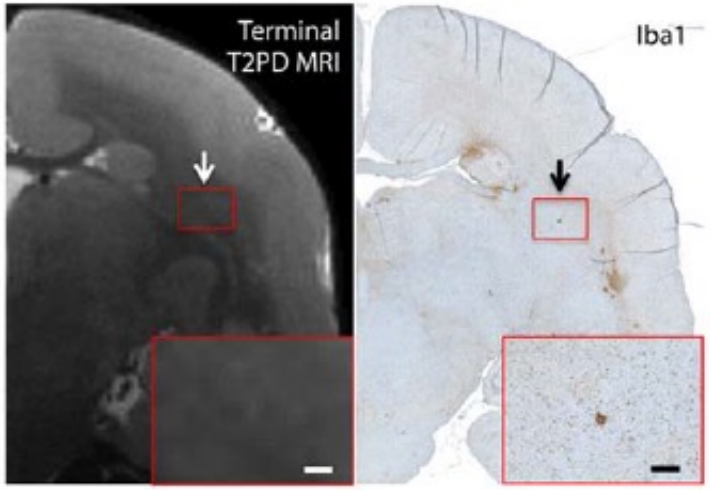


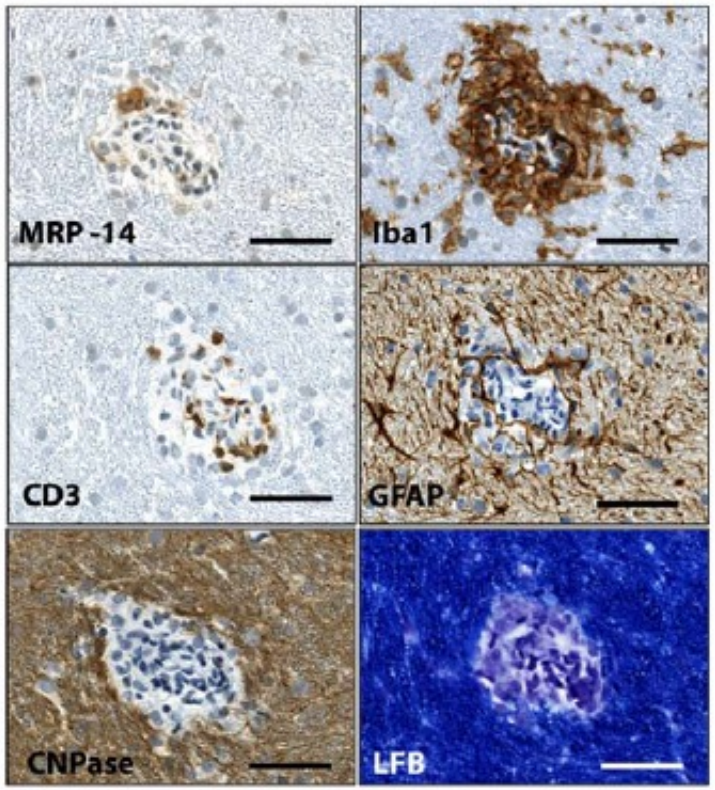


Pathological signature:

- Blood-derived MRP14^{+} early activated macrophages are absent
- Pale myelin staining suggesting **remyelination (lesion shrinkage)**.

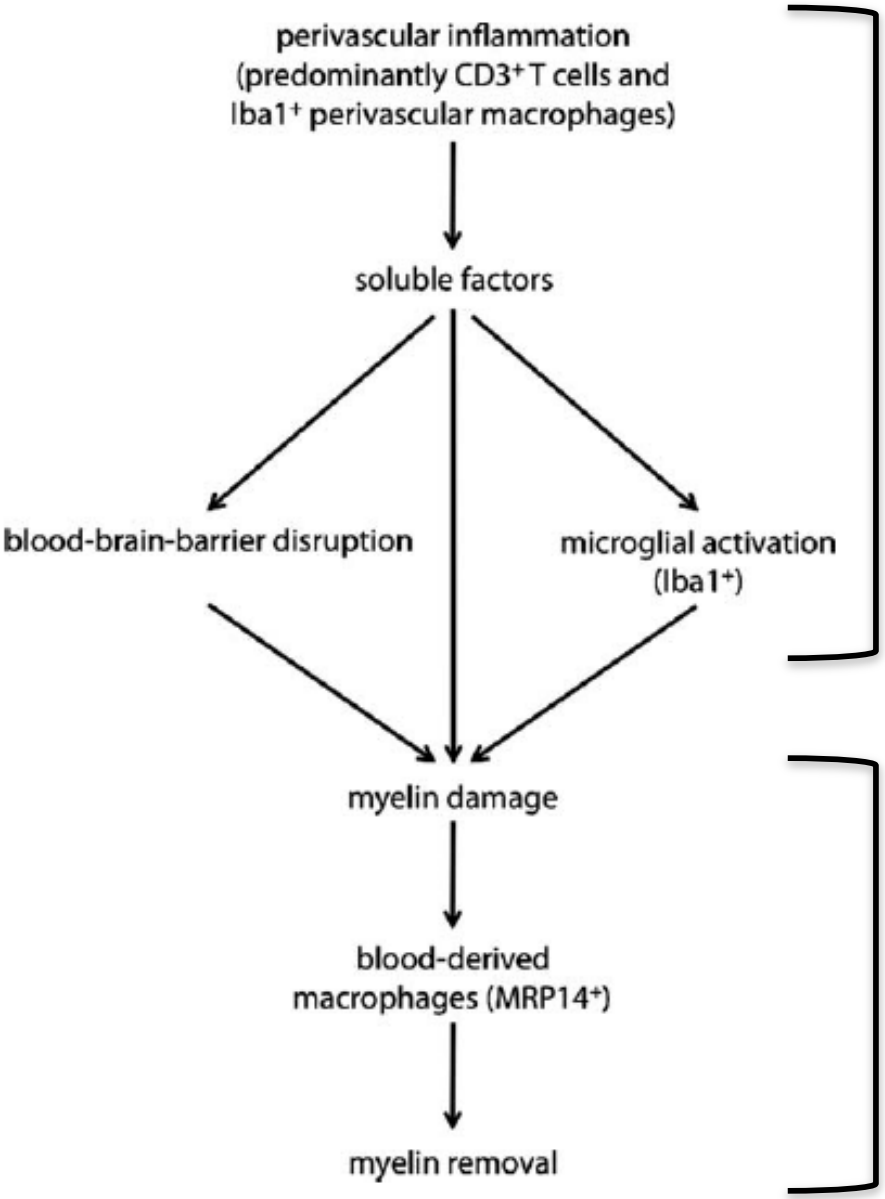
Nondemyelinated inflammatory nodules





Inflammatory nodules might precede lesion formation

Model of lesion formation in marmoset EAE



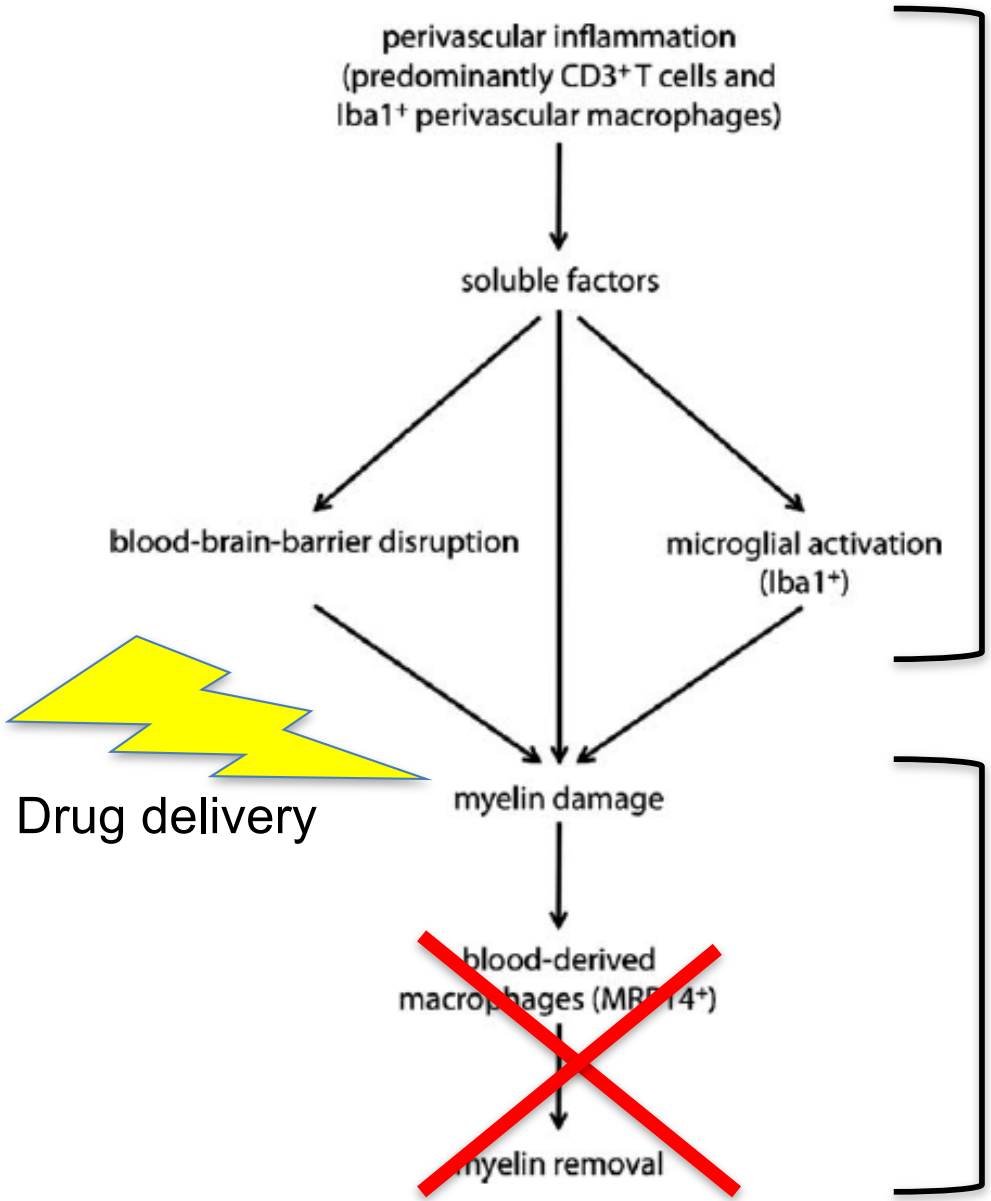
Nondemyelinated inflammatory nodules

Acute lesion (<1 week)

Subacute lesion (1 to 5 weeks)

Late subacute (>5 weeks)

Method for drug intervention study: stopping early inflammation



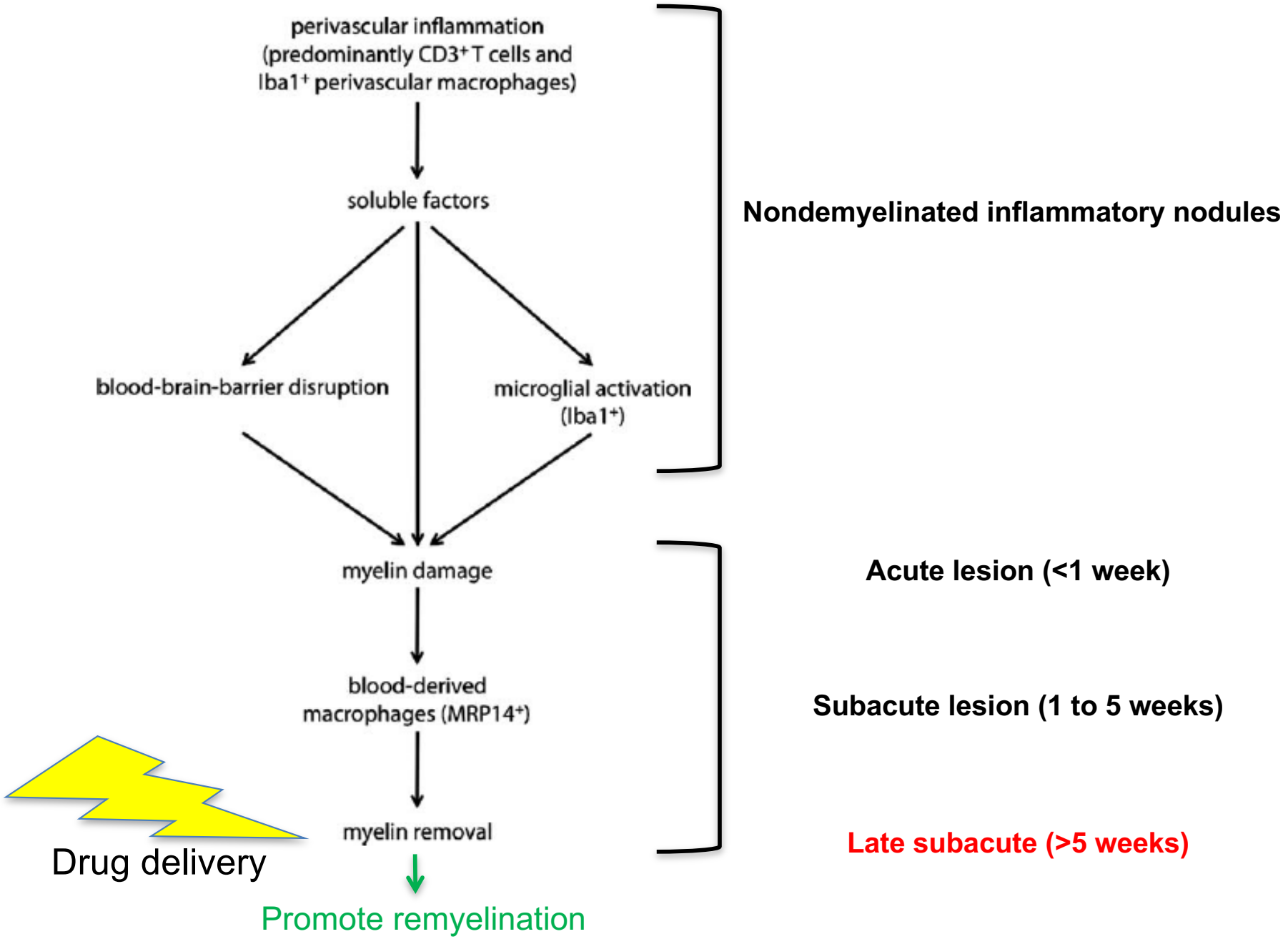
Nondemyelinated inflammatory nodules

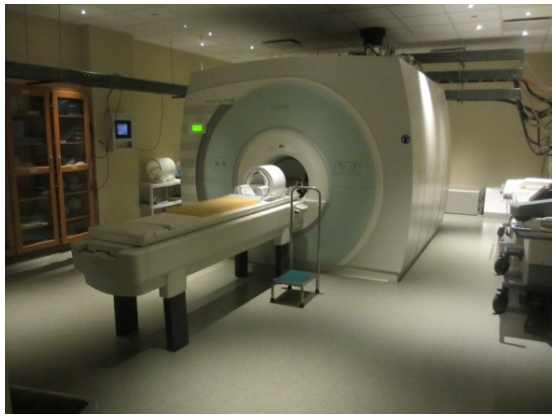
Acute lesion (<1 week)

Subacute lesion (1 to 5 weeks)

Late subacute (>5 weeks)

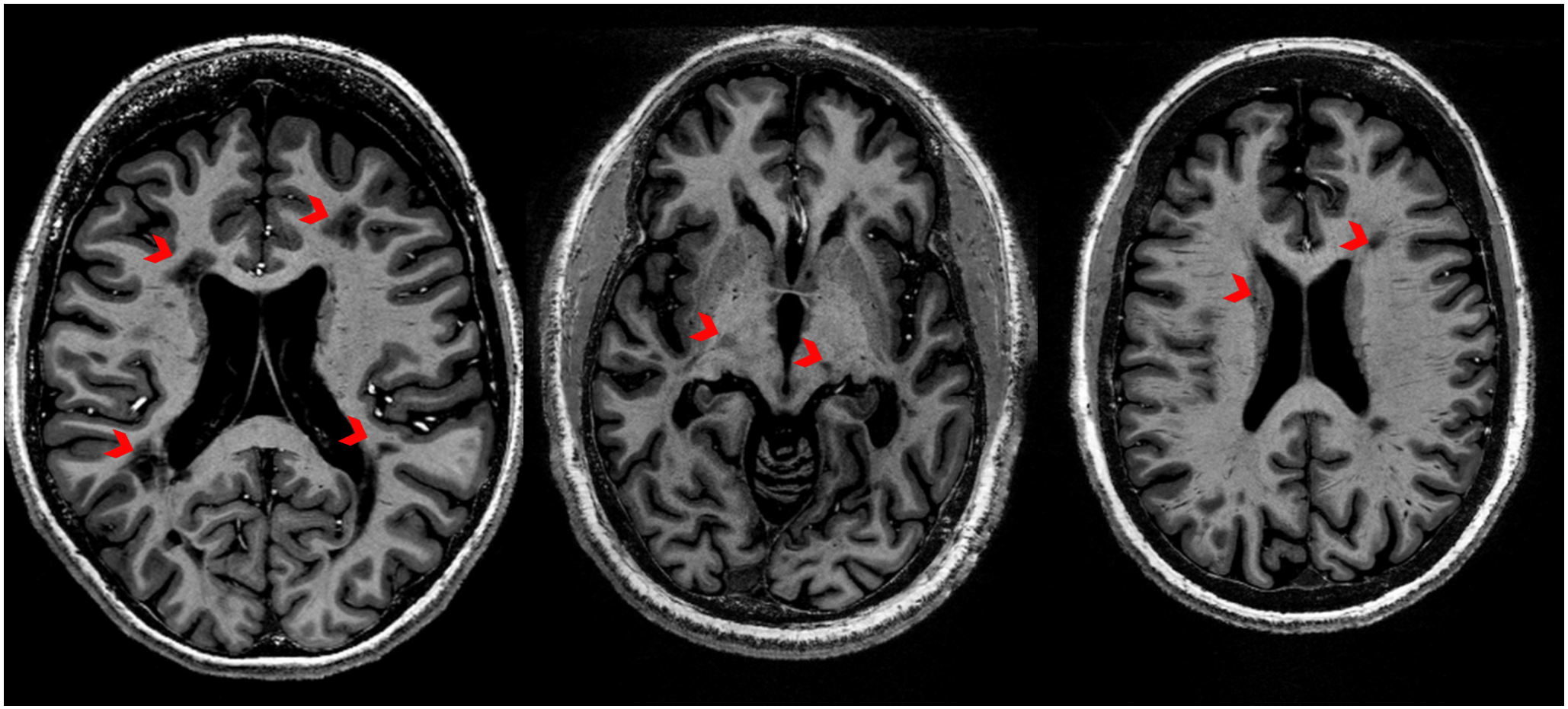
Method for drug intervention study: promoting tissue repair

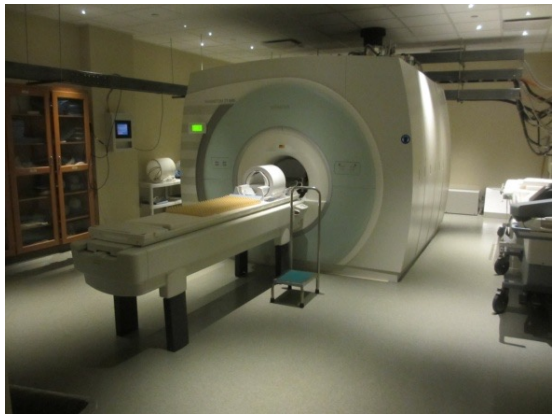




Advanced (7T) imaging of neurological diseases (MS)

1. To better detect *in vivo* MS pathology (MRIcroscopy)

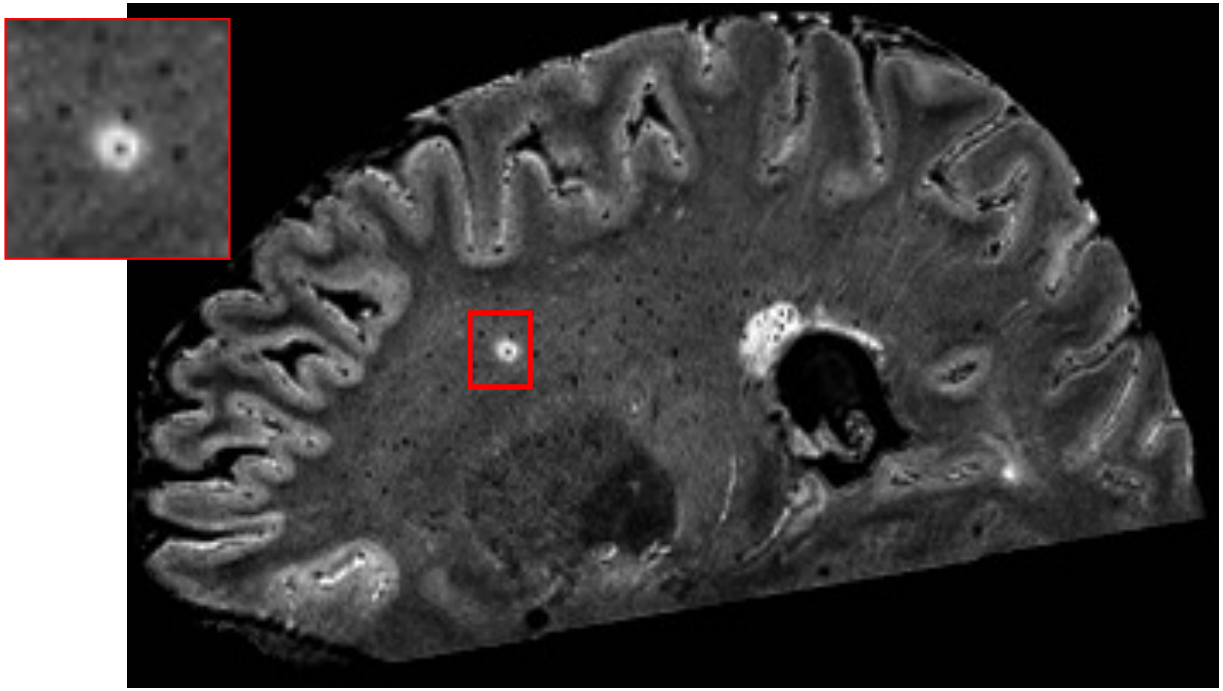


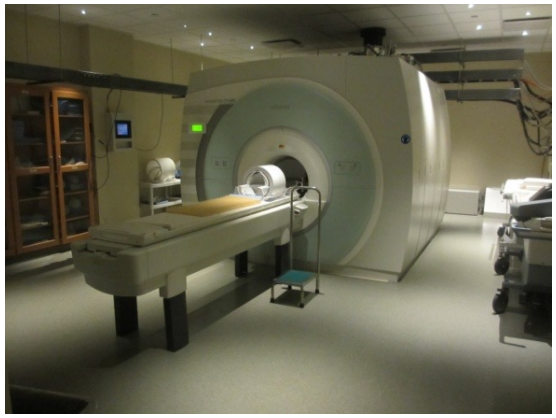


Advanced (7T) imaging of neurological diseases (MS)

1. To better detect *in vivo* MS pathology (MRIcroscopy)

2. To better diagnose MS by MRI (FLAIR*)



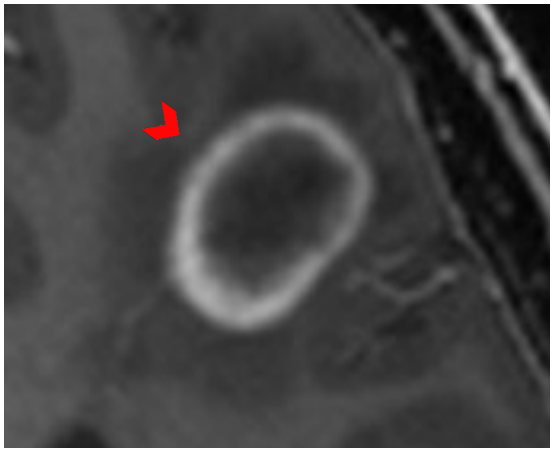


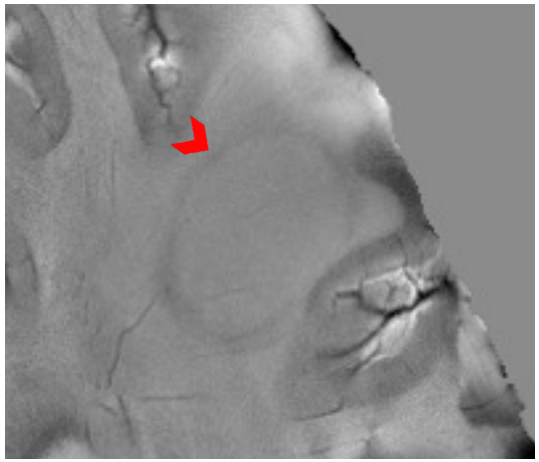
Advanced (7T) imaging of neurological diseases (MS)

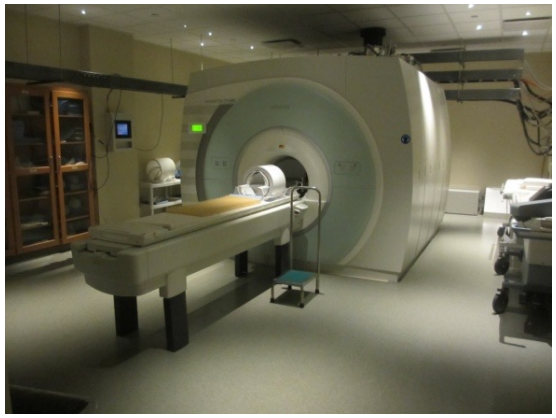
1. To better detect *in vivo* MS pathology (MRIcroscopy)

2. To better diagnose MS by MRI (FLAIR*)

3. To find new imaging markers of MS disease activity (phase rim)



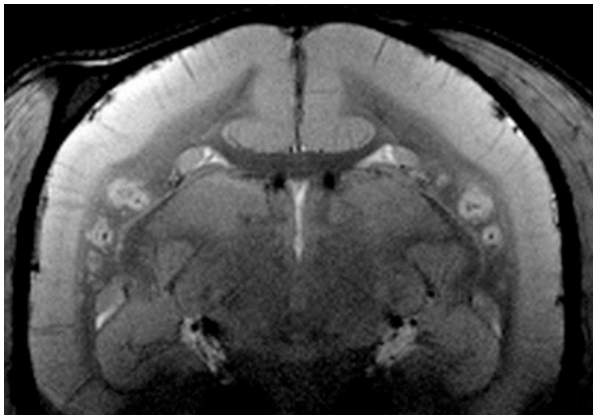




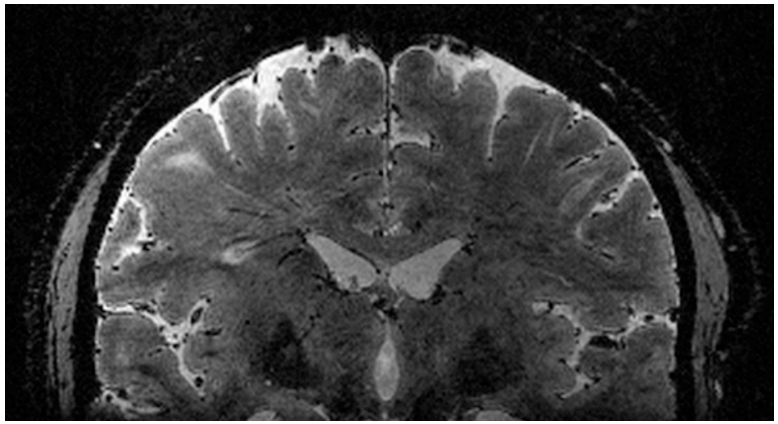
Advanced (7T) imaging of neurological diseases (MS)

1. To better detect *in vivo* MS pathology (MRIcroscopy)
2. To better diagnose MS by MRI (FLAIR*)
3. To find new imaging markers of MS disease activity (phase rim)
4. To conduct translational pre-clinical MS research (marmoset EAE)

marmoset EAE- T2* contrast - 7T



MS patient - T2* contrast - 7T



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