Studying central nervous system diseases with advanced MRI

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TNU

Mission statement:

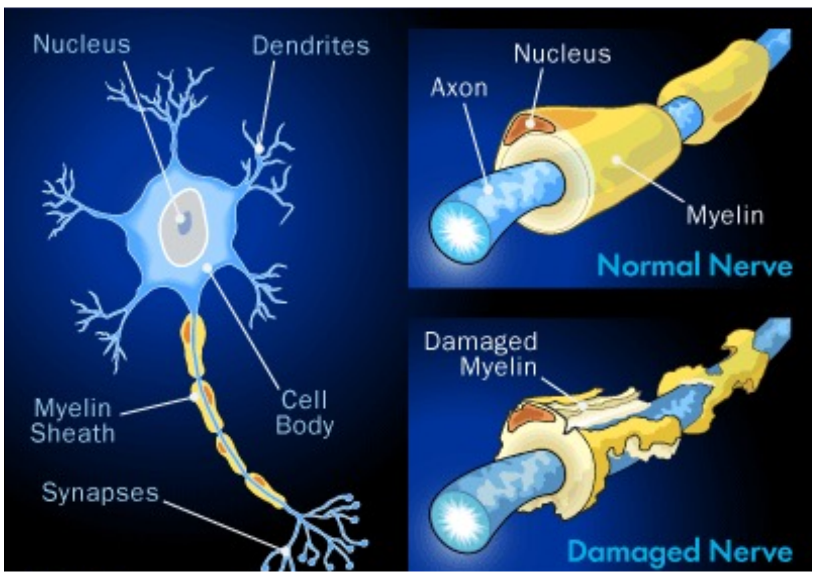
"Our research focuses on the use of **advanced MRI** techniques to **understand the sources of disability** in MS and on ways of adapting those techniques for use in **research trials** and **routine patient care**."

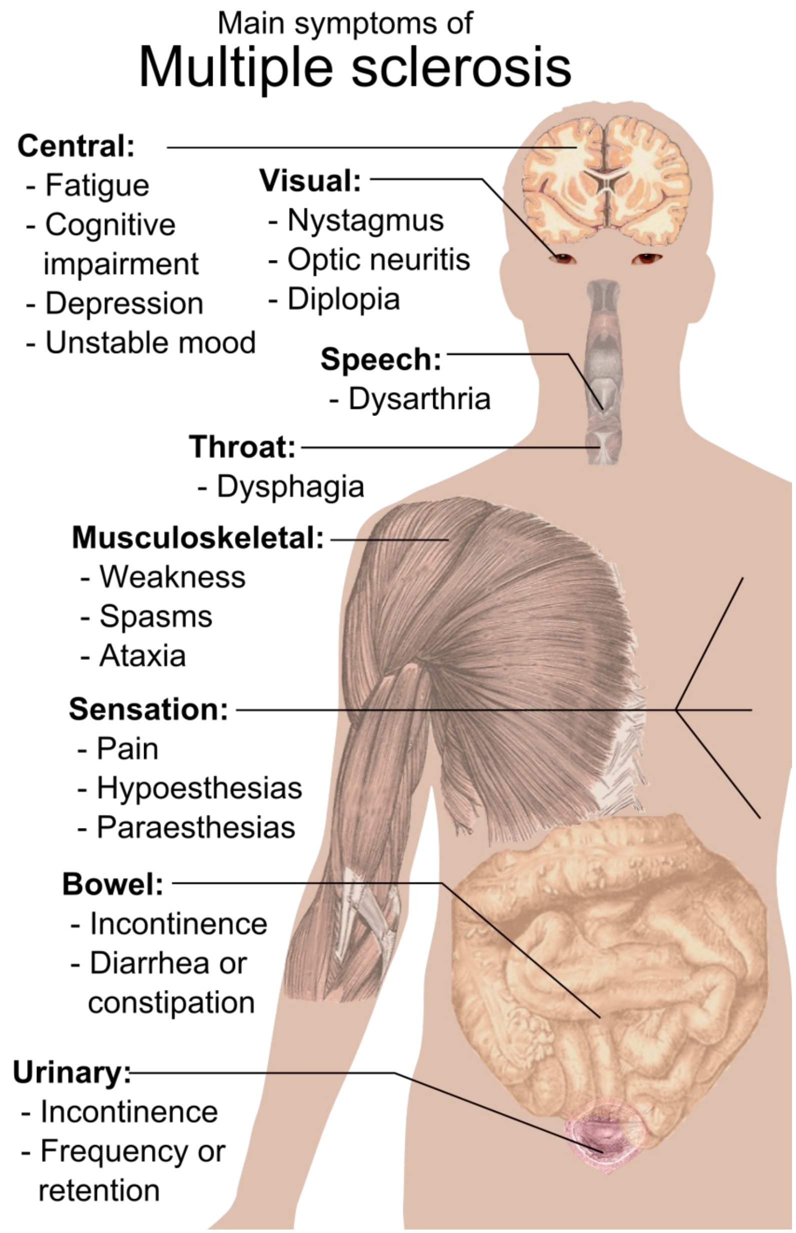
MS: a disabling disease of the central nervous system

Prevalence:
400,000 in the US

Origin:
Still unknown

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



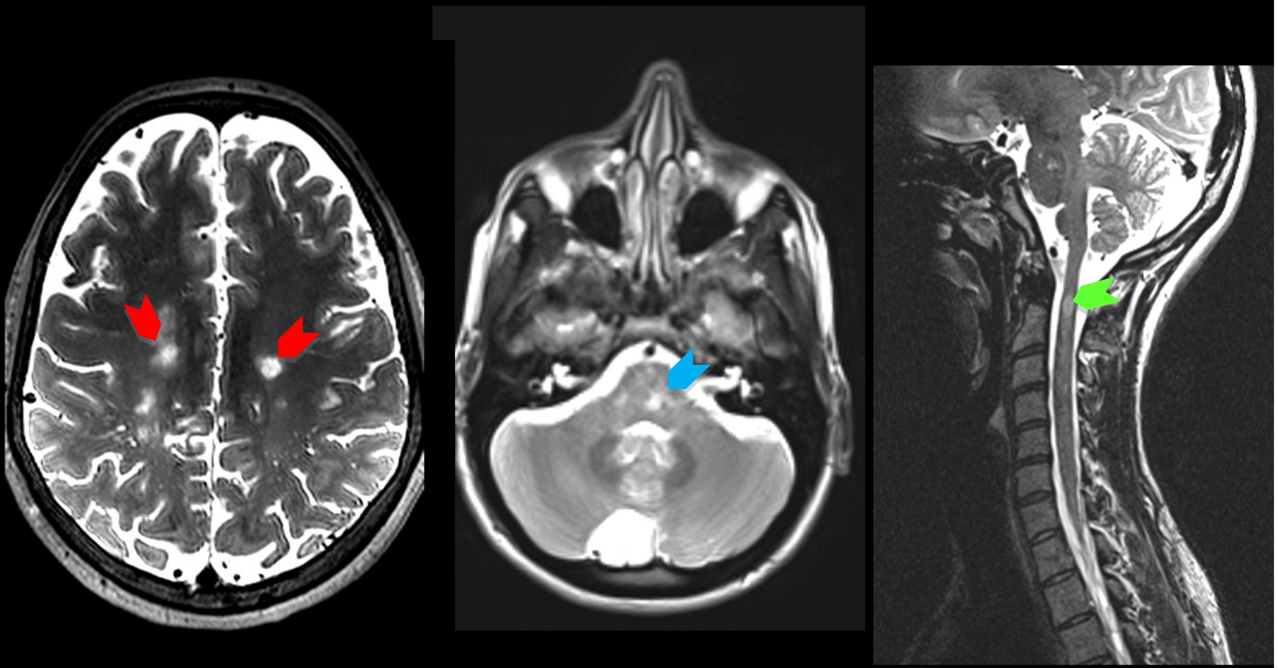


Many disease-modifying treatments exist **but still no cure…**

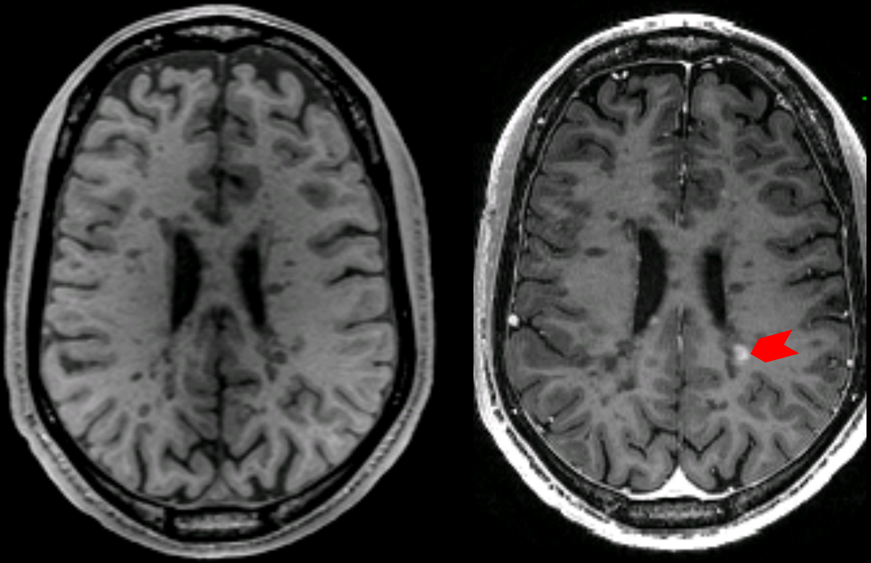
MRI and MS

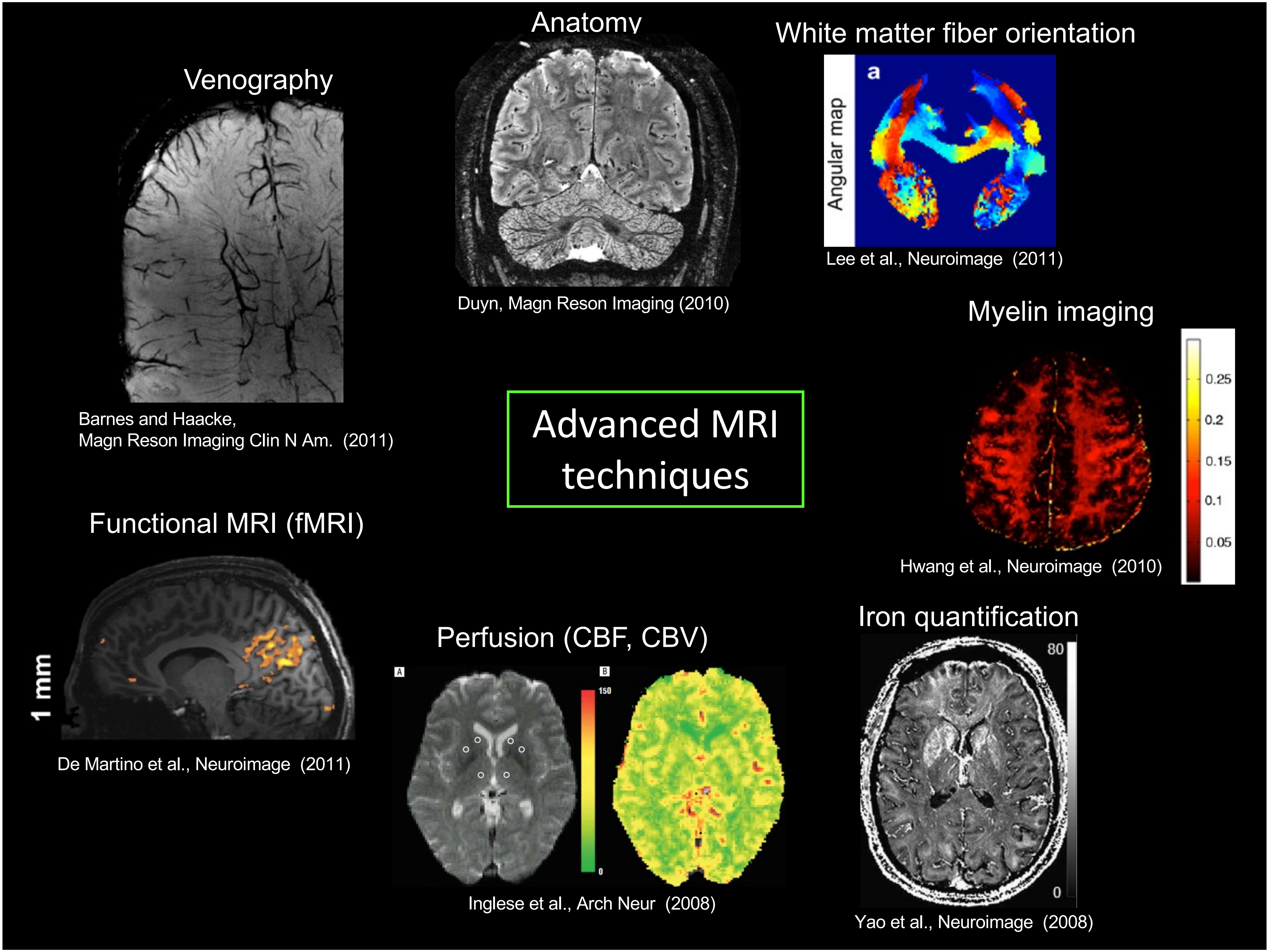
Clinical MRI is routinely used for **diagnosing** and **monitoring** the disease

- ❑ Dissemination in space:
  One or more lesions in two
  or more characteristic locations



- ❑ Dissemination in time:
  New T2 lesion and/or
  gadolinium-enhancing lesion (s)



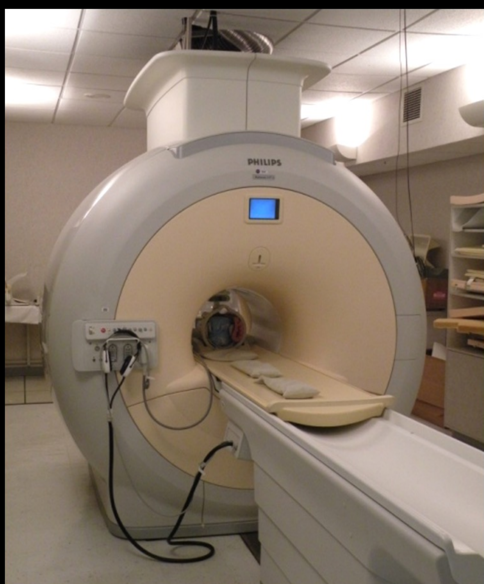

Advanced MRI techniques
Venography
Barnes and Haacke,
Magn Reson Imaging Clin N Am. (2011)
Anatomy
Duyn, Magn Reson Imaging (2010)
White matter fiber orientation
a
Angular map
Lee et al., Neuroimage (2011)
Myelin imaging
0.25
0.2
0.15
0.1
0.05
Hwang et al., Neuroimage (2010)
Functional MRI (fMRI)
1 mm
De Martino et al., Neuroimage (2011)
Perfusion (CBF, CBV)
A
B
150
0
Inglese et al., Arch Neur (2008)
Iron quantification
80
0
Yao et al., Neuroimage (2008)

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

7.0 T MRI

3.0 T MRI

1.5 T MRI

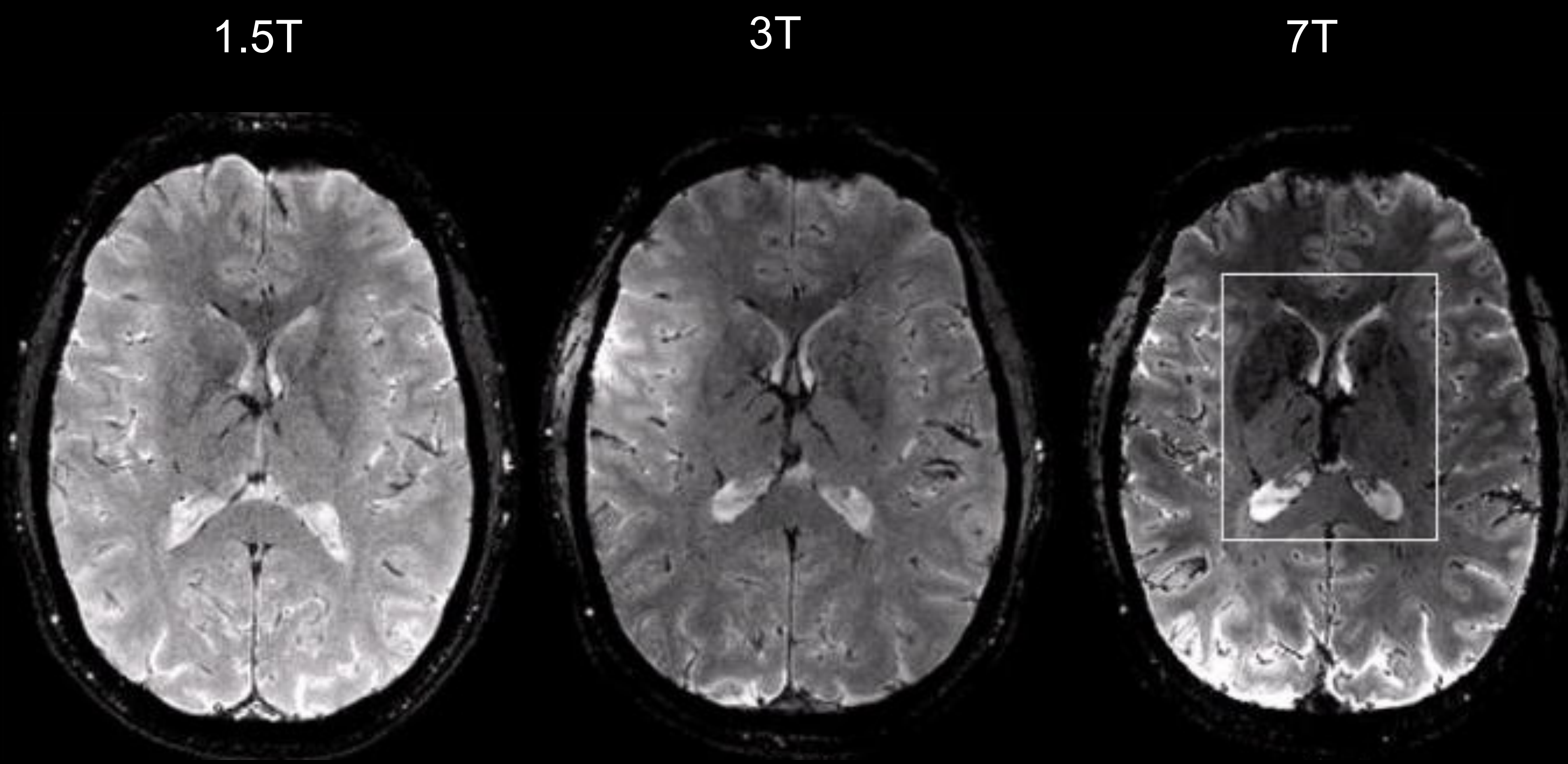


4,500 systems (US)

550 systems (US)

25 UHF systems (US)

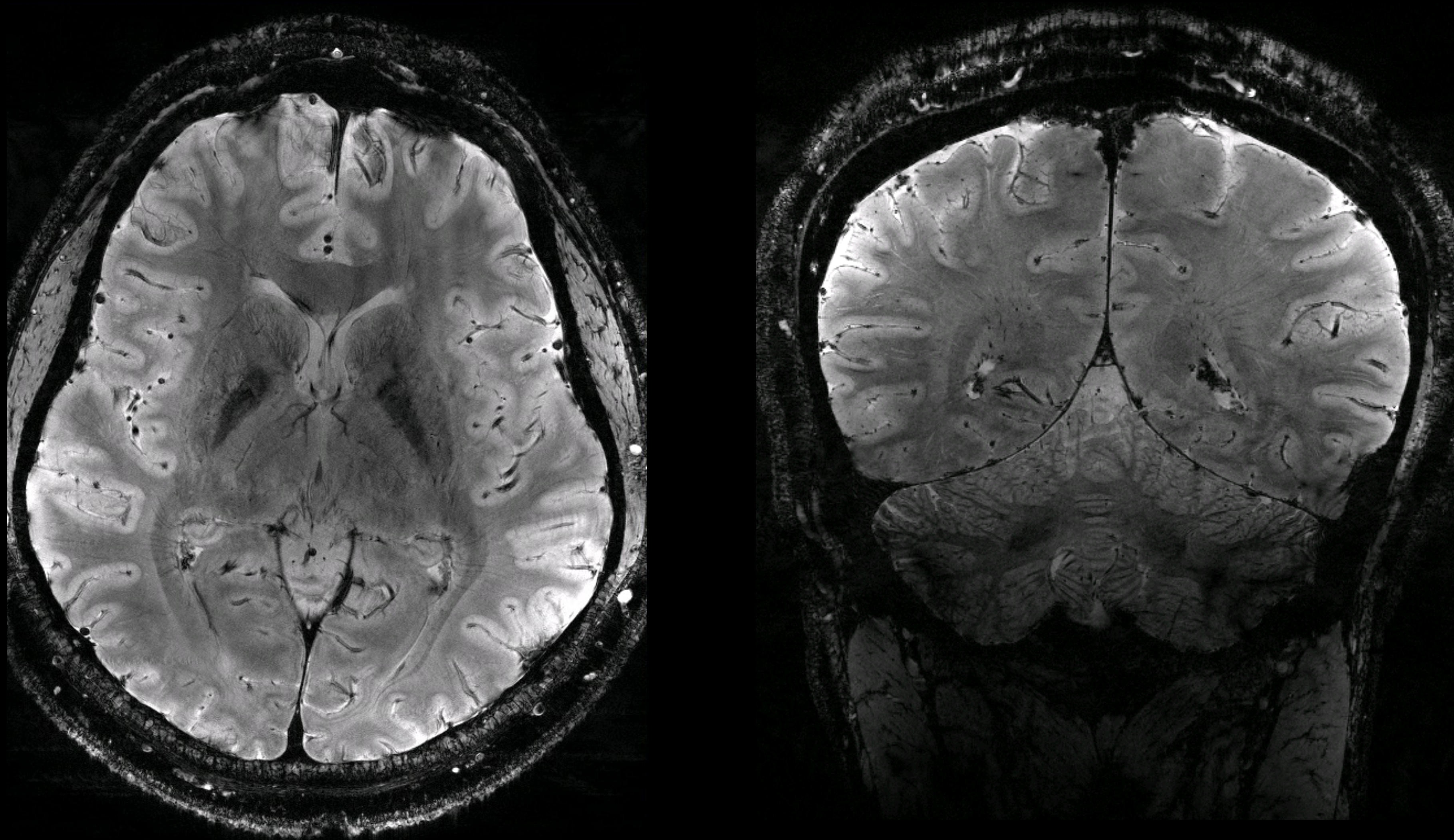
Advantages of UHF MRI



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

Yao et al., Neuroimage, 2009

MRIcroscope at 7T



Ultra-high image resolution
(250 x 250 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), **300+** 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).

7T MS brain protocol

- T_1w 3D MPRAGE
- Dynamic Contrast Enhancement - 3D FLASH
- T_2^*w / Phase - 2D Gradient Echo
- T_2^*w 3D multishot EPI (NIH sequence -Souheil Inati, PhD)
- T_2w 3D FLAIR (WIP 692)
- T_1w 3D MP2RAGE (WIP 900)

Average scanning duration = 90 min

Why using 7T MRI for MS?

I. To better detect the pathology caused by MS

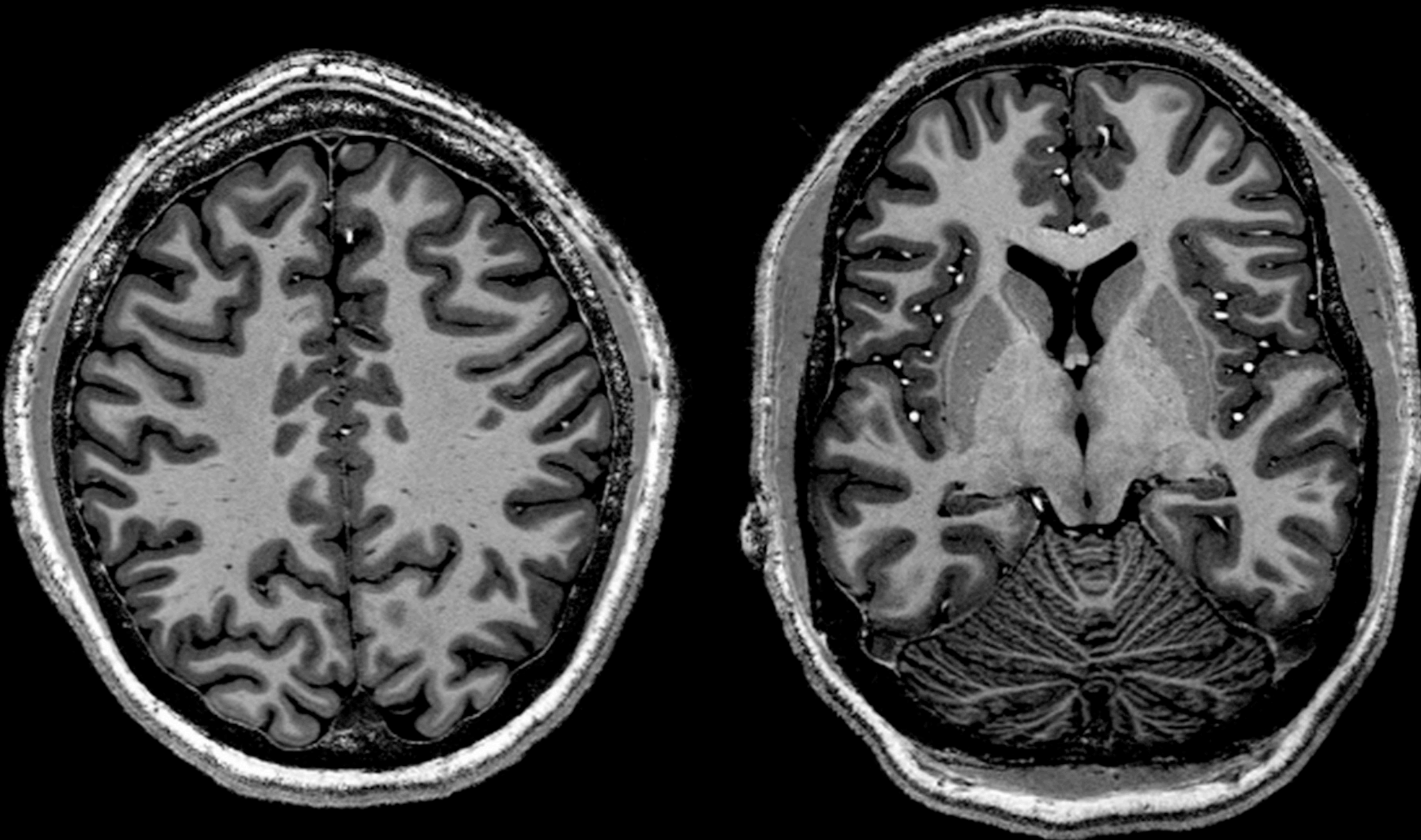
II. To find new imaging markers of disease activity

III. To improve the diagnosis of MS by MRI

IV. To conduct translational imaging research

I. Better detection of disease pathology using the 7T **MRIcroscope**

Healthy brain

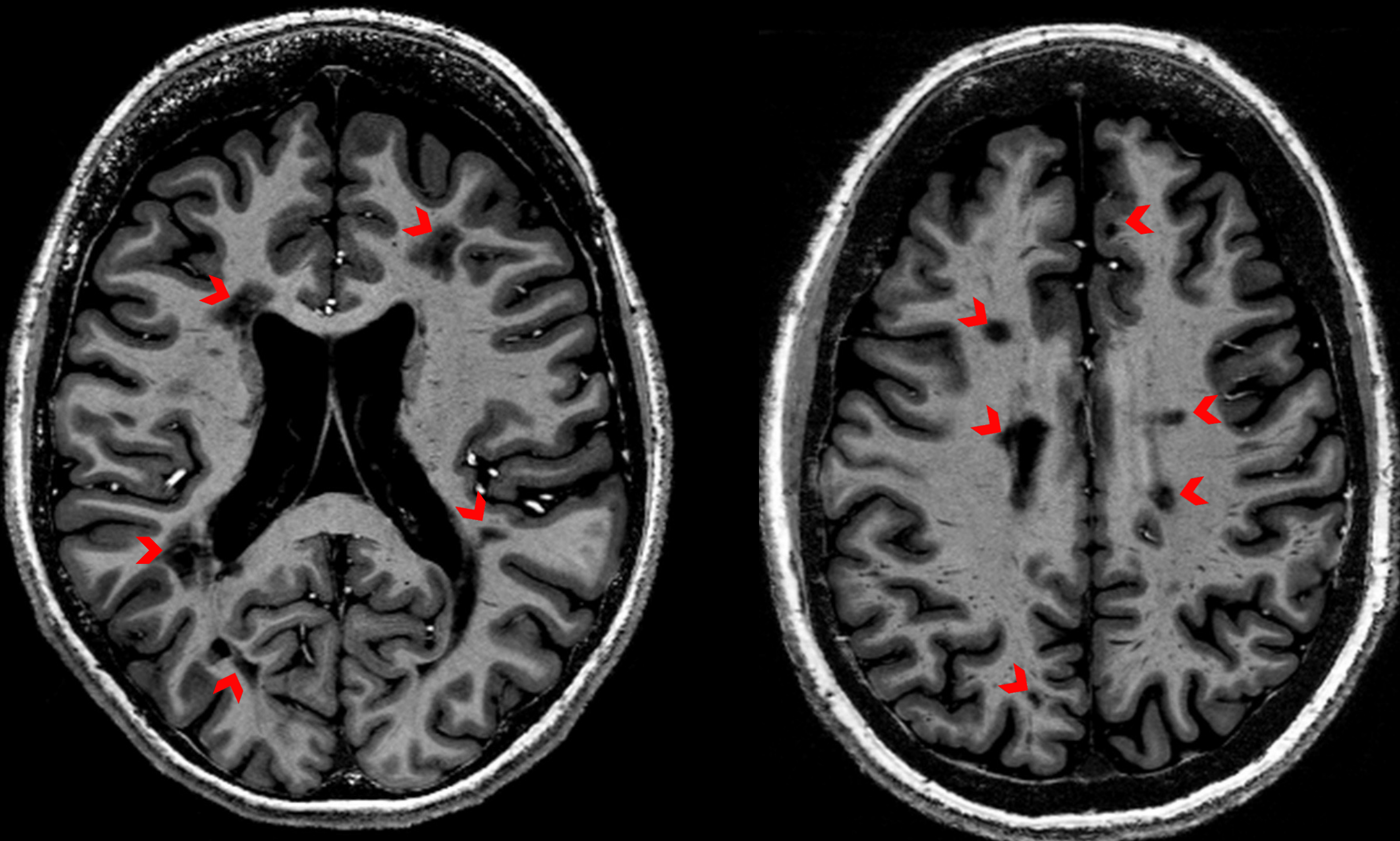


7T T1w MP2RAGE

voxel size = 0.5 mm isotropic

White matter MS lesions

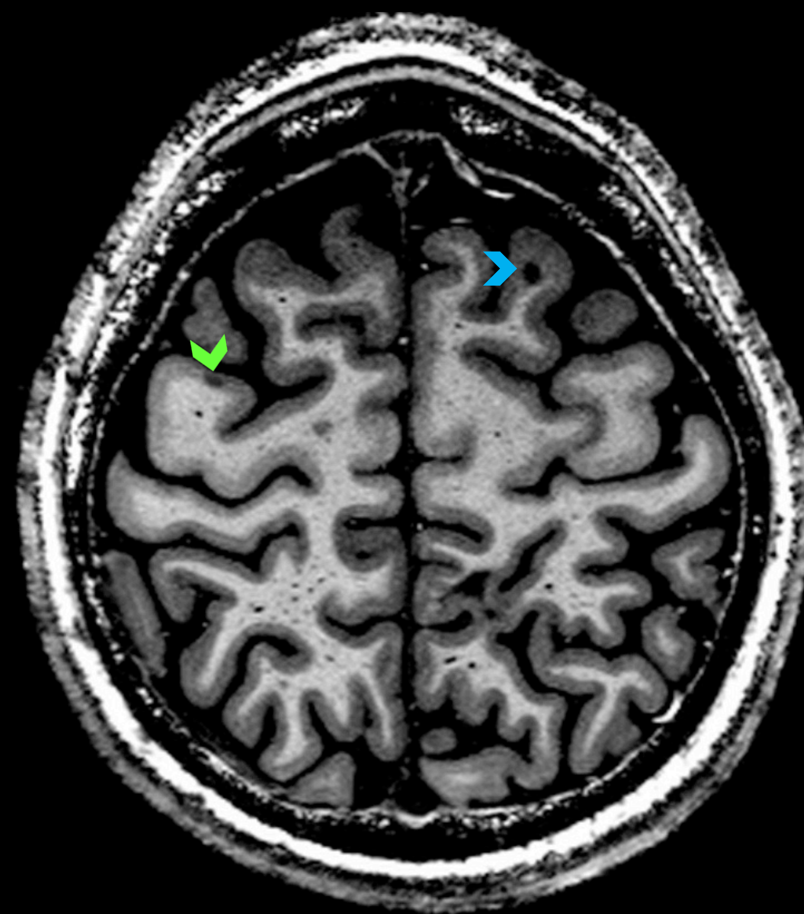
Also well detected with clinical MRI (≤3T)



7T   T1w MP2RAGE
voxel size = 0.5 mm isotropic

Grey matter MS lesions

Poorly detected with clinical MRI (≤3T)

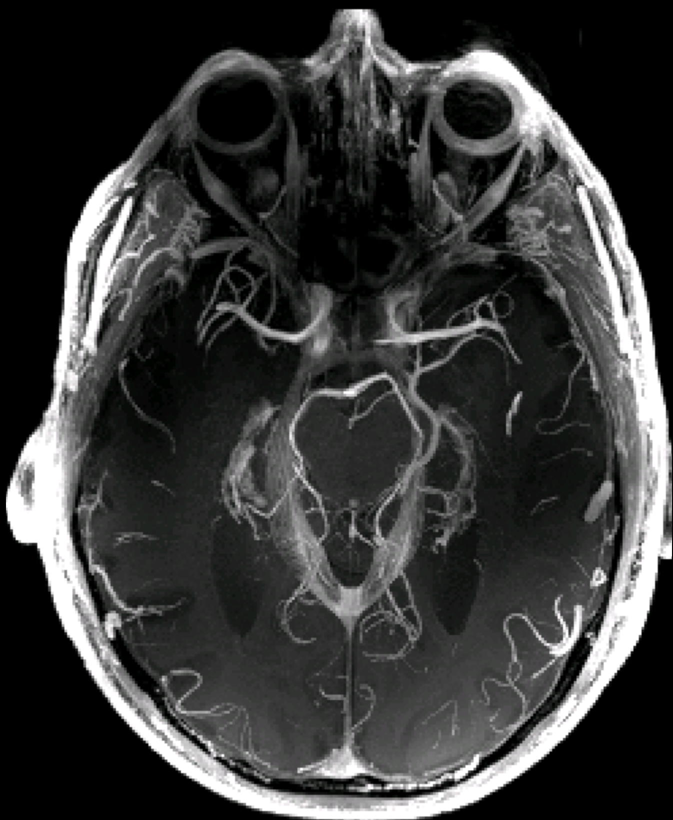


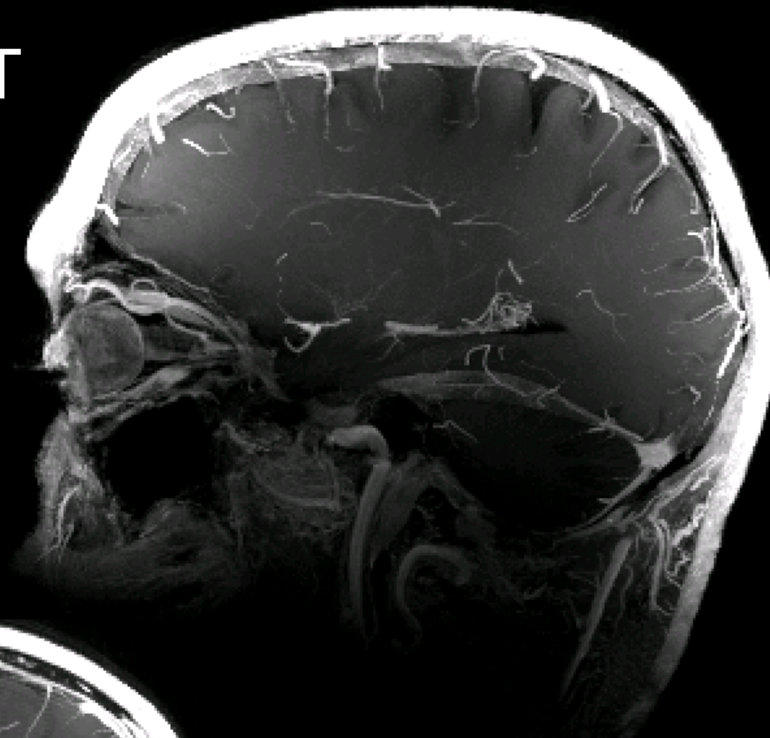
7T T1w MP2RAGE
voxel size = 0.5 mm isotropic

II. New imaging markers of disease activity

inflammation, demyelination/remyelination, axonal damage,…

Gadolinium-based contrast agent @ 7T

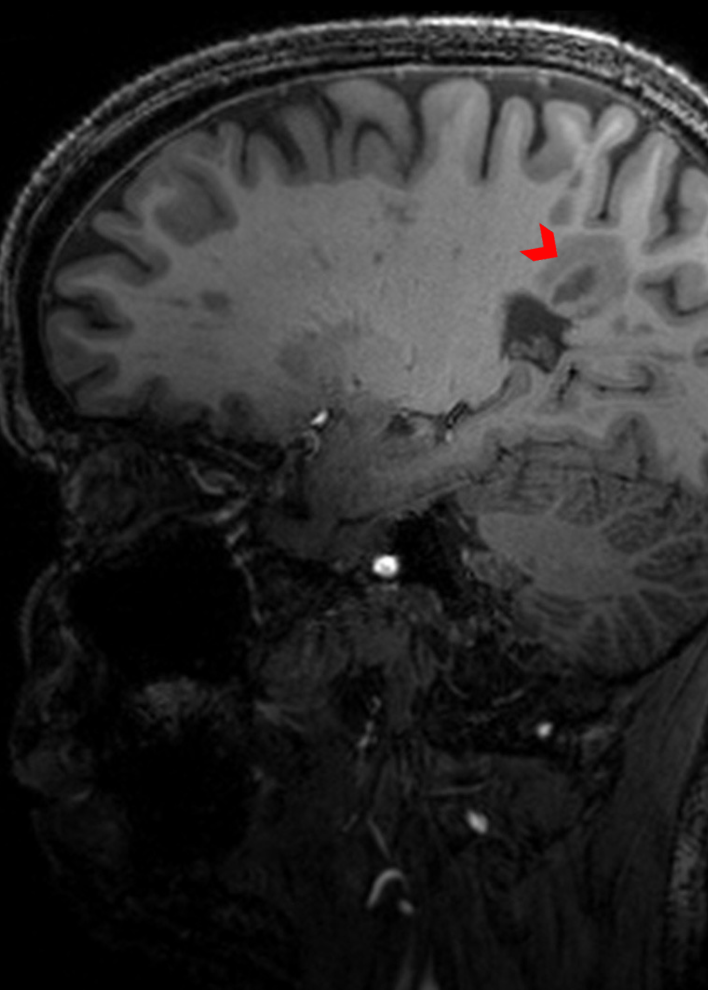




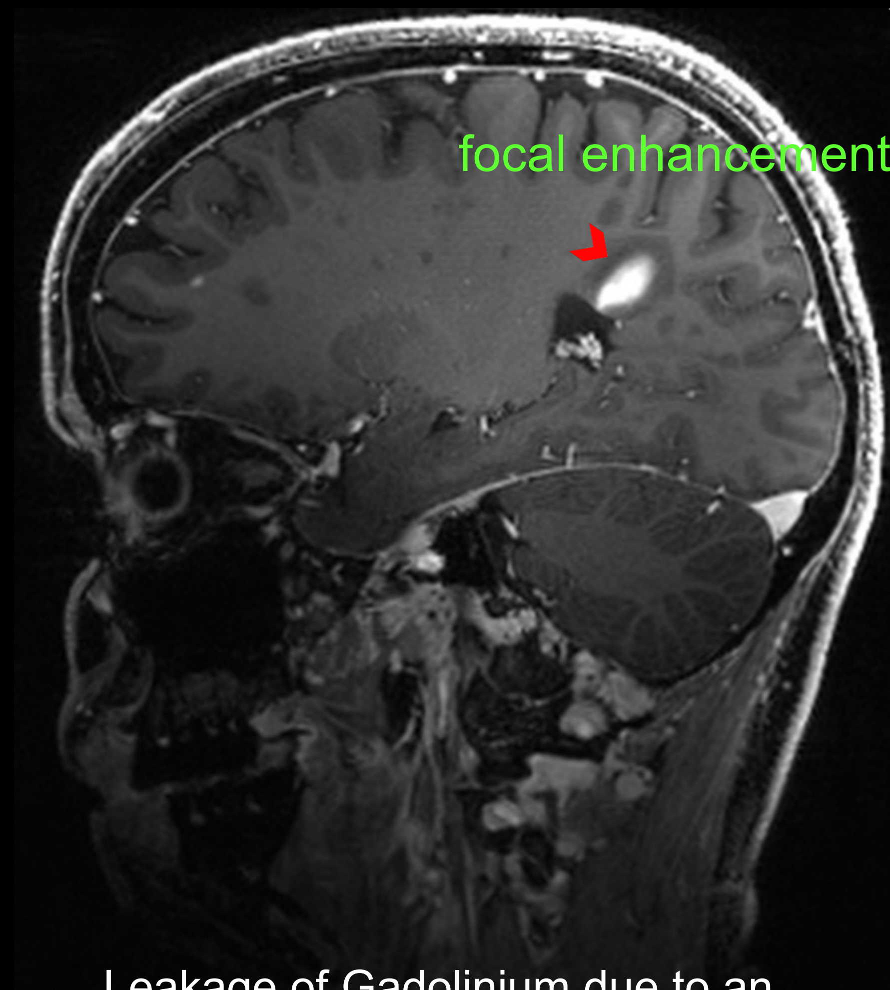
T1w 3D MPRAGE
voxel size = 0.7 mm isotropic
Single dose of Gadavist (0.1 mL/kg)
Maximum Intensity Projection

Newly active MS lesions

pre-injection



5 min post-injection

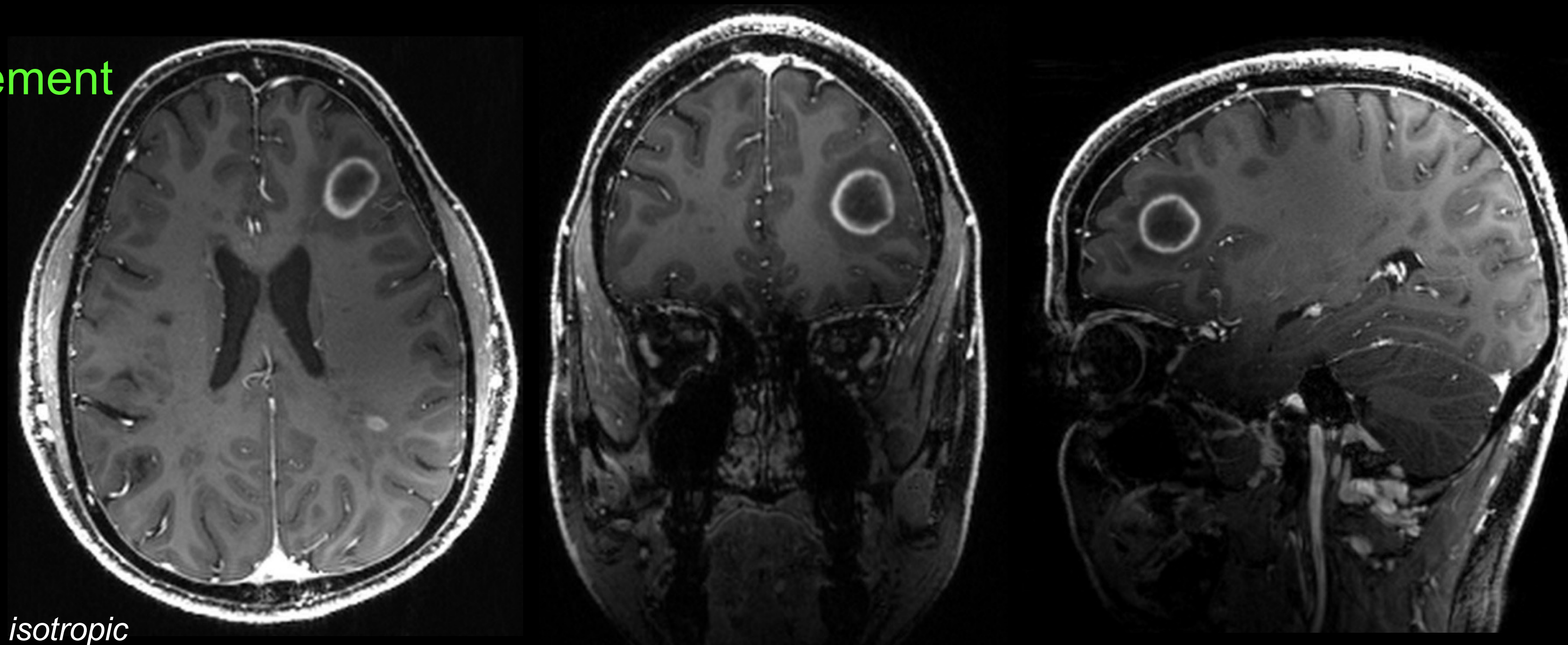


Leakage of Gadolinium due to an
open blood-brain-barrier

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

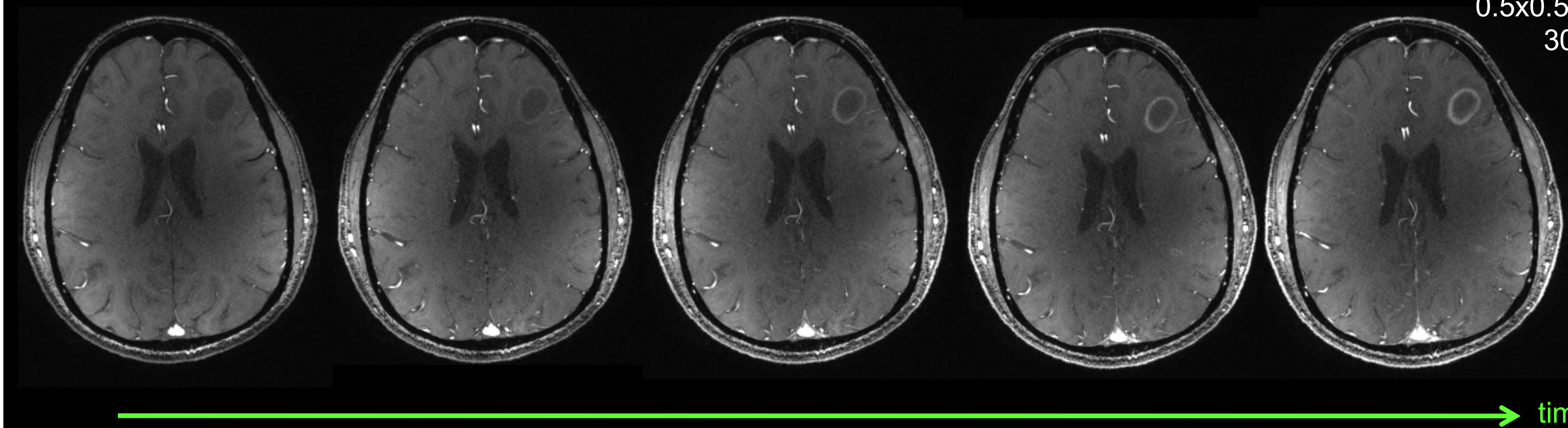
Active MS lesions

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

Gaitan et al., Ann Neurol 2011

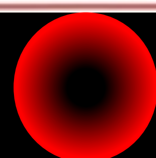
Gaitan et al., Mult Scler 2013

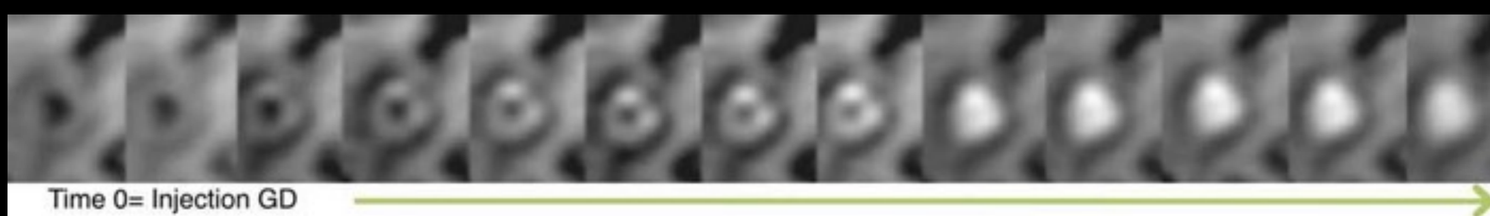
Day 1

Centrifugal DCE pattern

Day 5

Centripetal DCE pattern

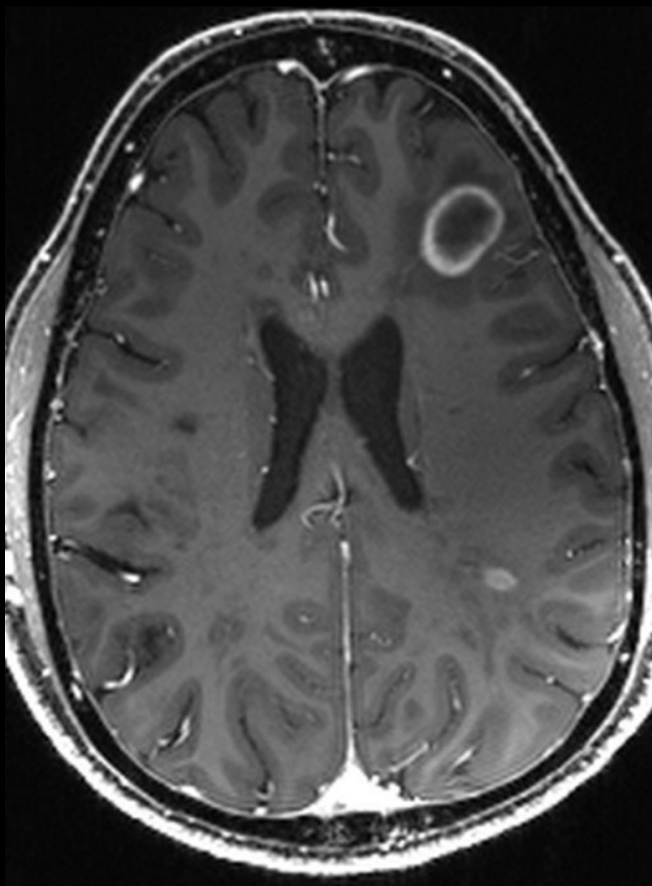




Day 25

Centripetal DCE pattern

Ring-enhancing MS lesions



T1w MPRAGE
0.7 mm isotropic

Magnitude (T2*w) image

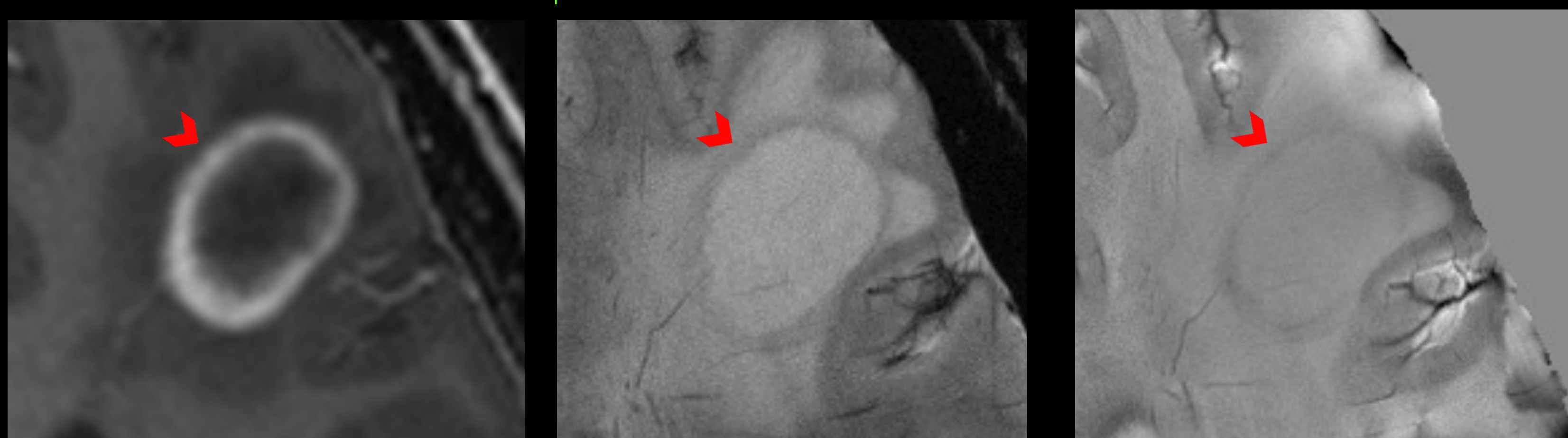
(processed) Phase image

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.

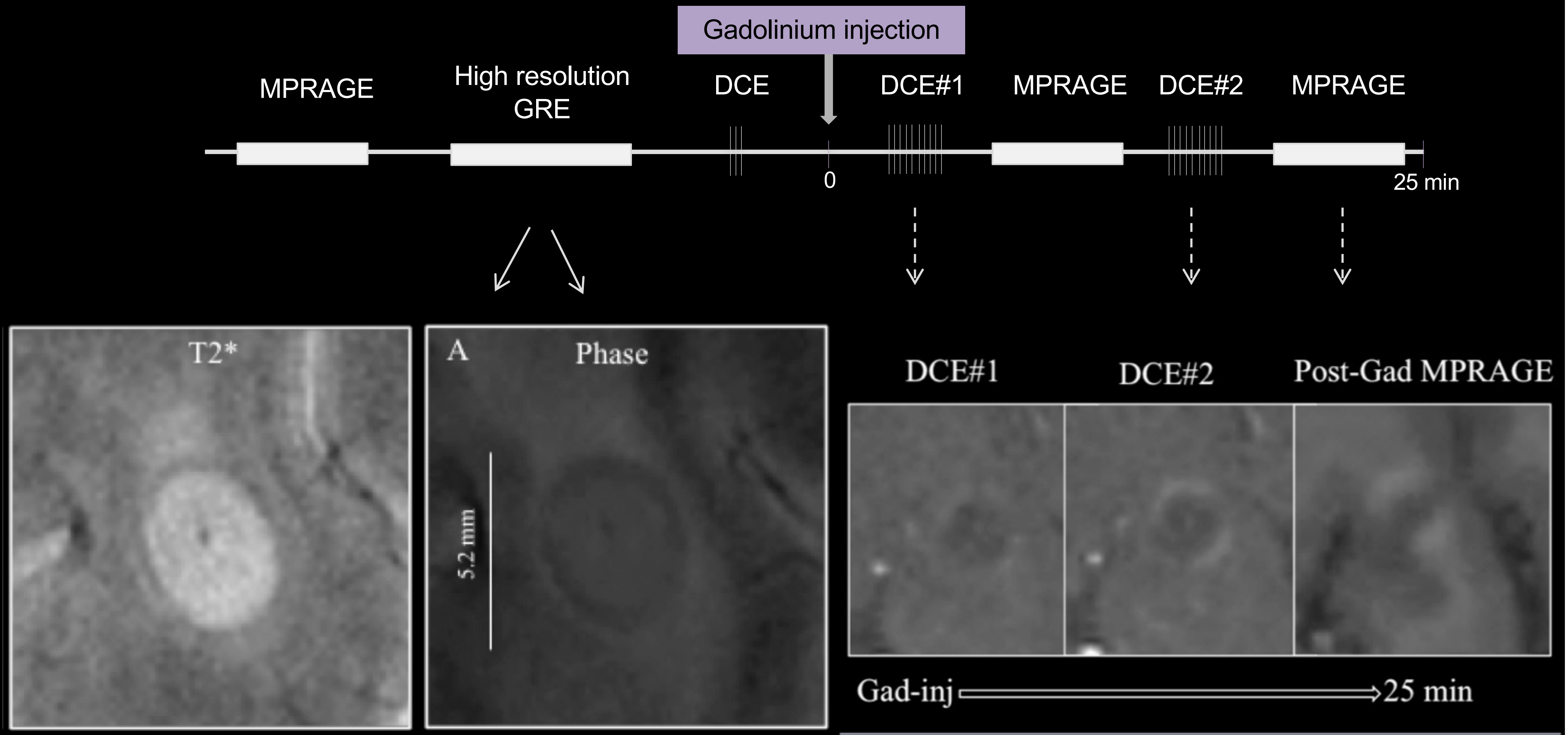
Results: Of 49 contrast-enhancing lesions, 44 could be analyzed. Centrifugal DCE lesions appeared isointense or hypointense on phase images, whereas centripetal DCE lesions showed thin, hypointense phase rims that clearly colocalized with the initial site of contrast enhancement. This pattern generally 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

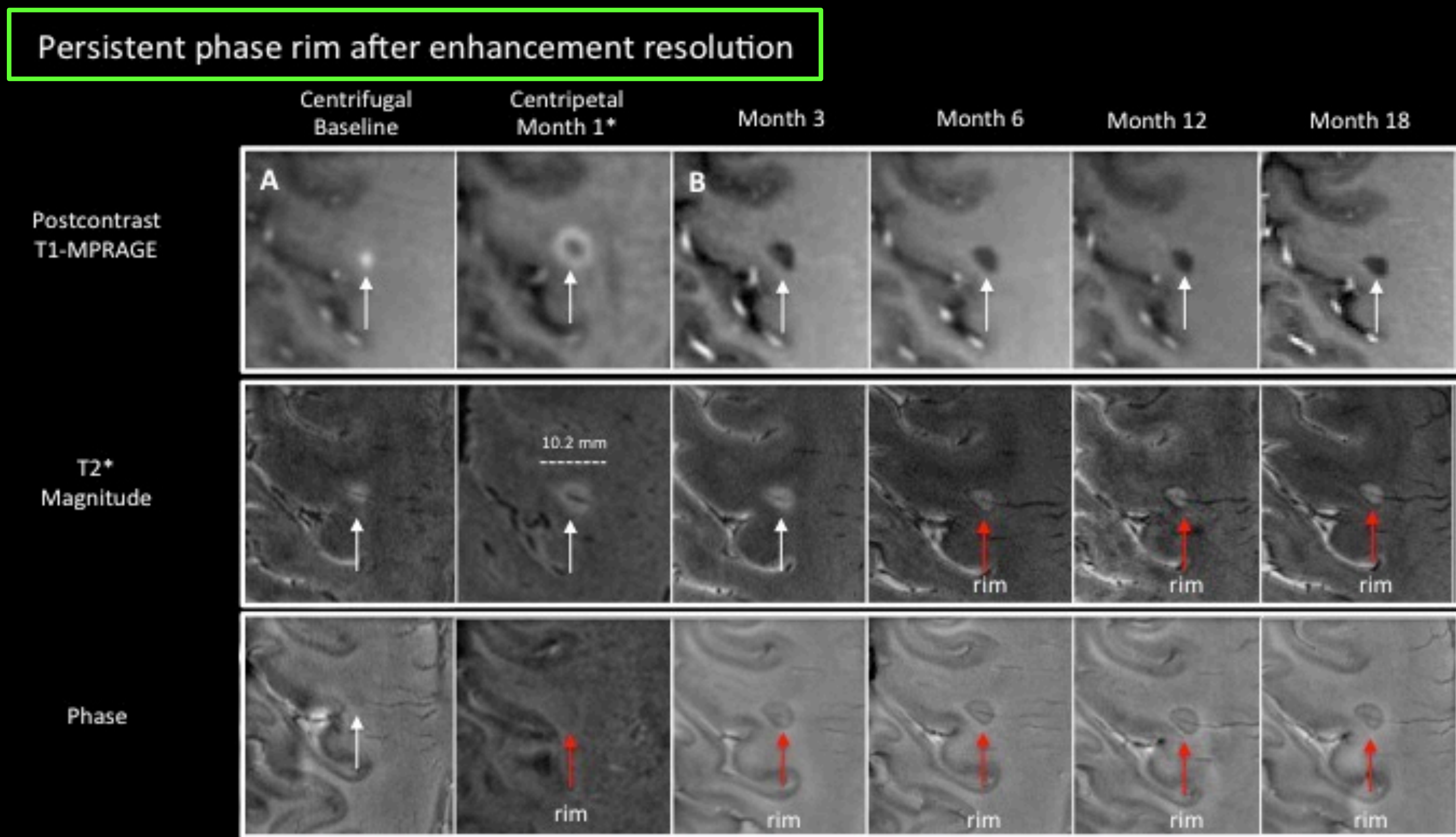
Absinta et al., Ann Neurol 2013

16 patients scanned, 44 enhancing lesions analyzed



New finding: a thin (paramagnetic) rim co-localizes with ring-enhancement in active MS lesions

ongoing 7T follow-up study
(unpublished work)



Chronic inflammation ?

ongoing 7T follow-up study
(unpublished work)

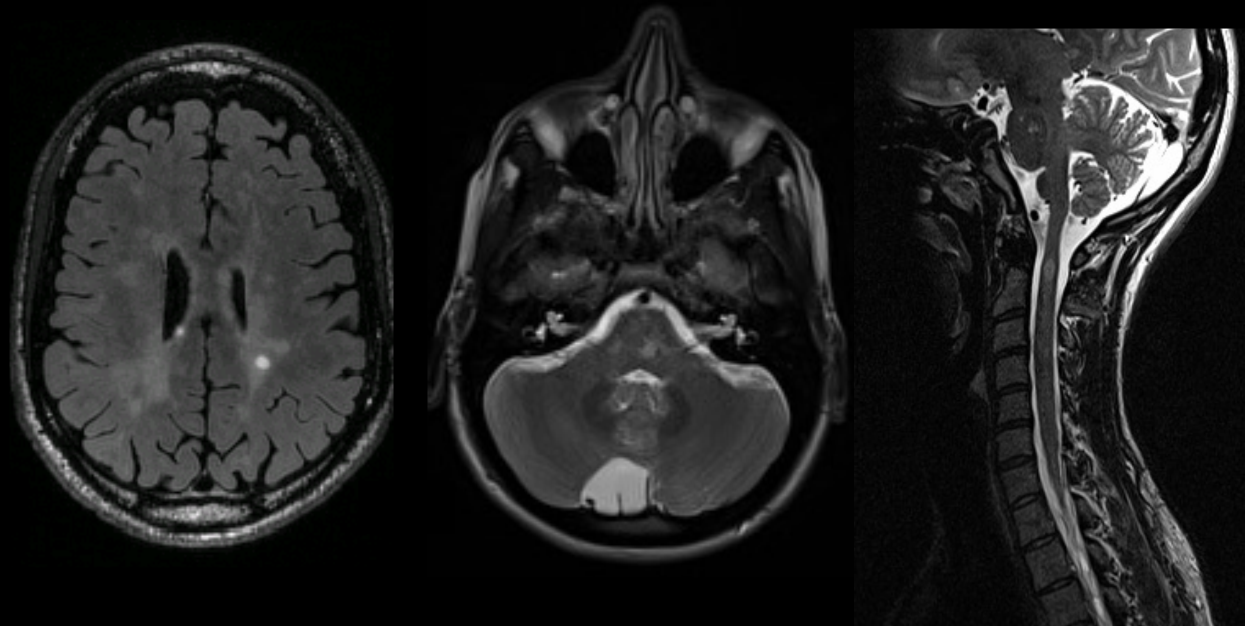
Repair ?

Our hypothesis:
Thin rim is a marker of acute/chronic inflammation
(biomarker for clinical trials?)

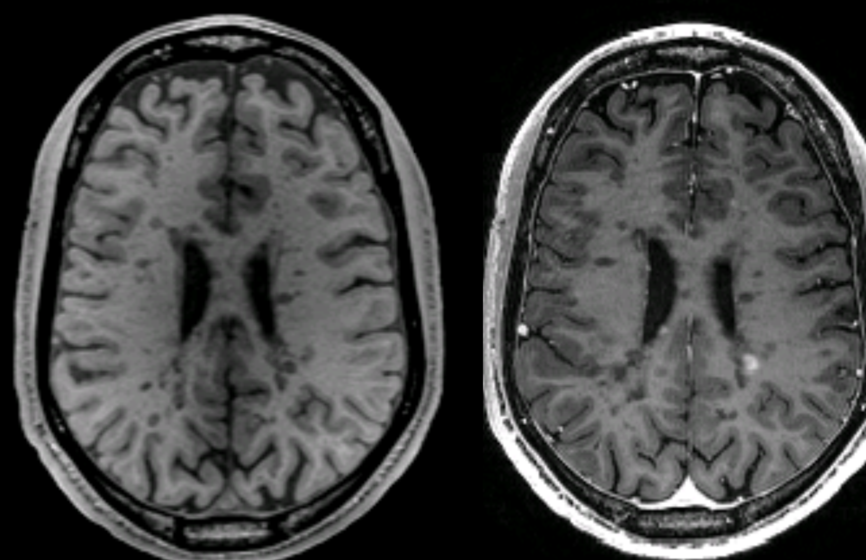
III. Additional imaging criteria for disease diagnosis

DIS and DIT in MS

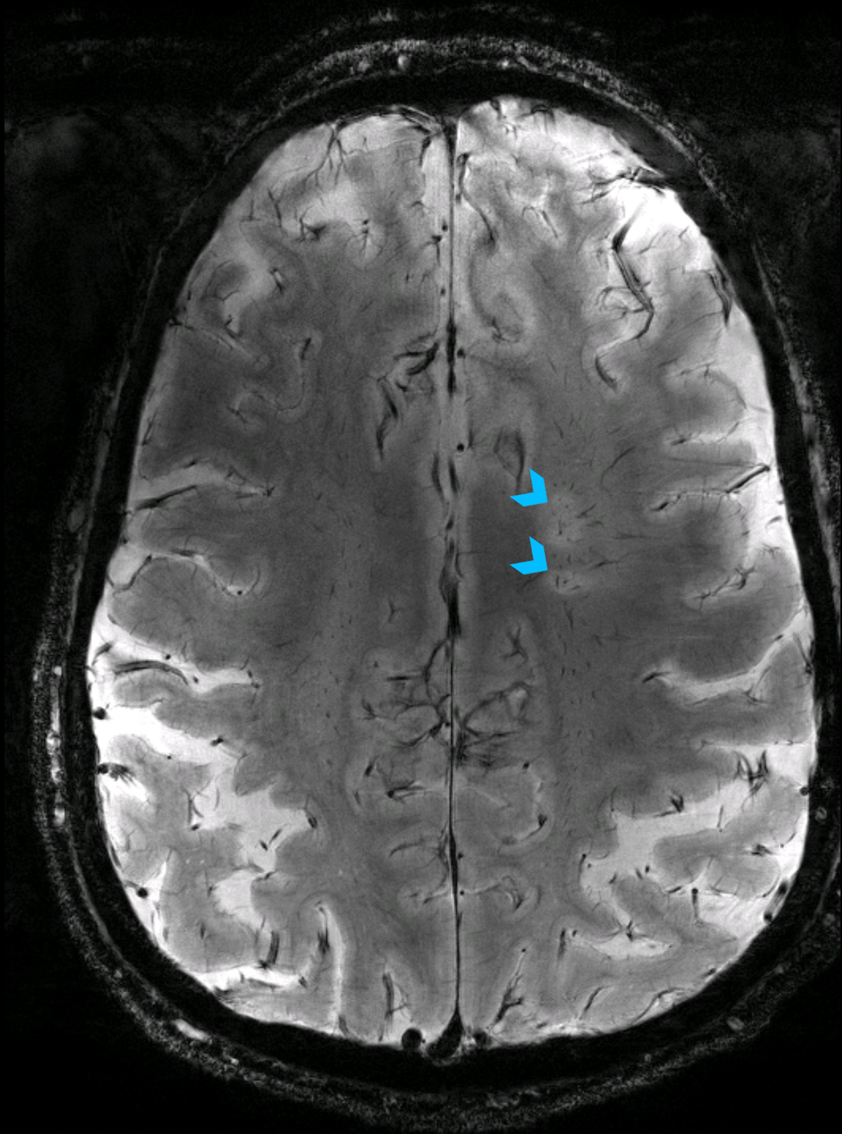
Dissemination in space



Dissemination in time



Parenchymal veins and MS lesions



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

Minimum Intensity Projection

Central vein in MS

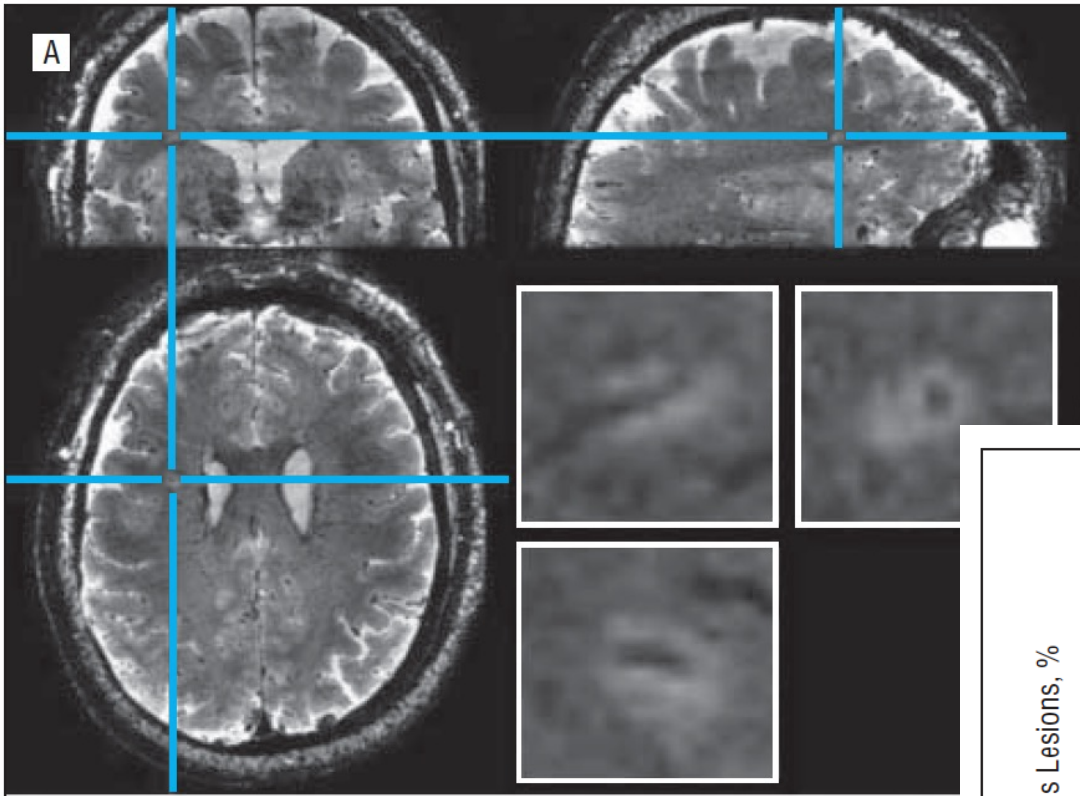
Mistry *et al.*, JAMA Neurol (2013)

ORIGINAL CONTRIBUTION

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

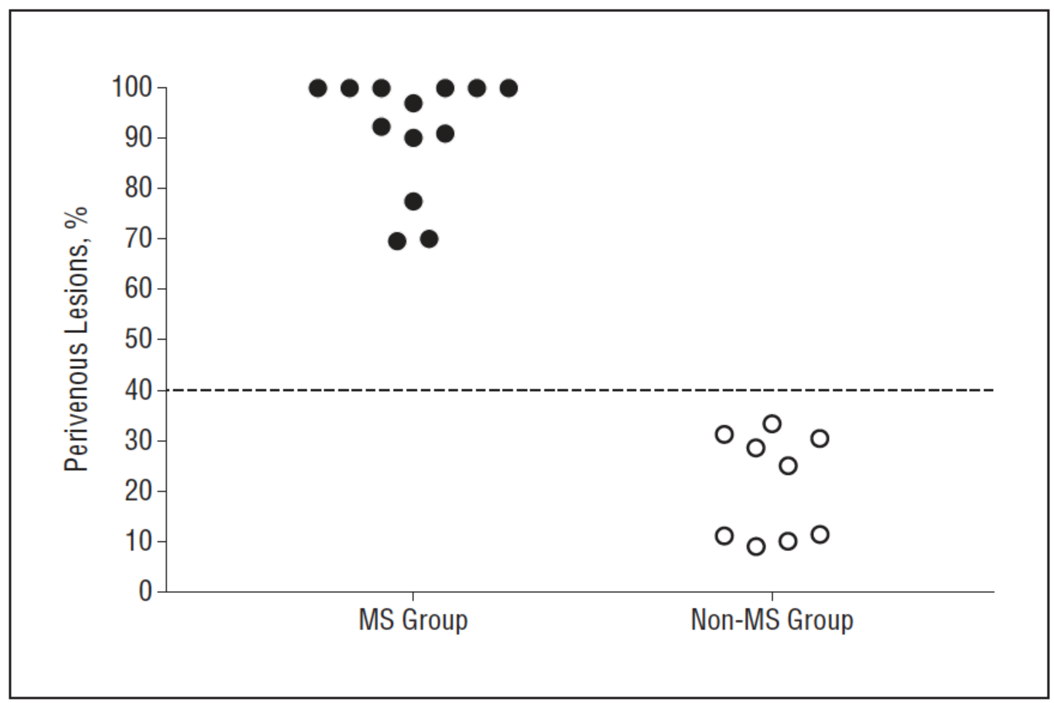
A Pathologically Specific Diagnostic Biomarker for Inflammatory Demyelination in the Brain

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



Philips Achieva 7T system

22 patients (13 MS and 9 other diseases)

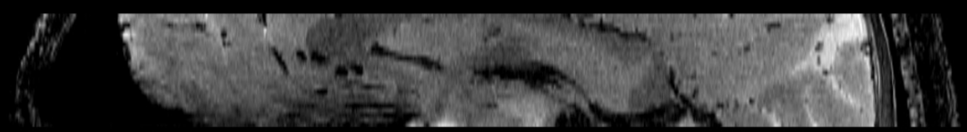


Venocentric lesions: an MRI marker of MS?

- Lane *et al*., Characterization of Multiple Sclerosis Plaques Using Susceptibility-Weighted Imaging at 1.5 T: Can Perivenular Localization Improve Specificity of Imaging Criteria?, J Comput Assist Tomogr (2015)
- Kilsdonk *et al*., Improved differentiation between MS and vascular brain lesions using FLAIR* at 7 Tesla, European Radiology (2014)
- Kulchling et al., Identical lesion morphology in primary progressive and relapsing–remitting MS –an ultrahigh field MRI study. Mult Scler (2014)
- Maggi et al., SWI enhances vein detection using gadolinium in multiple sclerosis, Acta Rad (2014)
- Kilsdonk *et al*., Morphological features of MS lesions on FLAIR* at 7 T and their relation to patient characteristics, Journal of Neurology (2014)
- Quinn *et al*., Venocentric Lesions: An MRI Marker of MS?, Front. Neurol (2013)
- Luo et al., Gradient echo magnetic resonance imaging correlates with clinical measures and allows visualization of veins within multiple sclerosis lesions, Mutl Scler (2013)
- Dixon *et al*., Optimisation of T_2*-weighted MRI for the detection of small veins in multiple sclerosis at 3 T and 7 T. Eur J Radiol (2013)
- Kau *et al*., The "central vein sign": is there a place for susceptibility weighted imaging in possible multiple sclerosis?. Eur Radiol (2013)
- Mistry *et al*.,Central veins in brain lesions visualized with high-field magnetic resonance imaging: a pathologically specific diagnostic biomarker for inflammatory demyelination in the brain, JAMA Neurol (2013)
- Tallantyre *et al*., Ultra-high-field imaging distinguishes MS lesions from asymptomatic white matter lesions. Neurology (2010)

Limitations of conventional T2* imaging at 7T

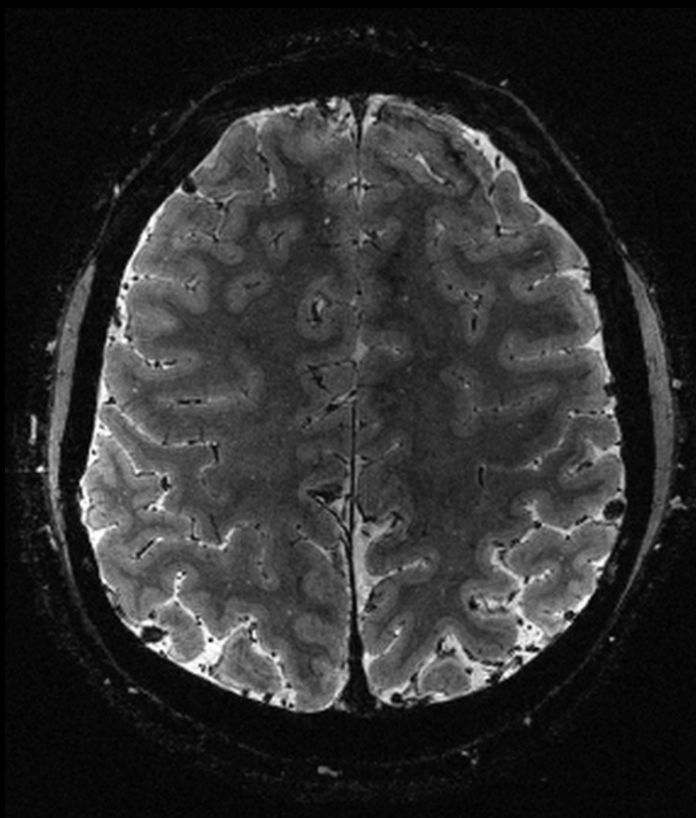
T2*w 2D Gradient Echo (GRE)
0.25 x 0.25 x 1 mm
2.5 cm per slab (25 slices)
9 min per slab

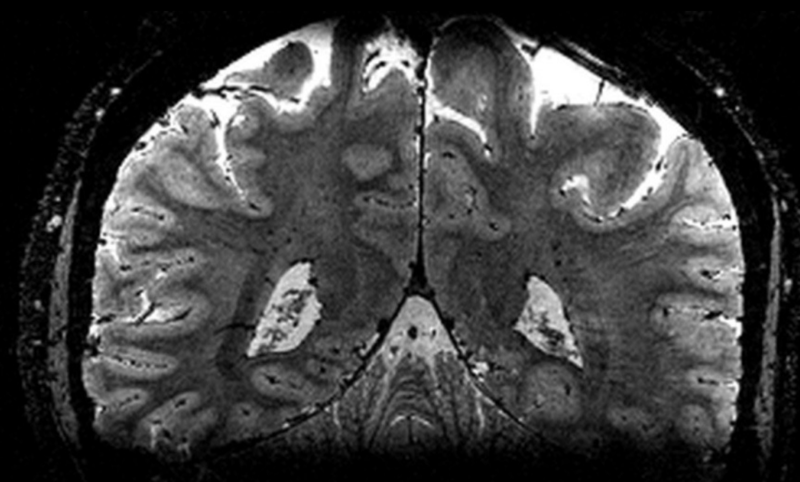


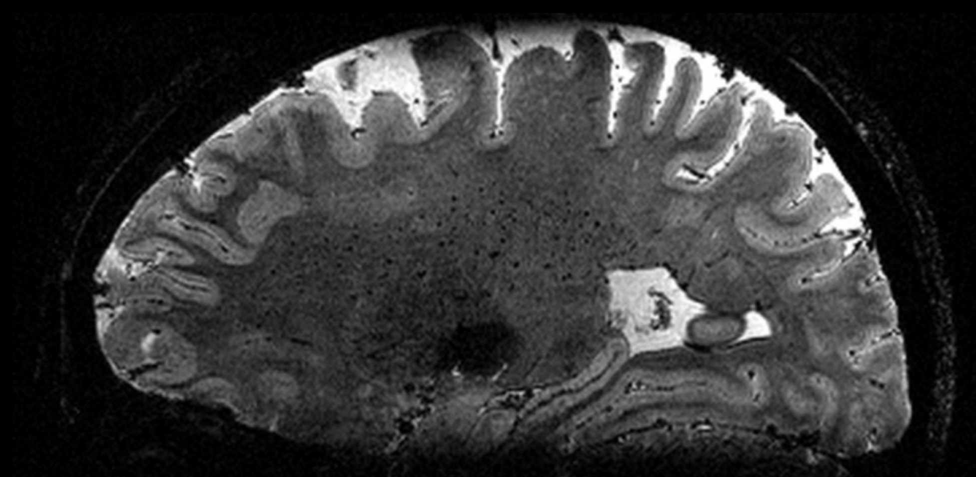
Whole brain would take > 45 min !

Rapid T2* imaging @ 7T

T2*w 3D multishot EPI
(NIH sequence)
0.5 mm isotropic
3 min 40 s per slab
8.8 cm per slab (176 slices)

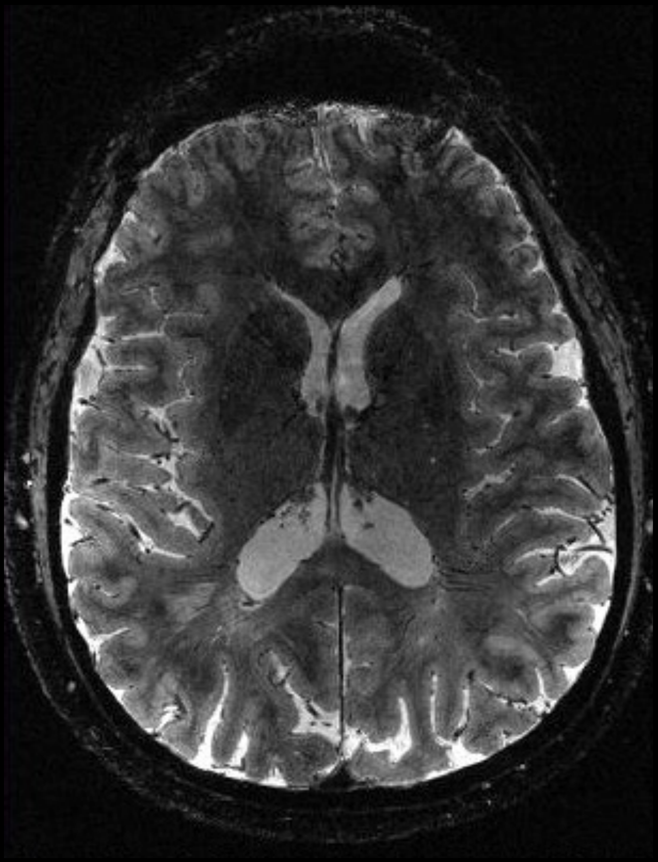


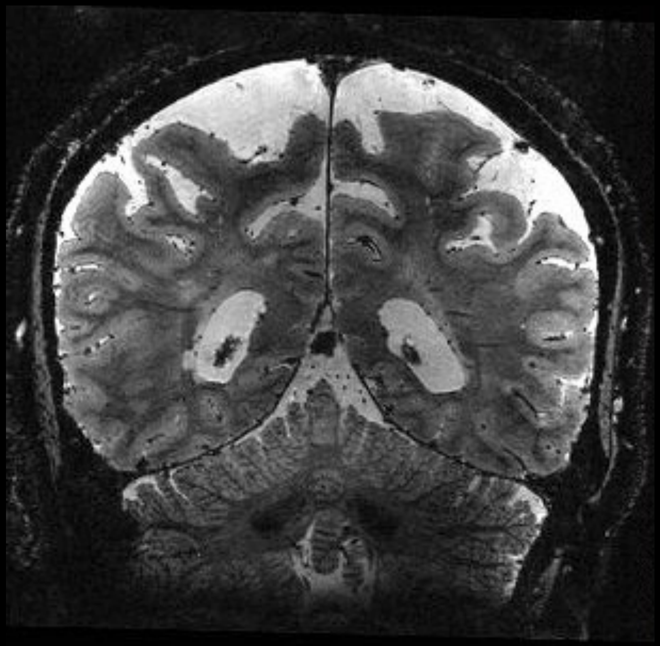


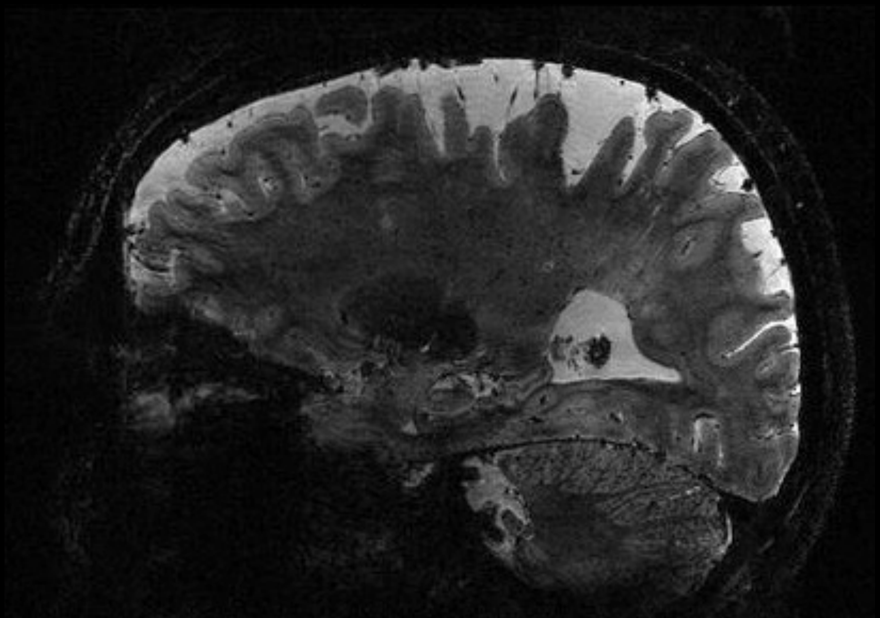


Rapid whole-brain T2* imaging @ 7T

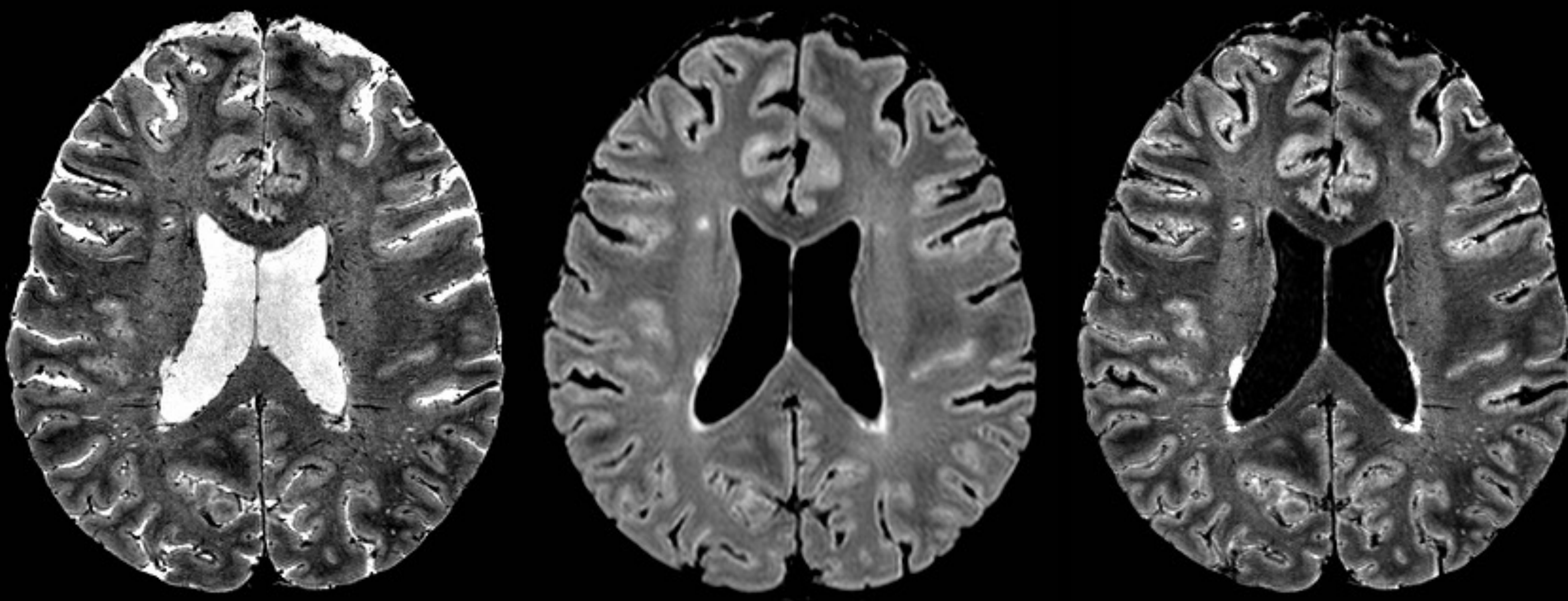
Whole brain in less than 8 min!







A new combined MR contrast: FLAIR*

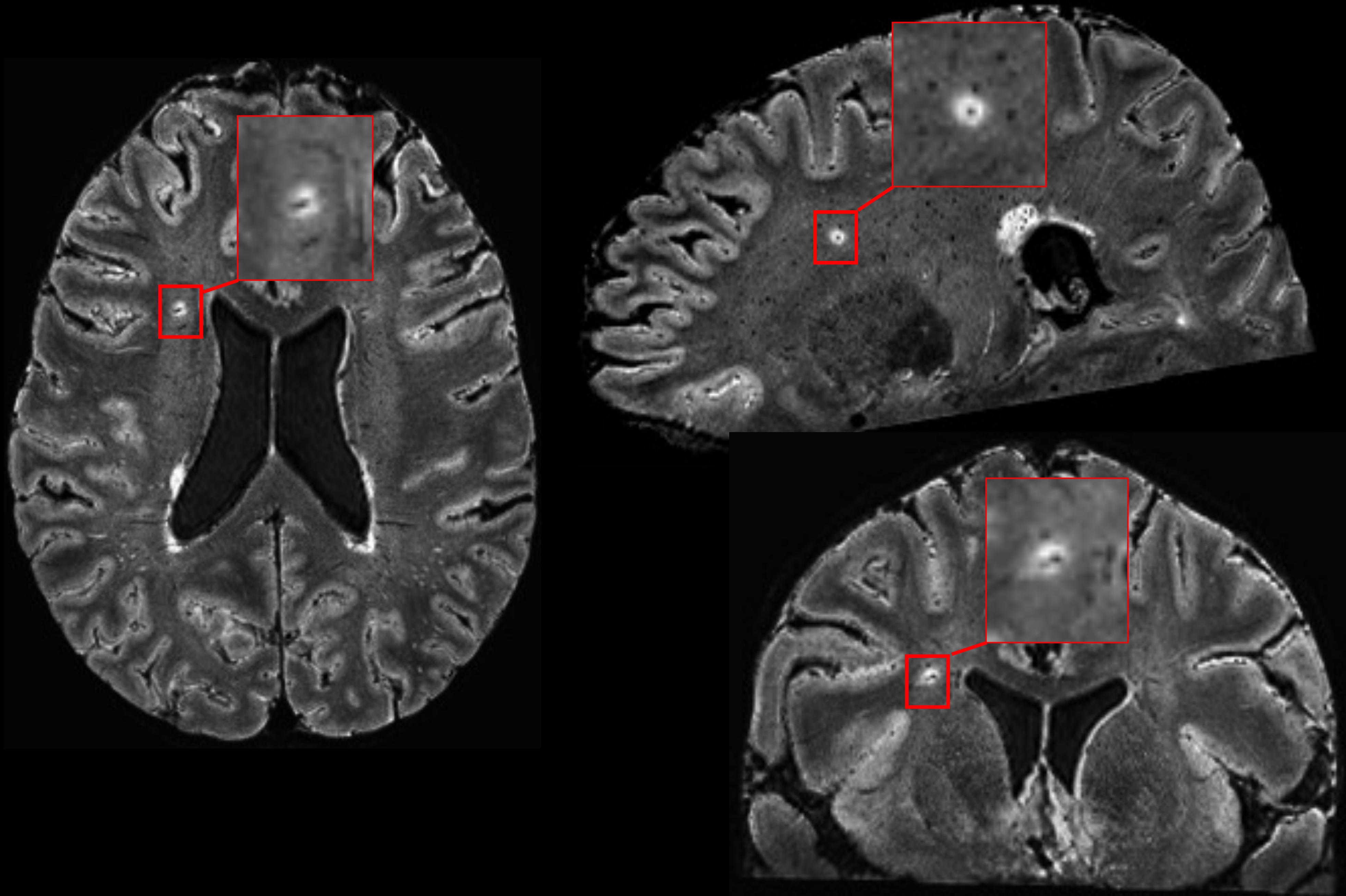


T2* 3D EPI (NIH)
0.5 mm iso

FLAIR (WIP 692)
0.8 mm iso

FLAIR* (NIH)
0.5 mm iso

FLAIR* @ 7T



ORIGINAL RESEARCH ■ TECHNICAL DEVELOPMENTS

Radiology

FLAIR*: A Combined MR Contrast Technique for Visualizing White Matter

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

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. Kilsdonk · Mike P. Wattjes · Alexandra Lopez-Soriano · Joost P. A. Kuijer · Marcus C. de Jong · Wolter L. de Graaf · Mandy M. A. Conijn · Chris H. Polman · Peter R. Luijten · Jeroen J. G. Geurts · Mirjam I. Geerlings · Frederik Barkhof

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. Kilsdonk · Alexandra Lopez-Soriano · Joost P. A. Kuijer · Wolter L. de Graaf · Jonas A. Castelijns · Chris H. Polman · Peter R. Luijten · Jeroen J. J. G. Geurts · Frederik Barkhof · Mike P. Wattjes

FLAIR* today

- Recently cited by an international panel as a valuable technique for improving the specificity of MRI diagnosis of MS

  Rovira et al., MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis – clinical implementation of the diagnostic process, Nat. Rev. Neurol., online July 2015

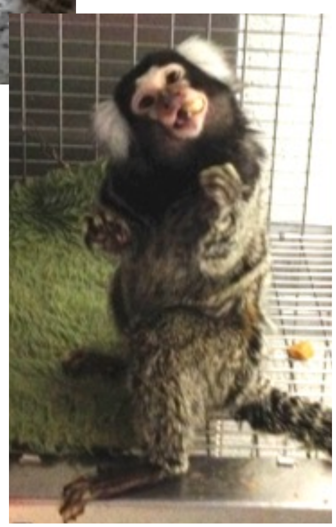
- Available on 1.5T, 3T and 7T platforms (Siemens & Philips scanners)

- Already distributed across multiple MS imaging centers (US & Europe)

- Currently being used to investigate the role of central veins in different neurological diseases (MS, vasculitis, migraine, HIV,…)

VI. Relating to translational imaging 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**

First EAE induction in marmosets

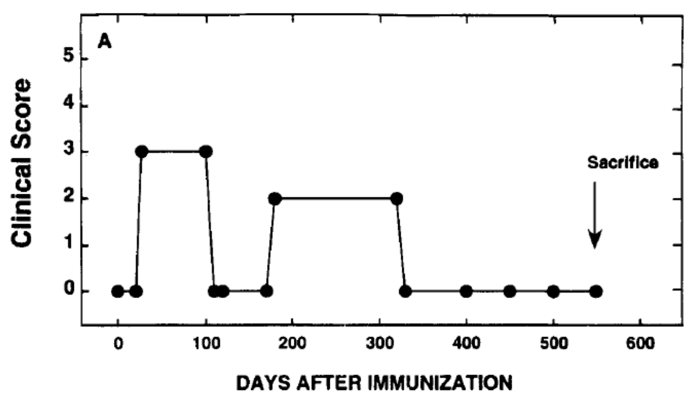
Massacesi L, Genain CP, Lee-Parritz D, Letvin NL, Canfield D, Hauser SL. Active and passively induced experimental autoimmune encephalomyelitis in common marmosets: a new model for multiple sclerosis. Ann Neurol. **1995**.

Induction

200 mg of human brain WM homogenate
+
CFA
(3 mg/mL of *Mycobacterium Turberculosis*)
+
10^{10} inactivated *Bordetella pertussis*

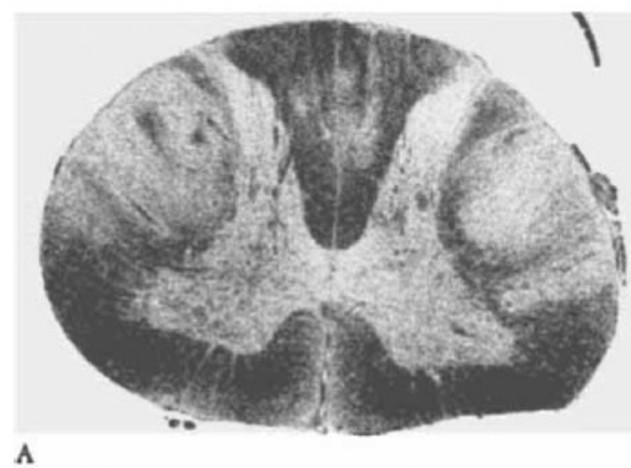
Clinical presentation

"chronic relapsing-remitting course, mild neurological signs, and complete recovery from initial attack"



Pathology

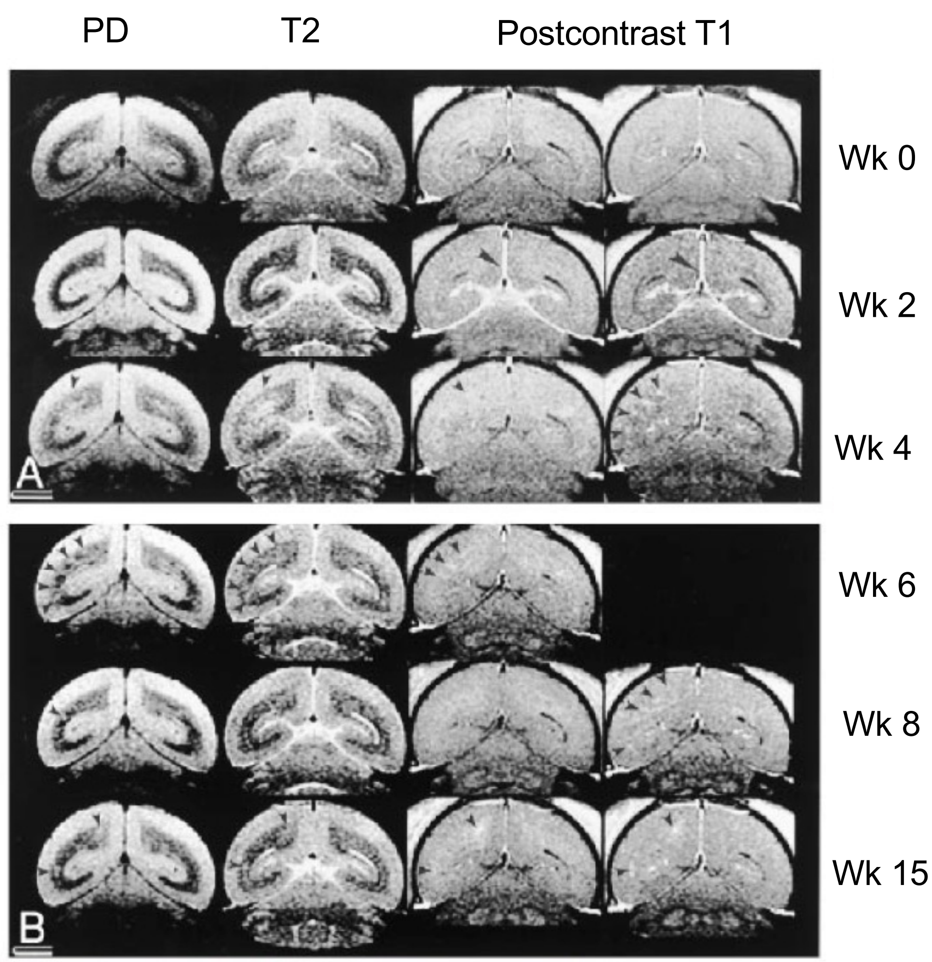
"scattered perivascular inflammatory infiltrates surrounded by large concentric areas of demyelination and associated with intense macrophage infiltration and mild astrogliosis"



First MRI study of marmoset EAE

Jordan EK, McFarland HI, Lewis BK, Tresser N, Gates MA, Johnson M, Lenardo M, Matis LA, McFarland HF, Frank JA. Serial MR imaging of experimental autoimmune encephalomyelitis induced by human white matter or by chimeric myelin-basic and proteolipid protein in the common marmoset. AJNR Am J Neuroradiol. **1999**.

1.5 T human scanner

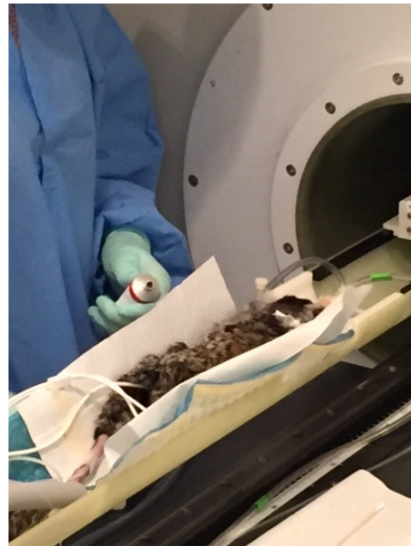


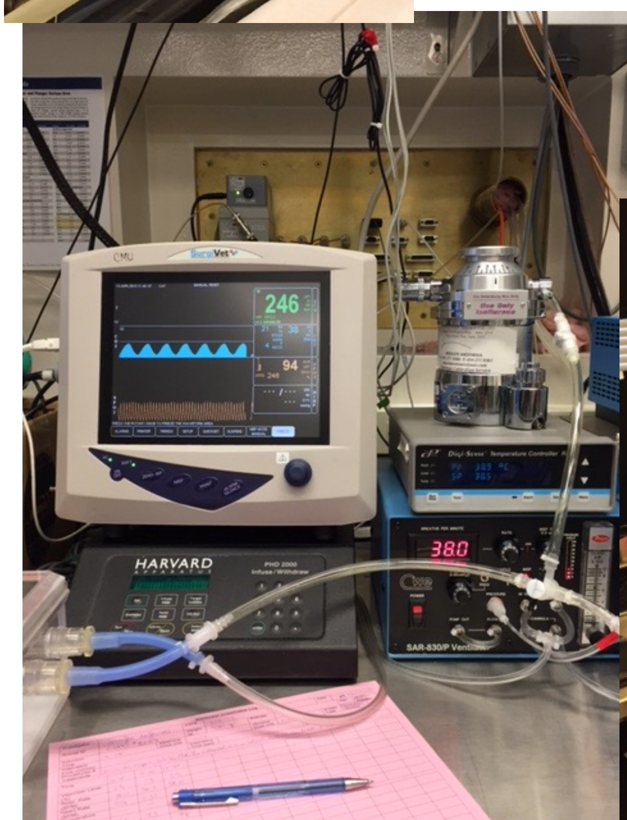
Dynamic presentation of MRI lesions
(distribution, size and enhancement) resembles RRMS

Today's MR imaging of marmoset EAE

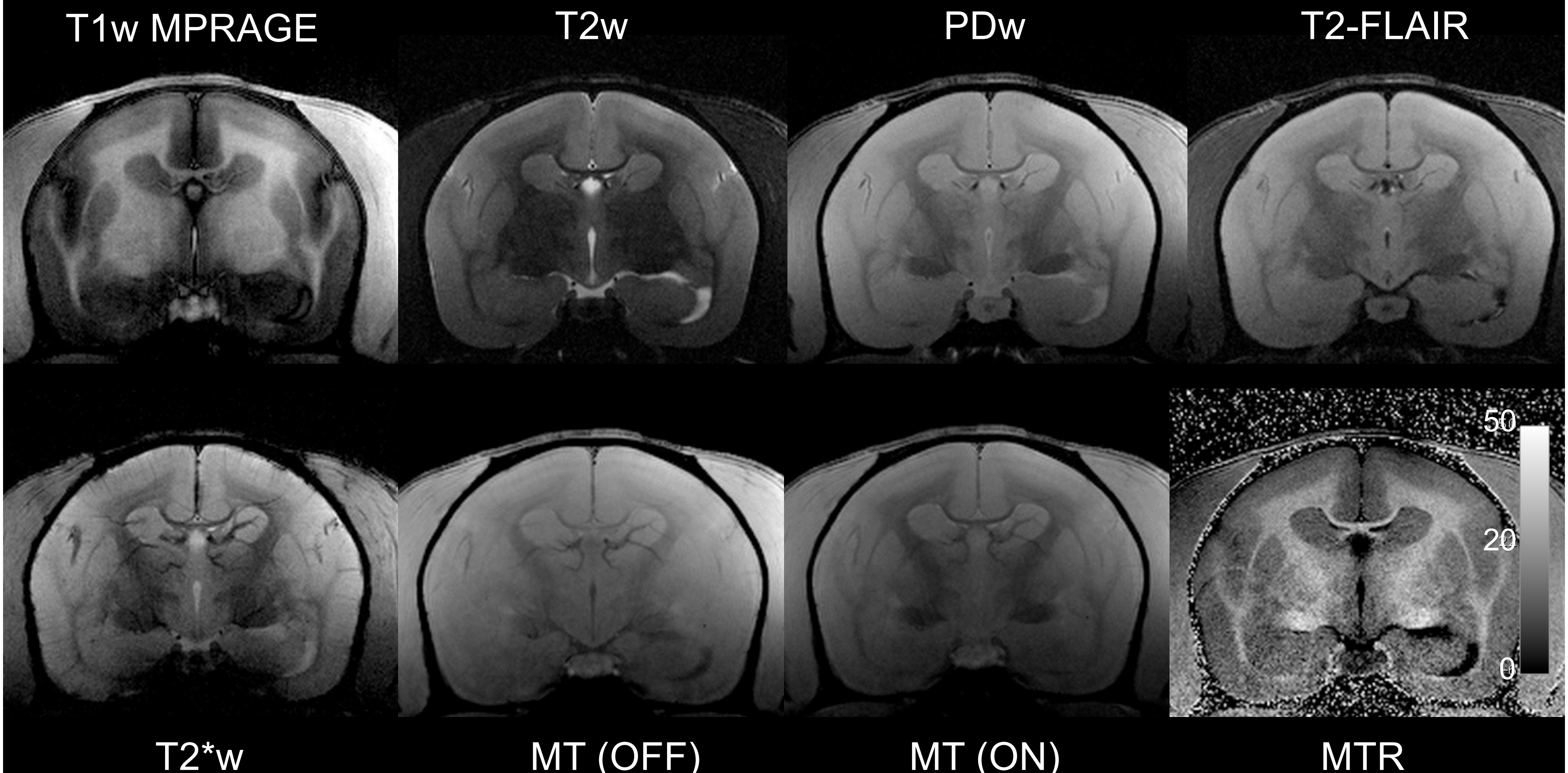
7T Bruker scanner

Cerebral Microcirculation Unit
PI: Afonso Silva, PhD



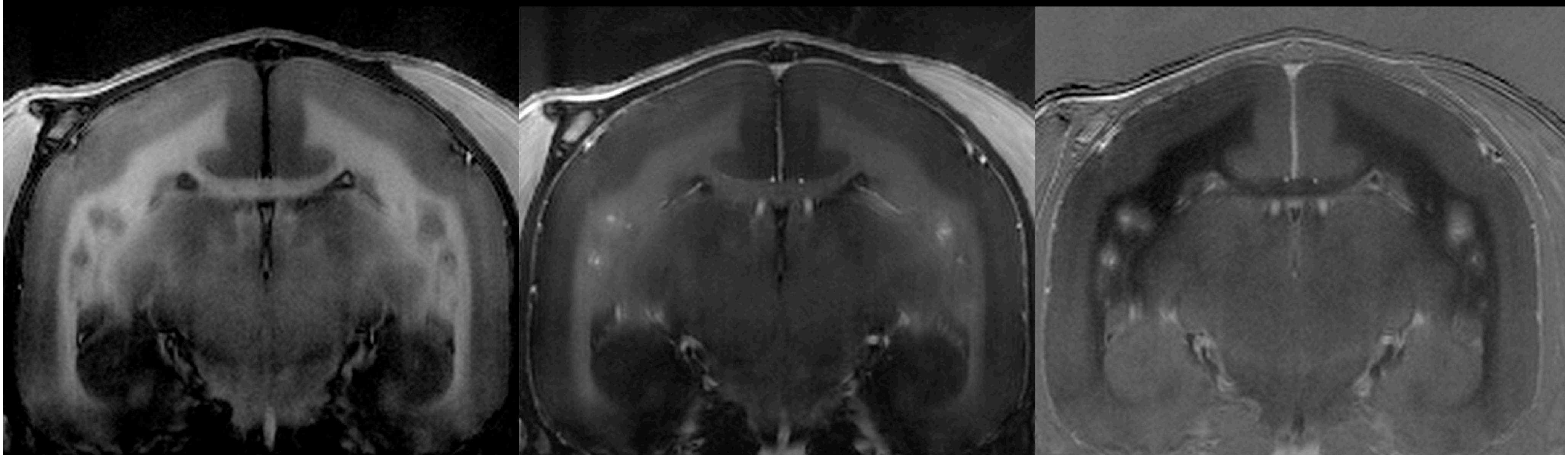


Protocol 1: Multi-contrast MRI



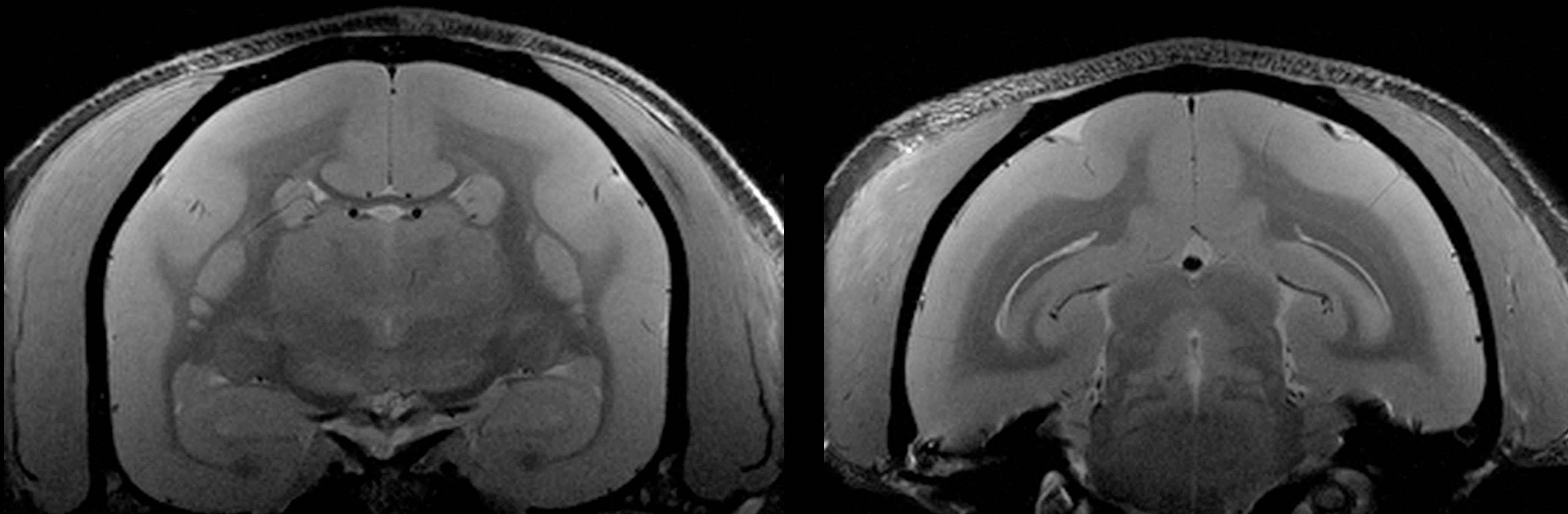
Voxel size =150 μm x 150 μm x 1 mm
Total scan time = 60 min

MRI with contrast agent



Triple-dose (0.3 mL / kg) of Gadavist

Protocol 2: High-resolution MRI



Voxel = 125 μm x 125 μm x 600 μm

Study #1: Effects of human herpesvirus 6 in marmoset EAE

Collaboration with Viral Immunology Section (PI: Steven Jacobson, PhD)

Hypothesis:
Marmosets inoculated with HHV6 will demonstrate an accelerated, more aggressive EAE disease course compared to EAE controls

Study design:
12 animals distributed in 3 groups & followed **bi-weekly by MRI**

Group 1: EAE induction only (HWM + CFA)

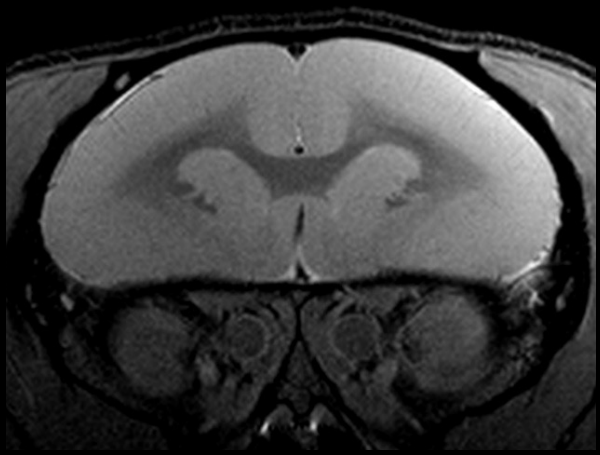
Group 2: HHV-6A inoculation following by EAE induction

Group 3: HHV-6B inoculation following by EAE induction

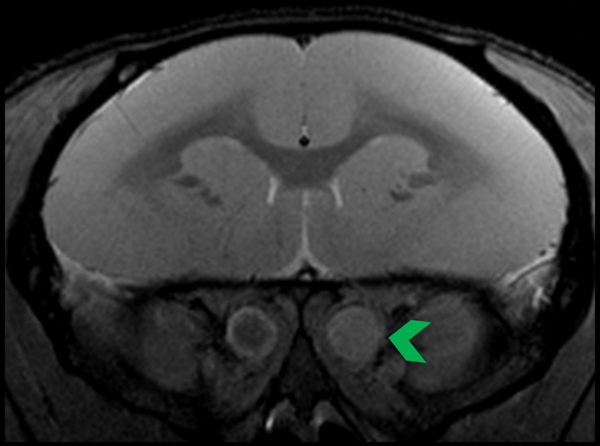
MRI outcomes:
Time of first lesion appearance & lesion load

MRI findings: optic nerve lesion

Baseline



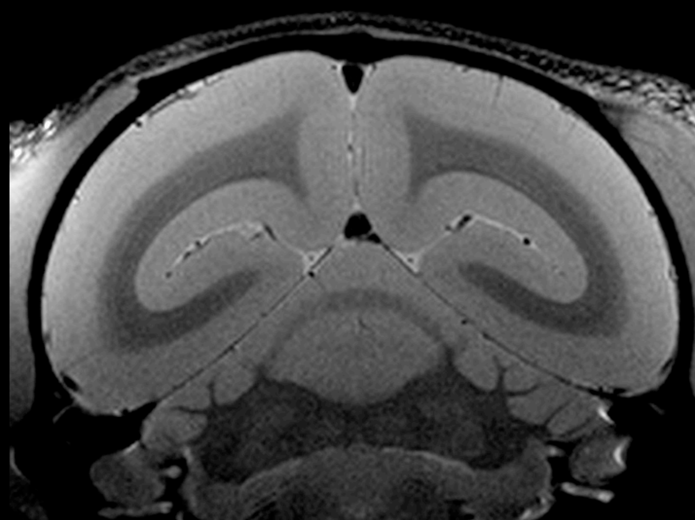
Follow-up



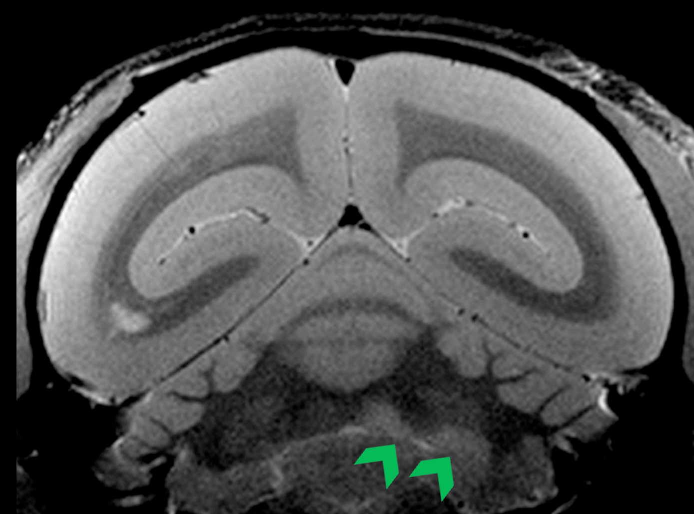
Clinical exam:
Afferent pupillary defect of the right eye
(optic neuritis)

MRI findings: Cerebellar lesions

Baseline

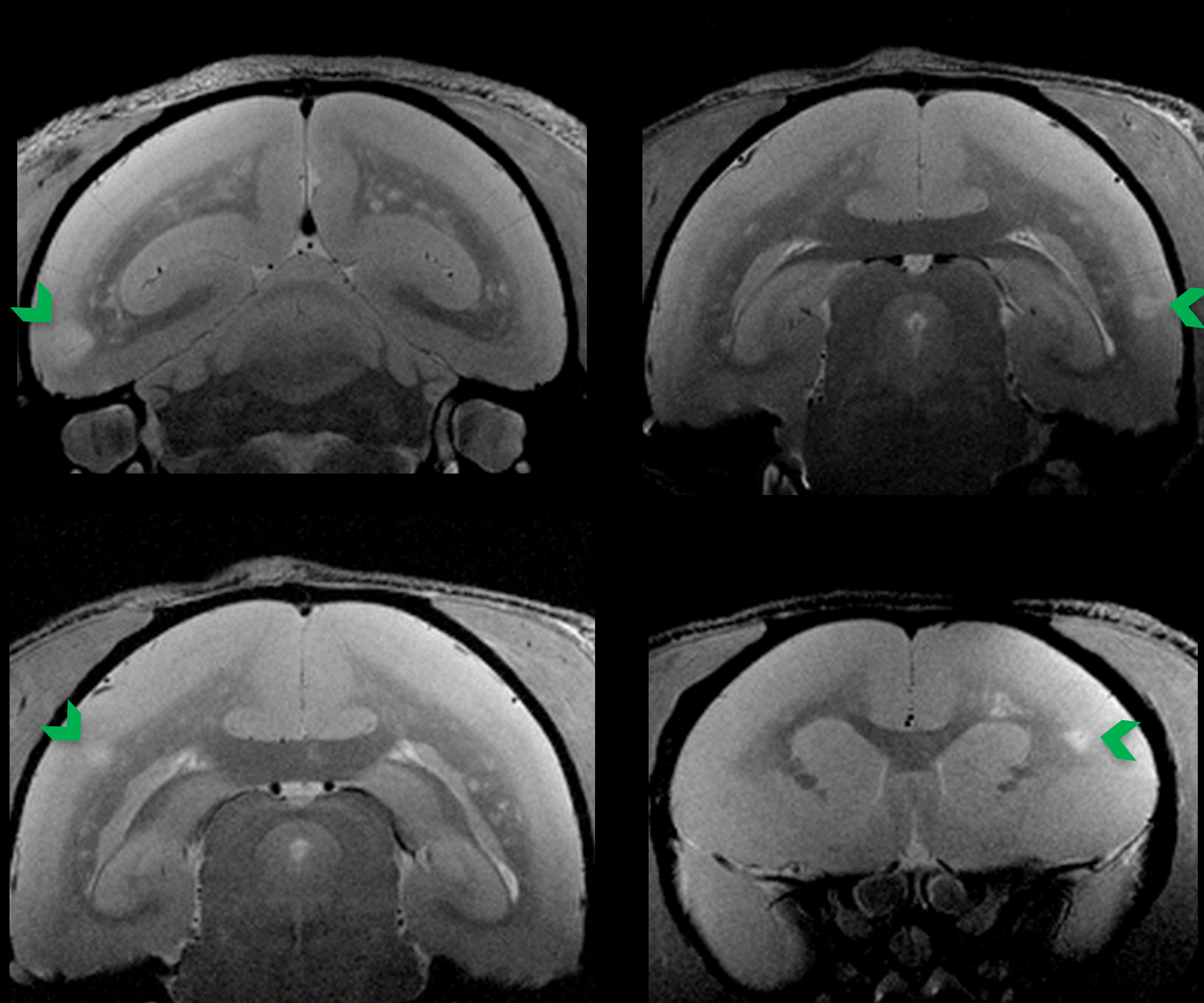


Follow-up



Clinical exam:
Severe cerebellar ataxia
(poor balance, instability of gait, trouble regulating run/stop)

MRI findings: (leuko)cortical lesions



Observed for the time by *in vivo* MRI !

Study #2: Effects of high-dose steroids in marmoset EAE

Collaboration with Vertex pharmaceuticals

Hypothesis:

Animals receiving high-dose steroidal treatment will demonstrate a reduced inflammatory activity compared to controls and have a milder disease course

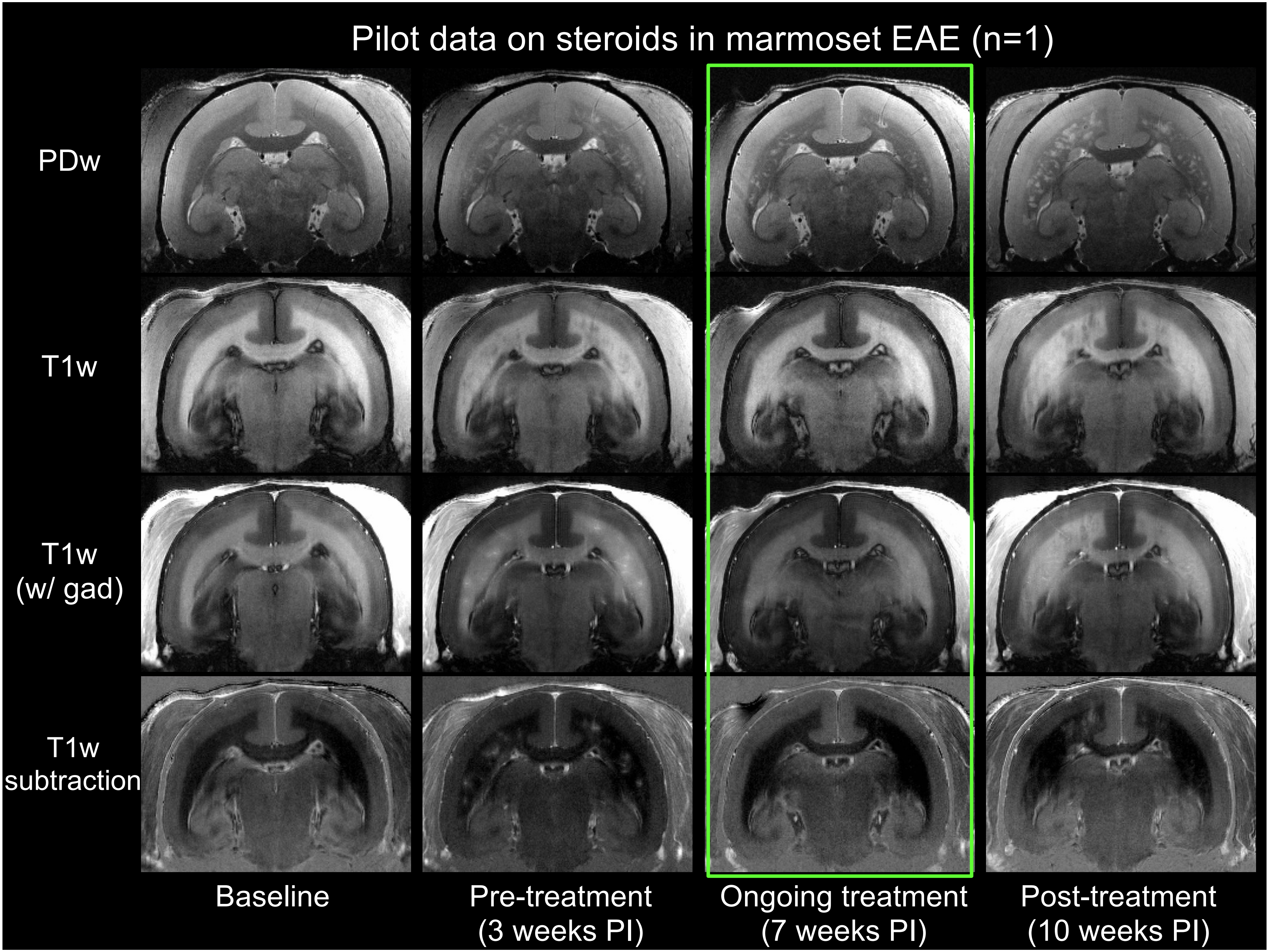
Study design:

2 pairs of twins (n=4) distributed in 2 groups & followed biweekly by MRI

- Group 1 (n=2): EAE (WMH+CFA)
- Group 2 (n=2): EAE + steroids

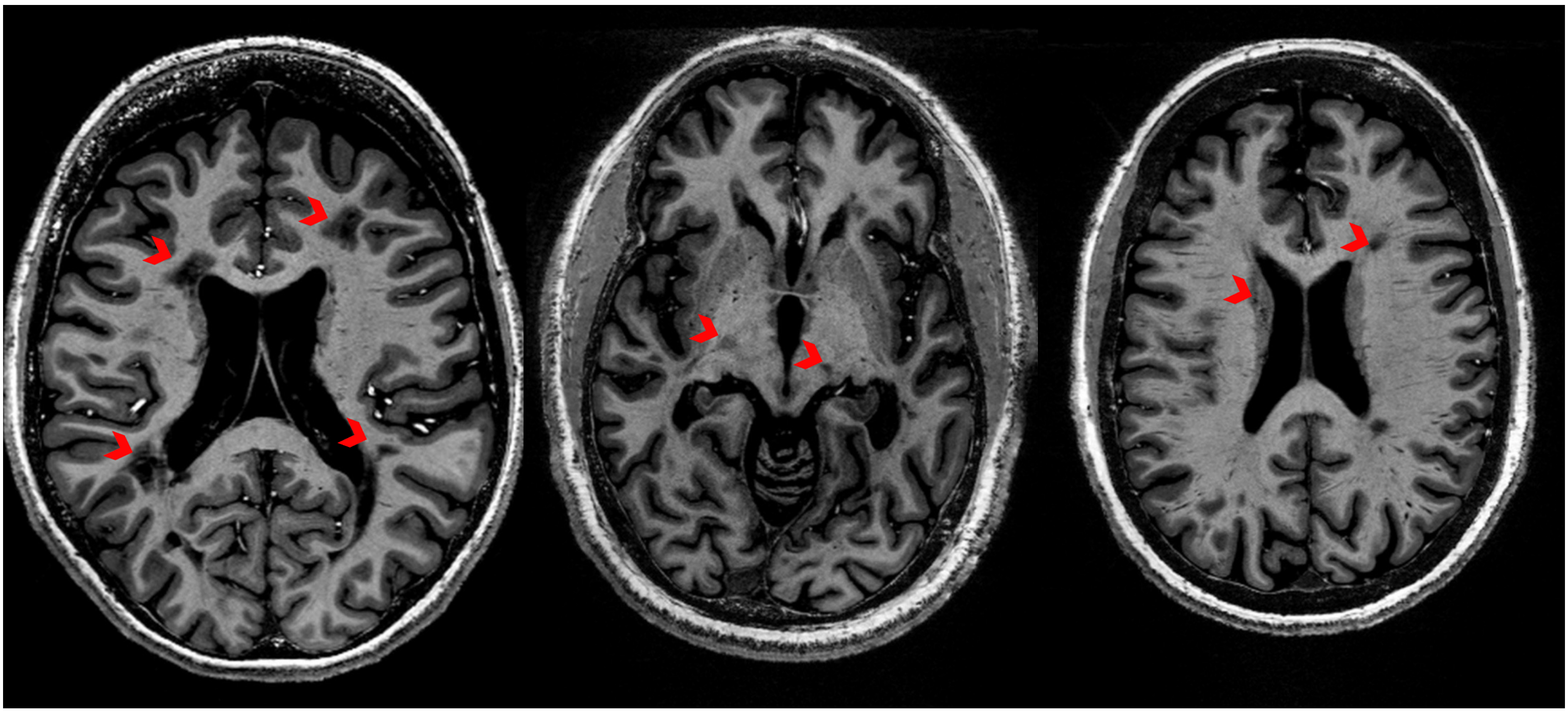
MRI outcomes:

Number of gad-enhancing lesions & lesion load


Pilot data on steroids in marmoset EAE (n=1)
PDw
T1w
T1w (w/ gad)
T1w subtraction
Baseline
Pre-treatment (3 weeks PI)
Ongoing treatment (7 weeks PI)
Post-treatment (10 weeks PI)

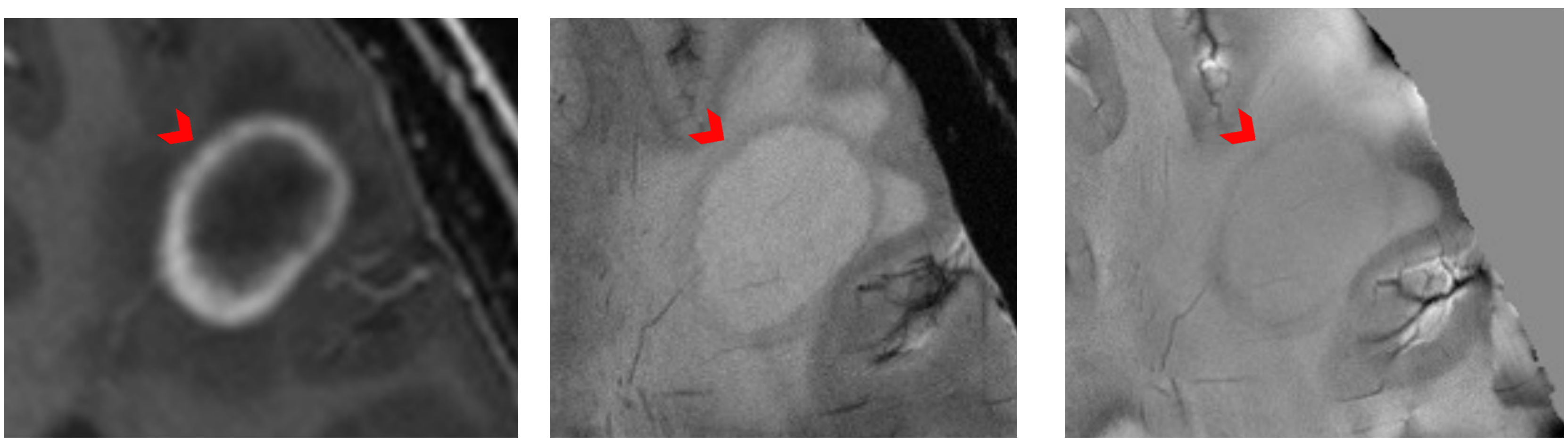
Advanced (7T) imaging of neurological diseases (MS)

1. To better detect the pathology caused by disease



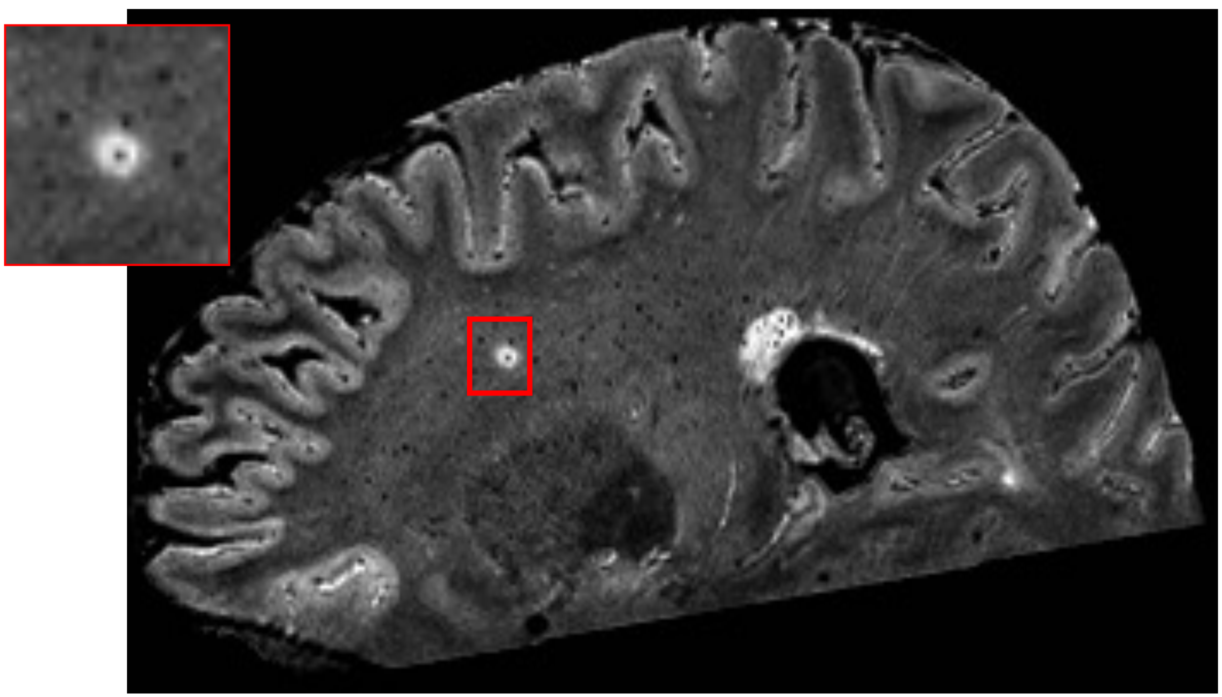
Advanced (7T) imaging of neurological diseases (MS)

1. To better detect the pathology caused by disease
2. To find new imaging markers of disease activity



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

1. To better detect the pathology caused by disease
2. To find new imaging markers of disease activity
3. To improve the diagnosis of disease by MRI



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

1. To better detect the pathology caused by disease
2. To find new imaging markers of disease activity
3. To improve the diagnosis of disease by MRI
4. To relate with preclinical imaging research

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