National Institute of Neurological Disorders and Stroke

Studying central nervous system (CNS) diseases with advanced MRI

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Mission statement:

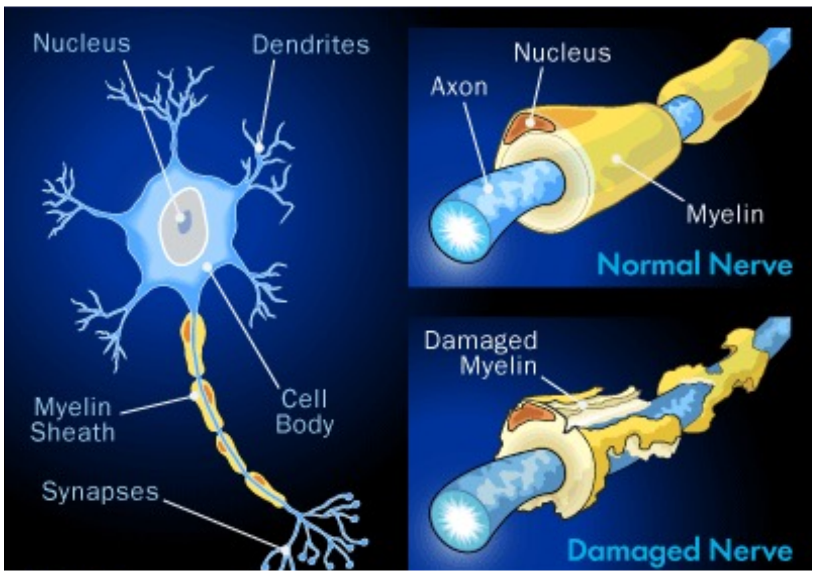
"Our research focuses on the use of **advanced MRI** techniques to understand the sources of disability in **multiple sclerosis** and on ways of adapting those techniques for use in **research trials** and **routine patient care**."

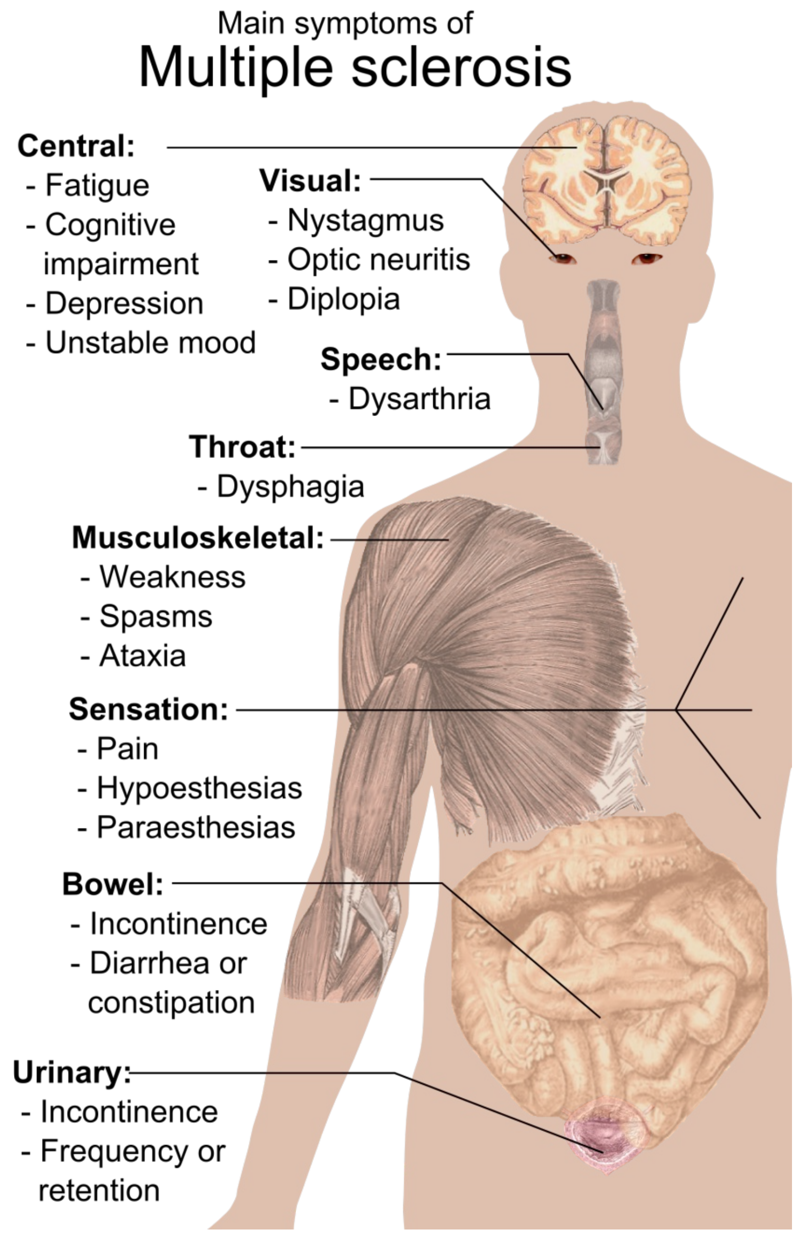
MS: a disabling disease of the central nervous system

Prevalence:
400,000 in the US, 2.5 million worldwide

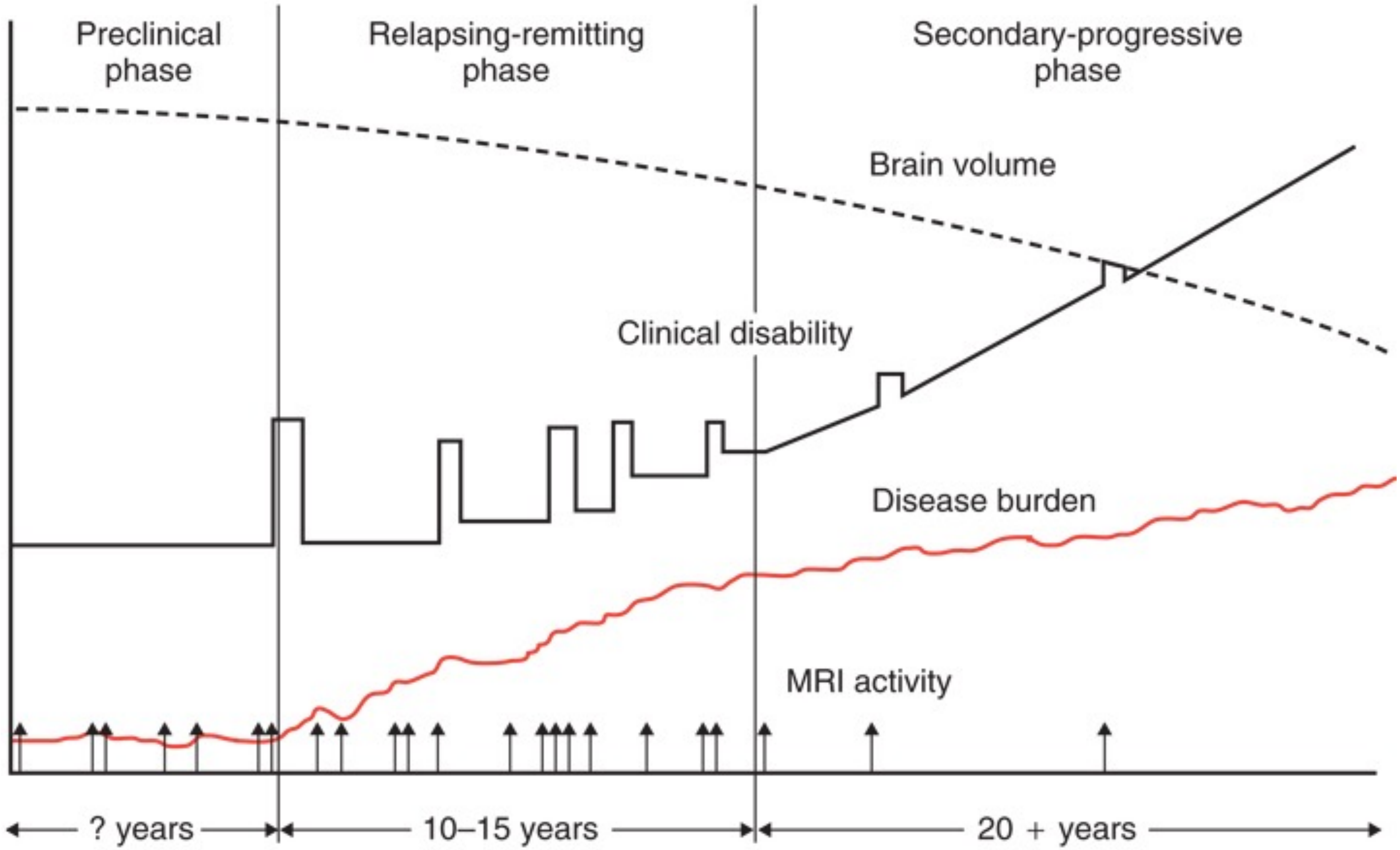
Origin:
Still unknown

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



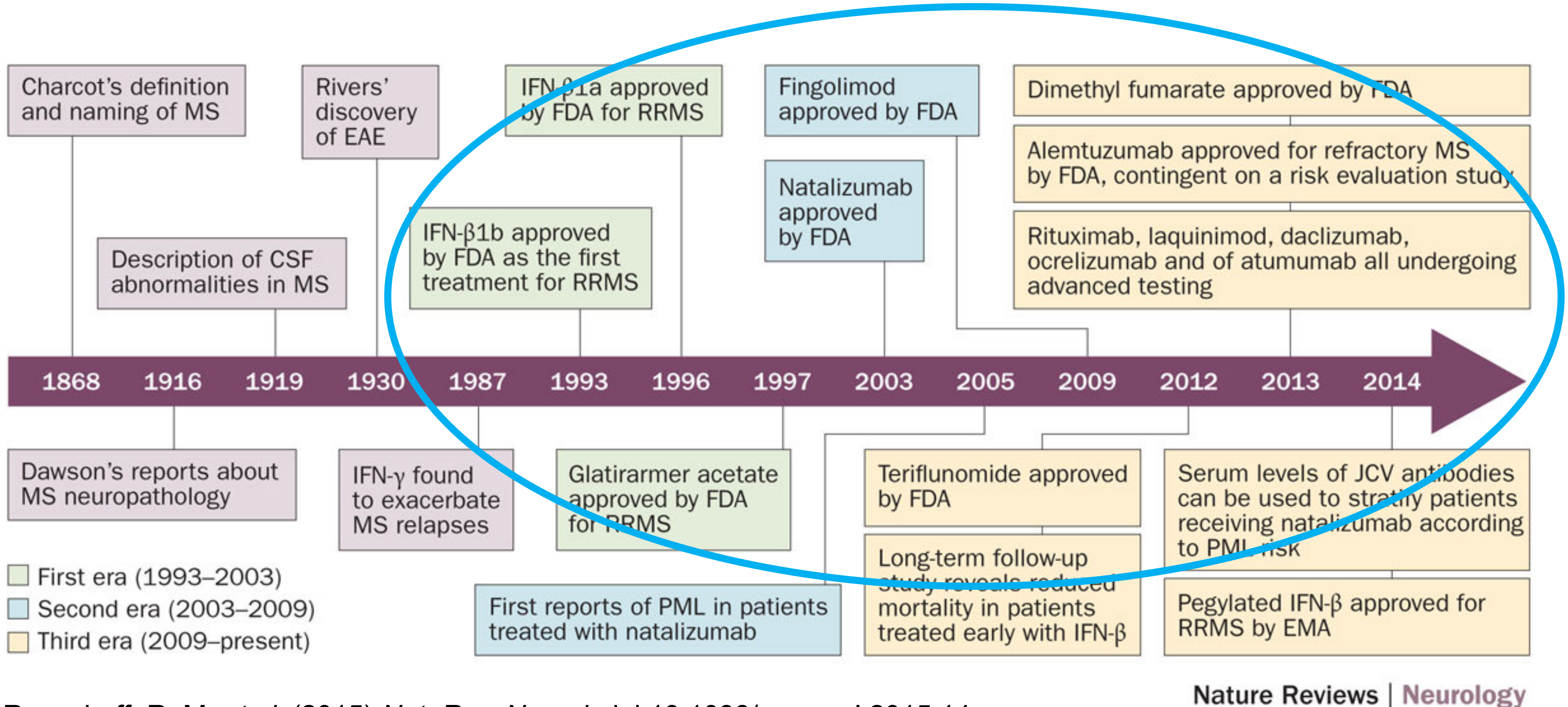


Typical clinical and magnetic resonance imaging (MRI) course of MS



http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/multiple_sclerosis/

Timeline for the development of disease-modifying drugs for MS



Ransohoff, R. M. *et al.* (2015) *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2015.14

- 15 FDA-approved DMTs primarily targets the early inflammatory phase of disease (RRMS)
- As the disease progresses, response to DMTs typically declines
- **Early diagnosis and treatment are of key importance to limit the impact of MS !**

Diagnosing MS

○ No single test can diagnose MS

○ Medical history, neurologic exam and lab tests help rule out other diseases and confirm the MS diagnosis.

○ 2010 McDonald Criteria to demonstrate CNS lesions disseminated in space (DIT) and time (DIS)

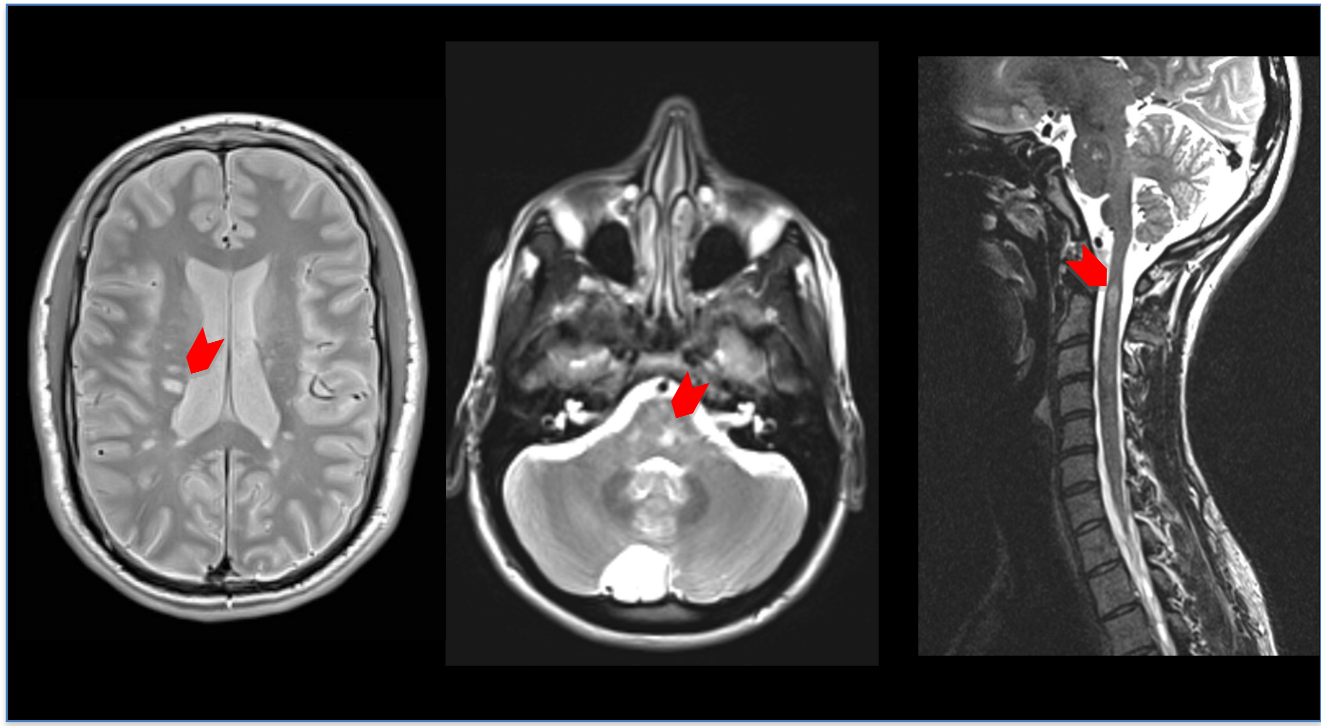
Clinical Findings at Presentation		
Episodes from History	Objective Clinical Signs	Additional Data Needed From MRI or Clinical Follow-up
2 Attacks	2 Lesions	None†
2 Attacks	1 Lesion	Evidence of DIS‡
1 Attack	2 Lesions	Evidence of DIT§
1 Attack	1 Lesion	Evidence of both DIS and DIT

Diagnosis of MS can be made in typical clinically isolated syndrome (CIS) patients based on a single MRI

2010 McDonald MRI criteria

Dissemination in space (DIS)

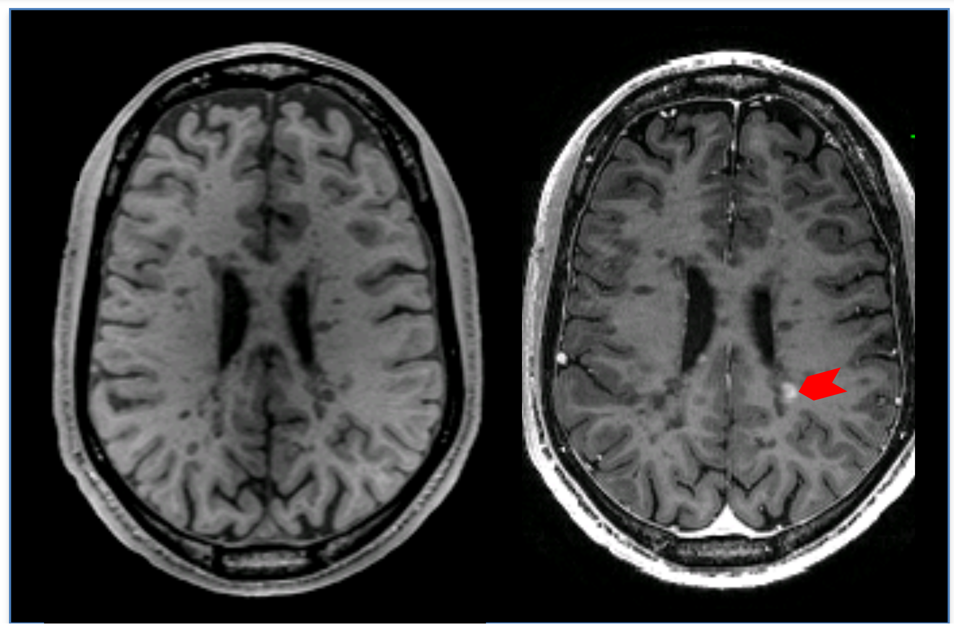
One or more T2 lesions in two or more characteristic locations (periventricular, juxtacortical, infratentorial, spinal cord)



Dissemination in time (DIT)

New T2 lesion and/or gadolinium-enhancing lesion(s) on follow-up scan

Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing T2 lesion on any one scan



Misdiagnosis of MS is common…

- Misdiagnosis of MS is common (5%-35%)

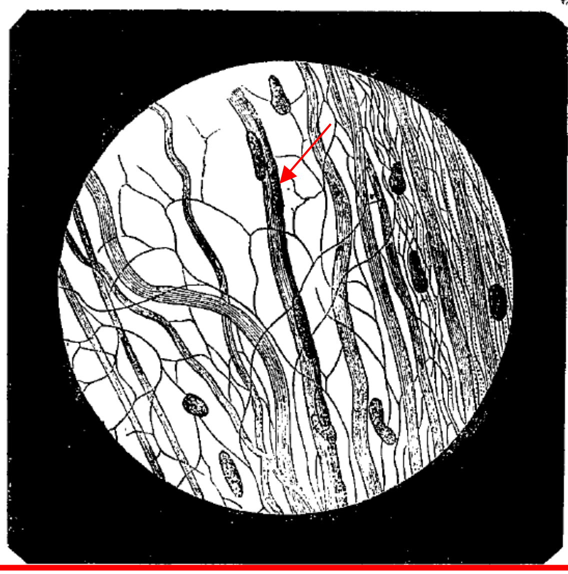
- Misdiagnosis expose patients to unnecessary disease modifying therapies (harmful side effects).
  Important economic consequences to healthcare system
  (5% of 400,000 of US patients => 1 billion USD/year for DMTs)

- Sensitivity and specificity of McDonald criteria are imperfect

- MS mimics show MRI lesions in the CNS
  (migraine, fibromyalgia, small vessel ischemic cerebrovascular disease, neuromyelitis optica spectrum disorders,…)

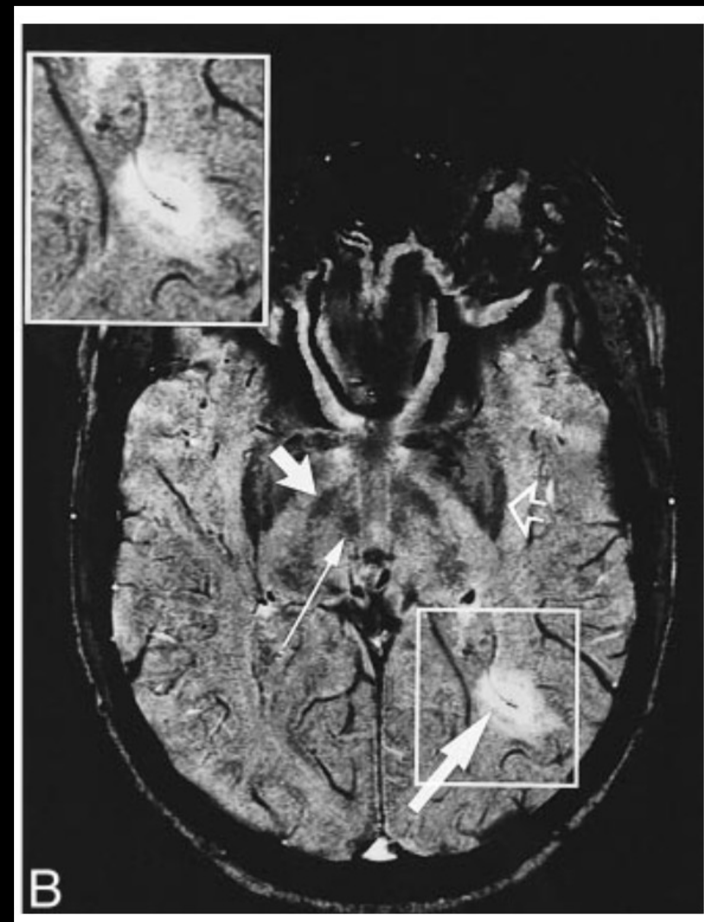
Solomon & Weinshenker, Curr Neurol Neurosci Rep (2013) 13:403
Solomon et al., Neurology (2012) 78:1986-91

Central veins in MS plaques



IG. 1. — Elle représente une préparation fraîche, provenant du centre d'une plaque scléreuse, coloriée par le carmin et traitée par dilacération. Au centre, vaisseau capillaire portant plusieurs noyaux. A droite et à gauche, cylindres d'axe, les uns volumineux, les autres d'un très-petit diamètre, tous dépouillés de leur myéline. Le vaisseau capillaire et les cylindres d'axe étaient fortement colorés par le carmin. Les cylindres d'axe ont des bords parfaitement lisses, ne présentant aucune ramification. Dans l'intervalle des cylindres d'axe, minces fibrilles de formation récente, à peu près parallèles les unes aux autres dans la partie droite de la préparation, formant à gauche et au centre, une sorte de réseau résultant, soit de l'enchevêtrement, soit de l'anastomose des fibrilles. Celles-ci se distinguent des cylindres d'axe, 1° par leur diamètre qui est beaucoup moindre; 2° par les ramifications qu'elles offrent dans leur trajet; 3° parce qu'elles ne se colorent pas par le carmin. — Çà et là, noyaux disséminés. Quelques-uns paraissant en connexion avec les fibrilles conjonctives; d'autres ayant pris une forme irrégulière, due à l'action de la solution ammoniacale de carmin.

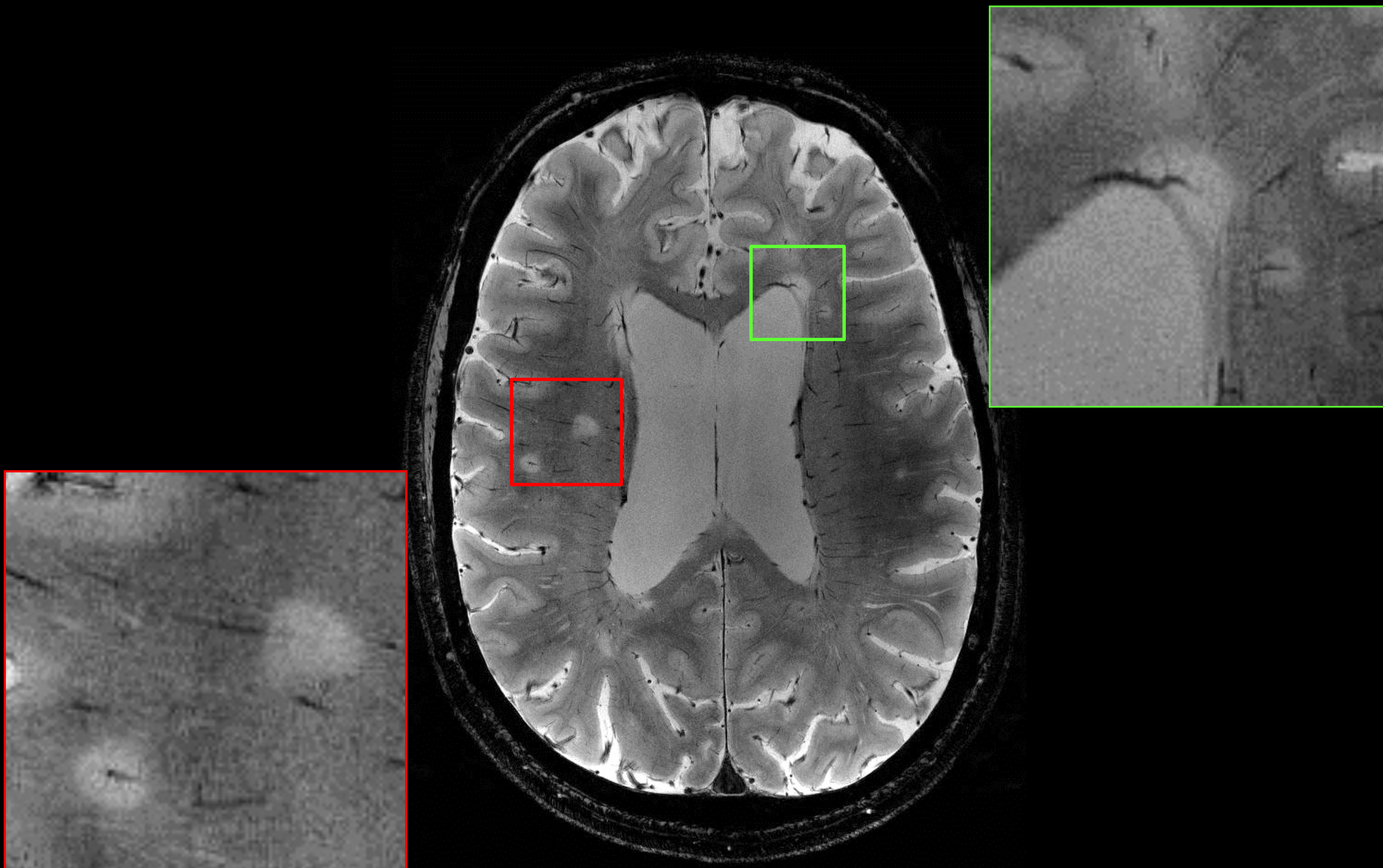
Charcot, 1868



Tan el al., AJNR (2000)

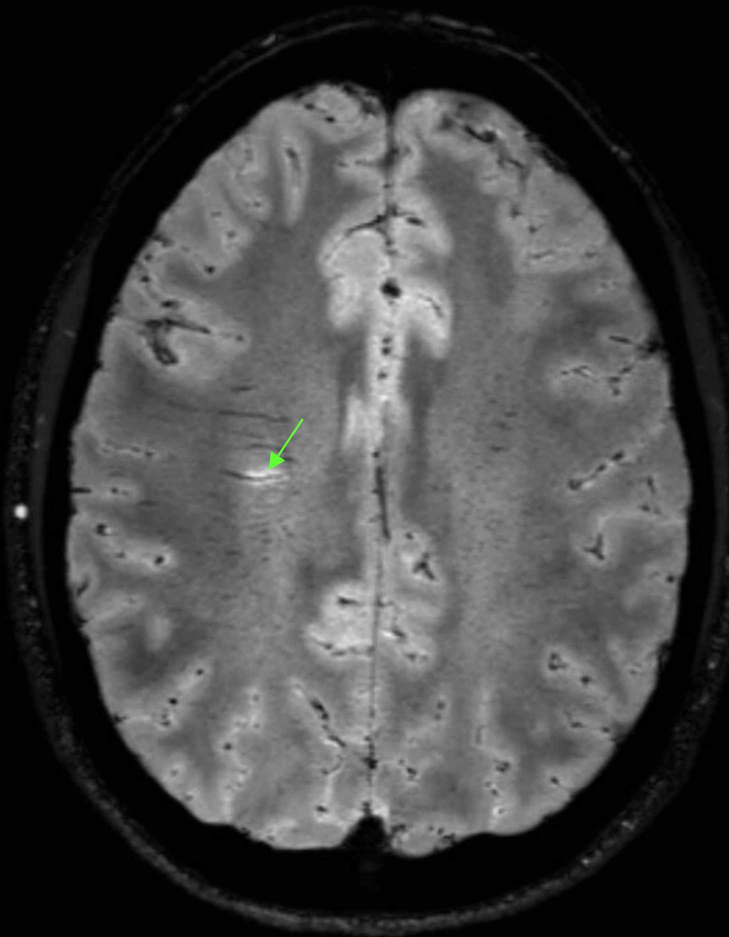
Susceptibility-Weighted imaging (SWI) @ 1.5T

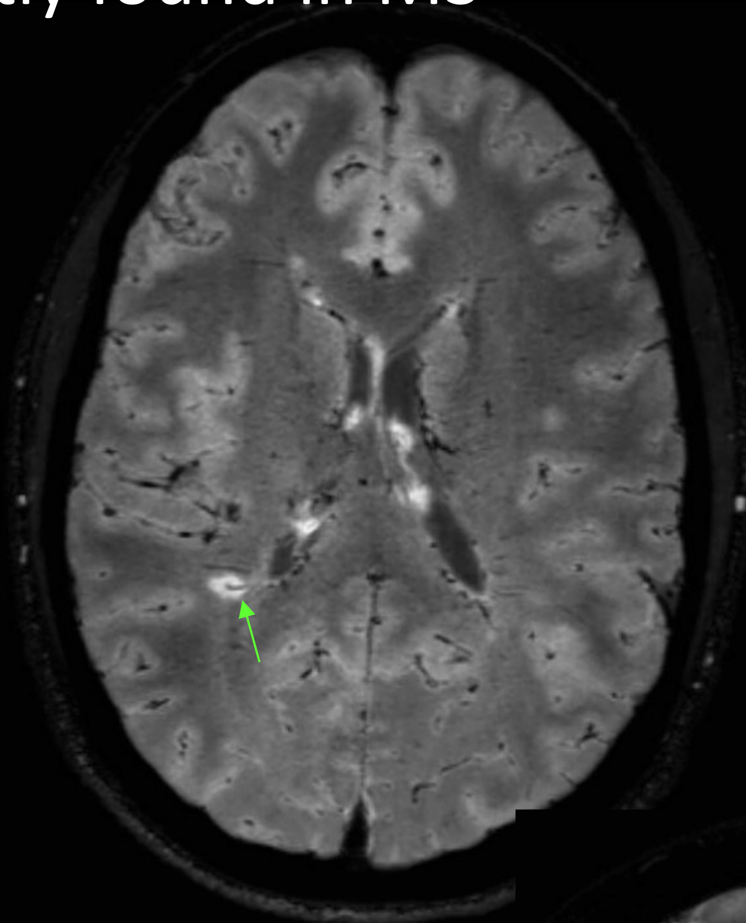
Central veins in MS plaques

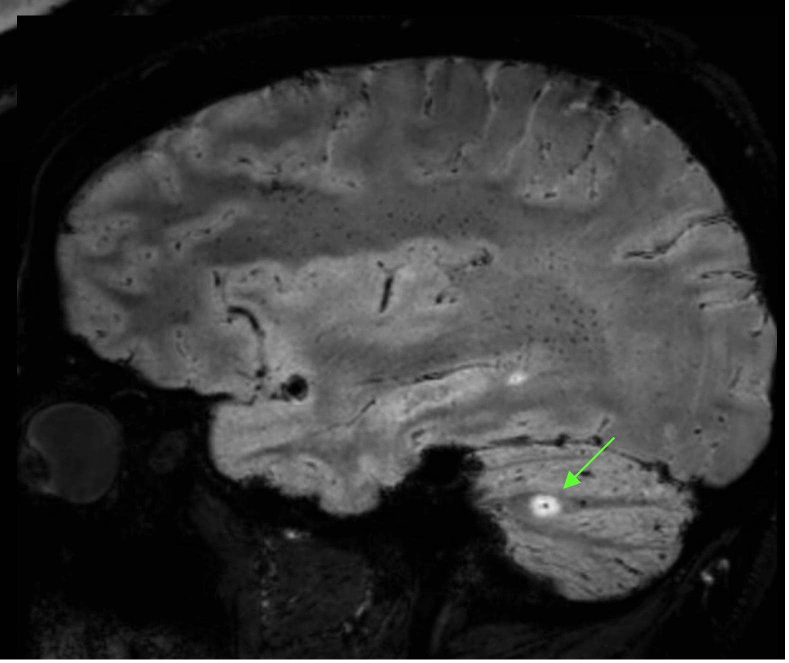


FMRIF 7T Siemens
T2-weighted*

Central veins frequently found in MS

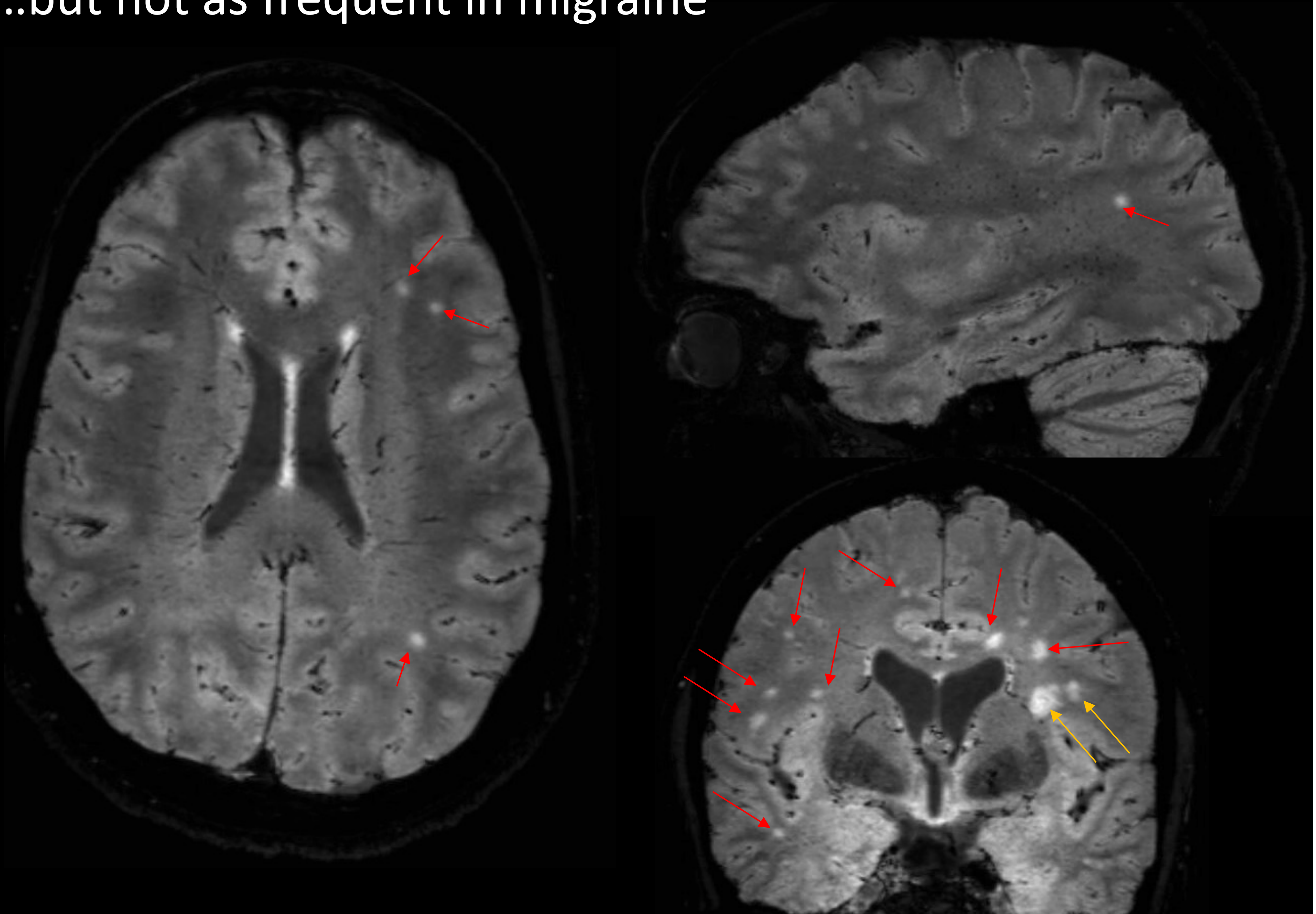






in collaboration with Andrew Solomon (UVM)
Solomon et al. Ann Clin Transl Neurol. (2015) ;3(2):82-7.

…but not as frequent in migraine



in collaboration with Andrew Solomon (UVM)
Solomon et al. Ann Clin Transl Neurol. (2015) ;3(2):82-7.

Prevalence of central veins in MS and its mimics

Disorders	Percentage of CV+ lesions	References
MS	78% (782/1,004) RR: 80% (394/490), PP:76% (277/362)	Kilsdonk et al., J Neurol (2014) Kuchling et al., Mutl Scler Journ (2014)
NMOSD	**mean:** **36%** [vs 90% for MS] **9%** (8/92 lesions)	Sinnecker et al. Neurology (2012) Kister et al. Mult Scler Int (2013)
Small vessel disease	**mean:** **22%** [vs 74% for MS] **median:** **6.1%** [vs 70% for MS]	Mistry et al., Mult Scler (2015) Samaraweera et al., J Neuroimaging (2016)
Migraine	**median:** **22%** [vs 84% for MS]	Solomon et al., ACTN (2015)
Susac's	**mean:** **54%** (vs 92% for MS)	Wuerfel et al., Mult Scler (2012)
Behcet's, SLE, APS	**13%** (40/103) [vs 80% (262/325) for MS]	Vuolo et al., Eur J of Neurol (2016)

The central vein sign for diagnosing MS ?

Sati et al. Nature Review Neurology (2017)

- ❑ Single-center studies reported a lower proportion of CV+ lesions in other diseases: NMO, SAD, CSVD, migraine.
- ❑ Need to investigate more MS mimics *(neurosarcoidosis, sjongren's, ADEM,…)*
- ❑ Need to define a CVS criterion *(% rule, select-lesion rule, combined DIT-DIS-CV+)*
- ❑ Need to validate in large multi-center imaging studies
  patients with a broad spectrum of neurological diseases
  patients at first clinical/radiological presentation (not yet diagnosed)
  patients with suspicion of misdiagnosis.

Typical brain MRI protocol for MS diagnosis

Rovira et al. Nature Review Beurology (2015). Consensus statement from MAGNIMS

- 2D or 3D high-resolution (1mm) isotropic T1-weighted (opt.)
- Axial proton-density and/or T2-weighted (mand.)
- Sagittal 2D or 3D T2-FLAIR (mand.)
- Injection of gadolinium-based contrast agent (mand.)
- 5 min “dead time”
- 2D or 3D contrast-enhanced T1-weighted (mand.)

Total scan time ~30 min

Typical brain MRI protocol for MS diagnosis

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- Sagittal 2D or 3D T2-FLAIR (mand.)
- Injection of gadolinium-based contrast agent (mand.)
- 5 min “dead time”

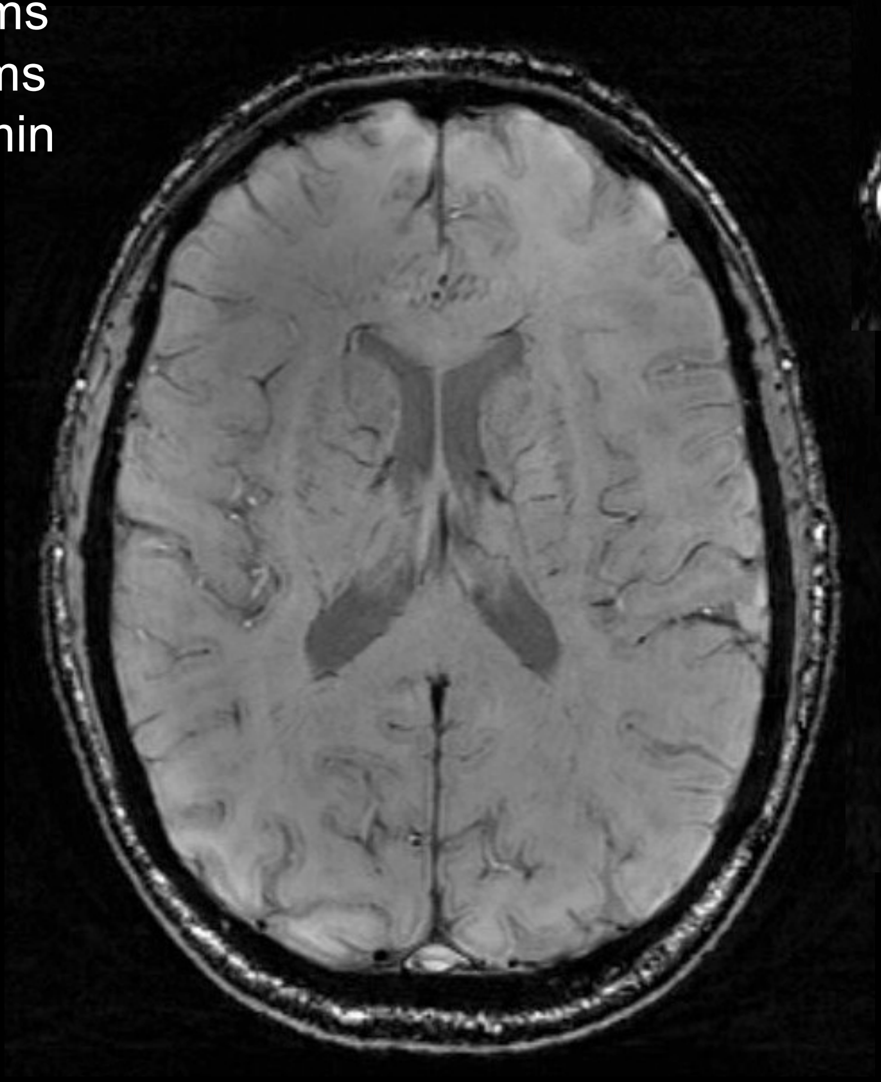
Add T2*-weighted/SWI sequence ?

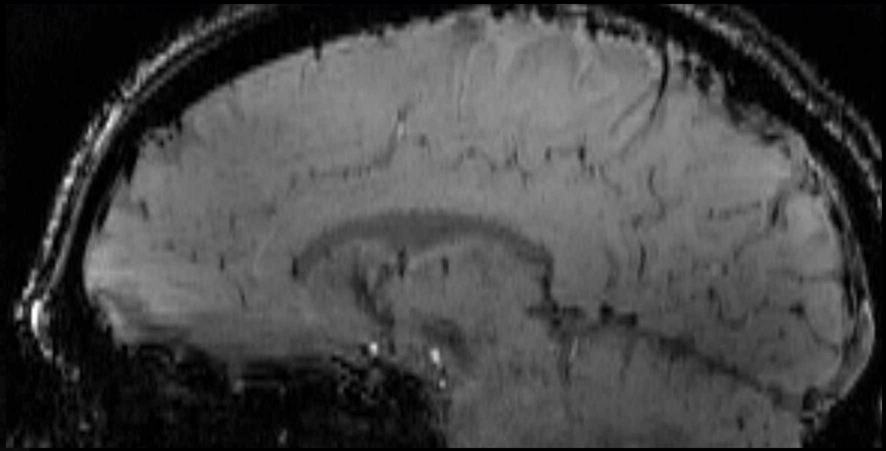
- 2D or 3D contrast-enhanced T1-weighted (mand.)

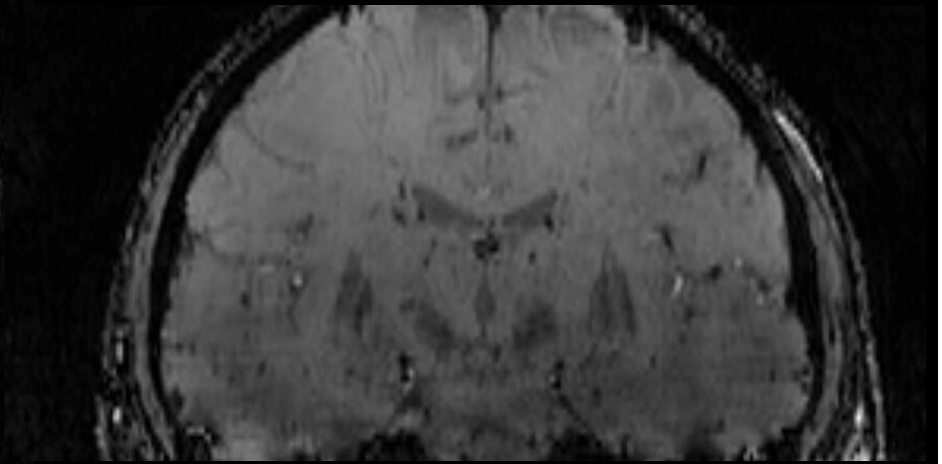
Total scan time ~30 min

Typical 3D GRE sequence for T2*w/SWI

3D spoiled Gradient-Echo (3D GRE)
in-plane res. = 0.68 x 0.68 mm
slice thick. = 1.4 mm
TR = 28 ms
TE = 20 ms
TA = ~5 min







Limited brain coverage
Anisotropic voxel dimensions

Rapid high-resolution T2* imaging using 3D segmented echo-planar-imaging (3D EPI)

3T Philips Achieva, 8-ch head coil

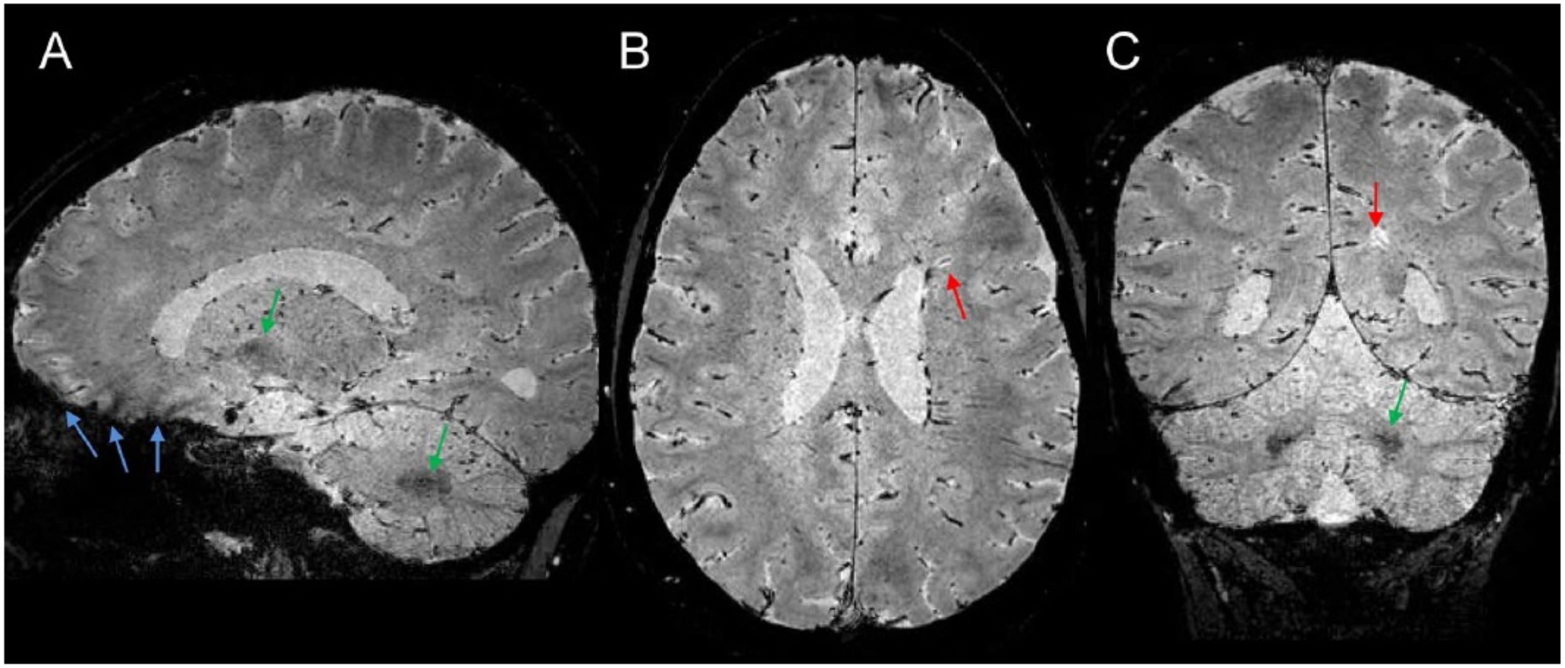
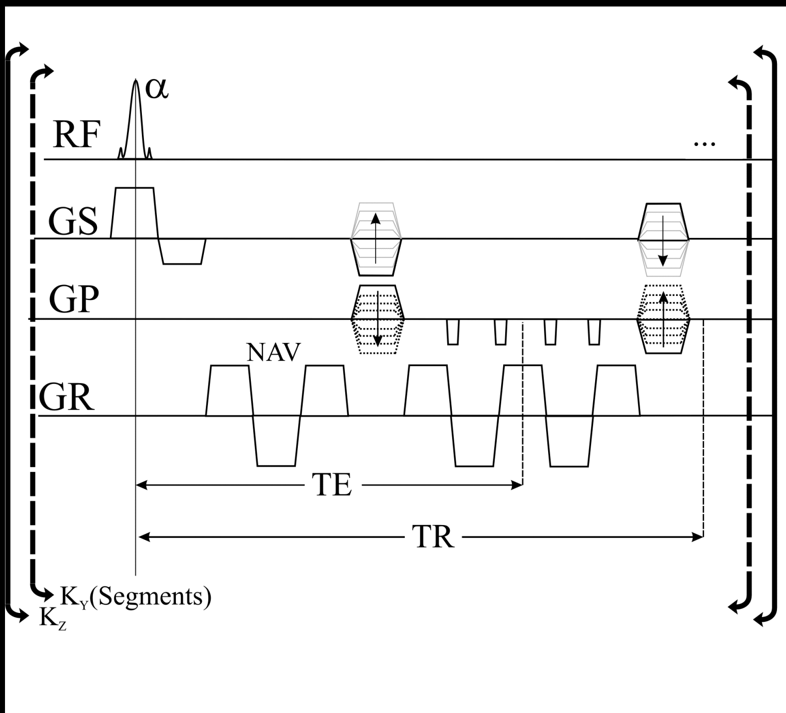
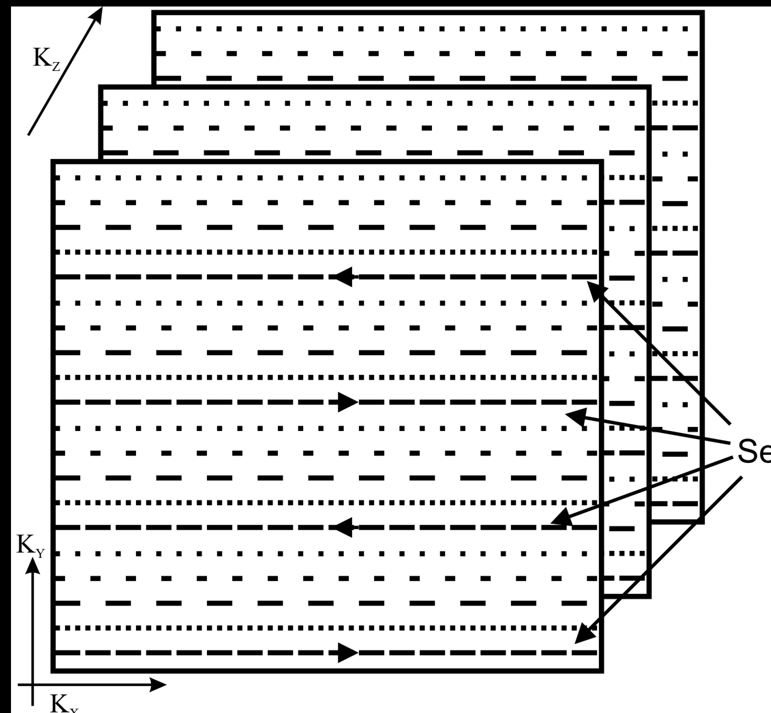


Figure 1. 3D-EPI magnitude images from one MS case acquired at 3 T using a voxel resolution of 0.55 × 0.55 × 0.55 mm³. 3D-EPI images are initially acquired in the sagittal plane (A) and then reformatted in the axial (B) and coronal (C) planes. Red arrows point to MS lesions in the white matter. Green arrows indicate globus pallidus and dentate nucleus. Blue arrows show areas of signal loss close to air/tissue interfaces (paranasal sinuses and mastoid air cells).

Sati et al., Mult Scler. 2014; 20(11):1464-70

A collaborative work between NIH (NINDS / NIMH/Clinical Center) and Siemens



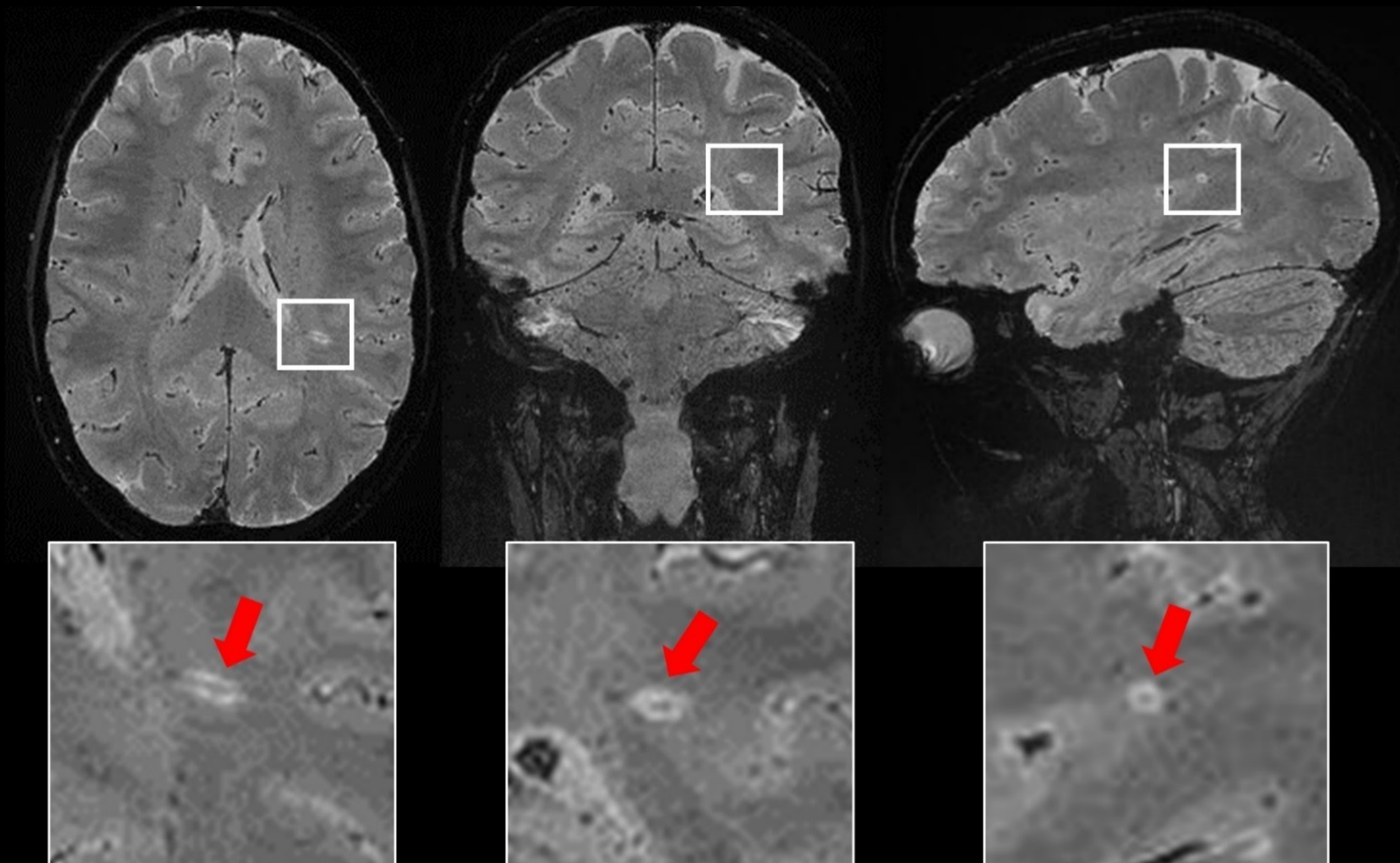


A more efficient way to sample k-space compared to conventional 3D GRE

Sati et al., Magnetom FLASH (2017)

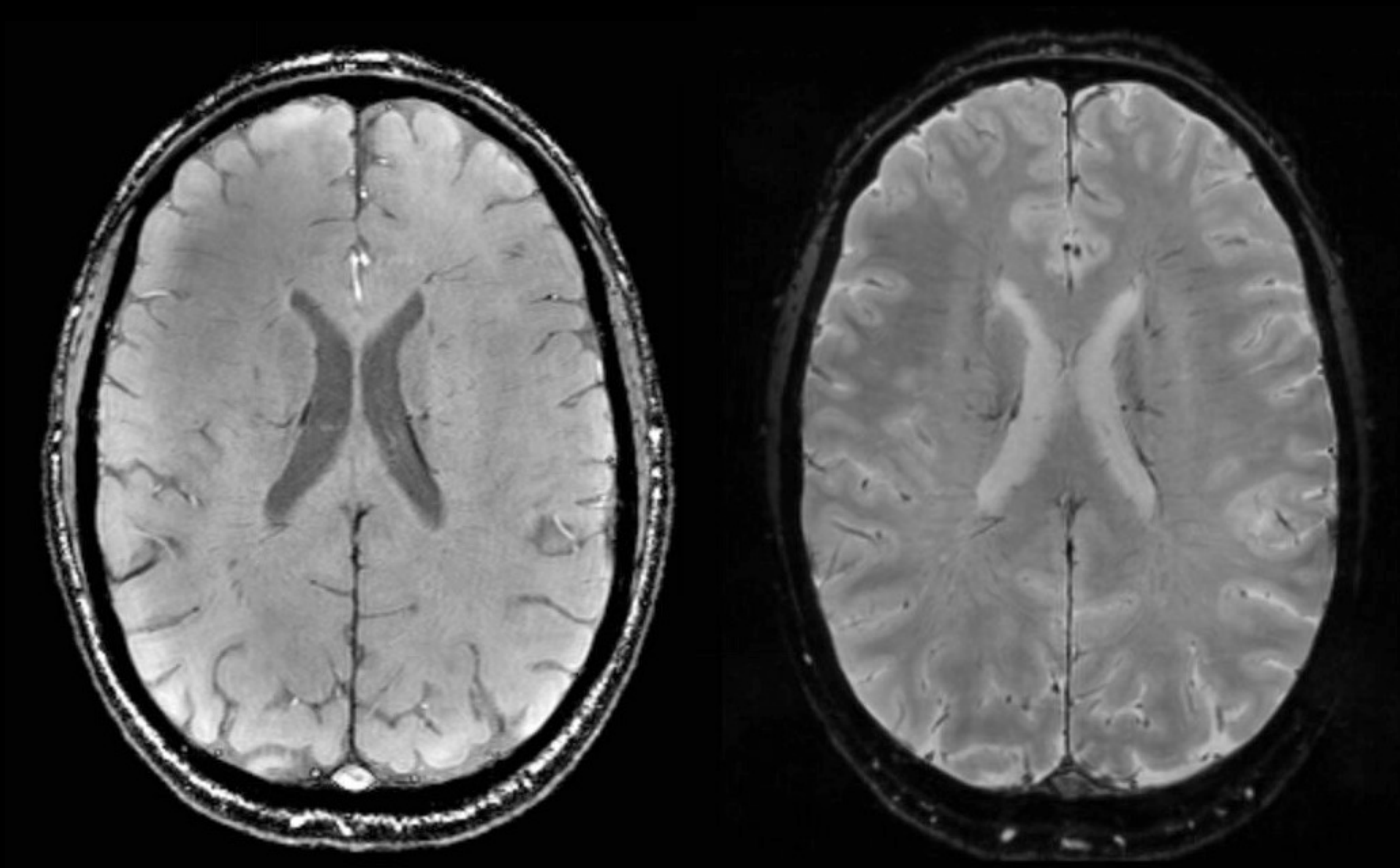
Whole-brain @ 0.65 mm iso in ~ 5 min

	Plane	TR (ms)	TE (ms)	FOV (mm)	Phase FOV (%)	Slices	Voxel size (mm)	Matrix	Phase direction	EPI factor	TA (mins)
1.5T MAGNETOM Area, Head/Neck 20 ch	Sag	64	37	228	94.1	256	0.75 iso	304	A >> P	15	5:23
3T MAGNETOM Biograph mMR, Head/Neck 16 ch	Ax	64	25	220	78.1	72	0.5 x 0.5 x 2.0	448	R >> L	15	1:30
	Sag	57	25	228	96.6	288	0.65 iso	352	A >> P	15	4:45
3T MAGNETOM Skyra, Head 32 ch & 3T MAGNETOM Prisma, Head 32 ch	Sag	64	35	250	81.3	256	0.65 iso	384	A >> P	15	5:46
7T research system, Head 32 ch	Ax	52	23	220	81.8	176	0.5 iso	440	R >> L	15	3:40



Sati et al., Magnetom FLASH (2017)

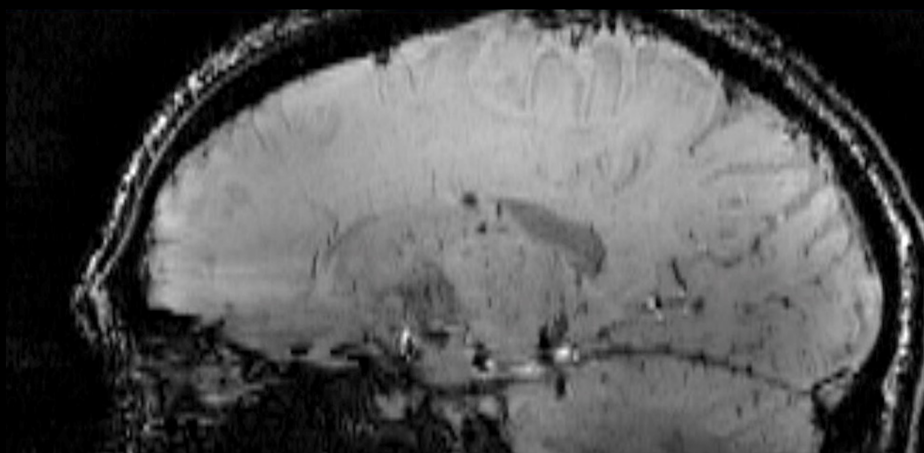
3D GRE vs 3D EPI

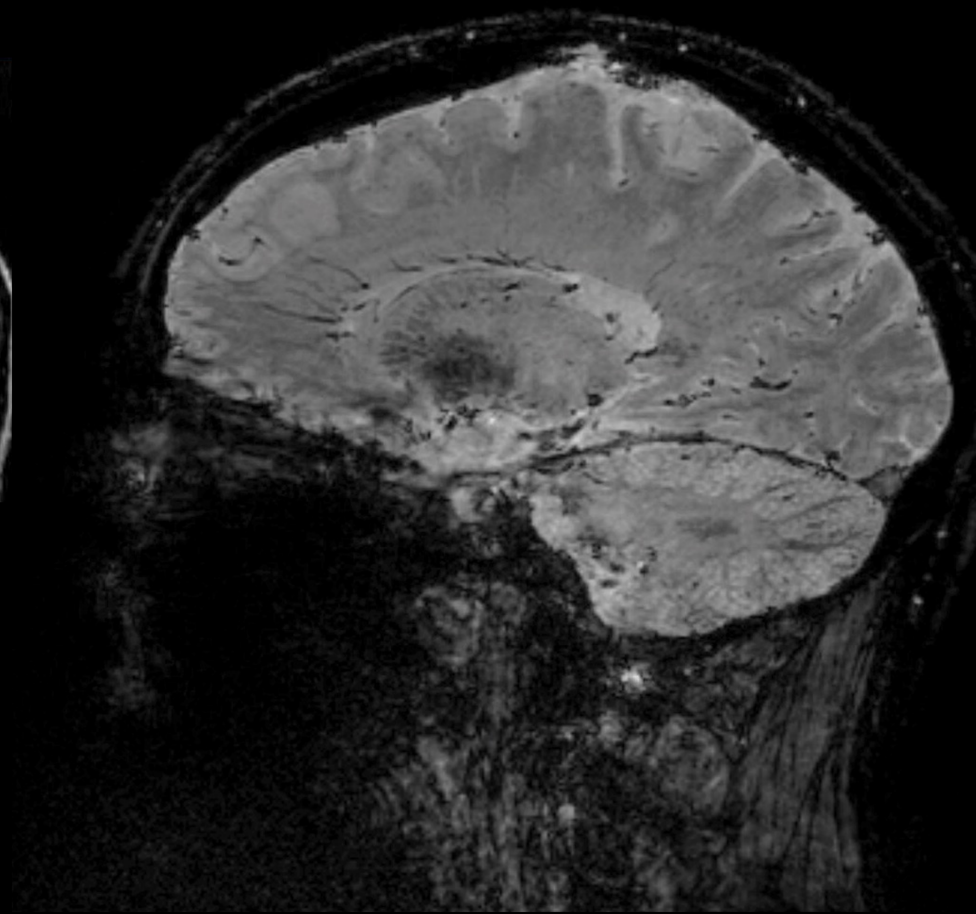


Same in-plane resolution (0.68 x 0.68 mm), same scan time (~ 5 min)

in collaboration with Andrew Derbyshire (NIMH)

3D GRE vs 3D EPI

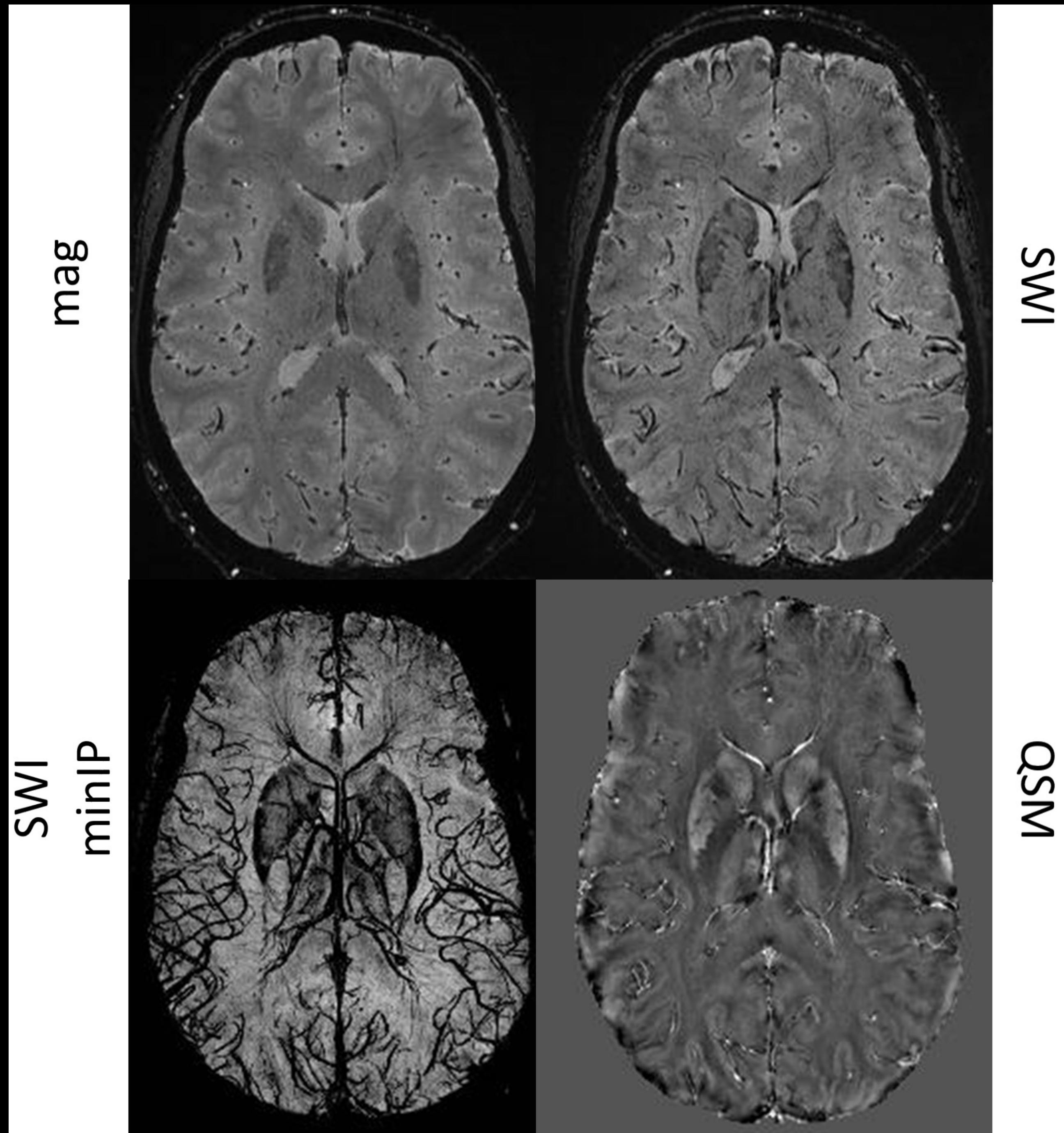




Same scan time (~ 5 min) but different slice thickness (1.4 mm vs 0.68 mm) and coverage (cerebrum vs whole brain)

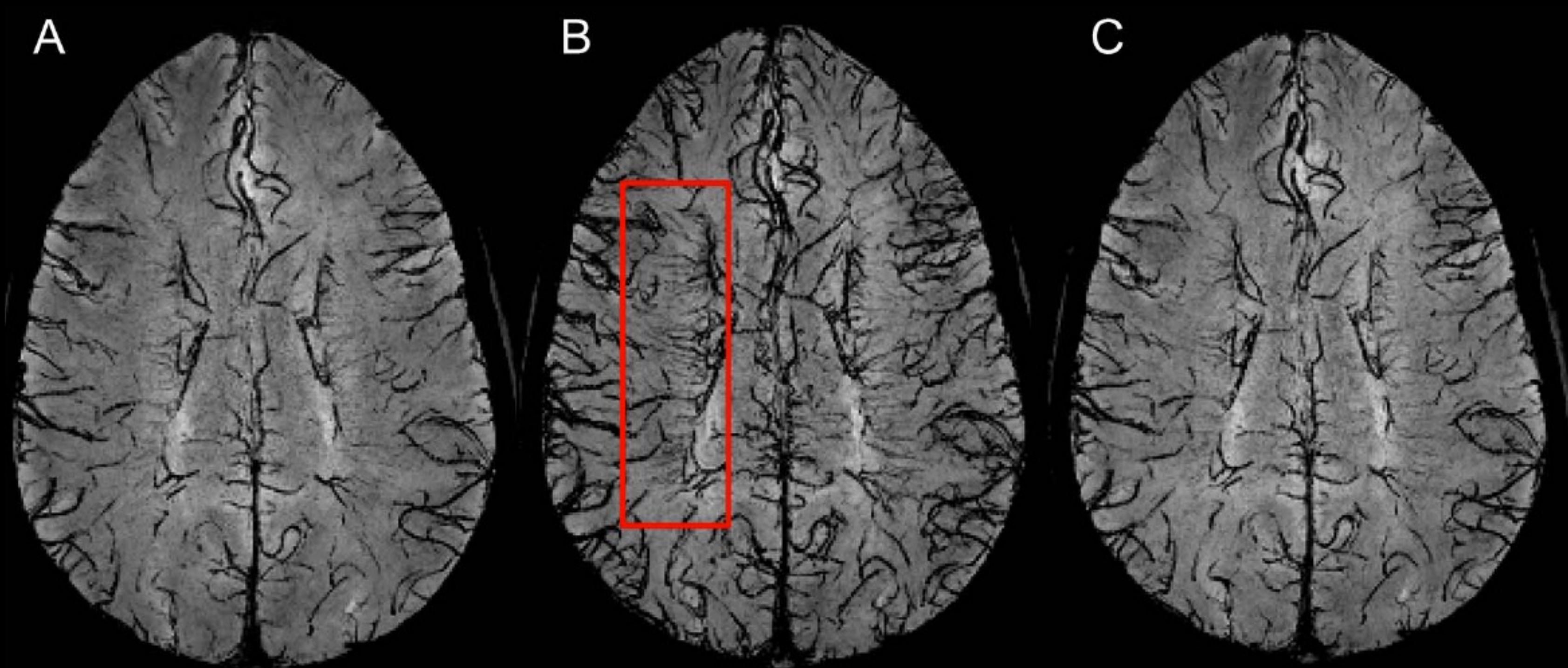
in collaboration with Andrew Derbyshire (NIMH)

Multi-contrast imaging with 3D EPI



Sati et al., Magnetom FLASH (2017)

Increased vein detection on 3DEPI with injection of GBCA

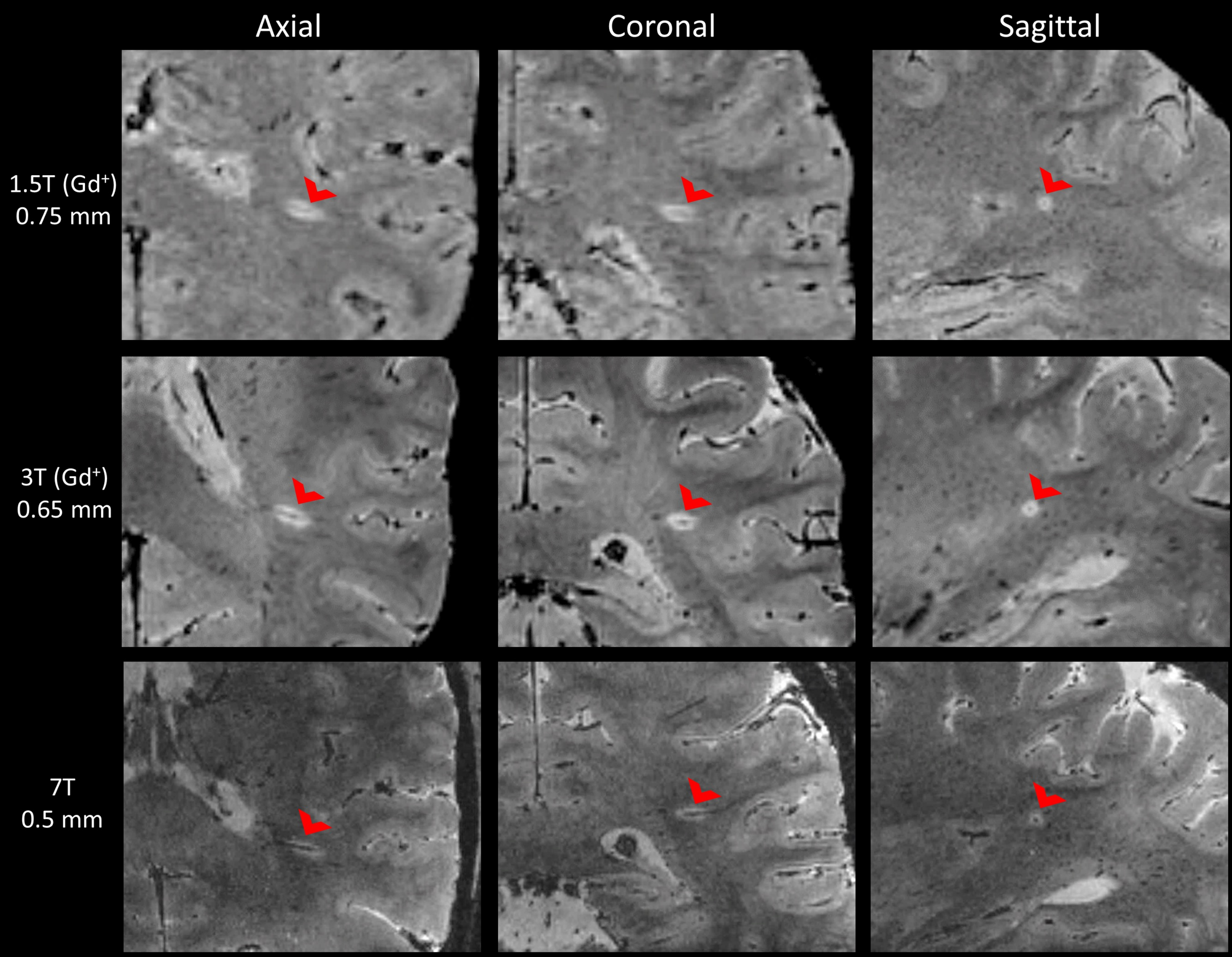


Pre-injection | During injection | Post-injection (15 min)

Injection of a single dose gadobutrol (0.1 mmol/kg) over a minute

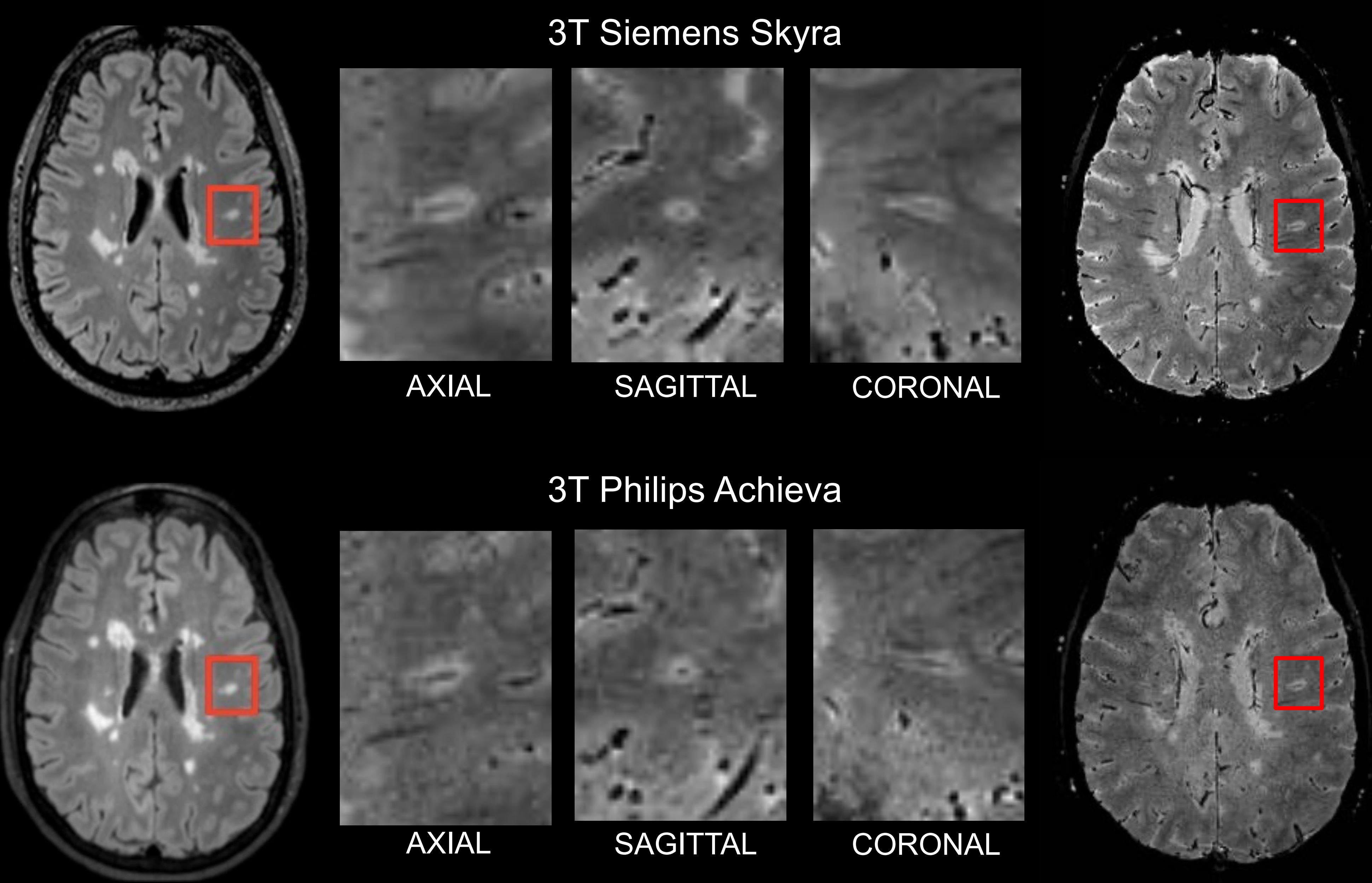
Sati et al., Mult Scler. 2014; 20(11):1464-70

Central vein detection at all field strengths with 3D EPI



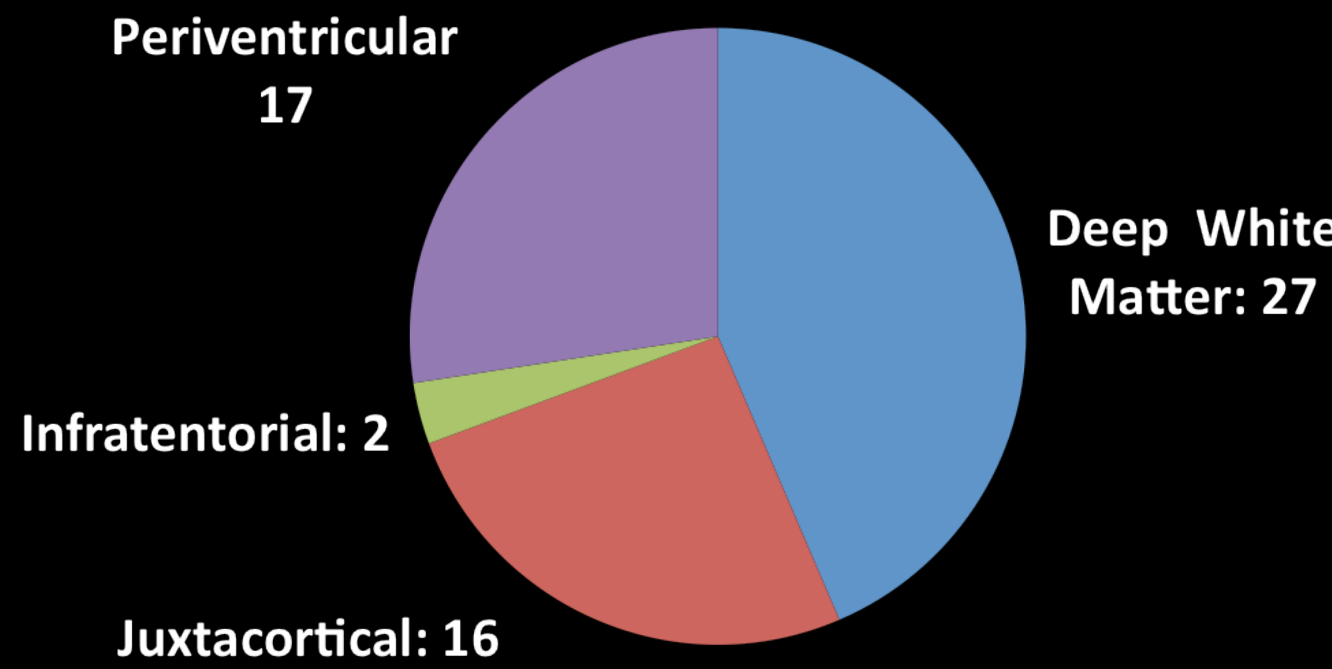
Sati et al., Magnetom FLASH (2017)

3D EPI applicable across MRI manufacturers



Fechner et al., ASNR conference (2017)

61 lesions analyzed on 3D EPI Siemens and Philips



- Excellent agreement between raters (59/61, 96.7%)
- Excellent agreement between scanners (56/59, 94.9%)

Fechner et al., ASNR conference (2017)

Dissemination of 3D EPI across MRI centers specialized in MS

[1] 3T Philips
[2] 3T Siemens

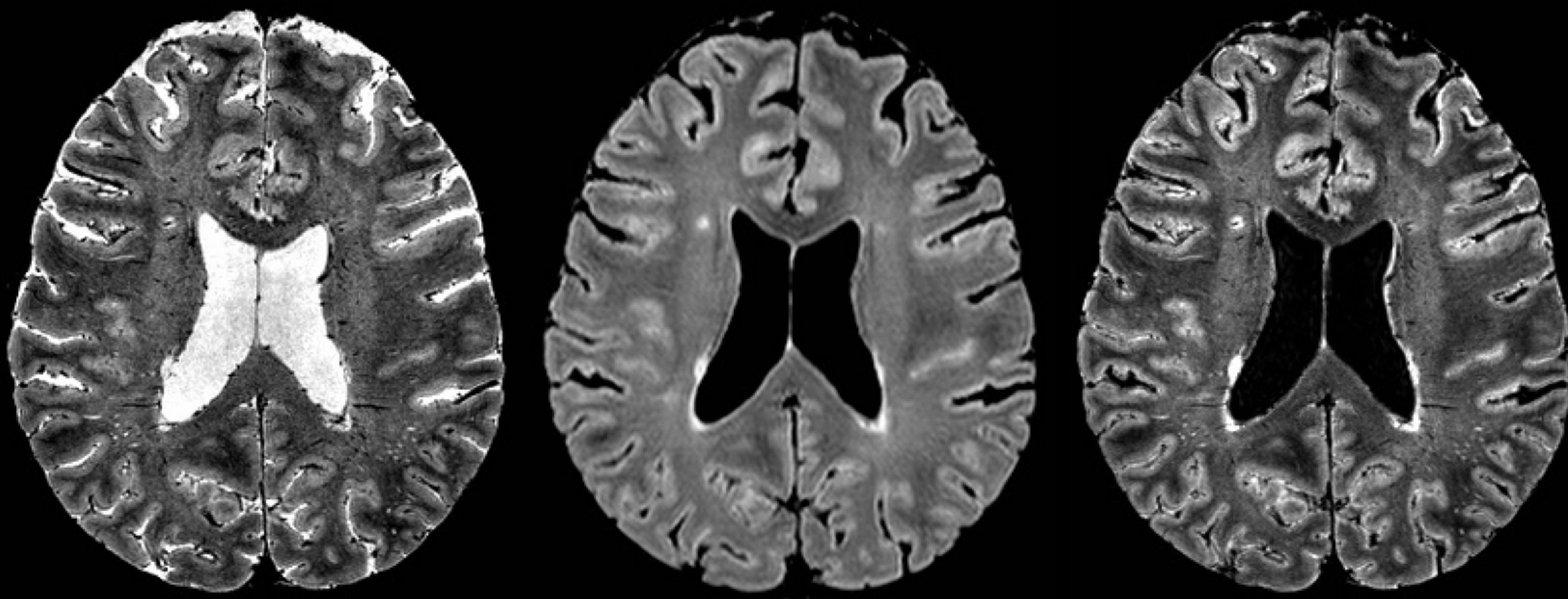
1. San Raffaele Ospedale[1] (Italy)
2. VU University Medical Center[1] (Netherlands)
3. Leiden University Medical Center[1] (Netherlands)
4. University of Nottingham[1] (UK)
5. Barts Health NHS Trust[1], Royal London Hospital (UK)
6. University of Florence[1] (Italy)
7. Universite Libre de Bruxelles[1] (Belgium)
8. Medical University of Graz[2] (Austria)
9. Fondation Rothschild[1], (France)
10. Johns Hopkins University[1] (Maryland, USA)
11. University of Texas Health Science Center at Houston[1] (Texas, USA)
12. Oregon Health & Science University[2] (Oregon, USA)
13. University of Vermont College of Medicine[1] (Vermont, USA)
14. St. Michael's Hospital, University of Toronto[2] (Ontario, Canada)
15. University of California San Francisco[2] (California, USA)
16. Cleveland Clinic Foundation[2], Cleveland (Ohio, USA)
17. University of South California[2] (California, USA)

Proposed brain MRI protocol for MS diagnosis

- 2D or 3D high-resolution (1mm) isotropic T1-weighted (opt.)
- Axial proton-density and/or T2-weighted (mand.)
- Sagittal 2D or 3D T2-FLAIR (mand.)
- Injection of gadolinium-based contrast agent (mand.)
- 5 min “dead time” — Replace with high-resolution 3D EPI
- 2D or 3D contrast-enhanced T1-weighted (mand.)

Total scan time ~30 min

FLAIR* for detecting CV+ lesions in the clinic



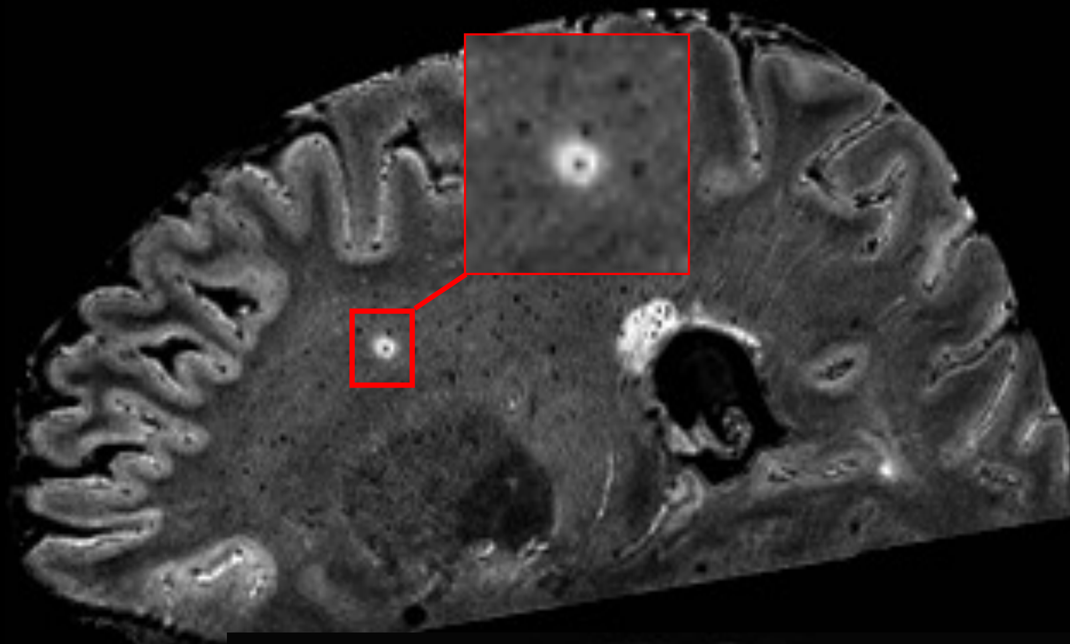
T2*-3D EPI

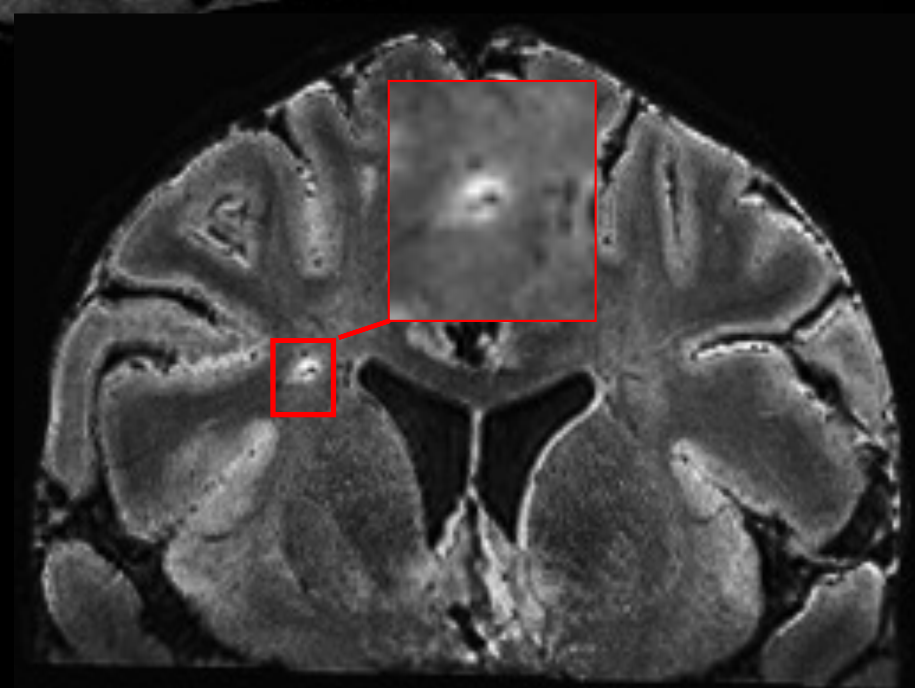
T2-FLAIR

FLAIR*

Sati et al., Radiology (2012)

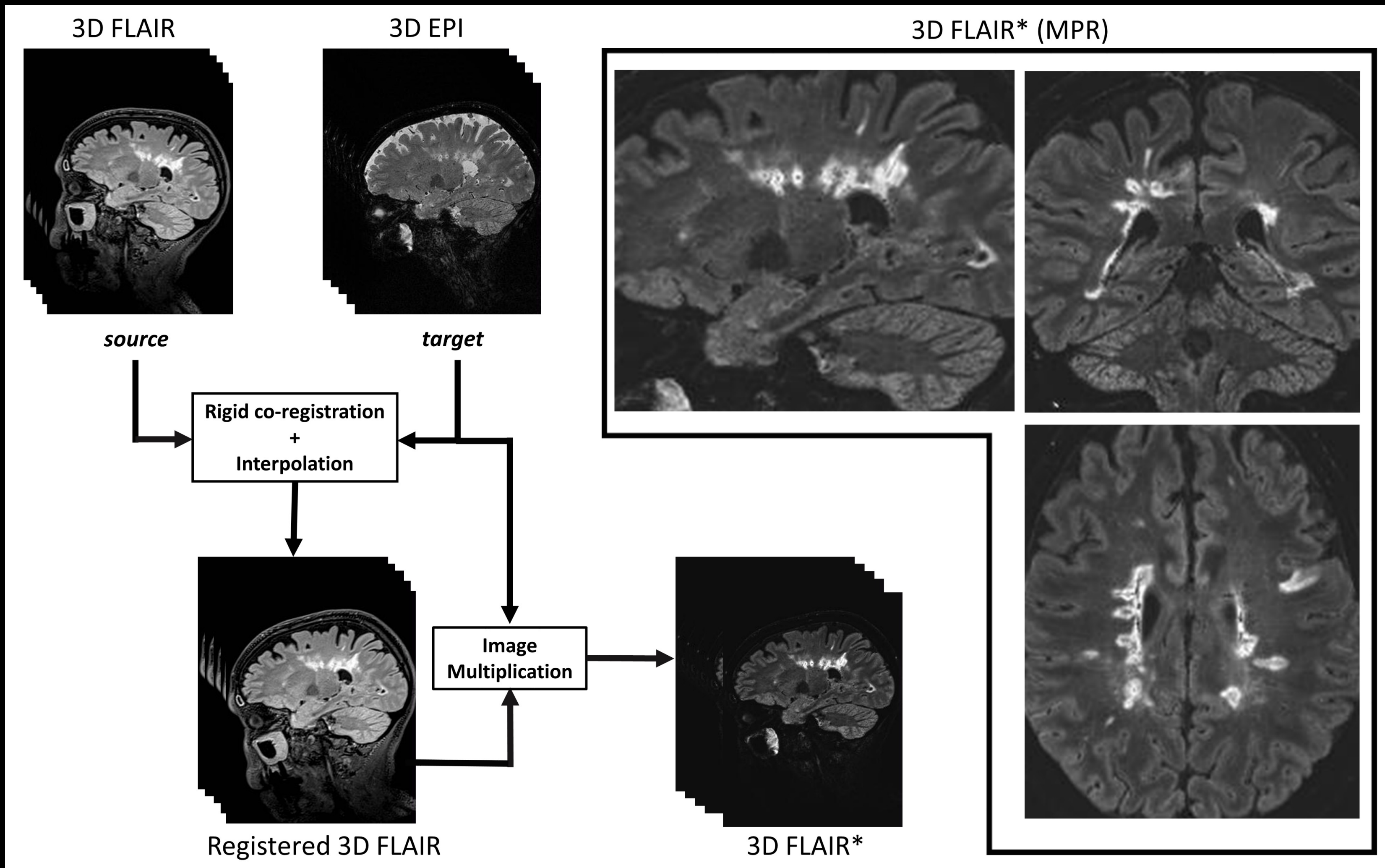
Multi-planar viewing with FLAIR*





Sati et al., Radiology (2012)

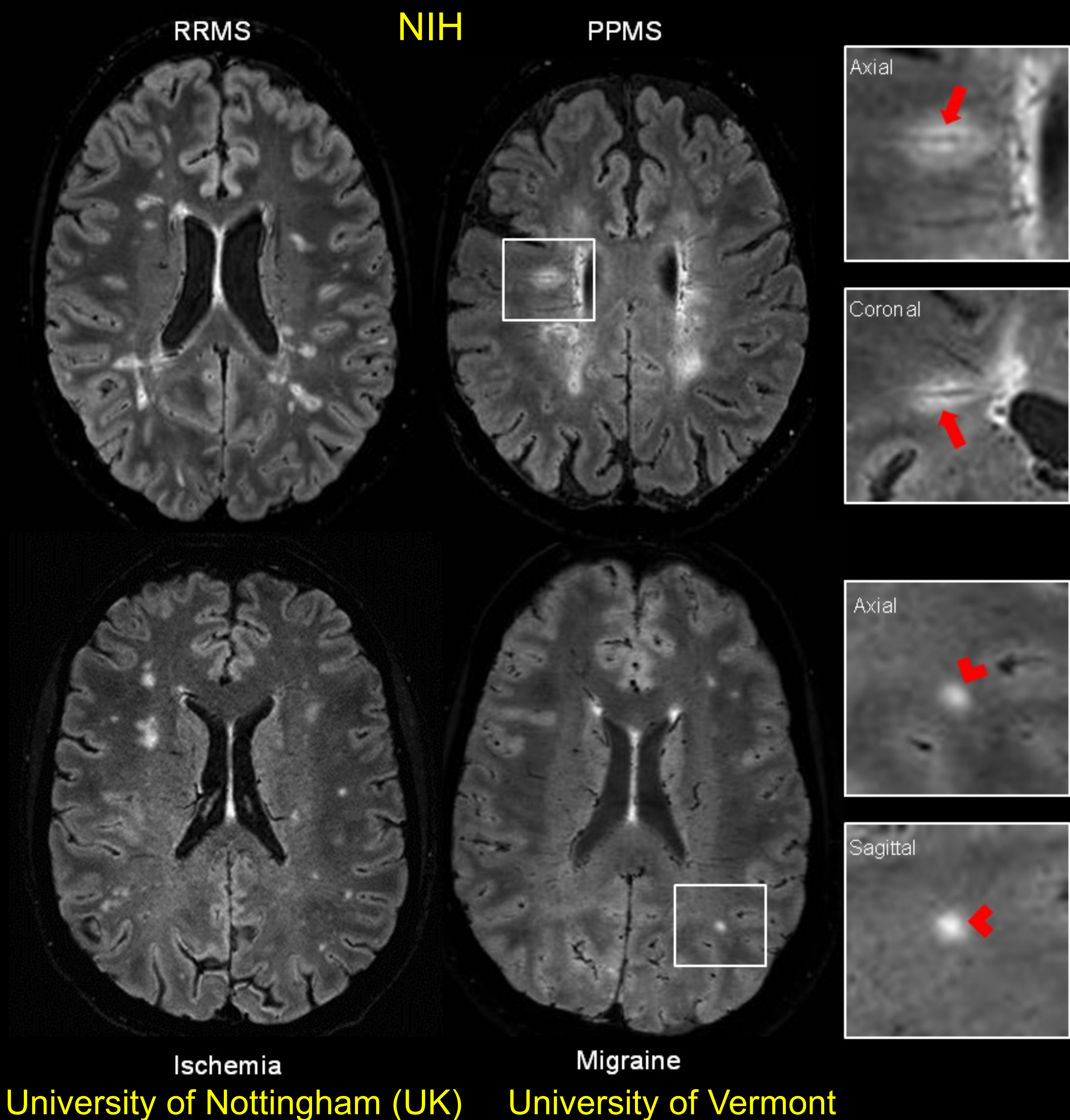
FLAIR* processing pipeline



Can be performed offline (pushed back to PACS), inline using advanced console (syngo.via Frontiers)

Sati et al., Radiology (2012)
Sati et al., Magnetom FLASH (2017)

FLAIR* in the (research) clinic



CentrAl Vein Sign in the early diagnosis of Multiple Sclerosis (CAVS MS)

NAIMS
NORTH AMERICAN IMAGING IN MULTIPLE SCLEROSIS

Prospective observational multi-center pilot study

6 imaging sites (**CCF**, JHU, UCSF, UofT, UVM, UTHealth) + 2 analysis sites (NIH, Penn)

60 patients / site

Primary Objective:
Determine the variability of 3T FLAIR* imaging across sites and across MRI scanners in subjects with a clinical or radiological suspicion of MS.

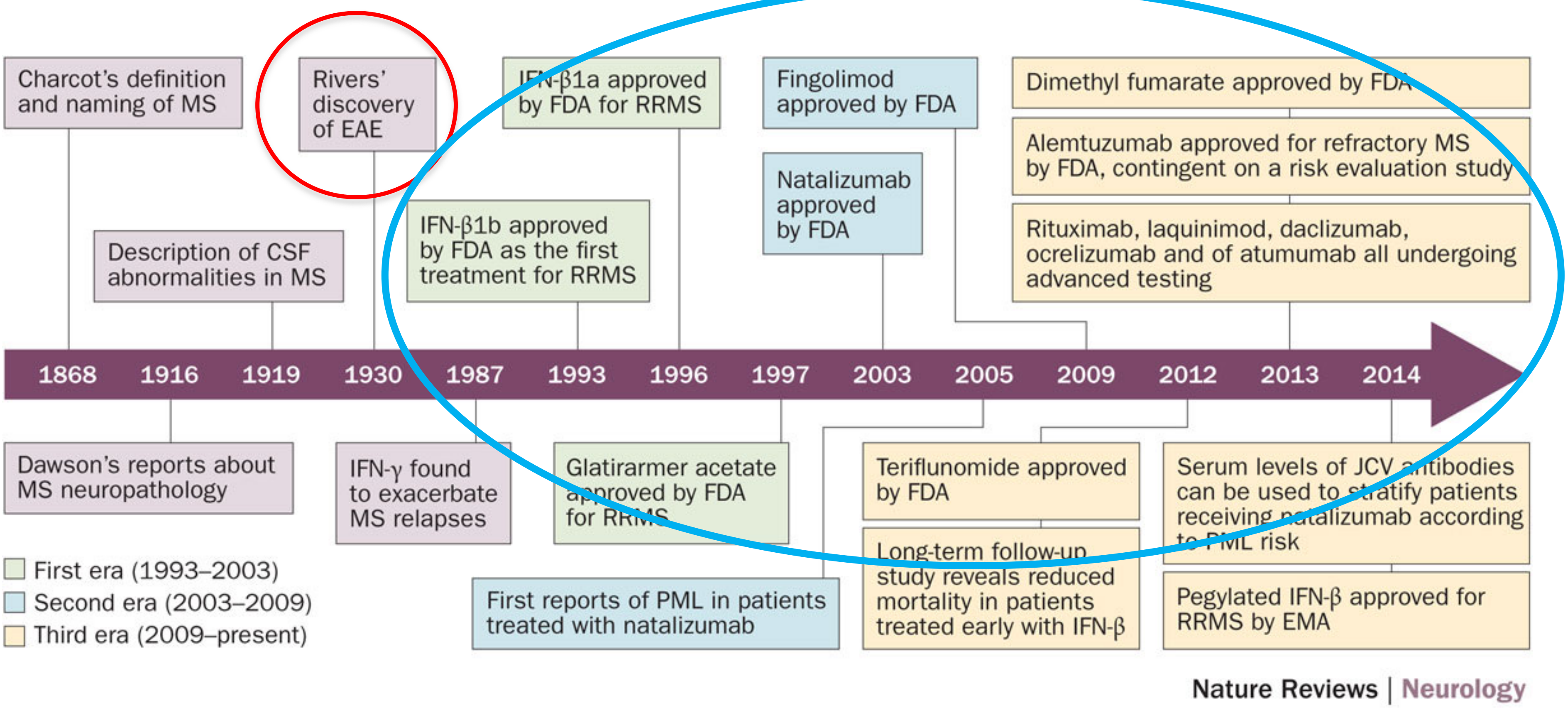
Secondary Objectives:

1. Investigate the difference in CNR identified in the primary objective between pre-contrast FLAIR* imaging and post contrast FLAIR* imaging to identify whether gadolinium injection is required for central vein detection

2. Determine the reproducibility of different methods for detection of positive CVS across sites.

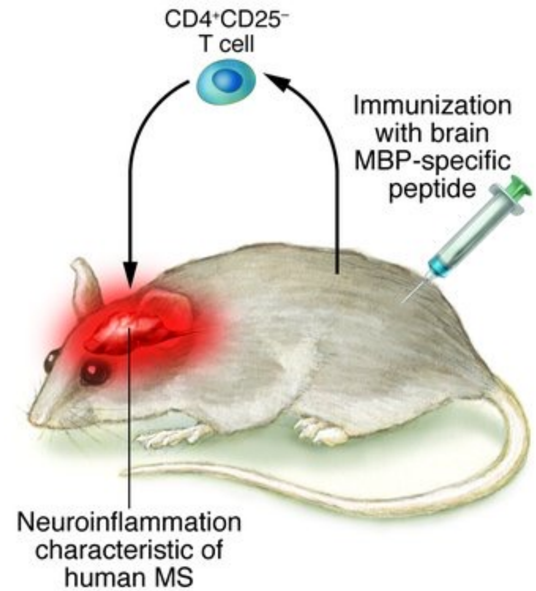
3. Determine the sensitivity and specificity of the different methods for the diagnosis of MS compared to the McDonald 2010 MS criteria.

Timeline for the development of disease-modifying drugs for MS



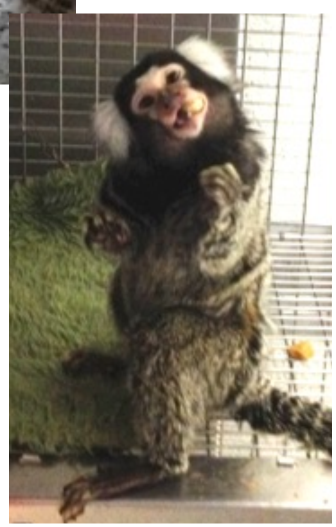
Ransohoff, R. M. *et al.* (2015) *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2015.14

Experimental autoimmune encephalomyelitis (EAE) as an animal model of MS



- Autoimmune aspects of MS can be modeled depending on animal species, strain, antigen, immunization protocol
- Rodent EAE models have been essential in developing successful MS therapies
- However, promising effects in rodent EAE models are often not reproduced in clinical trials (~10% success rate for CNS diseases)
- **Need for an animal model more closely related to MS immunologically and pathogenetically**

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**

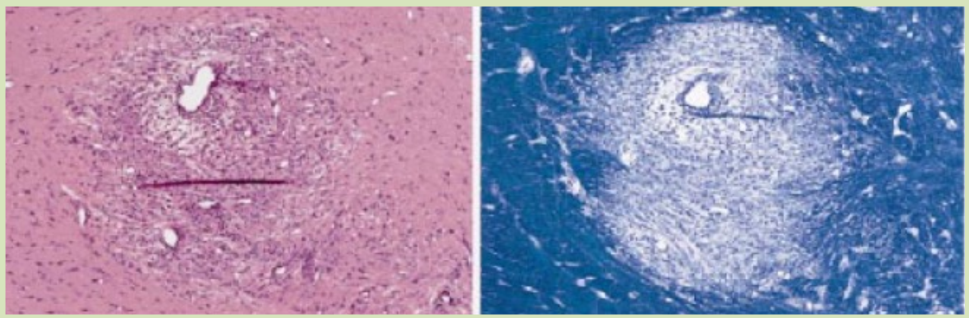
Marmoset EAE : a bridge between rodent EAE and MS

Kap et al. Drug Discovery Today (2016);21(8):1200-5

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

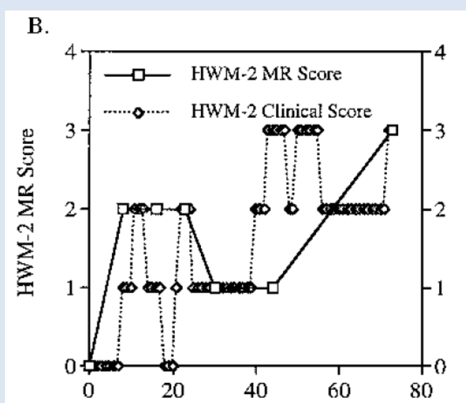
Pathology: scattered perivascular inflammatory infiltrates surrounded by large concentric areas of demyelination and associated with intense macrophage infiltration and mild astrogliosis. *Jordan EK et al., AJNR Am J Neuroradiol. 1999*

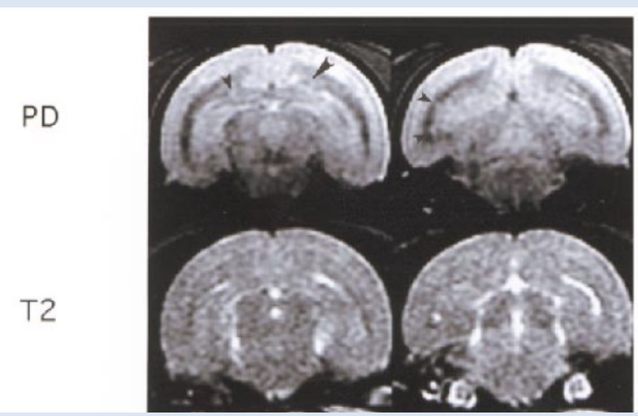
H&E
Dense perivascular mononuclear infiltration



LFB
Demyelination

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*

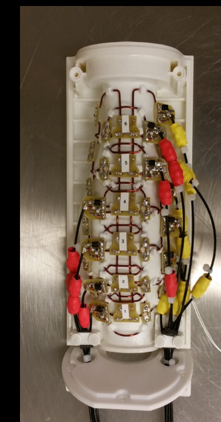


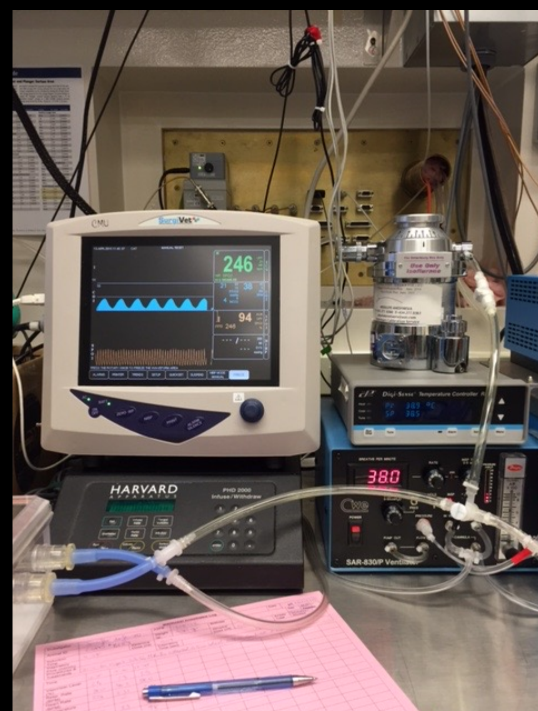


1.5T human MRI (NIH)

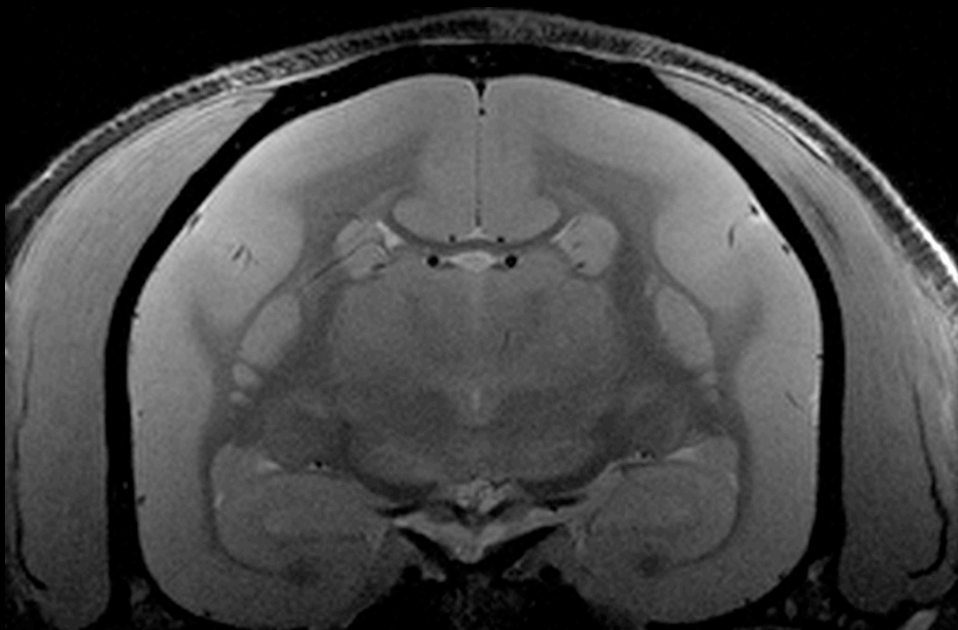
Ultra-high-field (7T) MRI of marmoset CNS

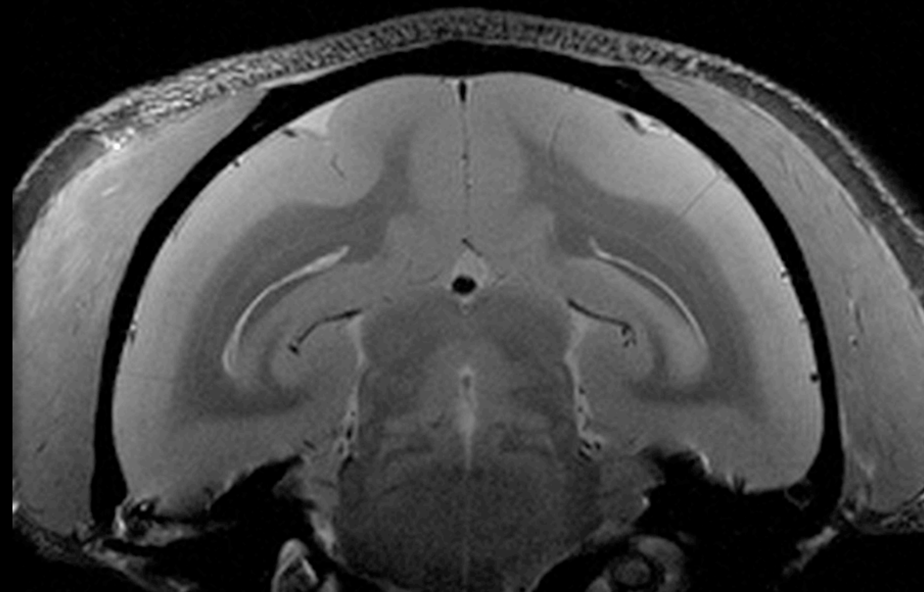
in collaboration with Afonso Silva's laboratory



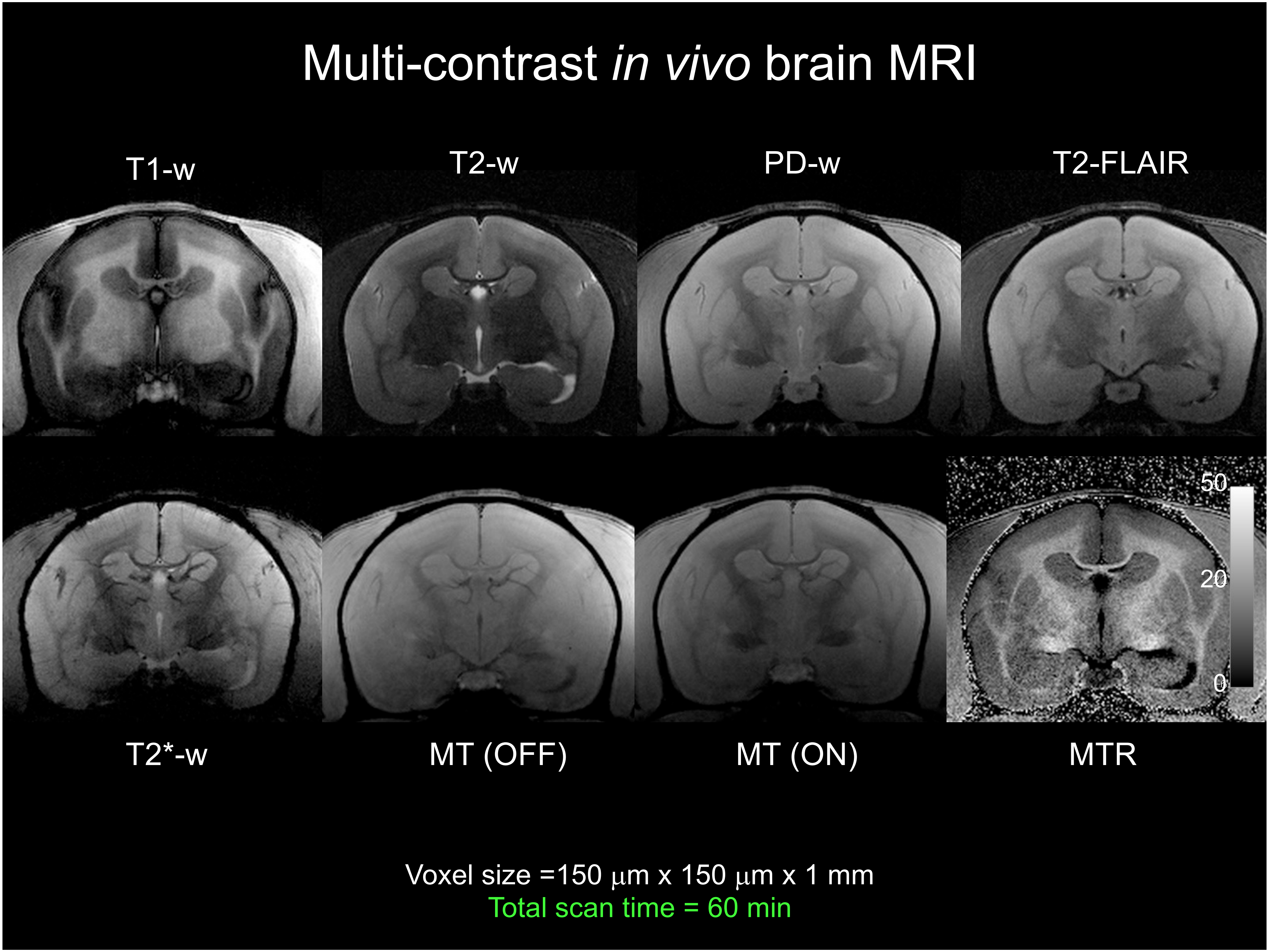


High-resolution *in vivo* 7T MRI of marmoset brain





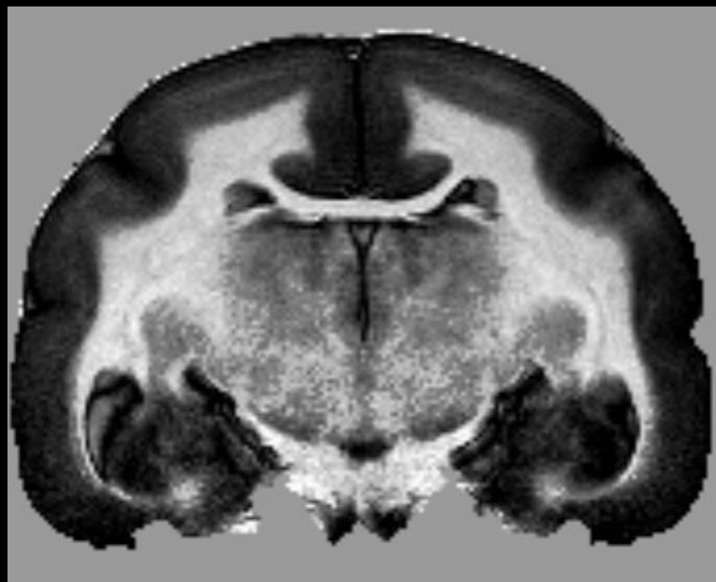
Proton-density weighted
(125 μm in-plane resolution)

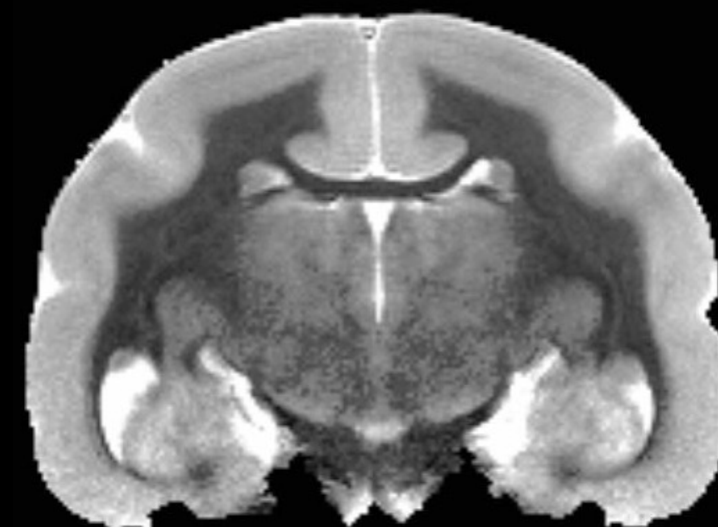

Multi-contrast *in vivo* brain MRI
T1-w
T2-w
PD-w
T2-FLAIR
50
20
0
T2*-w
MT (OFF)
MT (ON)
MTR
Voxel size =150 μm x 150 μm x 1 mm
Total scan time = 60 min

Advanced *in vivo* MRI of marmoset brain

in collaboration with Frank Ye (NIMH) and Steve Dodd (NINDS)

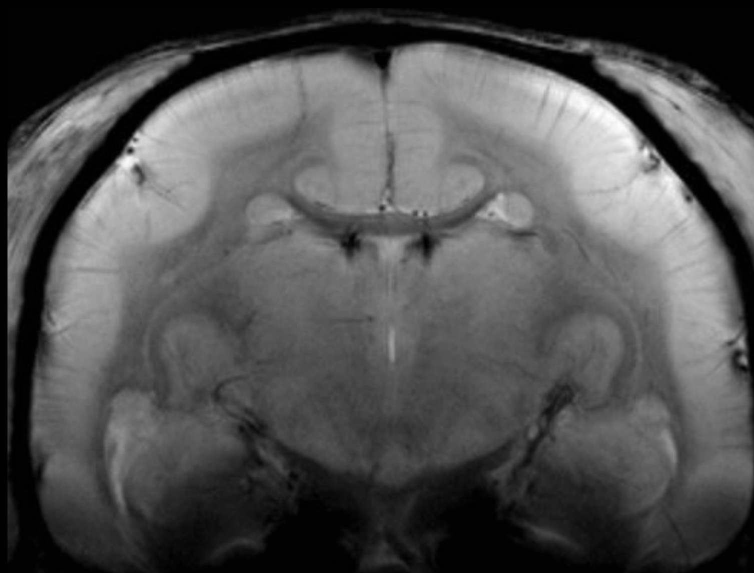
T1w
MP2RAGE





MP2RAGE
T1 map

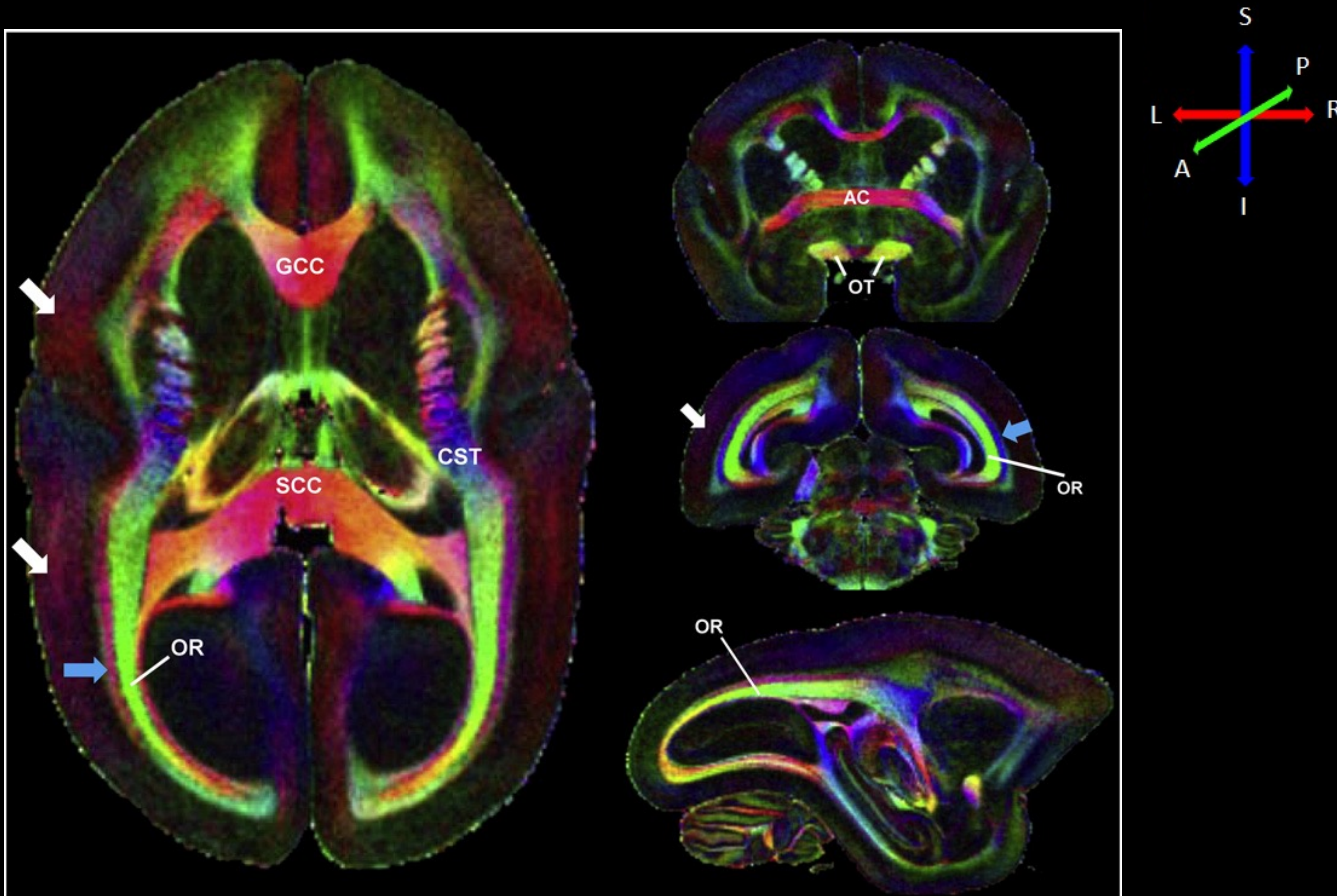
T2*w
T2* map



Phase
QSM

Nathanael Lee (grad student, TNS)

Postmortem MRI of marmoset brain



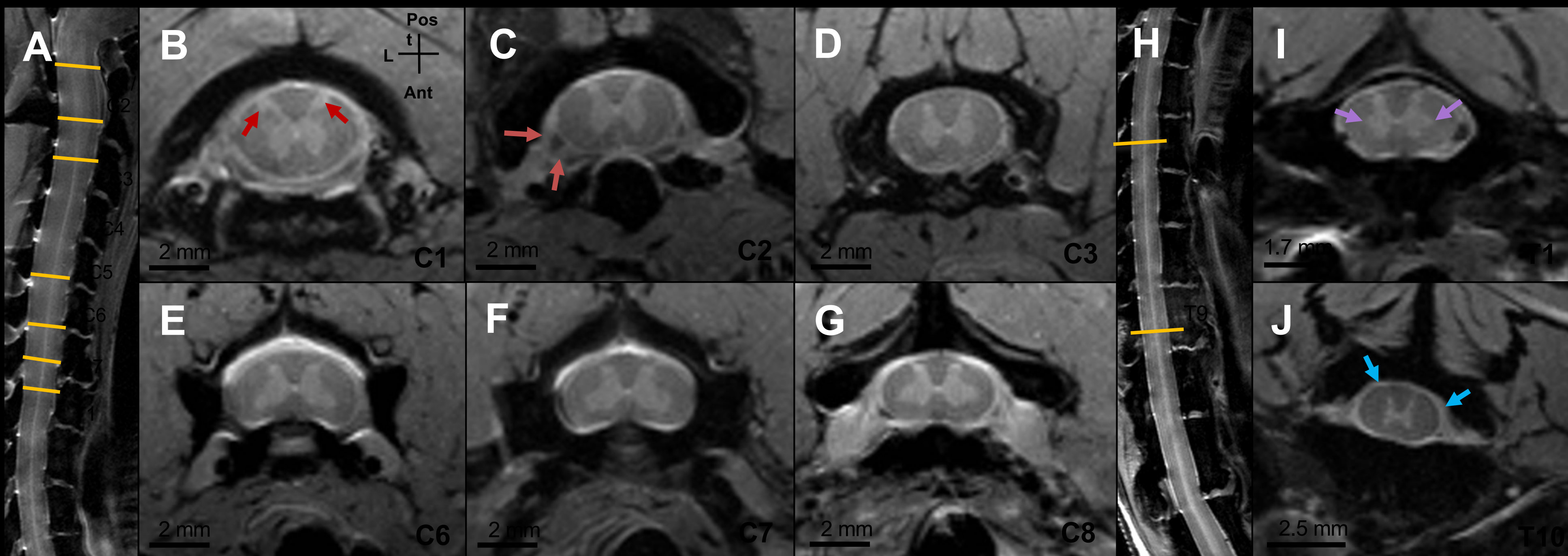
Sati et al., Neuroimage (2012); 59(2):979-85

In vivo spinal cord imaging of marmoset

Jennifer Lefeuvre (grad student, TNS)

Cervical cord

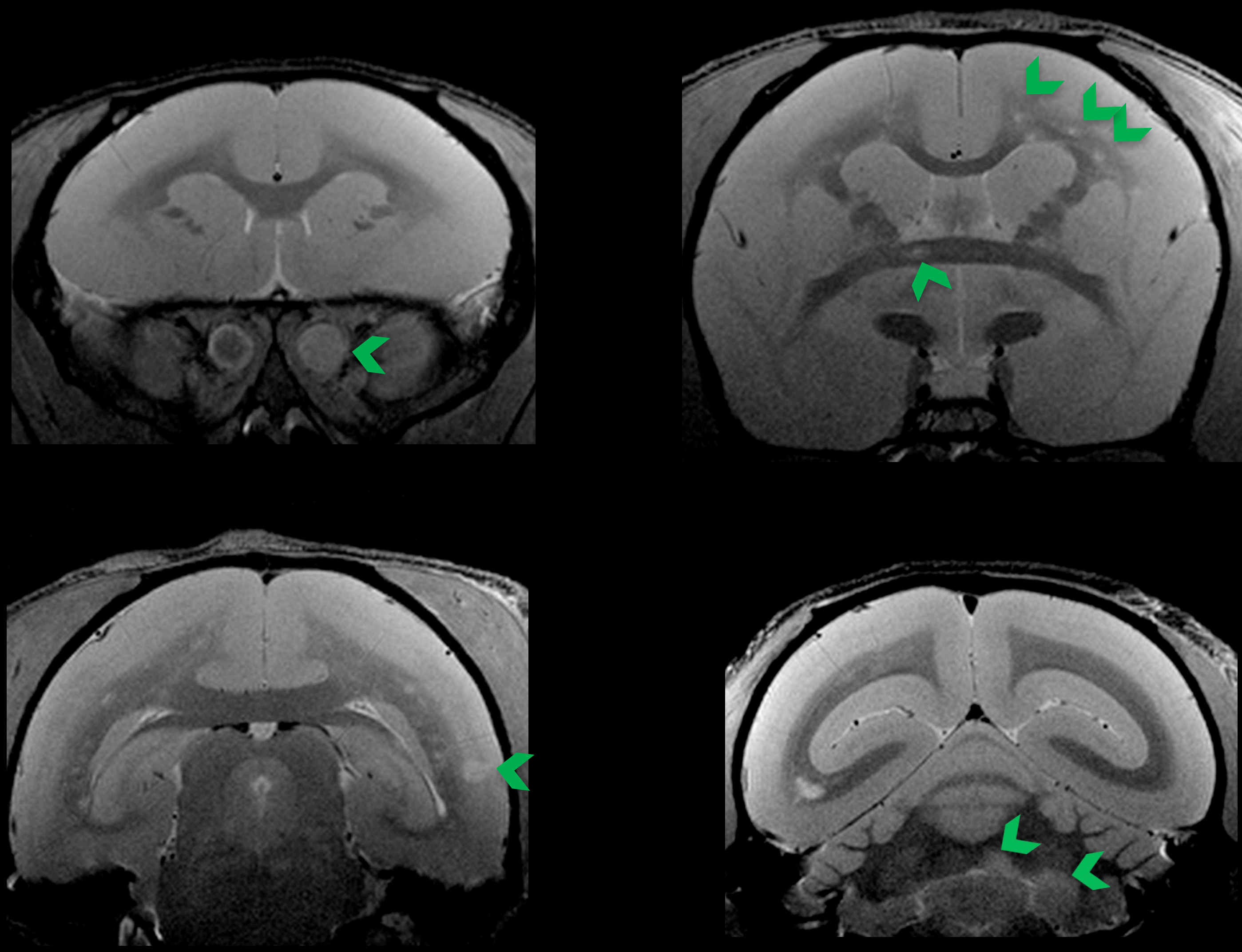
Thoracic cord



Proton-Density weighted
Sagittal: 0.125 x 0.125 x 0.6 mm and axial plane: 0.135 x 0.135 x 0.6 mm

Lefeuvre et al. ISMRM (2017)

Brain lesions in marmoset EAE by *in vivo* MRI

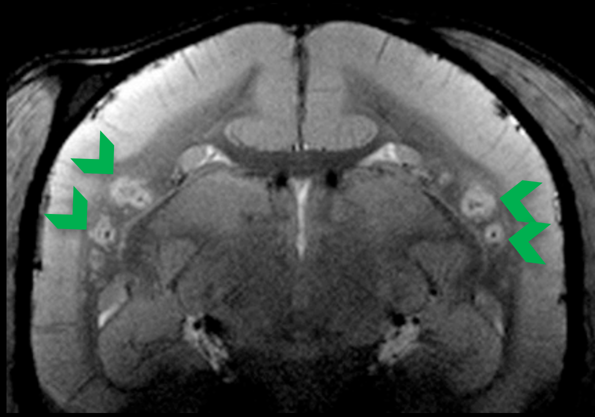


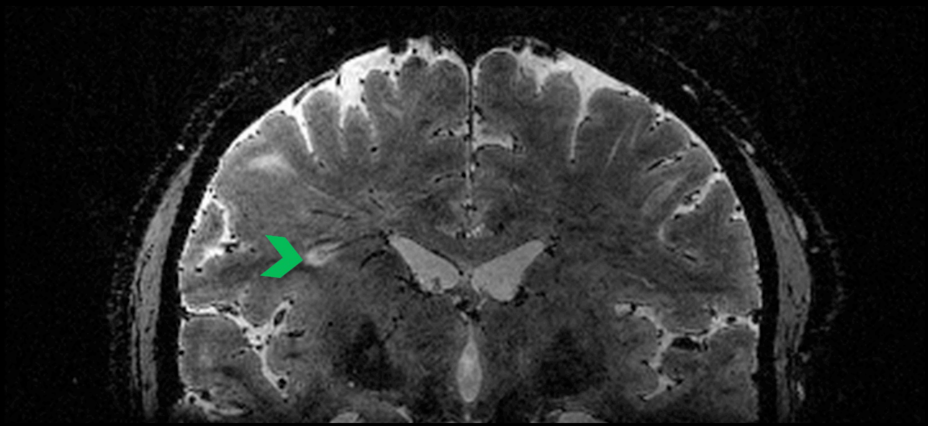
Absinta M, Sati P, Reich DS, Nature Review Neurology (2016); 12(6):358-68
Maggi P, Sati P, Massacesi L. Journal of Neuroimmunology (2017); 304:86-92

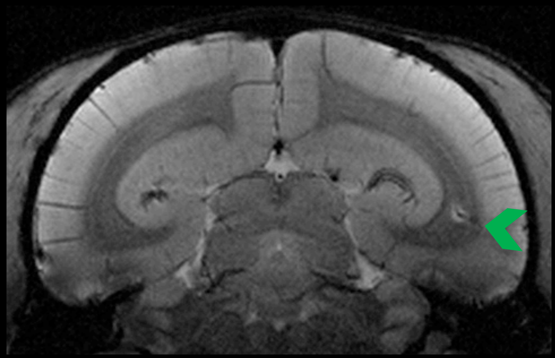
Central veins in EAE and MS lesions

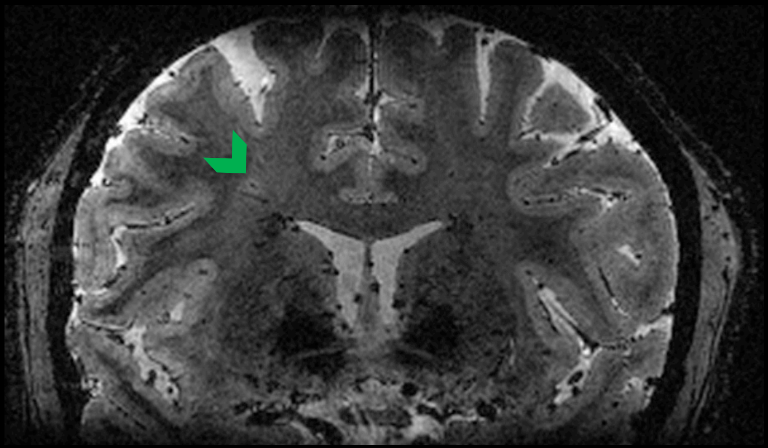
(T2*w - 7T Bruker)

(T2*w - 7T Siemens)









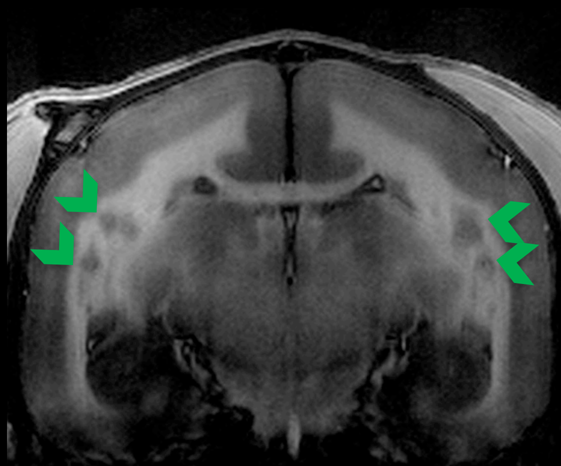
Gaitan et al., Multiple Sclerosis (2014): 20(1):64-71
Absinta M, Sati P, Reich DS, Nature Review Neurology (2016); 12(6):358-68
Maggi P, Sati P, Massacesi L. Journal of Neuroimmunology (2017); 304:86-92

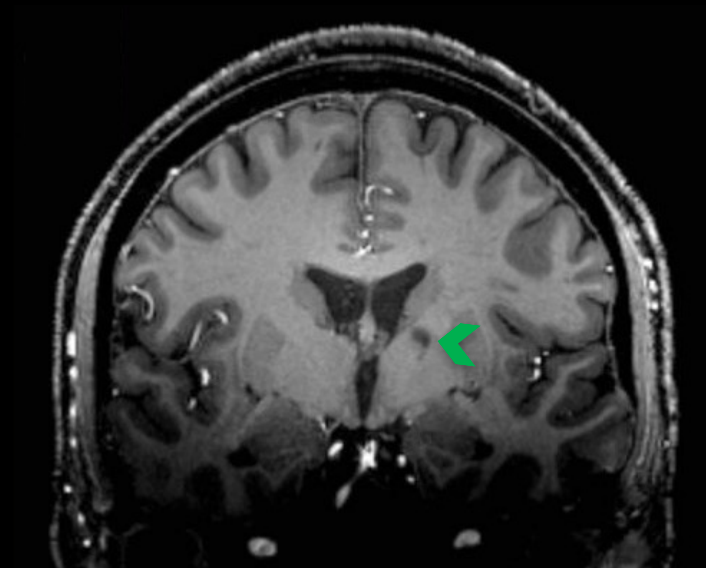
Acute lesions in EAE and MS

(T1w - 7T Bruker)

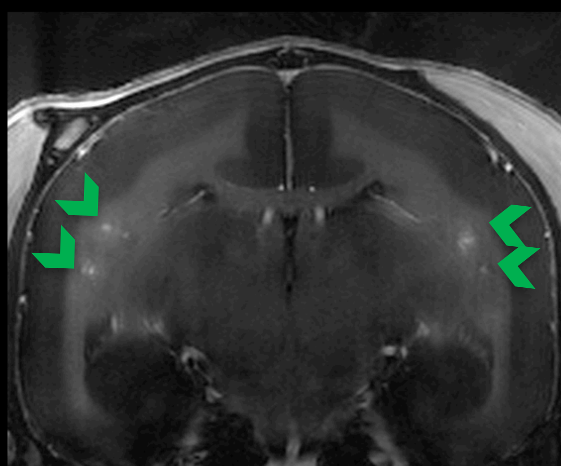
(T1w - 7T Siemens)

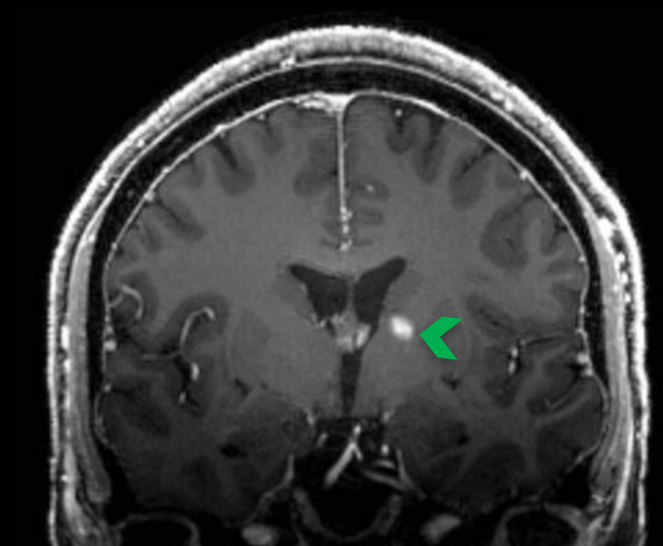
pre-injection





post-injection





Triple-dose gadobutrol (0.3 mL/kg)

single-dose gadobutrol (0.1 mL/kg)

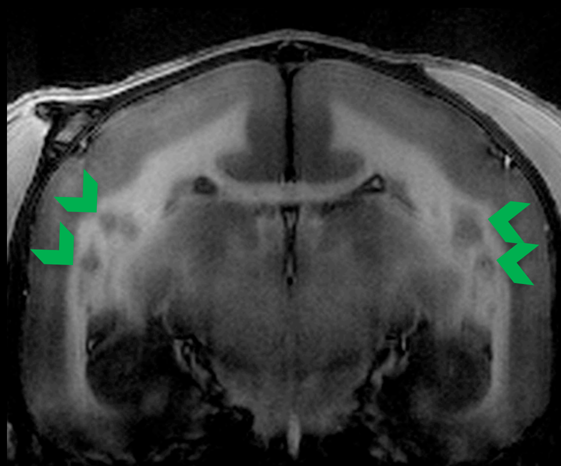
Absinta M, Sati P, Reich DS, Nature Review Neurology (2016); 12(6):358-68
Maggi P, Sati P, Massacesi L. Journal of Neuroimmunology (2017); 304:86-92

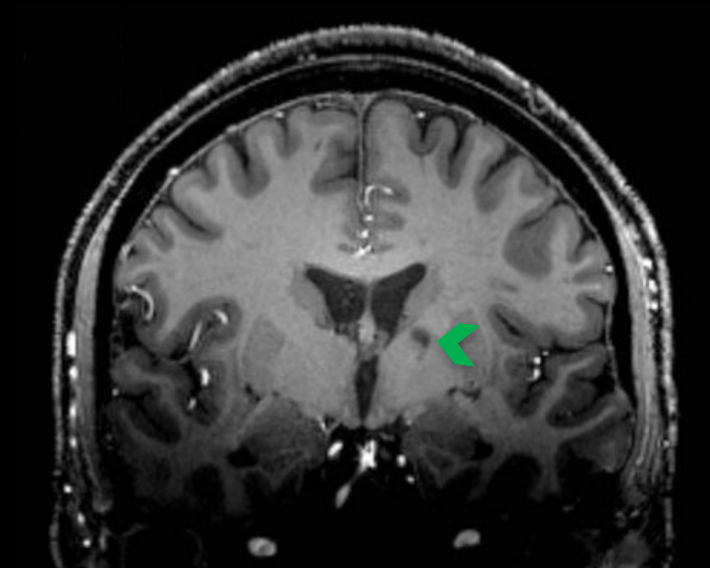
Acute lesions in EAE and MS

(T1w - 7T Bruker)

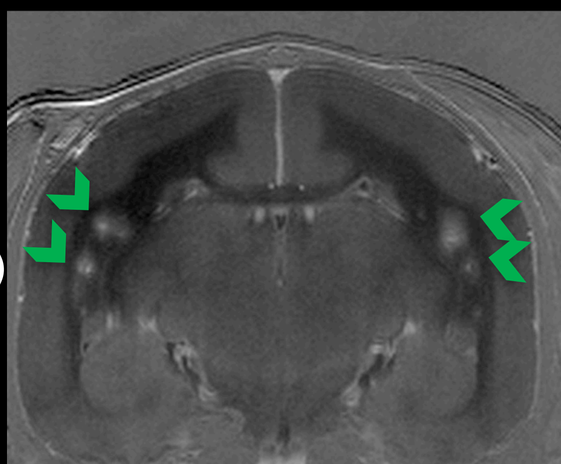
(T1w - 7T Siemens)

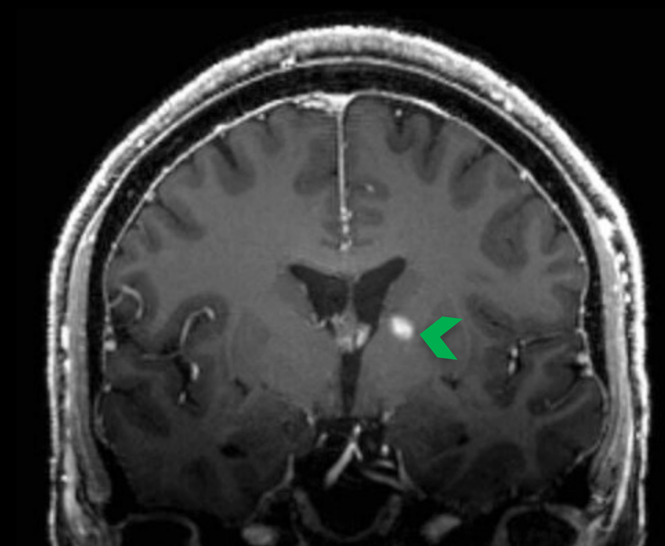
pre-injection





(difference image)





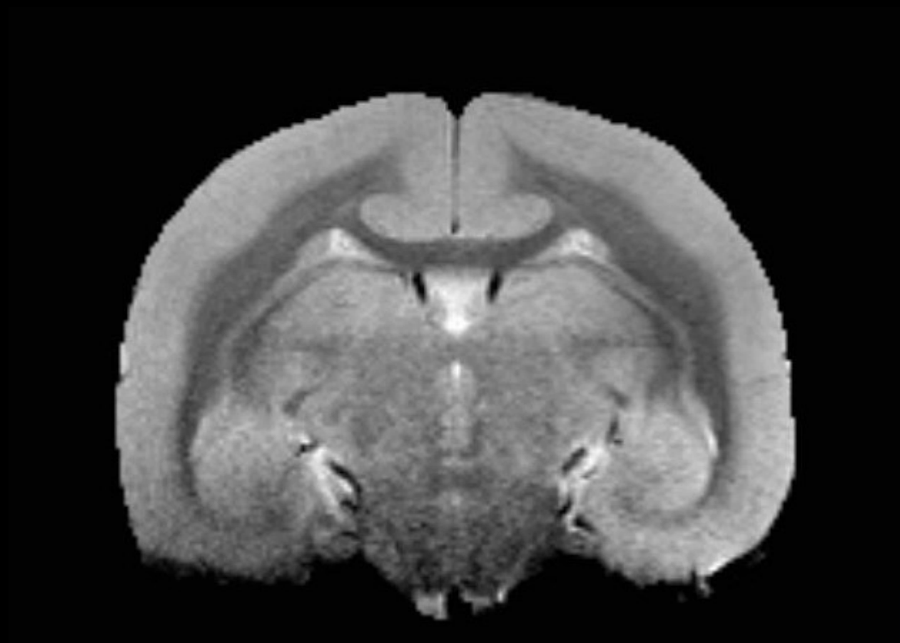
Triple-dose gadobutrol (0.3 mL/kg)

single-dose gadobutrol (0.1 mL/kg)

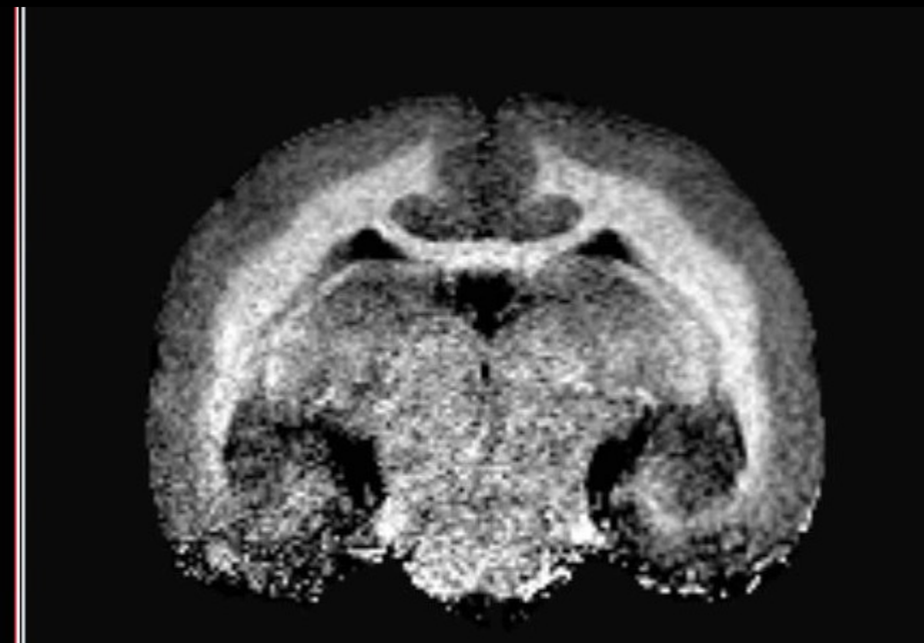
Absinta M, Sati P, Reich DS, Nature Review Neurology (2016); 12(6):358-68
Maggi P, Sati P, Massacesi L. Journal of Neuroimmunology (2017); 304:86-92

Serial brain MRI of marmoset EAE

Proton-Density Weighted



Magnetization Transfer Ratio

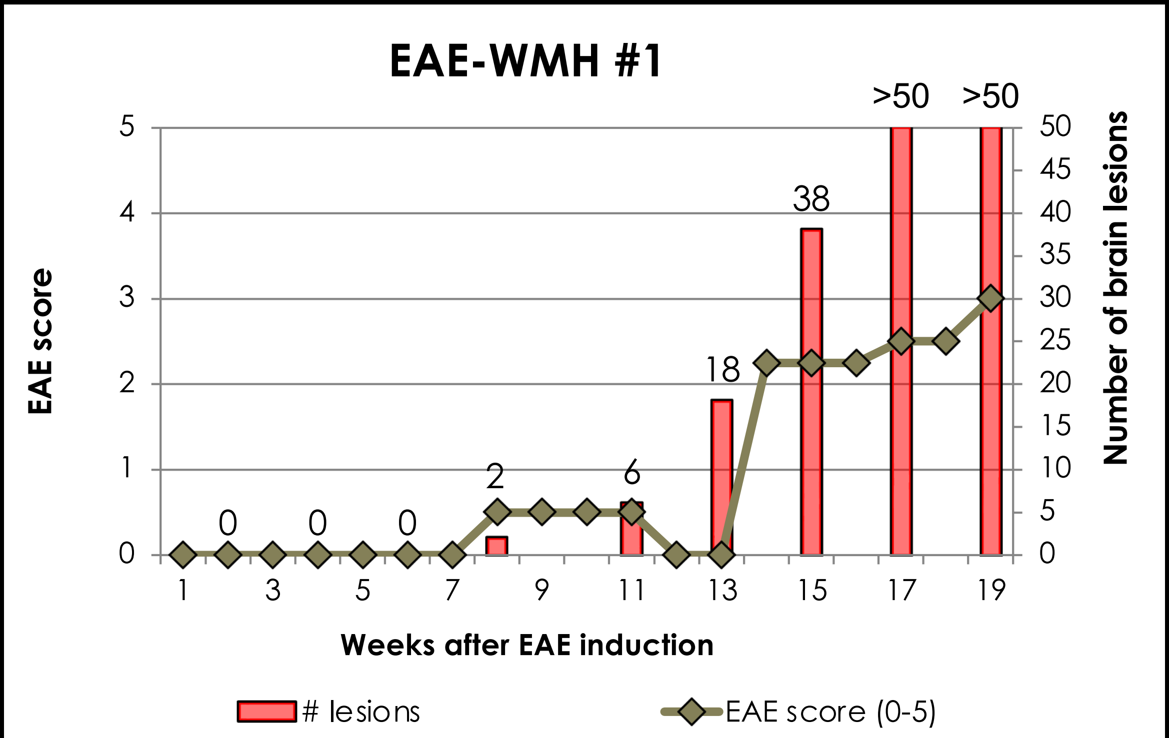


From baseline (healthy) until termination (severe disease)

Time series generated using home-built image processing pipeline

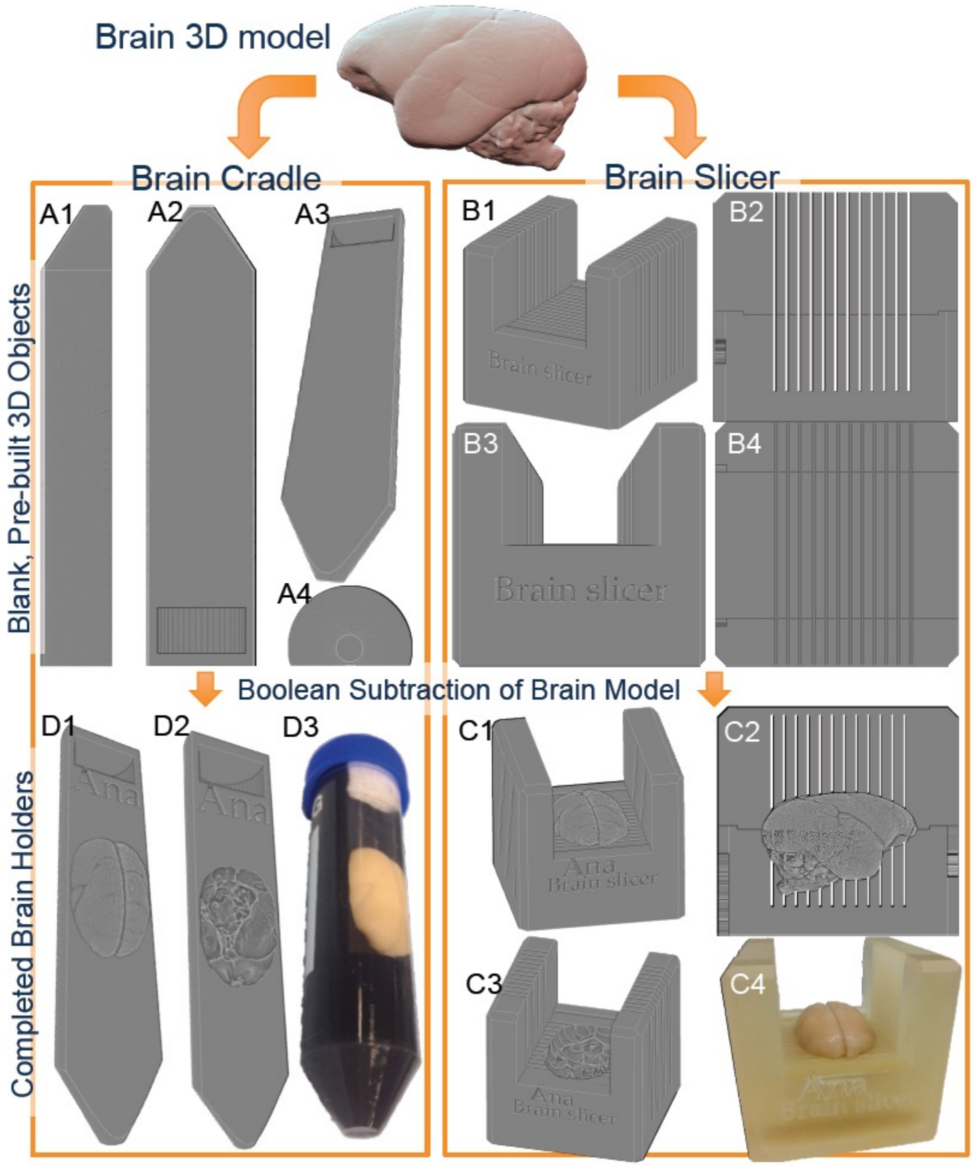
Nicholas Luciano (postbac, TNS), Blake Dewey (grad student, JHU)

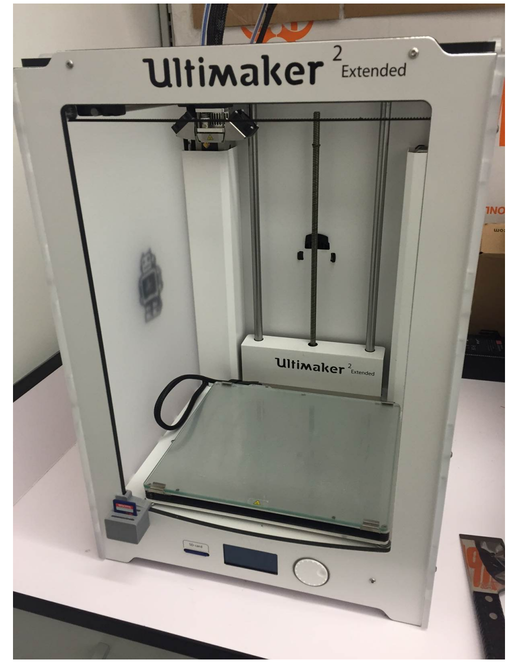
MRI as an outcome for marmoset EAE trials

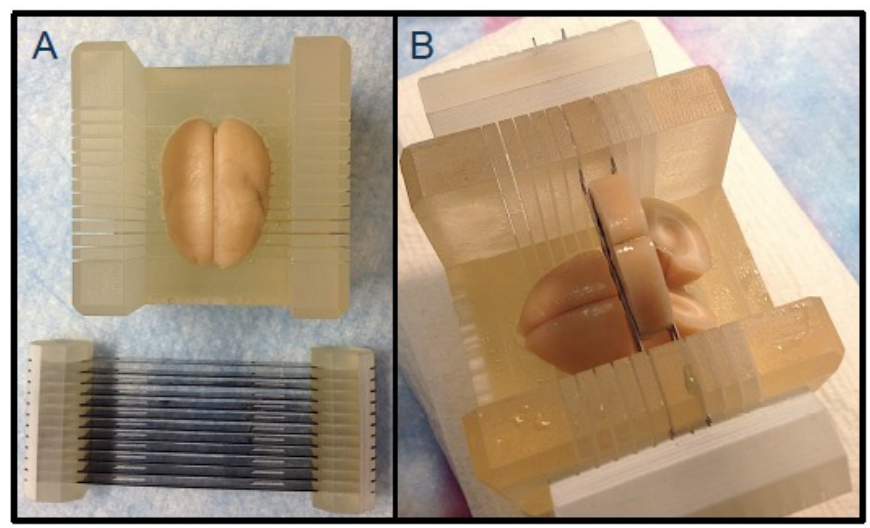


Clinical score, Lesion load, Lesion volume, # of enhancing lesions
(similar to human MS trials)

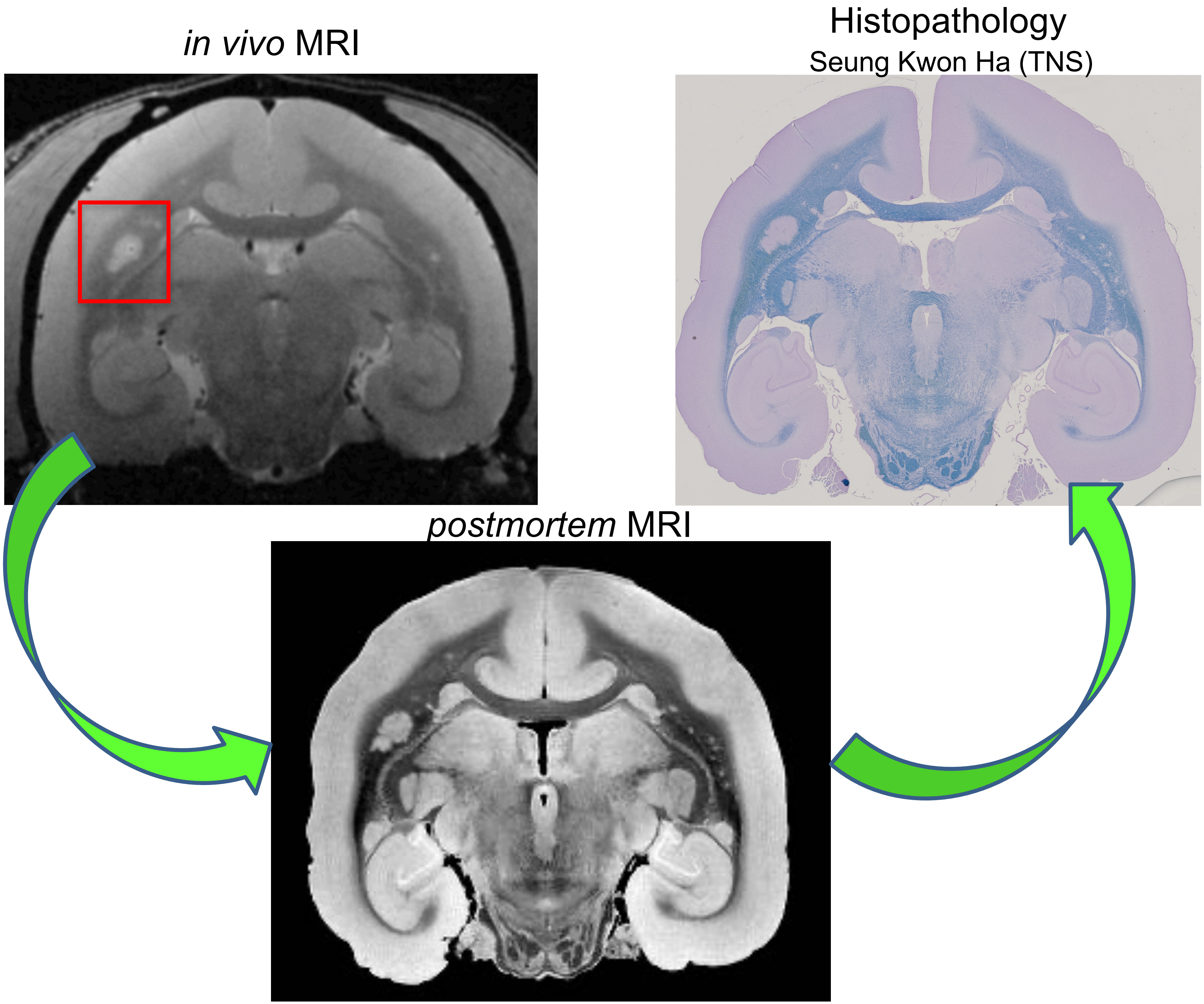
3D-printed marmoset brain holder and slicer





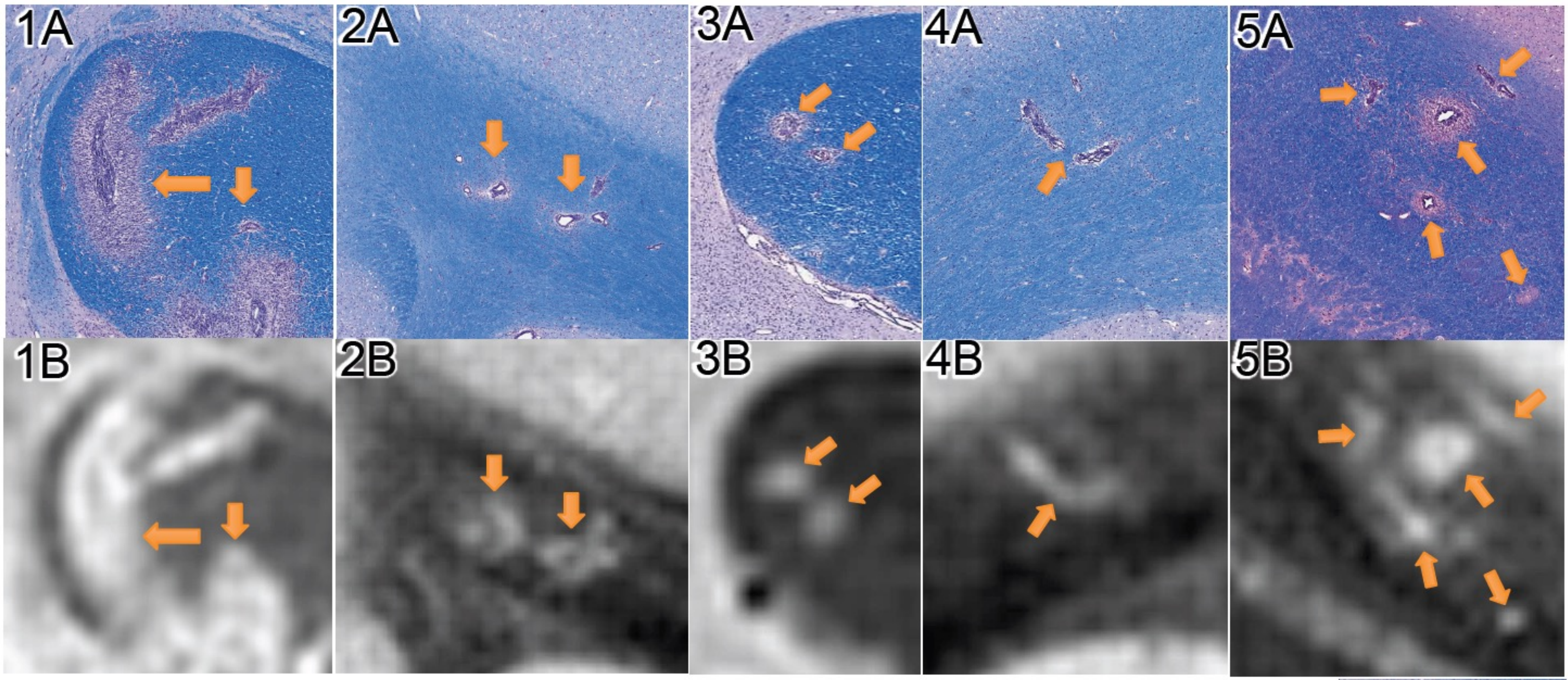


Guy et al., Journal of Neuroscience Methods (2016); 257:55-63
Luciano et al. Journal of Visualized Experiments (2016); 118



Guy et al., Journal of Neuroscience Methods (2016); 257:55-63
Luciano et al. Journal of Visualized Experiments (2016); 118

Method for validation of novel MRI markers

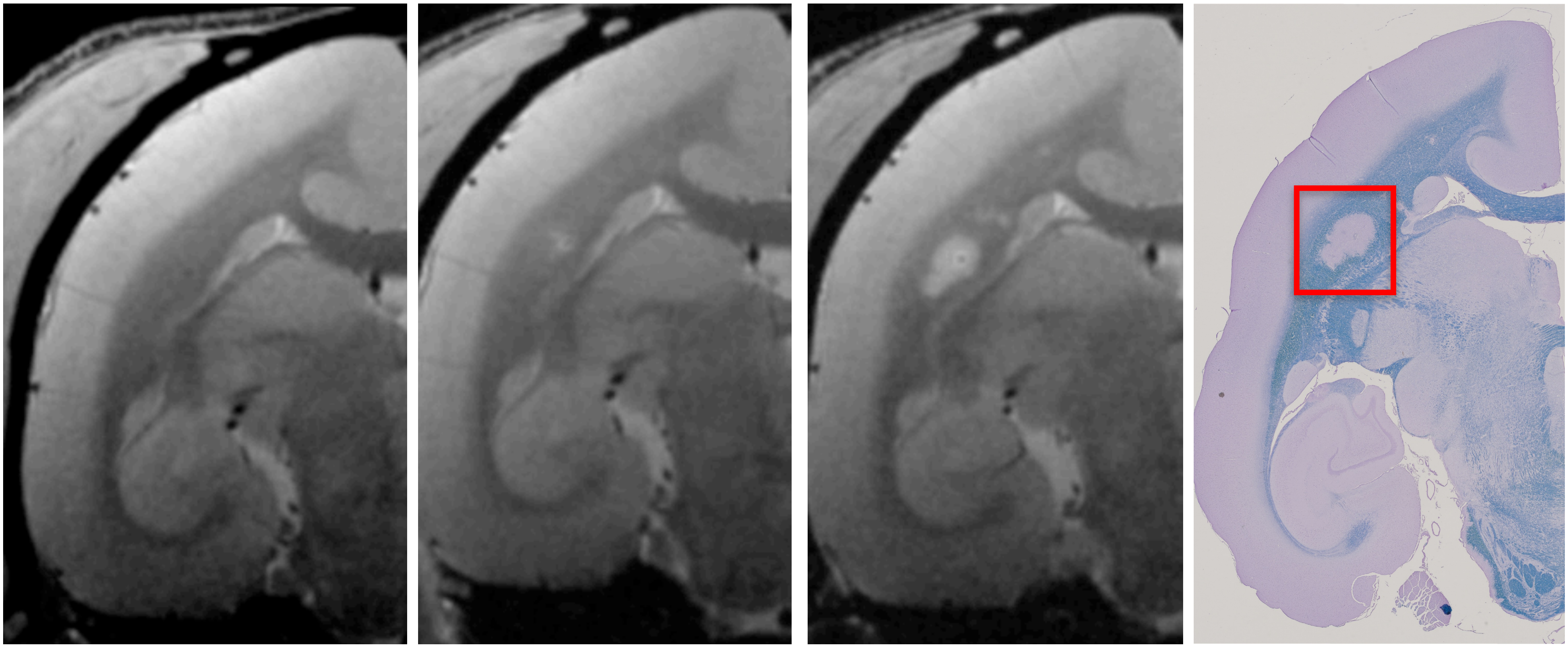


Guy et al., Journal of Neuroscience Methods (2016); 257:55-63
Luciano et al. Journal of Visualized Experiments (2016); 118

Method for unraveling the lesion formation process

“ Back in time” strategy

2 weeks before terminal MRI | 1 week before terminal MRI | Terminal MRI | Histopathology

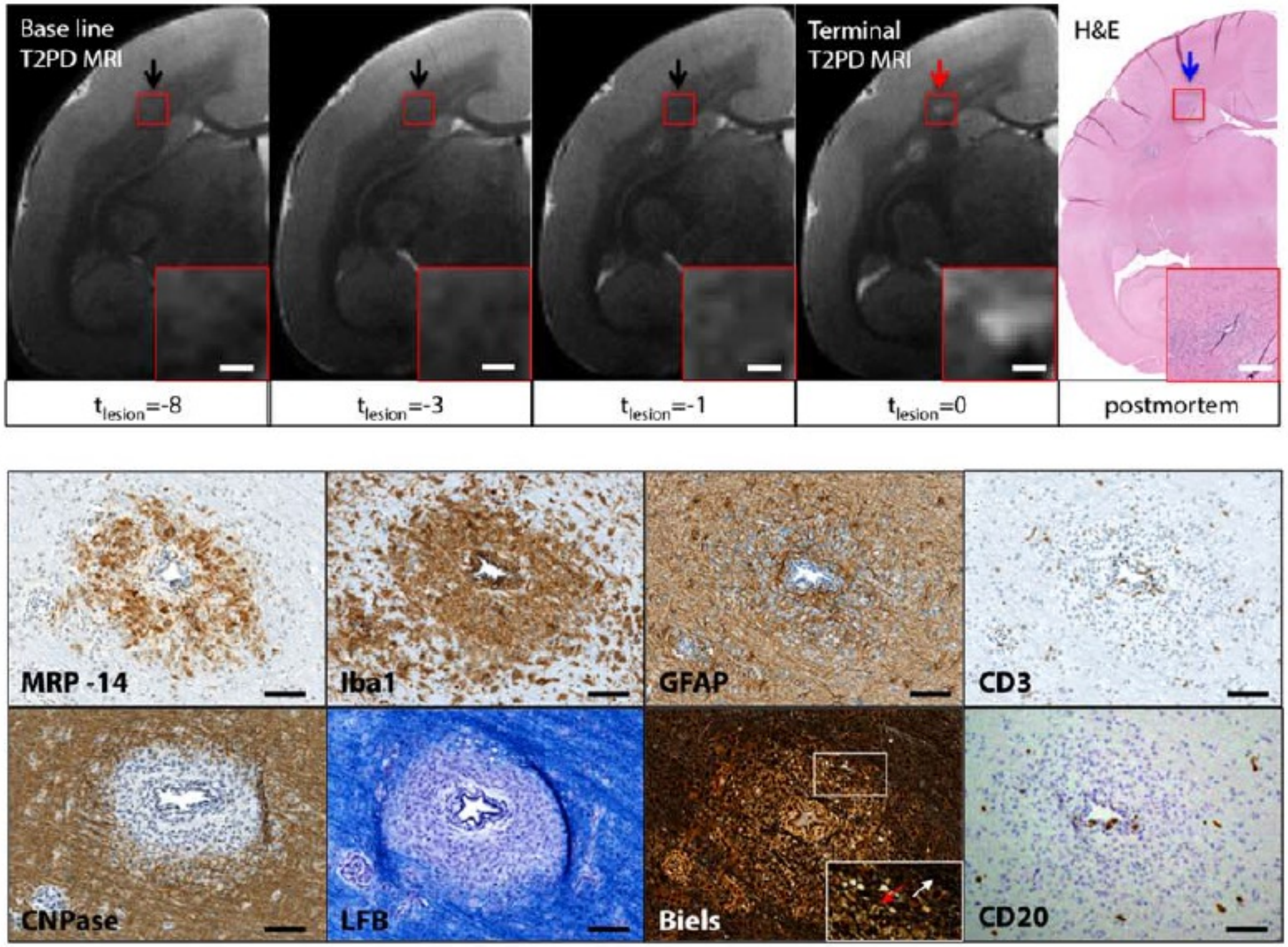


$t_{lesion} = -1$ | $t_{lesion} = 0$ | $t_{lesion} = +1$

Lesion age can be determined based on serial MRI

Maggi P et al. Annals of Neurology (2014); 76(4):594-608

Acute lesions (< 1 week old)

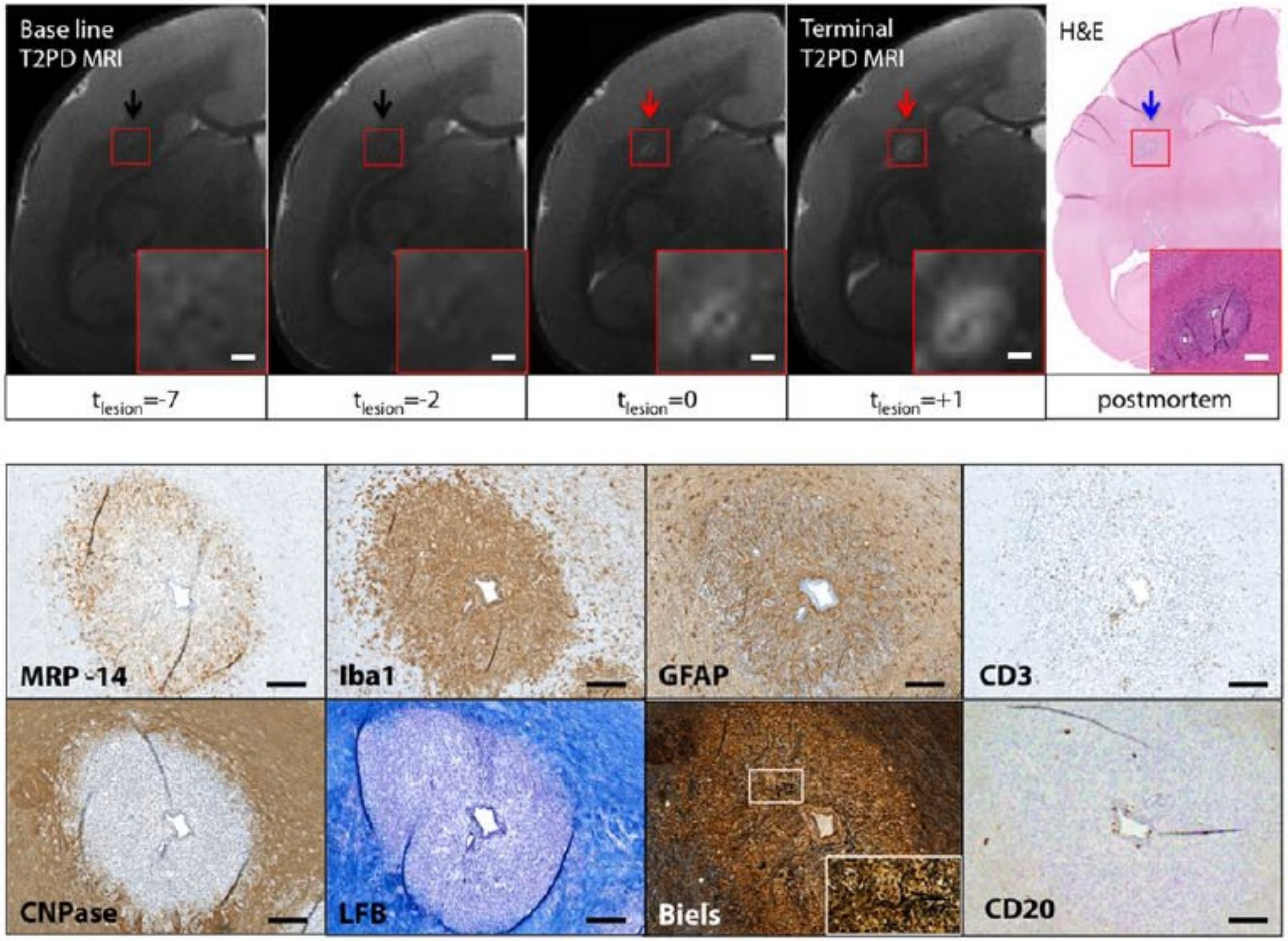


Pathological signature:

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

Maggi P et al. Annals of Neurology (2014); 76(4):594-608

Subacute lesions (1-5 week old)

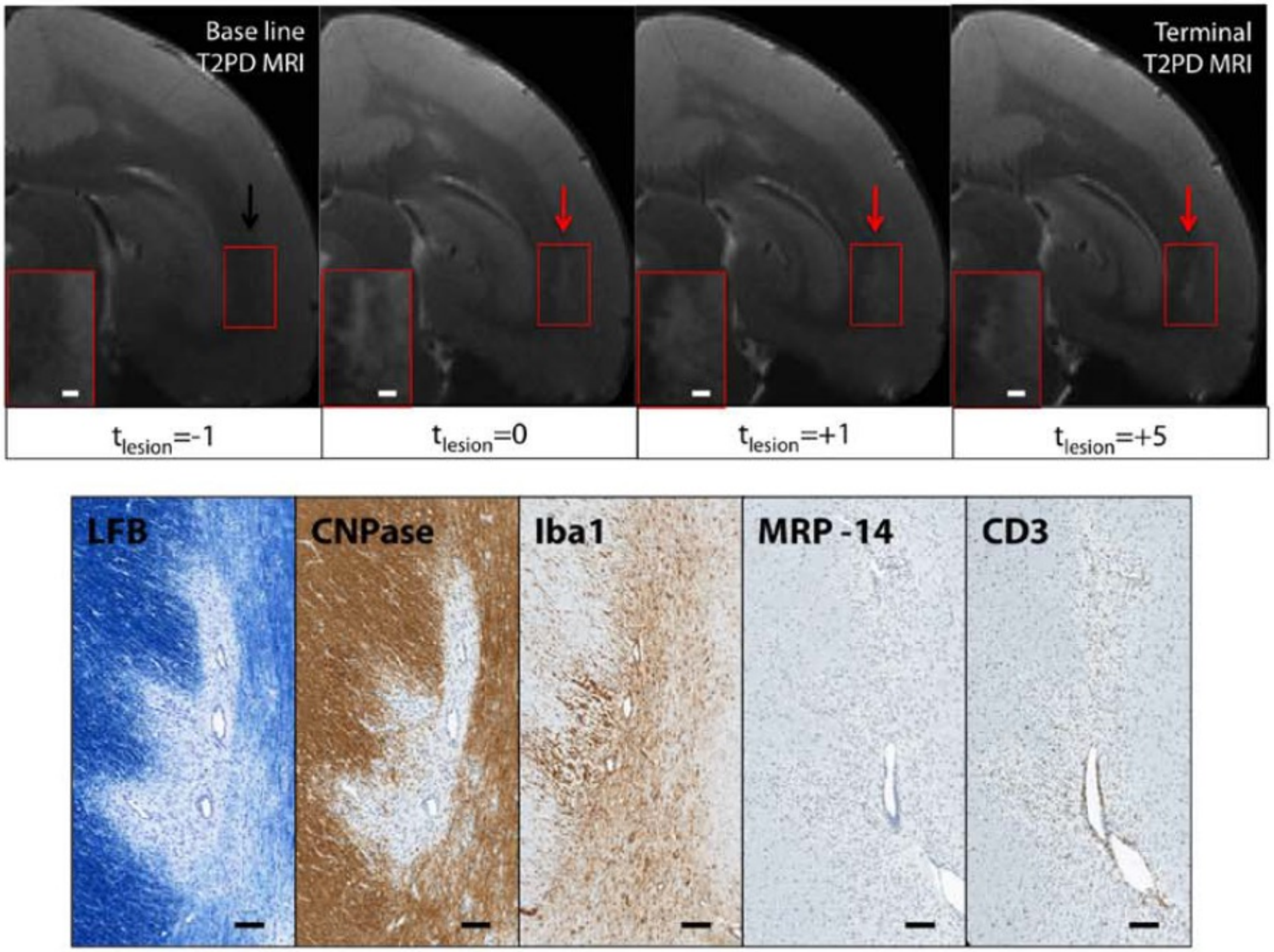


Pathological signature:

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

Maggi P et al. Annals of Neurology (2014); 76(4):594-608

Late subacute lesions (>5 week old)



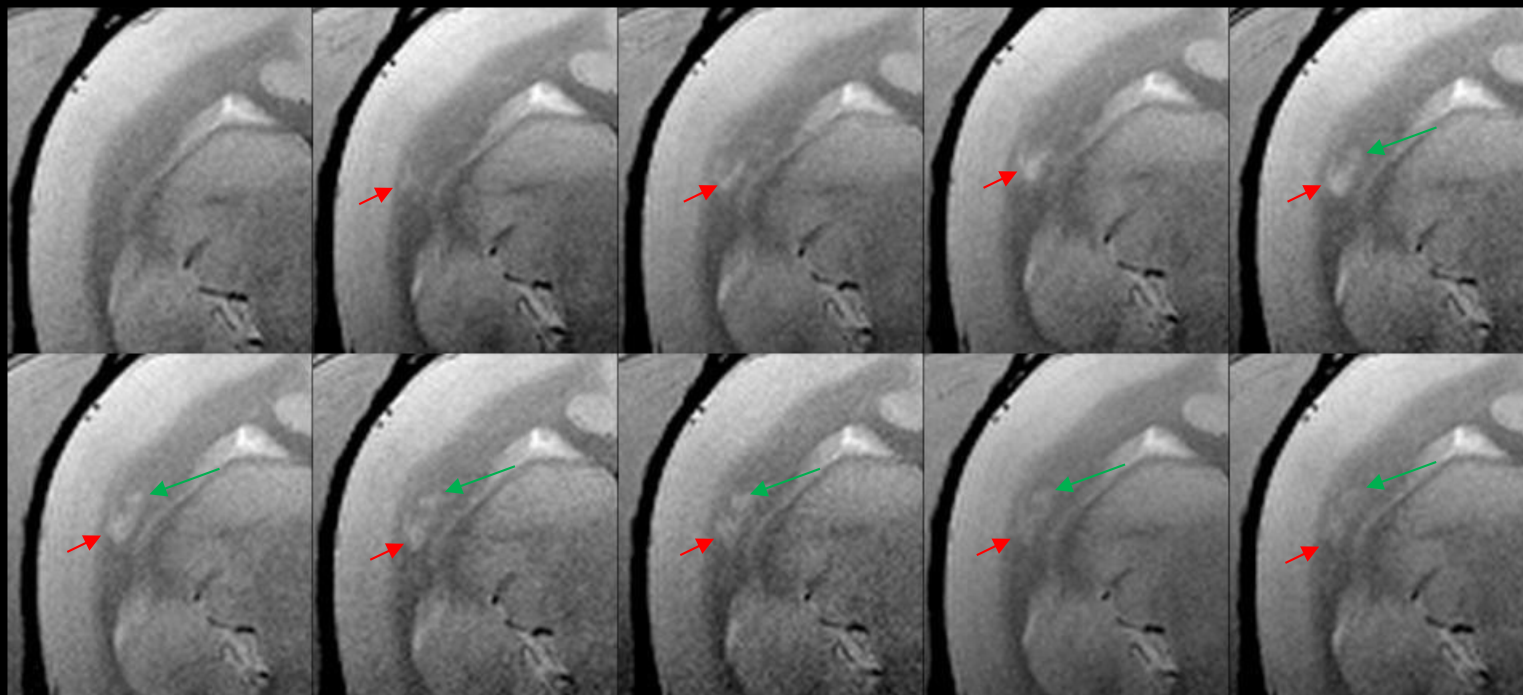
Pathological signature:

- Blood-derived MRP14^{+} early activated macrophages are absent
- Pale myelin staining suggesting **remyelination** at lesion edge

Maggi P et al. Annals of Neurology (2014); 76(4):594-608

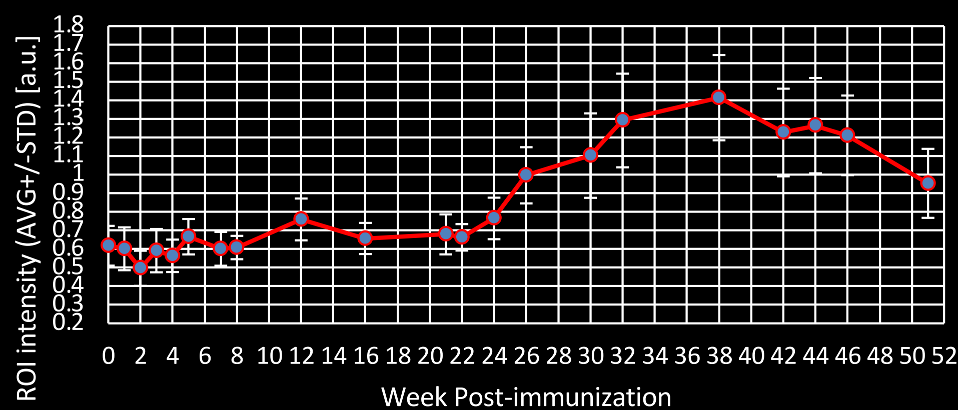
Spontaneous remyelination in marmoset EAE ?

Baseline | 26 wks PI | 30 wks PI | 32 wks PI | 38 wks PI

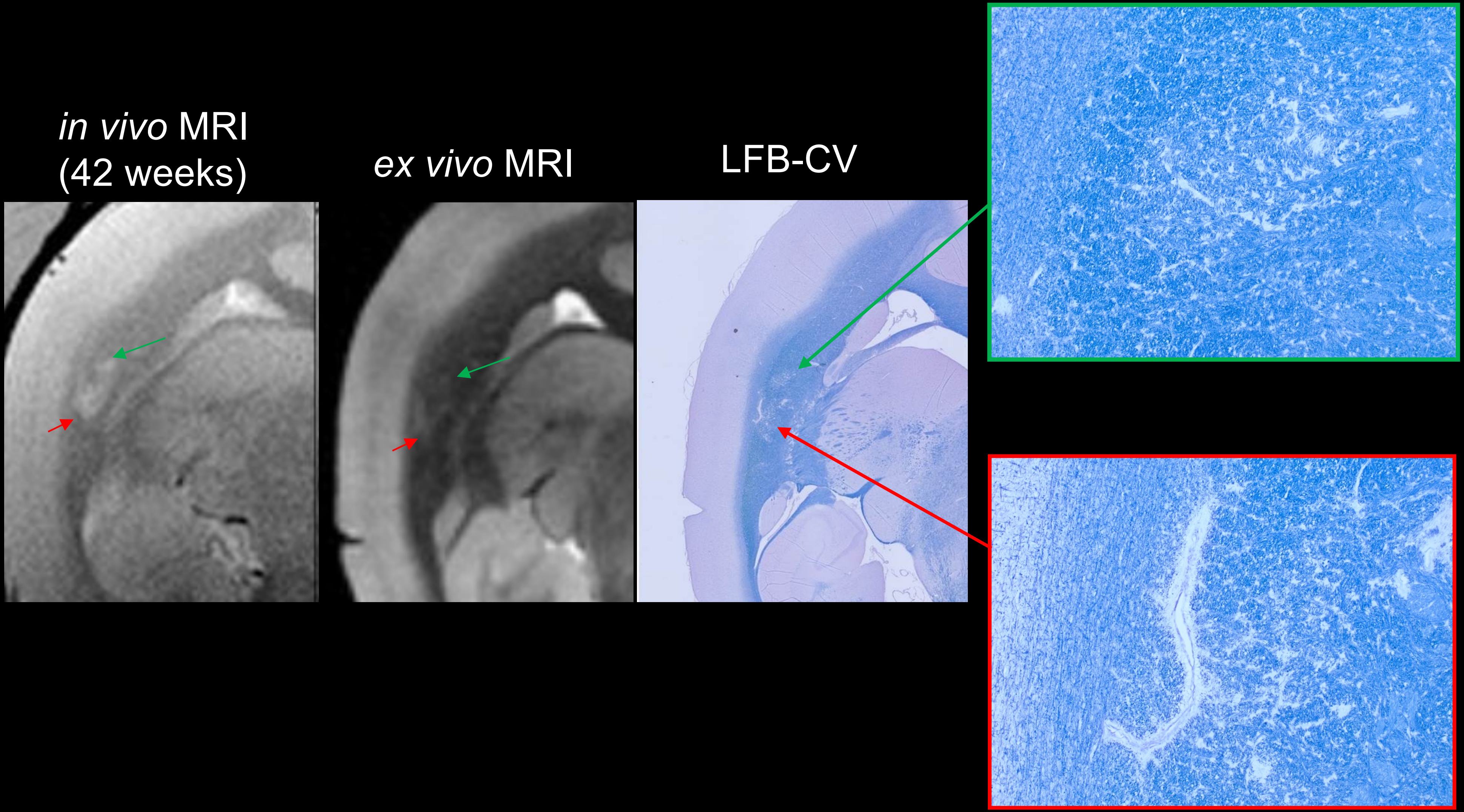


42 wks PI | 44 wks PI | 46 wks PI | 51 wks PI | 54 wks PI Terminal

Lesion intensity (normalized PDw) over time



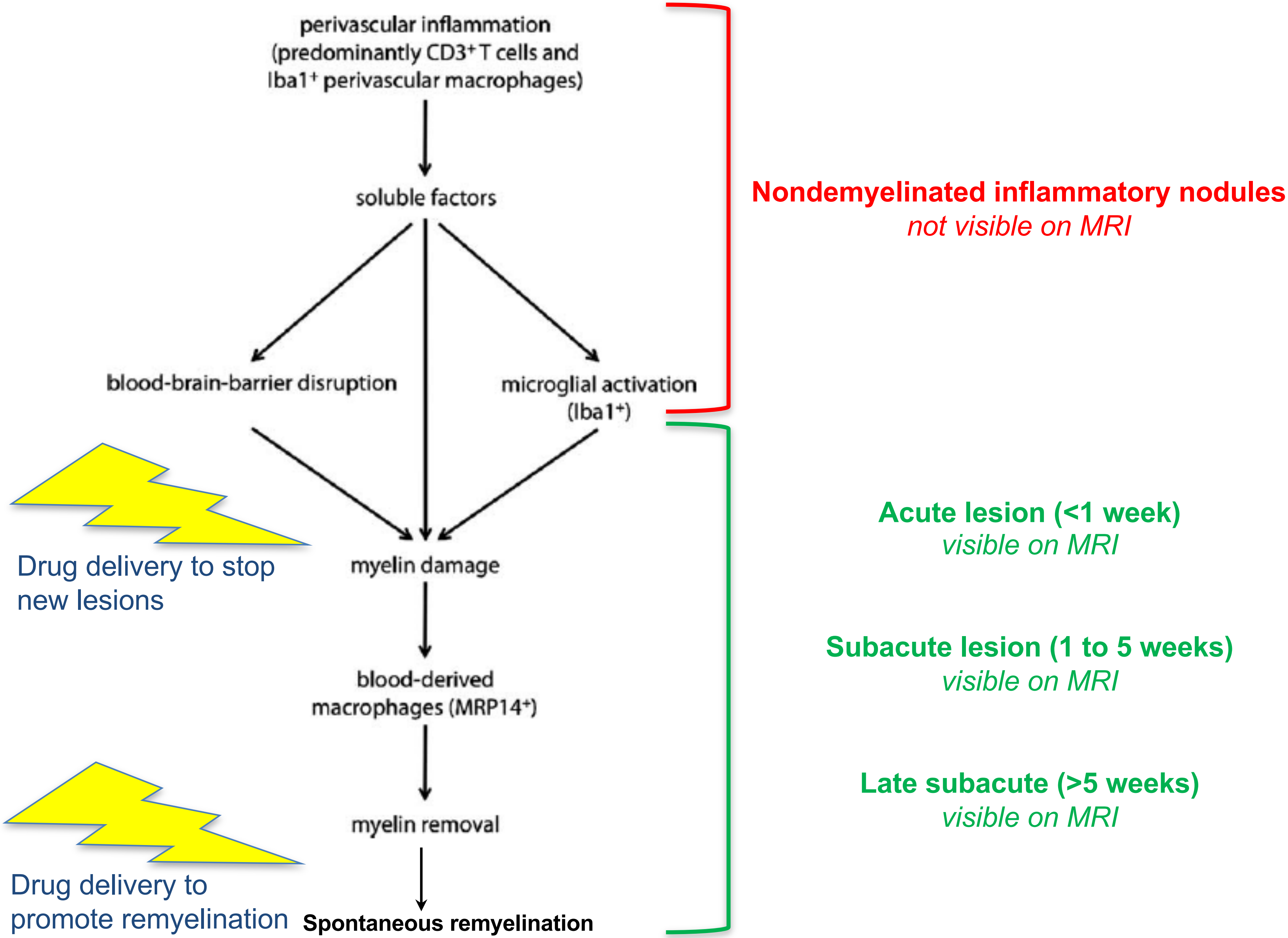
Spontaneous remyelination in marmoset EAE ? Yes, possibly!



Seung Kwon Ha, Nicholas Luciano (TNS), unpublished

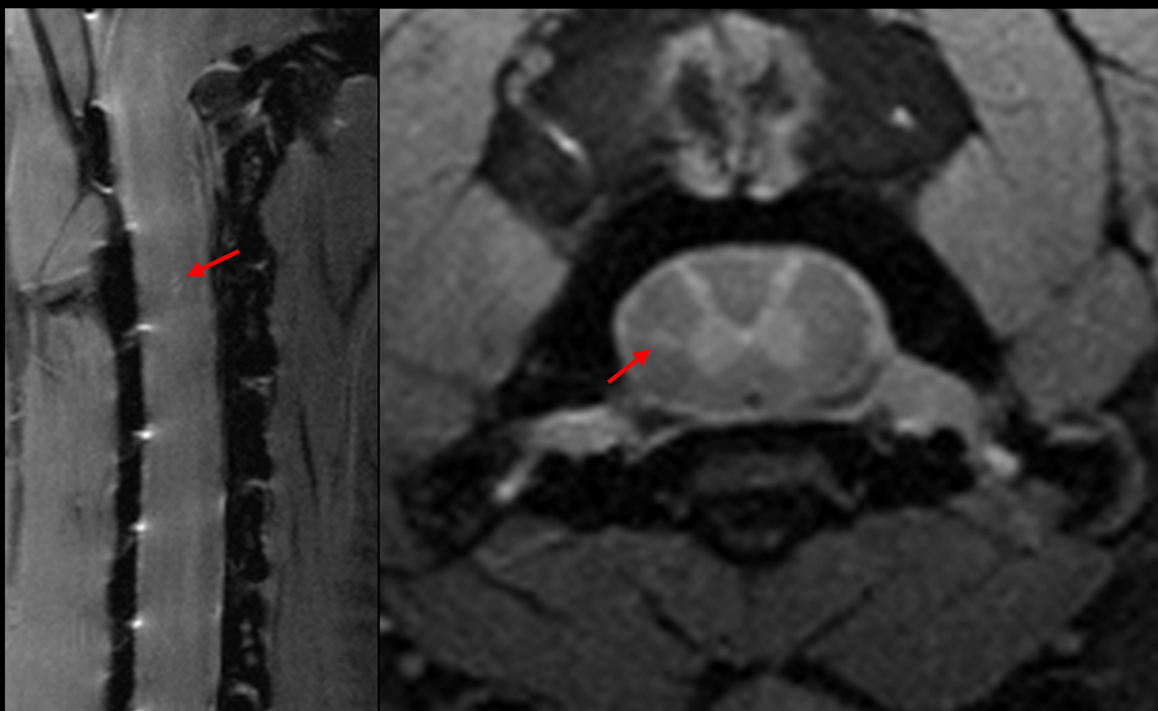
Model of lesion evolution in marmoset EAE

Maggi P et al. Annals of Neurology (2014); 76(4):594-608

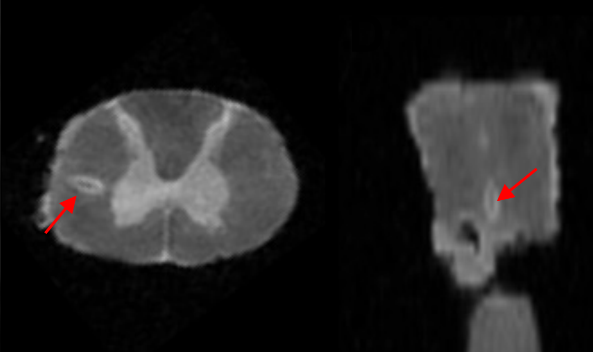


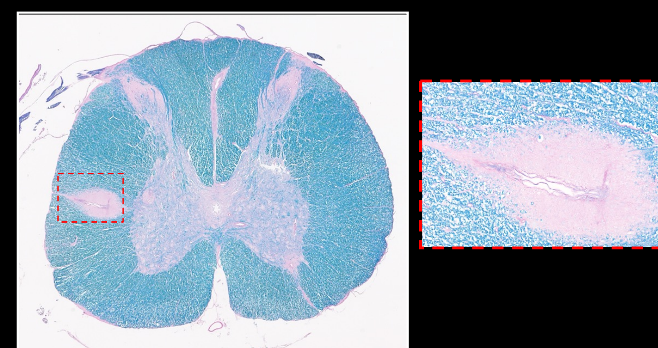
in vivo detection of spinal cord lesion in marmoset EAE

In vivo MRI



postmortem MRI





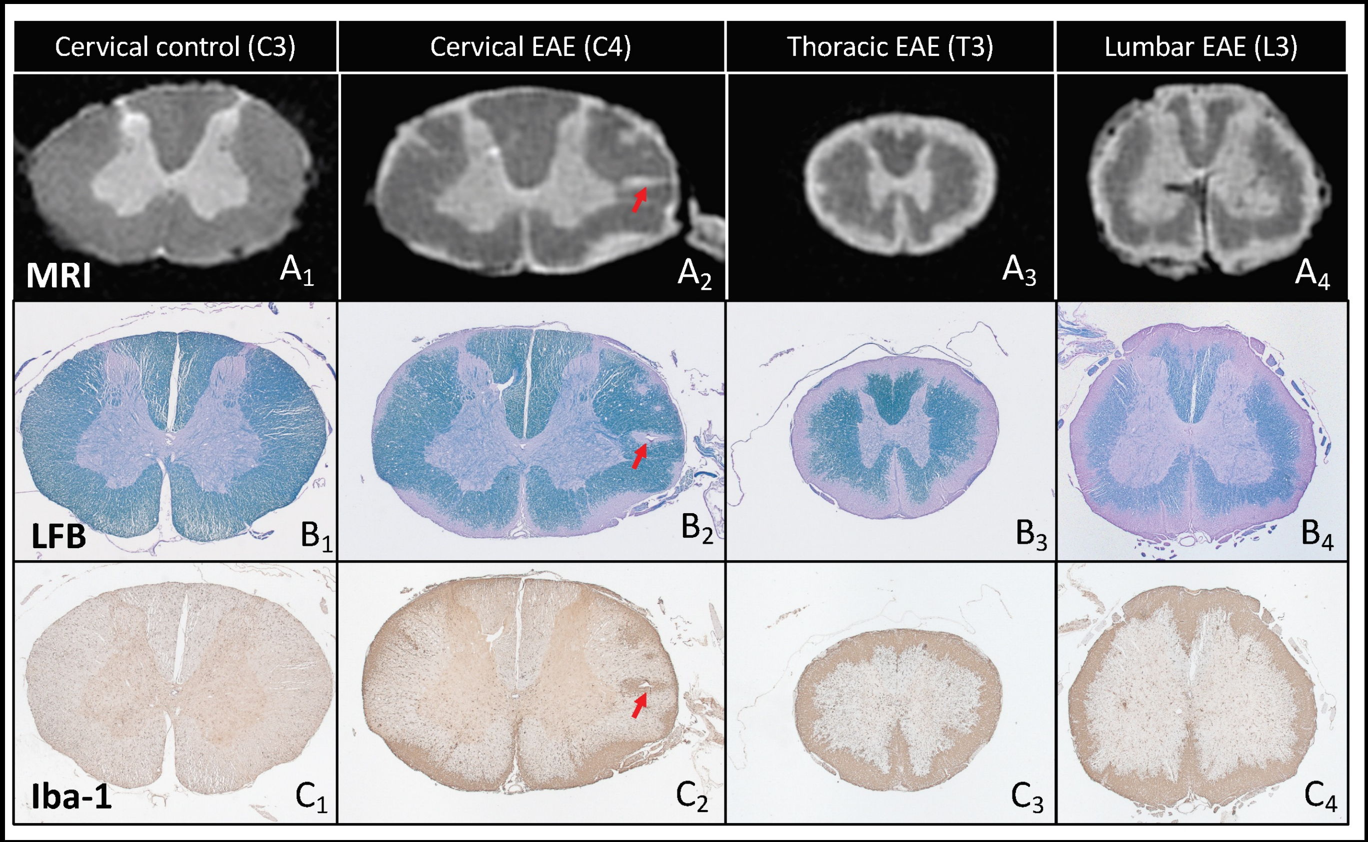
Histopathology

Seung Kwon Ha (TNS)

Lefeuvre et al. ISMRM (2017)

Frequent spinal cord damage in the marmoset EAE

12/12 investigated animals show inflammatory demyelinated lesions

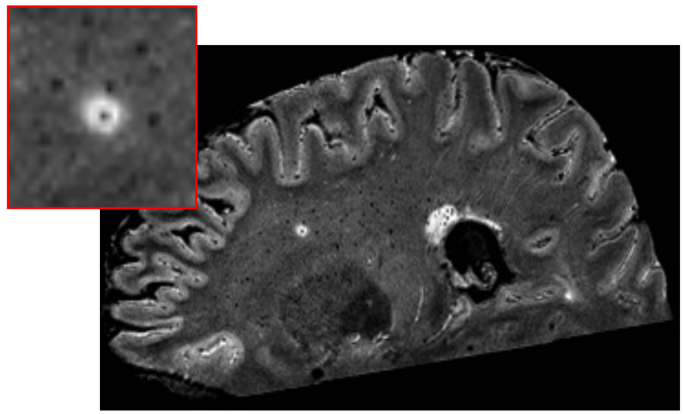


Lefeuvre et al. ISMRM (2016), manuscript in preparation

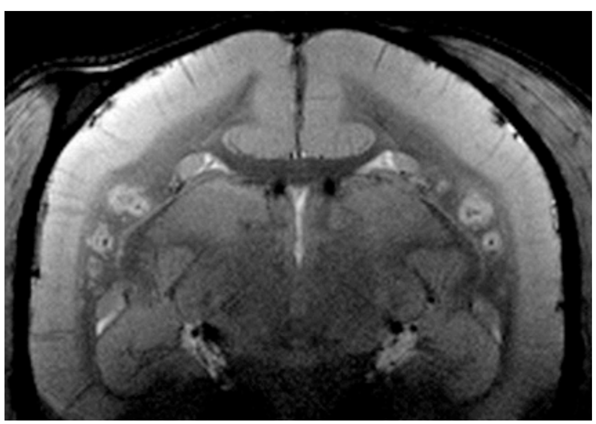
‘Take-home messages’

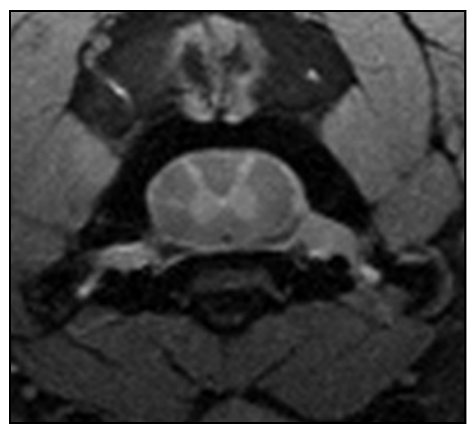
Studying central nervous system diseases with advanced MRI…

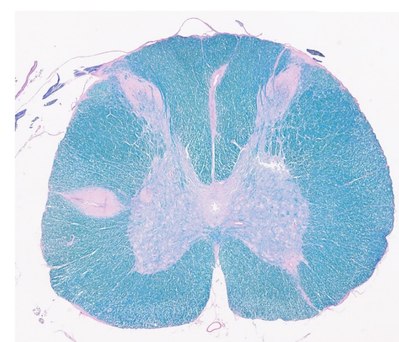
1. to improve MS diagnosis (Central Vein Sign, 3D EPI, FLAIR*)



2. to conduct translational preclinical MS research (marmoset EAE @ 7T)







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Jen Dwyer
Govind Nair

FMRIF/ NIMH
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Andrew Derbyshire
Sean Marrett
Staff Scientists/ MR Techs
Frank Ye

VIS
Steven Jacobson
Emily Leibovitch
Jeanne Billioux

CMS
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Cecil Yen
Wen-Yang Chiang
Lisa Zheng

AMRI
Jeff Duyn
Peter Van Gelderen
Jacco De Zwart

LFMI
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Hellmut Merkle
Steve Dodd

Siemens Healthineers
Gunnar Krueger
Sunil Patil
Himanshu Bhat
Tobias Kober

Vertex pharmaceuticals
Mac Johnson
Doug Bartels

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Thank you for your attention