Workshop in Multiple Sclerosis

Translating engineering innovation into the clinic

30th - 31st January 2018, University College London, London

THE CENTRAL VEIN SIGN

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The Central Vein Sign
Outline

- Background

- The Central Vein Sign in MS vs NMOSD

- Future work

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The Central Vein Sign in MS

1963

ON THE VESSEL-PLAQUE RELATIONS IN THE
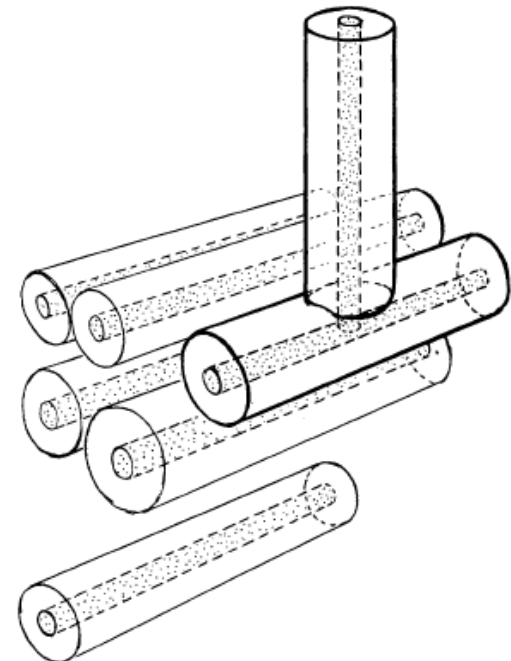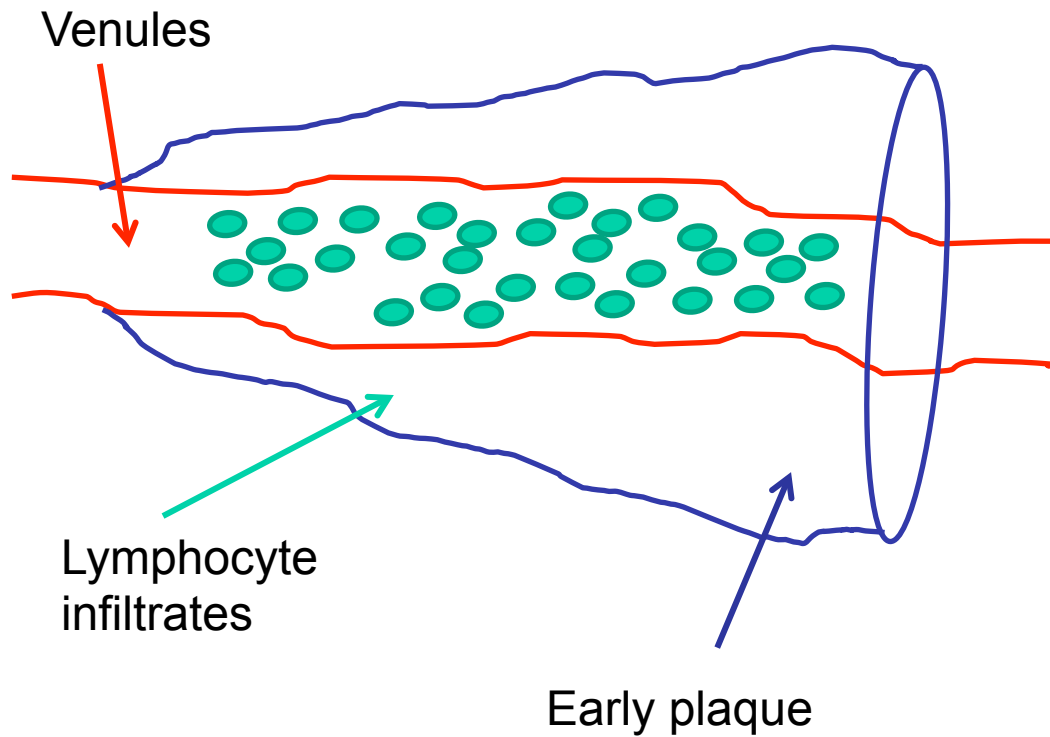BRAIN IN MULTIPLE SCLEROSIS

TORBEN FOG

Fig. 2.
Schematic drawing of periventricular plaque, composed of single perivascular cylinders.
Prolongation around a vessel perpendicular to the longitudinal axis is demonstrated.

The Central Vein Sign in MS

1963

Venules

Lymphocyte infiltrates

Early plaque

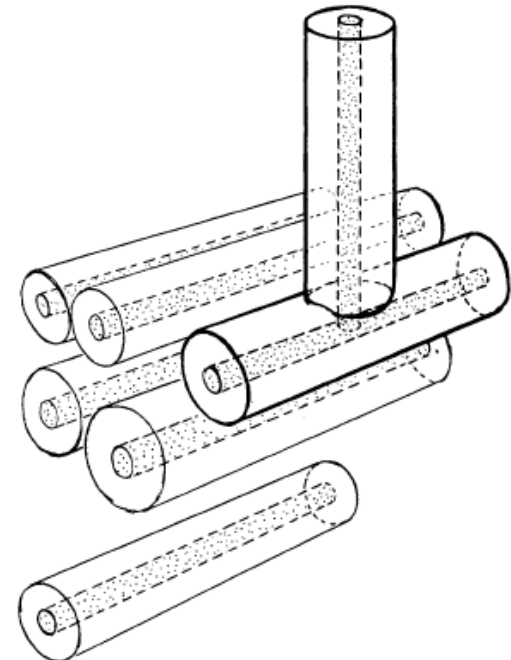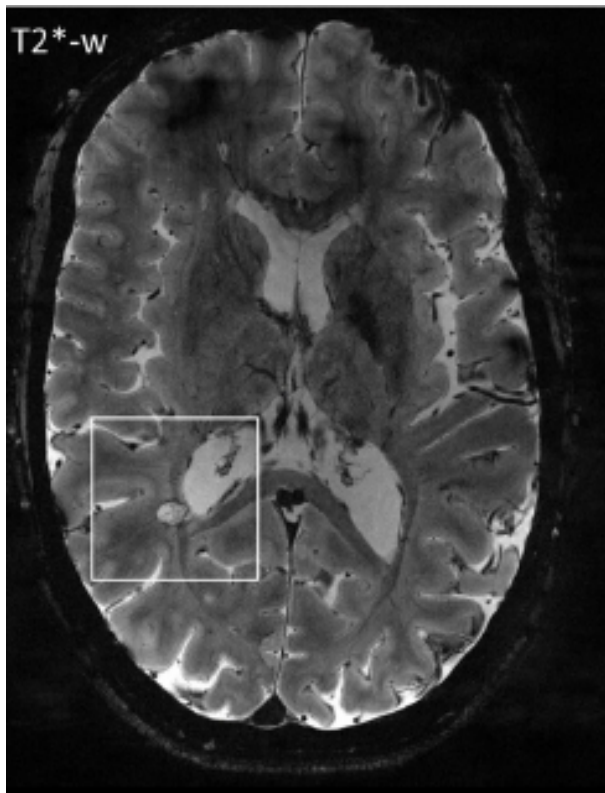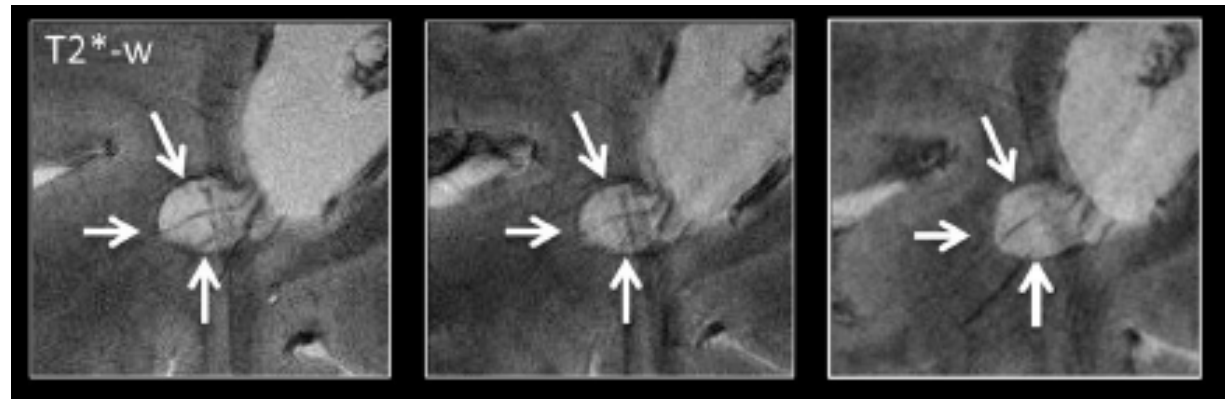ON THE VESSEL-PLAQUE RELATIONS IN THE BRAIN IN MULTIPLE SCLEROSIS

TORBEN FOG

Fig. 2.

Schematic drawing of periventricular plaque, composed of single perivascular cylinders. Prolongation around a vessel perpendicular to the longitudinal axis is demonstrated.
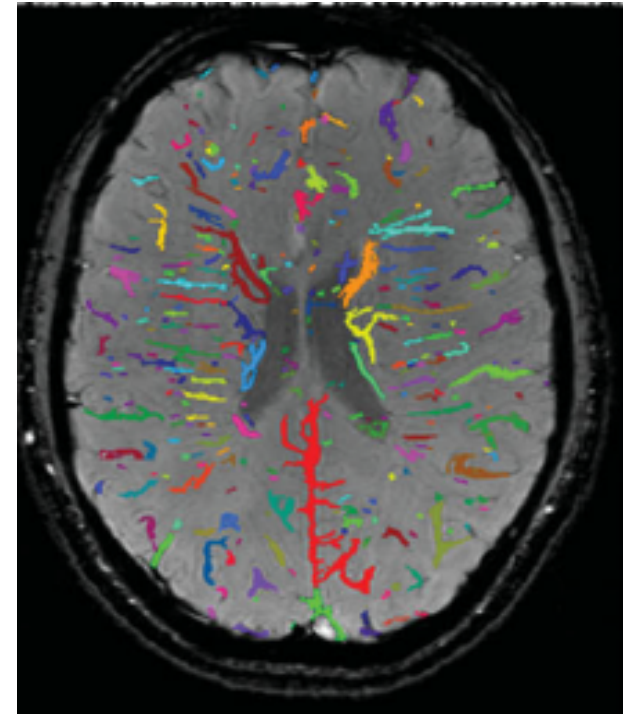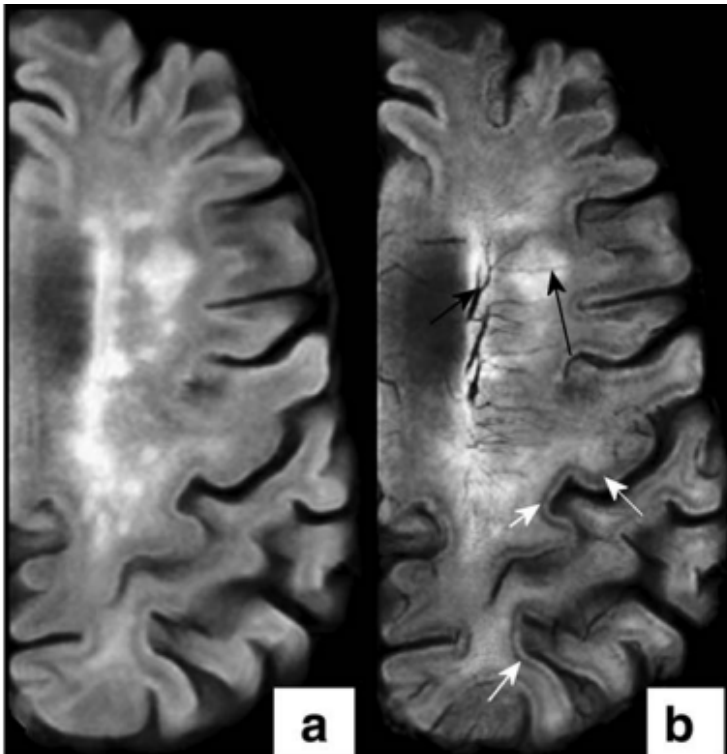
The Central Vein Sign in MS

7T T2*-weighted gradient-echo

Filippi et al, Lancet Neurol 2016

The Central Vein Sign in MS

Grabner et al. J. Magn. Reson. Imaging 2011

Susceptibility Weighted Imaging (SWI) a **3T** enhances the contrast between tissue and allows the visualization of the anatomic relationship between the cerebral WMLs and the penetrating veins.

The Central Vein Sign in MS

2016

EXPERT CONSENSUS DOCUMENT   NATURE REVIEWS | NEUROLOGY

The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative

Pascal Sati[1], Jiwon Oh[2,3], R. Todd Constable[4], Nikos Evangelou[5], Charles R. G. Guttmann[6], Roland G. Henry[7], Eric C. Klawiter[8], Caterina Mainero[9], Luca Massacesi[10], Henry McFarland[1], Flavia Nelson[11], Daniel Ontaneda[12], Alexander Rauscher[13], William D. Rooney[14], Amal P. R. Samaraweera[5], Russell T. Shinohara[15], Raymond A. Sobel[16], Andrew J. Solomon[17], Constantina A. Treaba[9], Jens Wuerfel[18], Robert Zivadinov[19], Nancy L. Sicotte[20], Daniel Pelletier[21] and Daniel S. Reich[1] on behalf of the NAIMS Cooperative

Box 2 | Radiological definition of a central vein

A central vein exhibits the following properties on $T2^*$-weighted images:

- Appears as a thin hypointense line or small hypointense dot
- Can be visualized in at least two perpendicular MRI planes, and appears as a thin line in at least one plane
- Has a small apparent diameter (<2 mm)
- Runs partially or entirely through the lesion
- Is positioned centrally in the lesion (that is, located approximately equidistant from the lesion's edges and passing through the edge at no more than two places), regardless of the lesion's shape

Exclusion criteria for lesions:

- Lesion is <3 mm in diameter in any plane
- Lesion merges with another lesion (confluent lesions)
- Lesion has multiple distinct veins
- Lesion is poorly visible (owing to motion or other MRI-related artefacts)

The Central Vein Sign in MS

High-priority areas for research:

*«The role in MS diagnosis of techniques to distinguish MS lesions from T2 hyperintensities in other condition (e.g. **central vein sign** on susceptibility weighted imaging)…is being explored»*

The Central Vein Sign
Outline

- Background

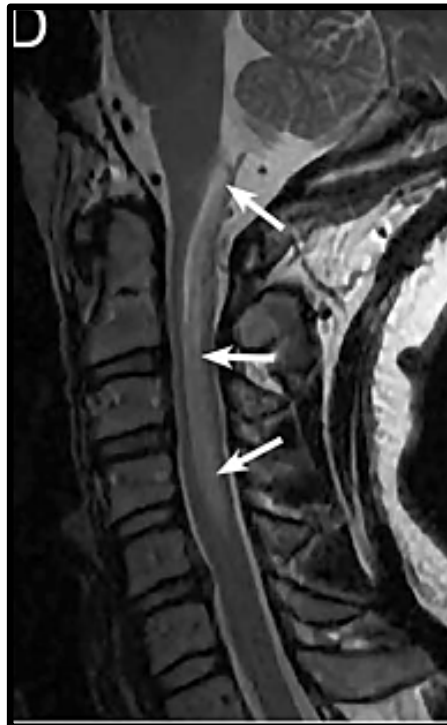- The Central Vein Sign in MS vs NMOSD

- Future work

The Central Vein Sign in MS vs NMOSD

Aim of the study

**To assess the discriminatory value of
the perivenous distribution of
brain white matter lesions in NMOSD and MS
on susceptibility weighted imaging (SWI) at 3T**

The Central Vein Sign in MS vs NMOSD

Neuromyelitis optica spectrum disorder (NMOSD) is a severe, disabling disease of the CNS primarily affecting spinal cord and optic nerves

Wingerchuk et al, Neurology 2015

The Central Vein Sign in MS vs NMOSD

NMOSD is different from Multiple Sclerosis (MS)

Table	Comparison of characteristic MRI findings between NMOSD and MS	
	NMOSD	**MS**
Spinal cord	Longitudinally extensive lesion (≥3 vertebral segments)	Short, often multiple lesions
	Central/gray matter involvement	Peripheral/asymmetrical/often posterior
	T1 hypointensity common on acute lesions	T1 hypointensity rare
Optic nerve	Long-length/posterior-chiasmal lesions	Short-length lesions
Brain	Periependymal lesions surrounding the ventricular system (wide-based along the ependymal lining)	Dawson fingers (perpendicular to ventricles)/S-shaped U-fiber lesions, inferior lateral ventricle and temporal lobe lesions
	Hemispheric tumefactive lesions	Cortical lesions
	Lesions involving corticospinal tracts	Perivenous lesions
	"Cloud-like" enhancing lesions	Ovoid or ring/open-ring enhancing lesions
Others	Normal-appearing tissue involvement may be limited to lesional tracts and associated cortex	Normal-appearing white matter manifests tissue damage using special MRI techniques
	Lesional *myo*-inositol reduced on MRS	Lesional *N*-acetyl-aspartate reduced on MRS

Abbreviations: MRS = magnetic resonance spectroscopy; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder.

MS-like lesions may appear in 10% to 12.5% of NMOSD patients

Kim et al, Neurology 2015

The Central Vein Sign in MS vs NMOSD

Treatments used in MS may exacerbate NMOSD

OBSERVATION

Interferon Beta Treatment in Neuromyelitis Optica

Increase in Relapses and Aquaporin 4 Antibody Titers

Jacqueline Palace, DM; Maria Isabel Leite, DPhil; Angela Nairne, MRCP; Angela Vincent, FRCPath

Arch Neurol. 2010;67(8):1016-1017

Failure of Natalizumab to Prevent Relapses in Neuromyelitis Optica

Ingo Kleiter, MD; Kerstin Hellwig, MD; Achim Berthele, MD; Tania Kümpfel, MD; Ralf A. Linker, MD; Hans-Peter Hartung, MD; Friedemann Paul, MD; Orhan Aktas, MD; for the Neuromyelitis Optica Study Group

Arch Neurol. 2012;69(2):239-245

MULTIPLE SCLEROSIS JOURNAL | MSJ

Case Study

Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder

Multiple Sclerosis Journal
18(1) 113–115
© The Author(s) 2012
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sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1352458511431973
msj.sagepub.com
⑤SAGE

Ju-Hong Min, Byoung Joon Kim and Kwang Ho Lee

The Central Vein Sign in MS vs NMOSD

Cohort description

	NMOSD(*)	RRMS(**)	HC
No. of patients	18	18	25
Gender (male/ female)	4/14	4/14	7/18
Age, y, mean [± SD]	52.5 [±2.8]	41.8 [±2.8]	37.1 [±2.4]
Disease duration, years, mean [± SD]	8.6 [± 7.3]	9 [± 6.4]	NA
EDSS, median (range)	5 (2 – 6.5)	2.5 (1 – 7.5)	NA

* 2006 Revised criteria for NMO

**2010 Diagnostic criteria for MS

The Central Vein Sign in MS vs NMOSD

Methods: image analysis

T2

PD

Symmetric affine registration

NiftyReg
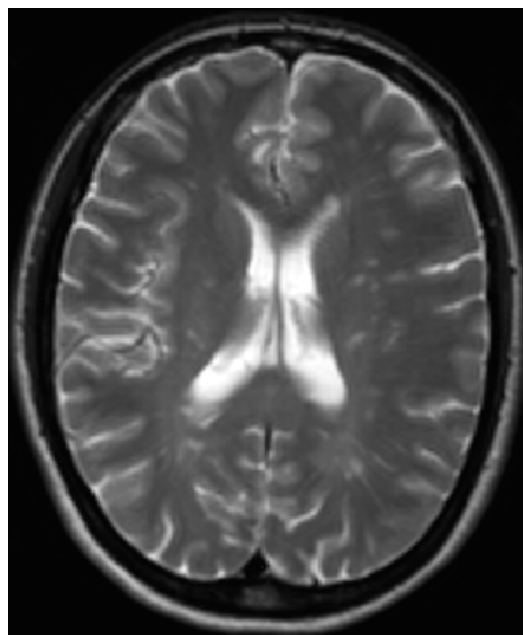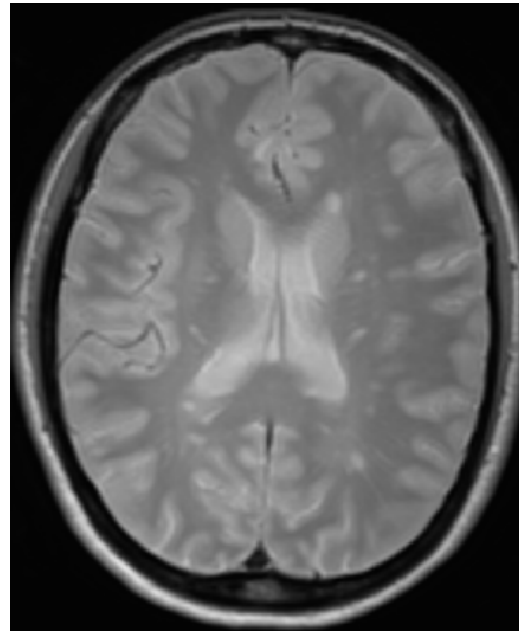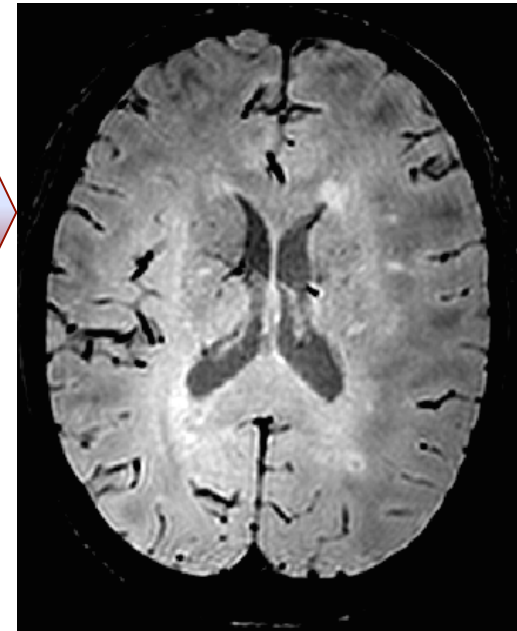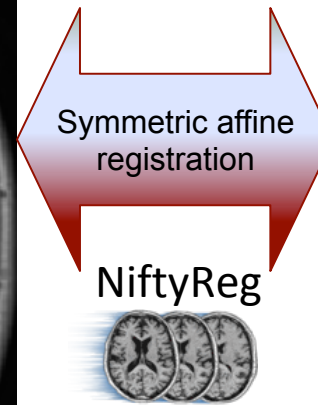
SWI

Brain MRI: Philips Achieva 3T
3D-FFE sequence with shifted echo
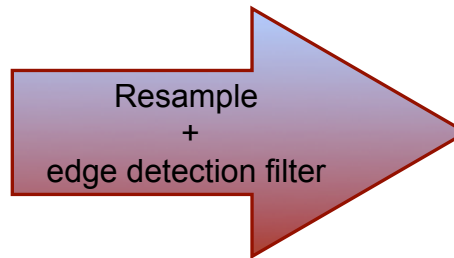(voxel size 1x1x1 mm^3, reconstructed to 0.5 x 0.5 x 0.5 mm^3).

The Central Vein Sign in MS vs NMOSD

Methods: image analysis

Manual lesion detection
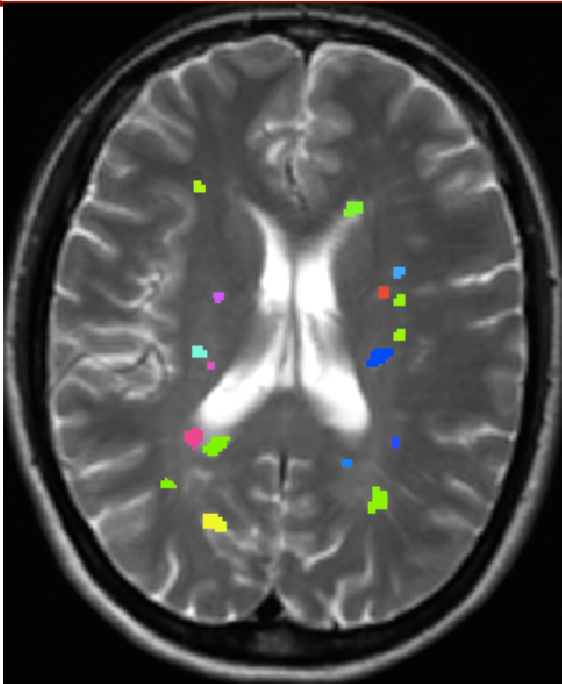
**Infratentorial
Periventricular
Subcortical**

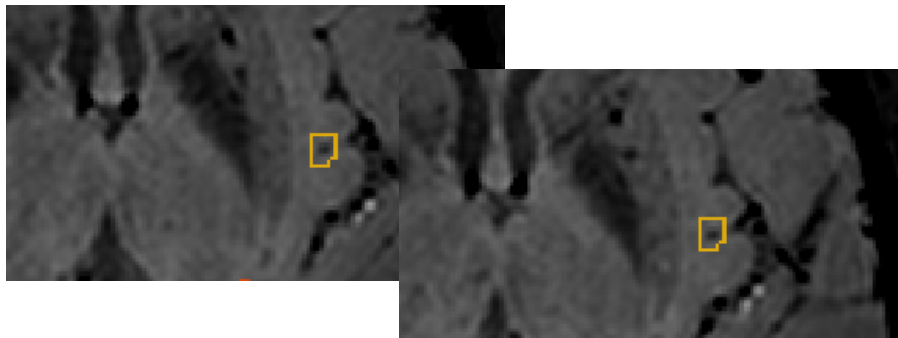Resample
+
edge detection filter

SWI + Lesion Mask
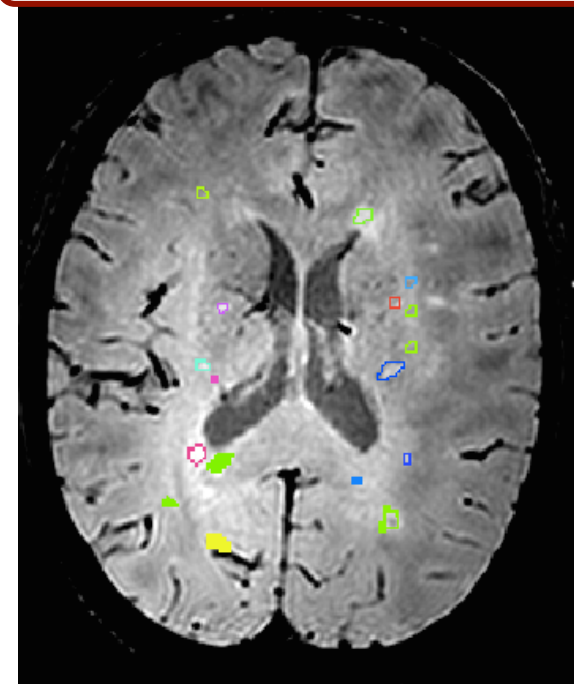
**Two readers blinded to
clinical data**

The Central Vein Sign in MS vs NMOSD

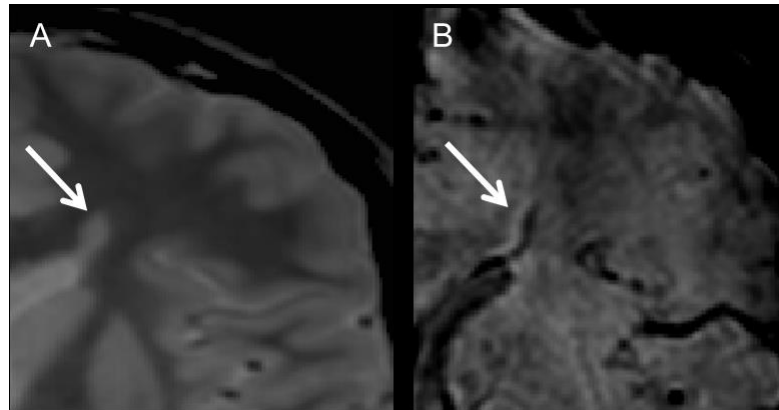## Methods: image analysis

Dark line coursing through the lesion
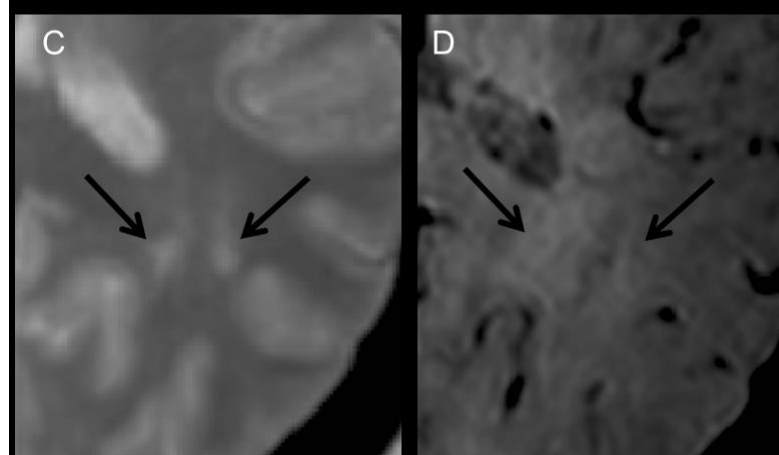

Dark dot tracked on contiguous slices

The Central Vein Sign in MS vs NMOSD
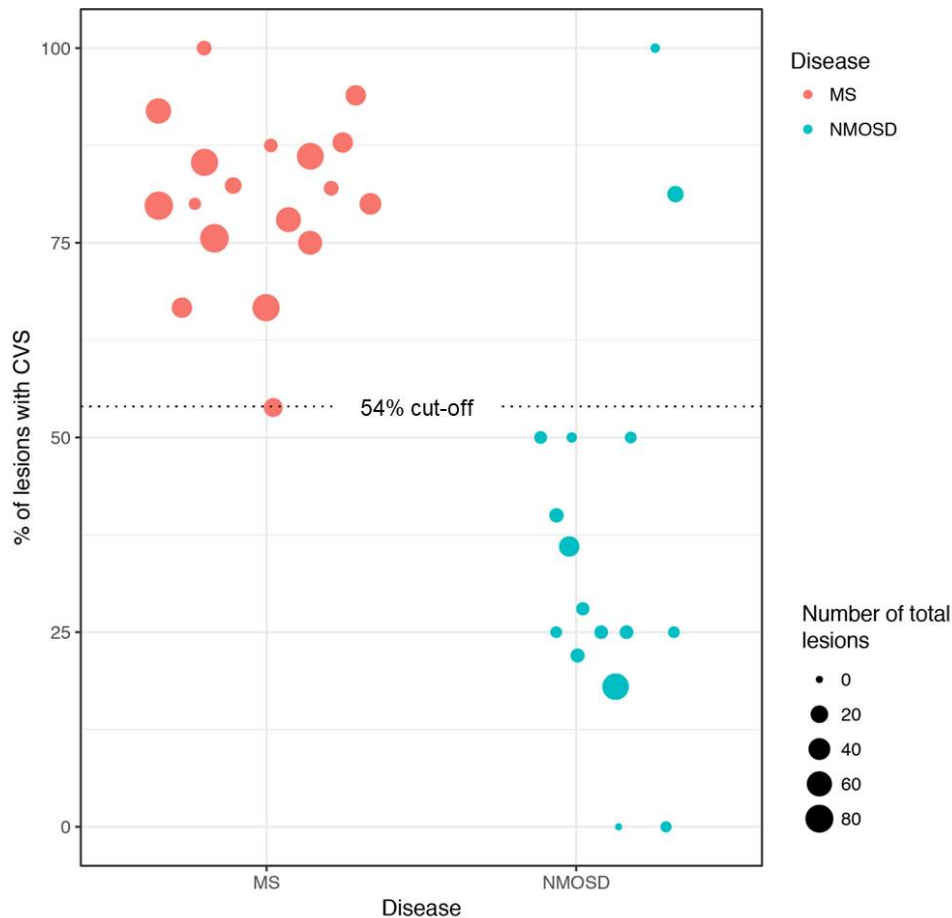
Results

**MS
80% CVS**

**NMOSD
32% CVS**

OR=1.10
95%CI 1.04 to 1.16, p=0.001

The Central Vein Sign in MS vs NMOSD

Results

Accuracy: 94/%
(95%CIs 81.34, 99.32, p<0.001, sensitivity/specificity: 90%/100%).

The Central Vein Sign in MS vs NMOSD

Conclusion

The CVS on SWI at 3T MRI may differentiate MS from NMOSD.

Limitation

Procedure time-consuming

The Central Vein Sign
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- Future work

Future work
Less time-consuming algorithms

«PICK 6»

1. If there are **six or more** morphologically characteristic lesions

2. if there are fewer than six morphologically characteristic lesions, but morphologically c h a r a c t e r i s t i c l e s i o n s **outnumber** non-perivenous lesions
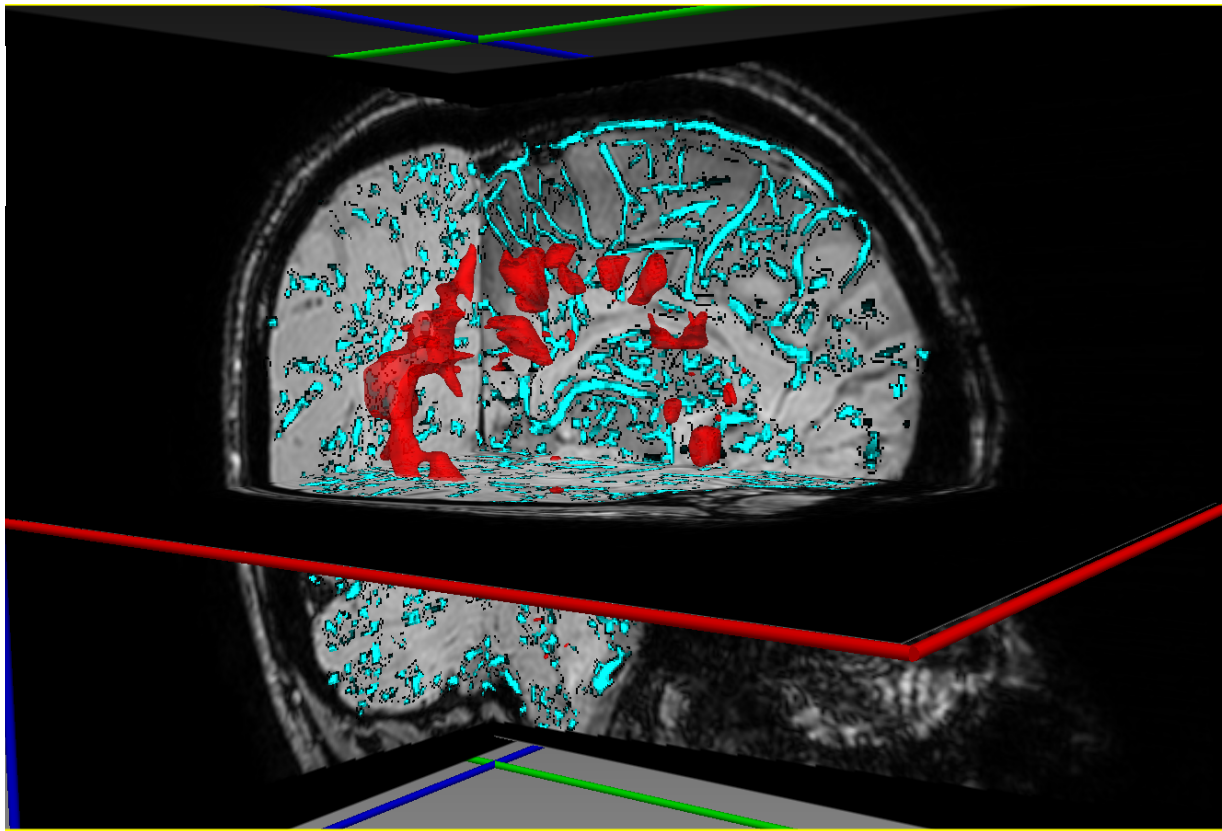
3. if **neither** of these conditions are met
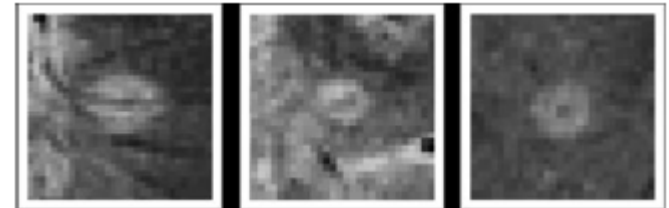
INFLAMMATORY DEMYELINATION

NO INFLAMMATORY DEMYELINATION

Mistry, MSJ 2016

Future work
Automatic vessel segmentation

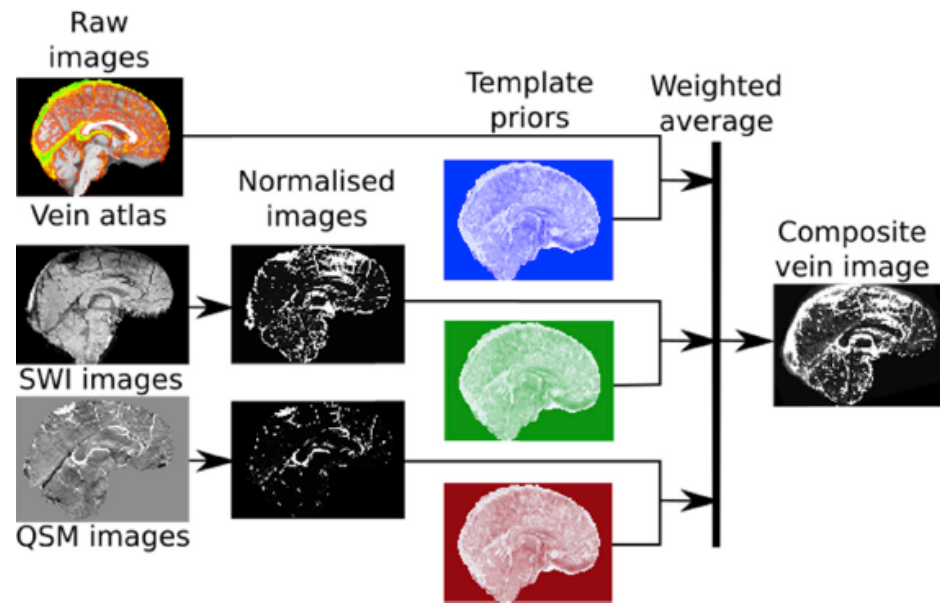Courtesy of F. Prados and M. Zuluaga

Future work
Automatic vessel segmentation

Vein anatomy

+

Image contrast

The accuracy of automated vein segmentations derived from the **composite vein image** was overwhelmingly superior to segmentations derived from SWI or QSM alone.

Ward et al ,Neuroimage 2018

THANK YOU