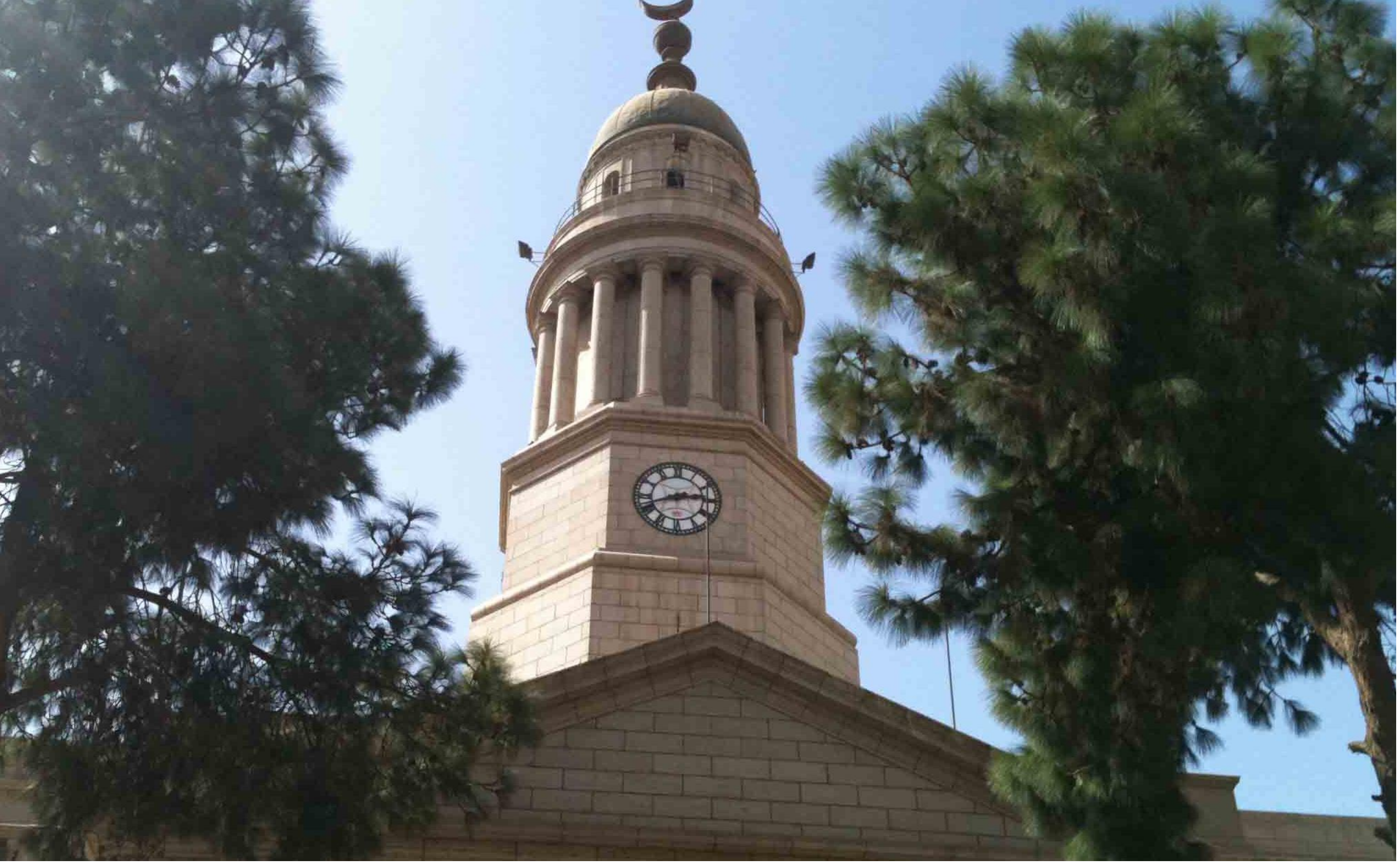
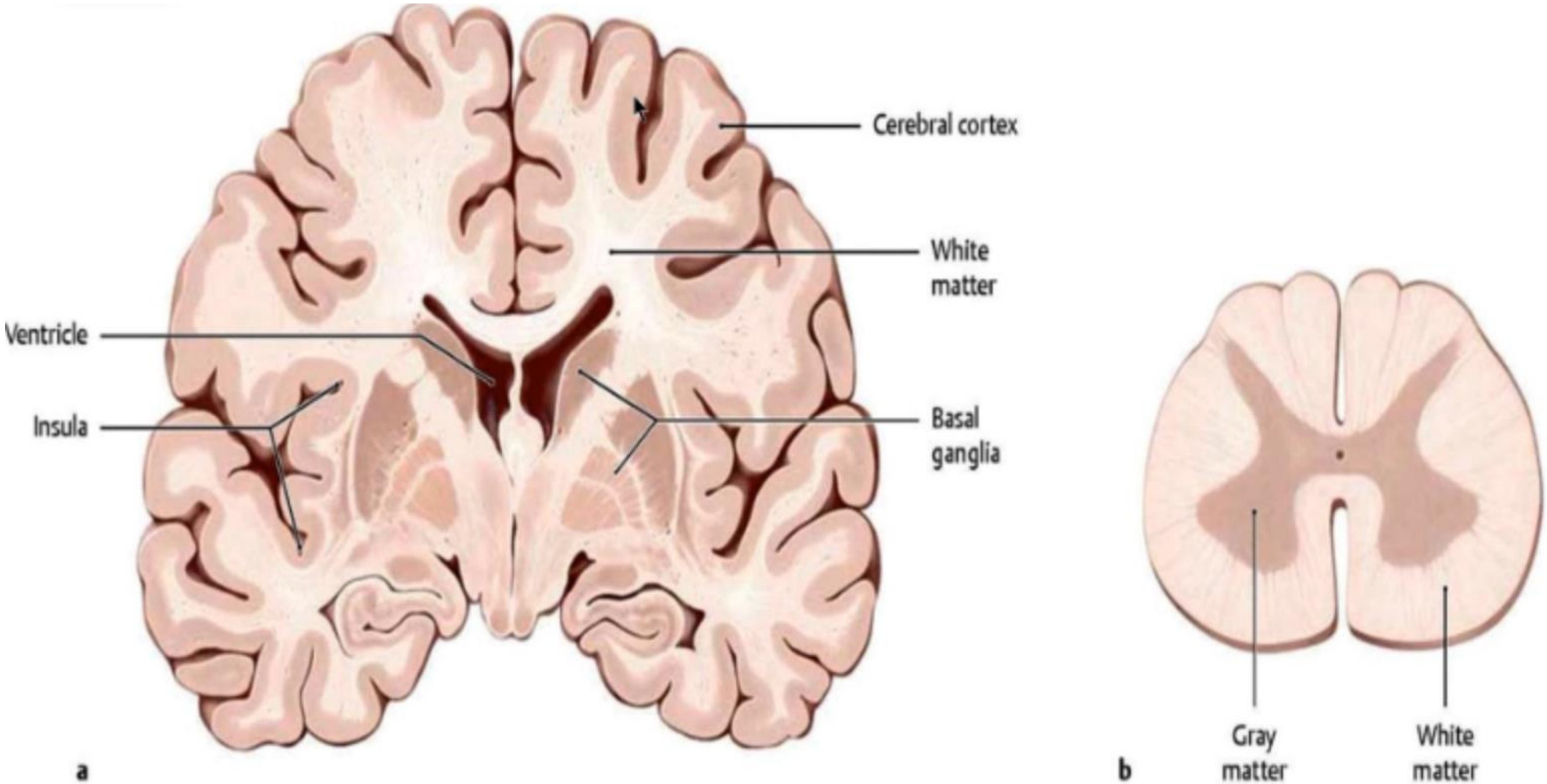


Grey Matter & MS

Amr Hassan MD,FEBN
Associate Professor of Neurology
Cairo University

Grey matter



Distribution of gray and white matter in the CNS

James w. Dawson, 1916

- *"...when an area [of demyelination] is confined to the cortex, the changes are, as a rule, not nearly so marked..."*

Dawson also wondered:

- *"Is then, the process that attacks the cortex different in its nature and origin from that which affects the rest of the central nervous system?".*

Dawson, J. D. The histology of disseminated sclerosis. *Trans. R. Soc. Edin.* **50**, 517–740(1916).

Grey matter involvement in MS

J. Neurol. Neurosurg. Psychiat., 1962, **25**, 315

The distribution of plaques in the cerebrum in multiple sclerosis

BETTY BROWNELL AND J. TREVOR HUGHES

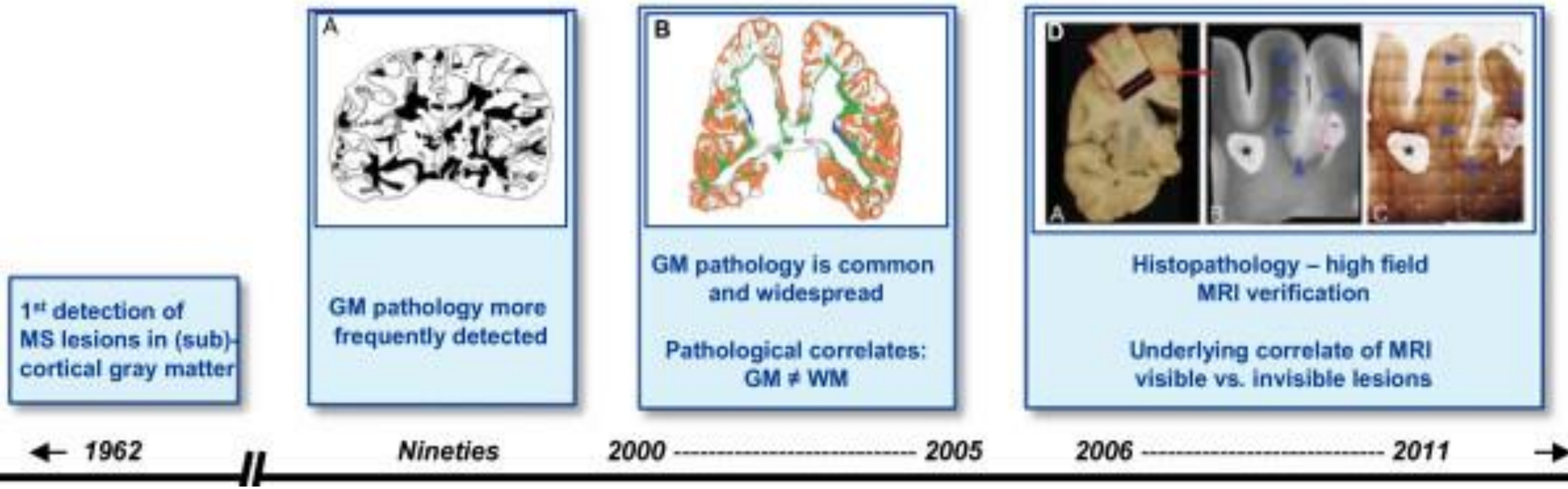
From the Departments of Neurology and Pathology, Radcliffe Infirmary, Oxford

TABLE II

DISTRIBUTION OF 1,594 CEREBRAL PLAQUES IN 22 CASES OF MULTIPLE SCLEROSIS

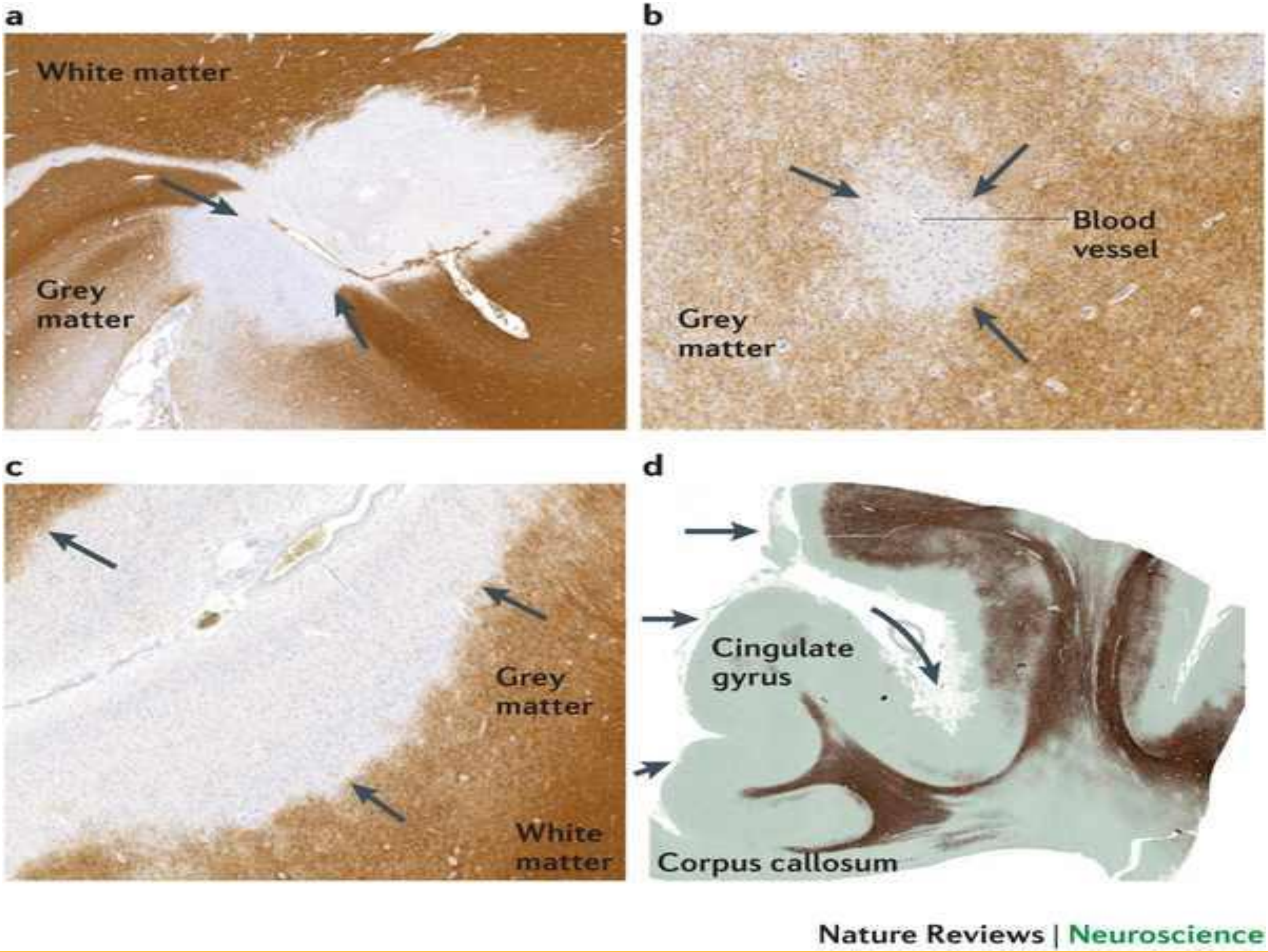
Position in Grey or White Matter	*Number of Plaques*
Cortex	80 (5%)
Central grey matter	65 (4%)
Junction of cortex and white matter	265 (17%)
White matter	1,184 (74%)

(HISTO)PATHOLOGY



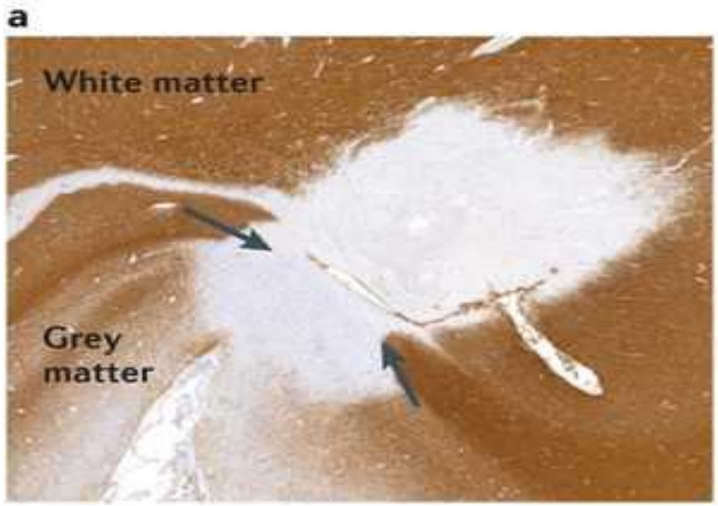
Bo et al, 2003

Types of grey matter lesions



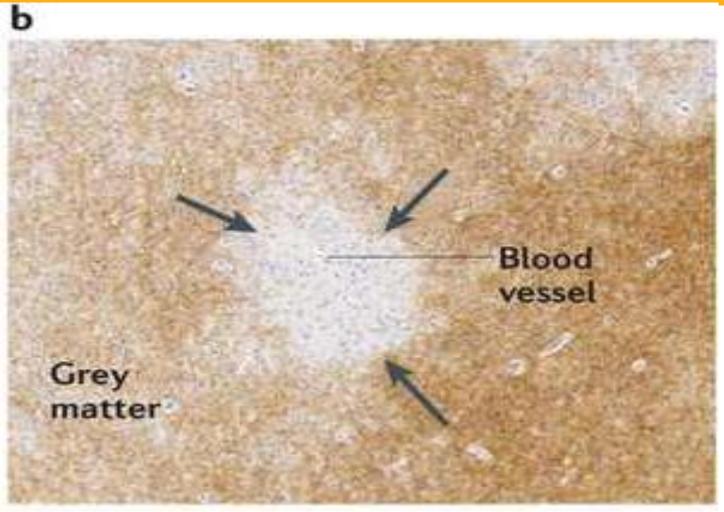
Calabrese et al, 2015. Exploring the origins of grey matter damage in multiple sclerosis. Nature reviews Neuroscience 16(3):147-58

Types of grey matter lesions



- **Type 1 (leukocortical):** **lesions extend through grey matter into the white matter and do not usually reach the surface of the brain.**

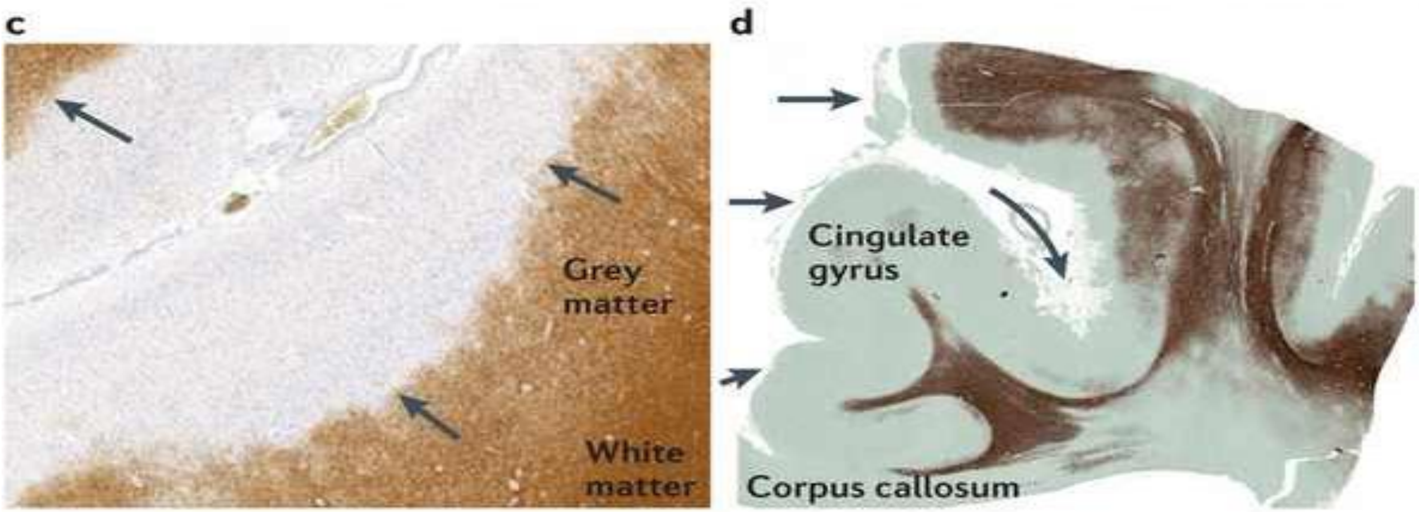
Types of grey matter lesions



- **Type 2 lesions (intracortical): having no contact with white matter or with the surface of the brain.**

Types of grey matter lesions

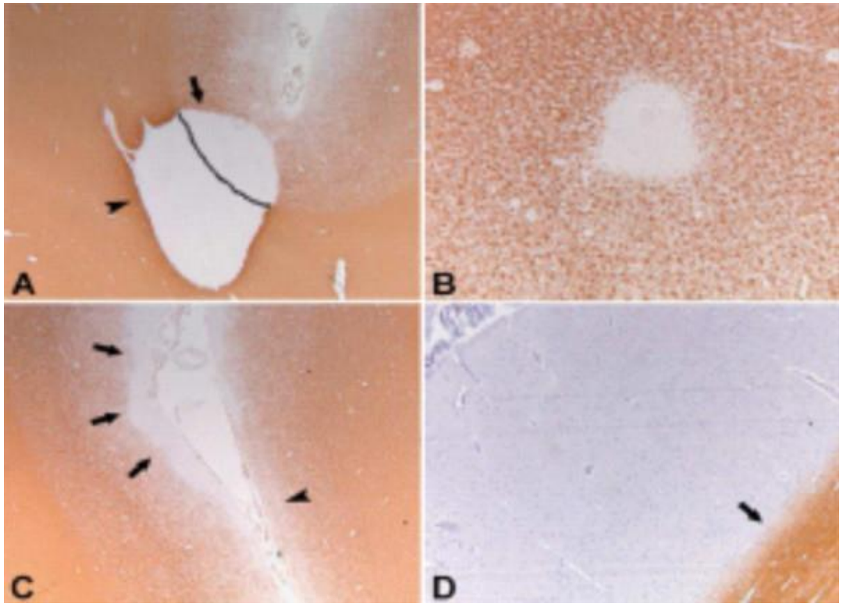
- **Type 3 lesions (Subpial) :** **extend inward from the surface of the brain (the superficial cortical layers).**



Calabrese et al, 2015. Exploring the origins of grey matter damage in multiple sclerosis. Nature reviews Neuroscience 16(3):147-58

Types of grey matter lesions

- **Type 4 lesions (Subpial) :** **extend through the whole width of the cortex without reaching into white matter.**



Calabrese et al, 2015. Exploring the origins of grey matter damage in multiple sclerosis. Nature reviews Neuroscience 16(3):147-58

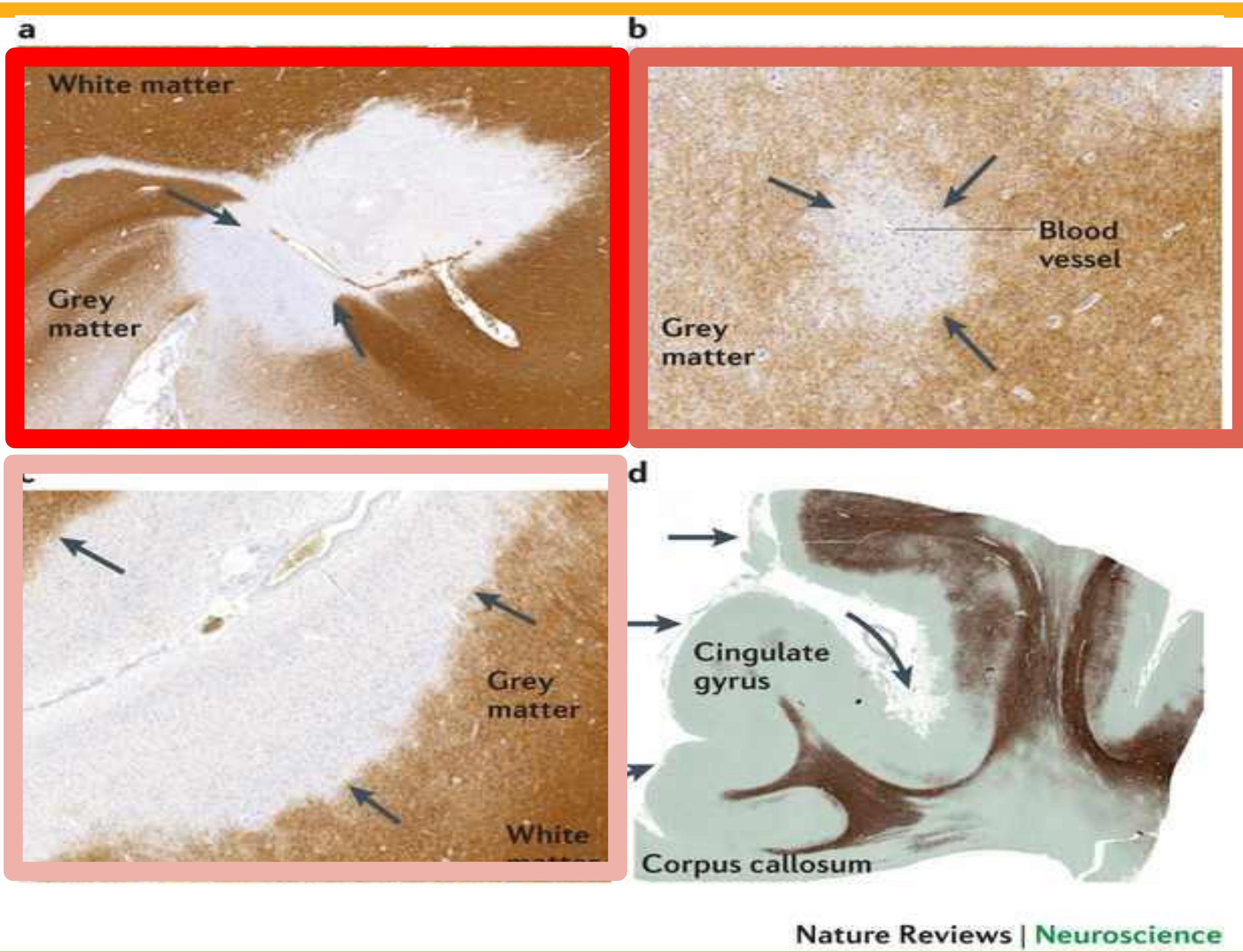
When compared with white matter lesions

Grey matter lesions are usually characterized by a relative lack of

- Parenchymal lymphocyte infiltration
- Deposition of antibody
- Complement proteins
- Blood–brain barrier disruption

Bø, L., Vedeler, C. A., Nyland, H. I., Trapp, B. D. & Mörk, S. J. Subpial demyelination in the cerebral cortex of multiple sclerosis patients. *J. Neuropathol. Exp. Neurol.* **62**, 723–732(2003).

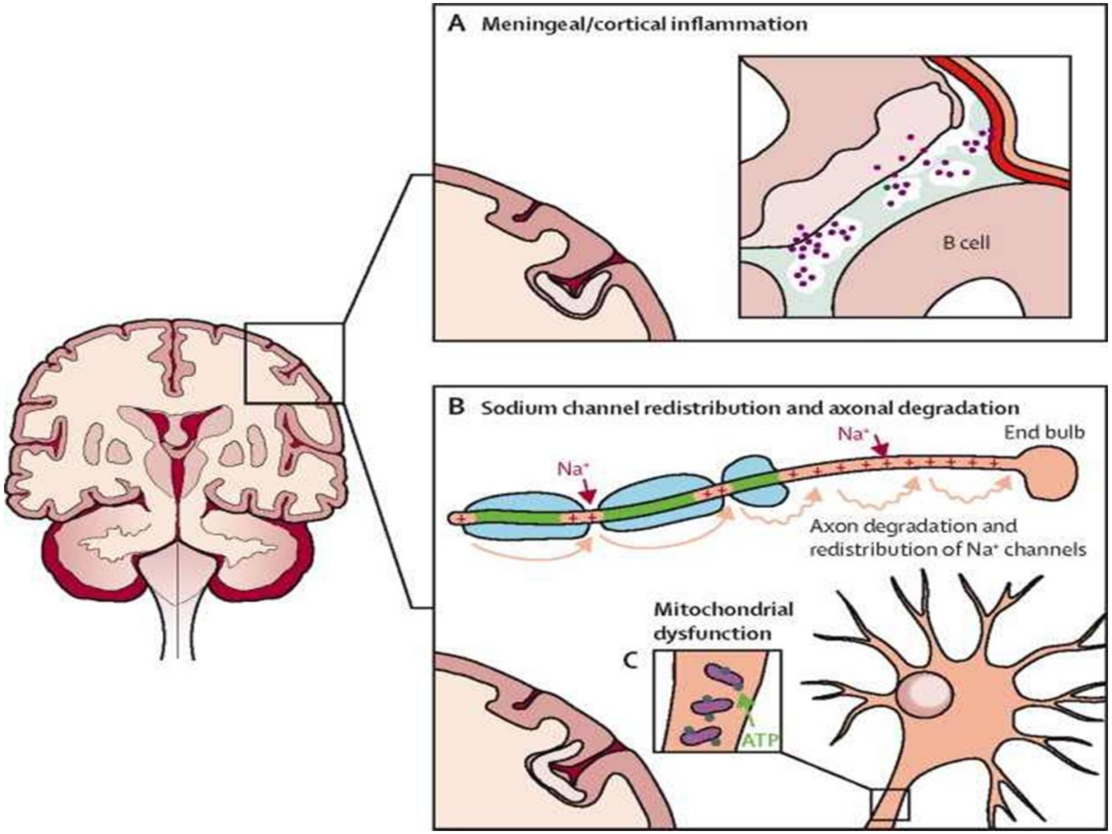
Types of grey matter lesions



Calabrese et al, 2015. Exploring the origins of grey matter damage in multiple sclerosis. Nature reviews Neuroscience 16(3):147-58

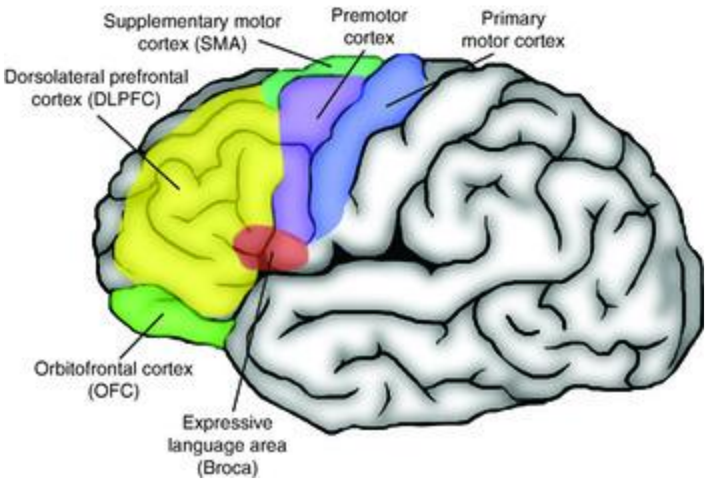
Preferential sites of grey matter lesions

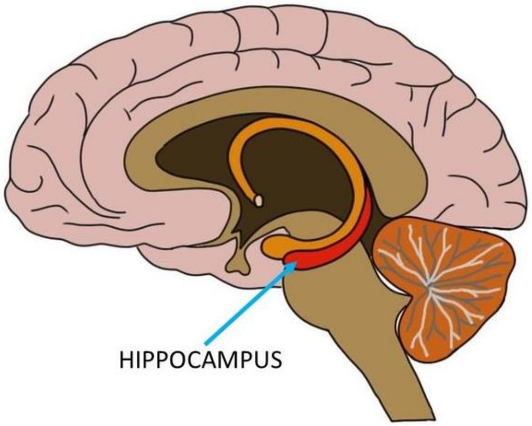
- Subpial demyelination and cortical atrophy are more pronounced within deep invaginations of the cortex.

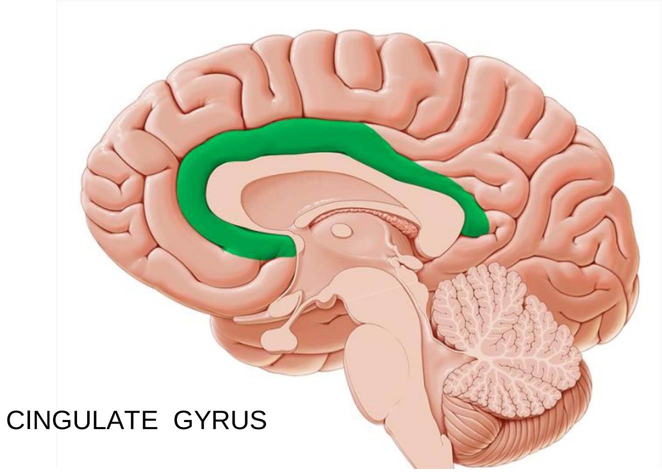


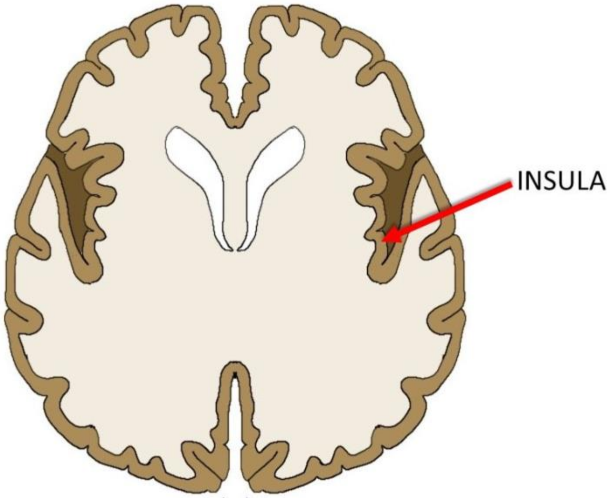
Wegner, C., Esiri, M. M., Chance, S. A., Palace, J. &Matthews, P. M. Neocortical neuronal, synaptic, and glial loss in multiple sclerosis. *Neurology* **67**, 960–967 (2006).

Preferential sites of grey matter lesions

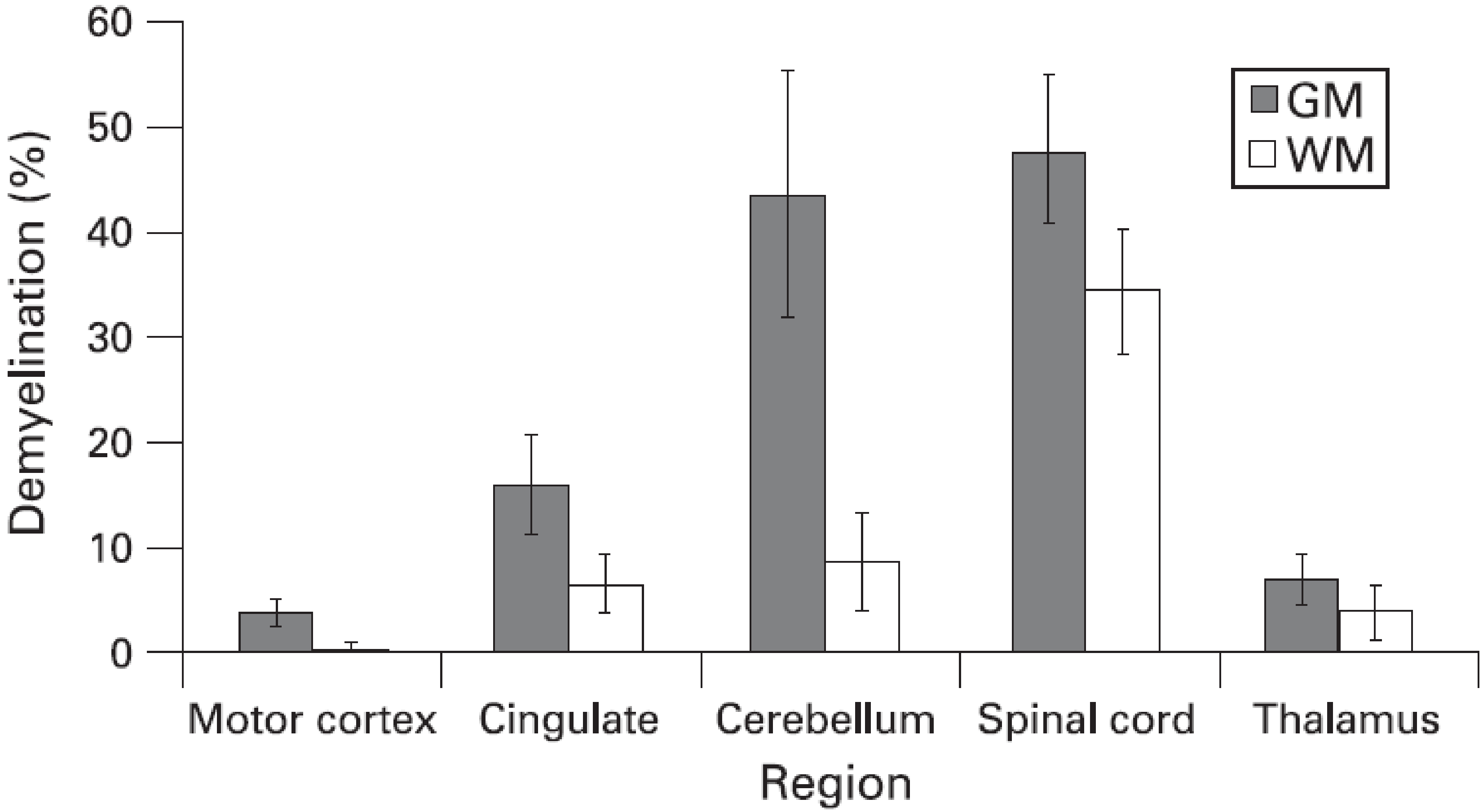






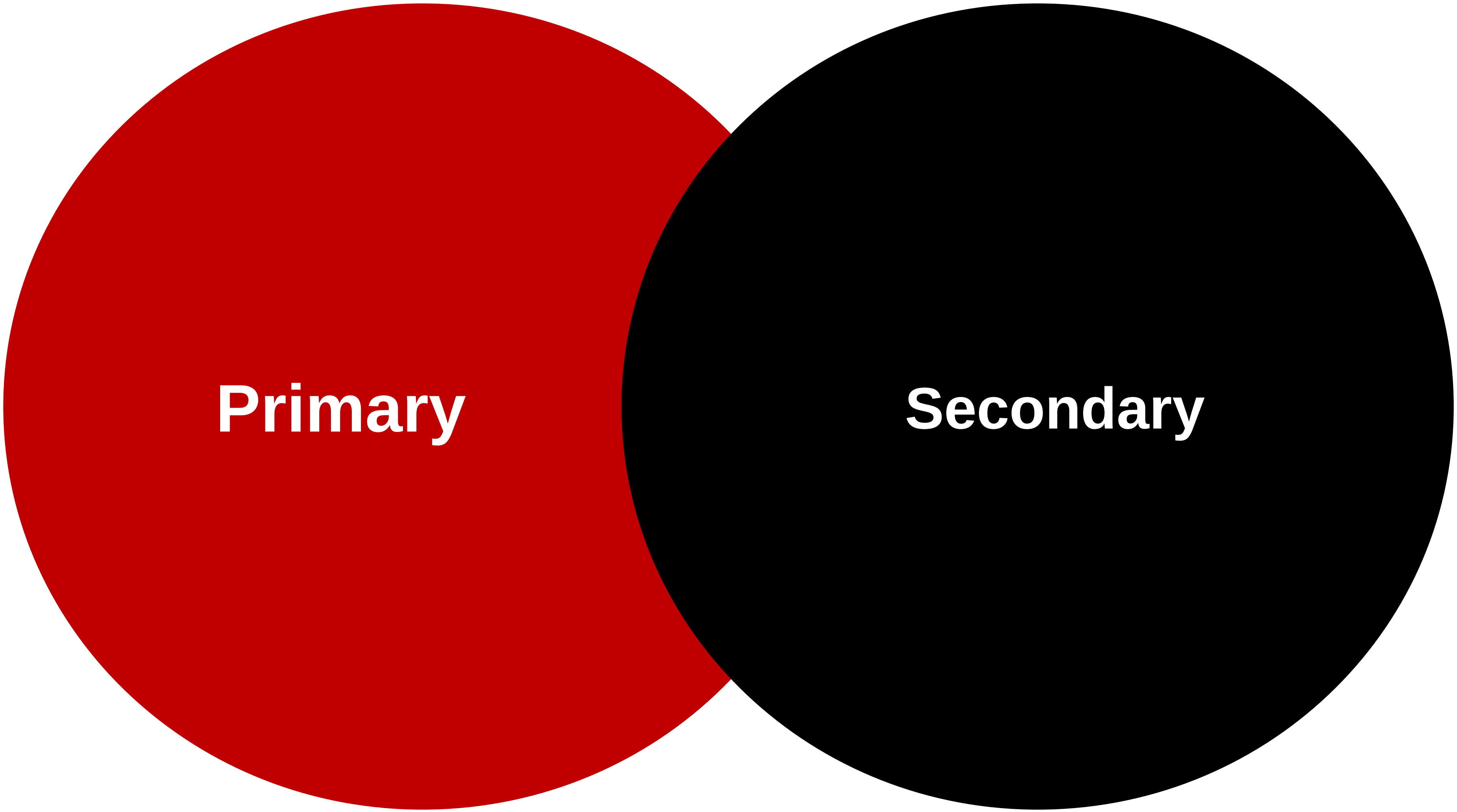


Grey matter and white matter pathology in multiple sclerosis

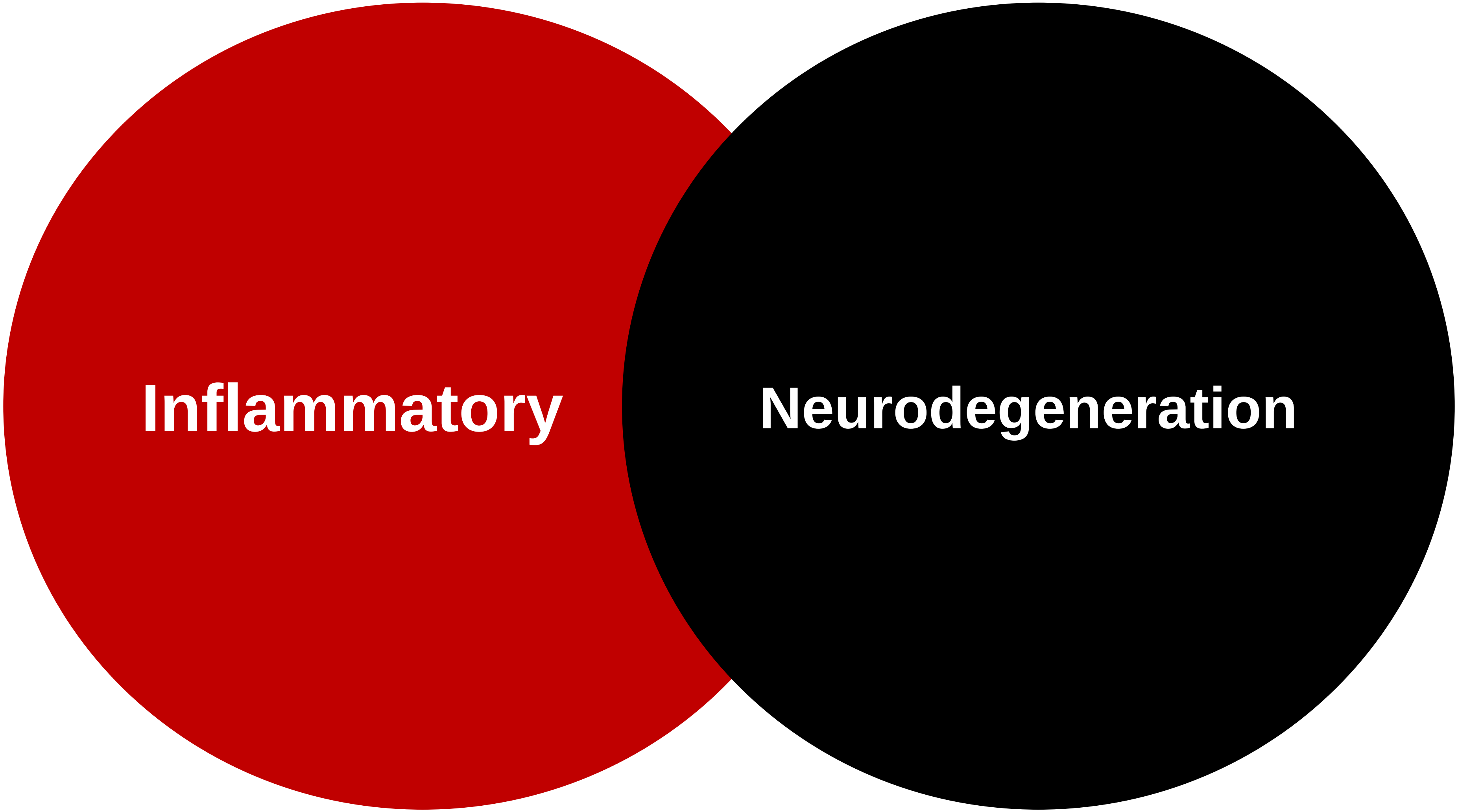


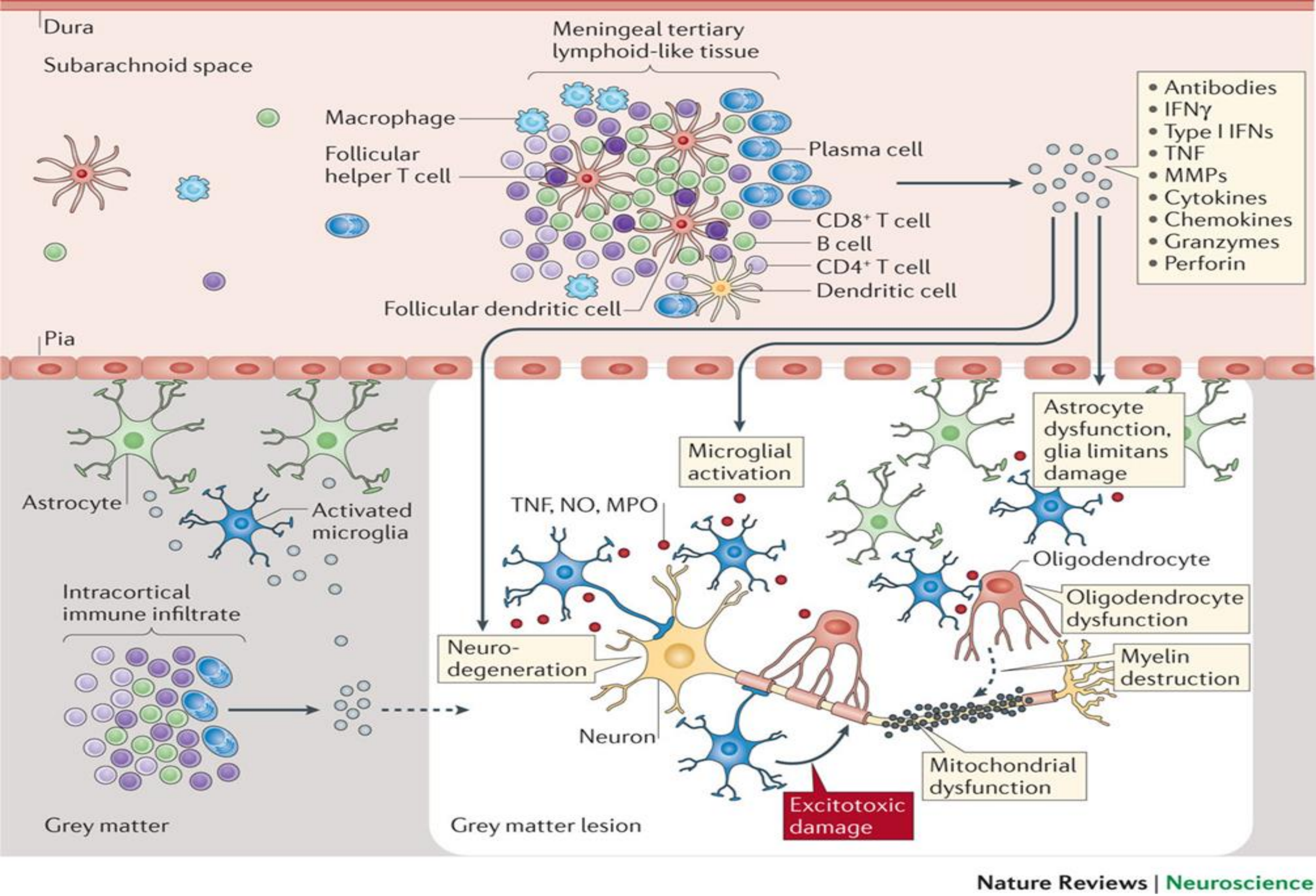
Gilmore, C. P. *et al*. Regional variations in the extent and pattern of grey matter demyelination in multiple sclerosis: a comparison between the cerebral cortex, cerebellar cortex, deep grey matter nuclei and the spinal cord. *J. Neurol. Neurosurg. Psychiatry* **80**, 182–187 (2009).

Grey matter pathology in multiple sclerosis

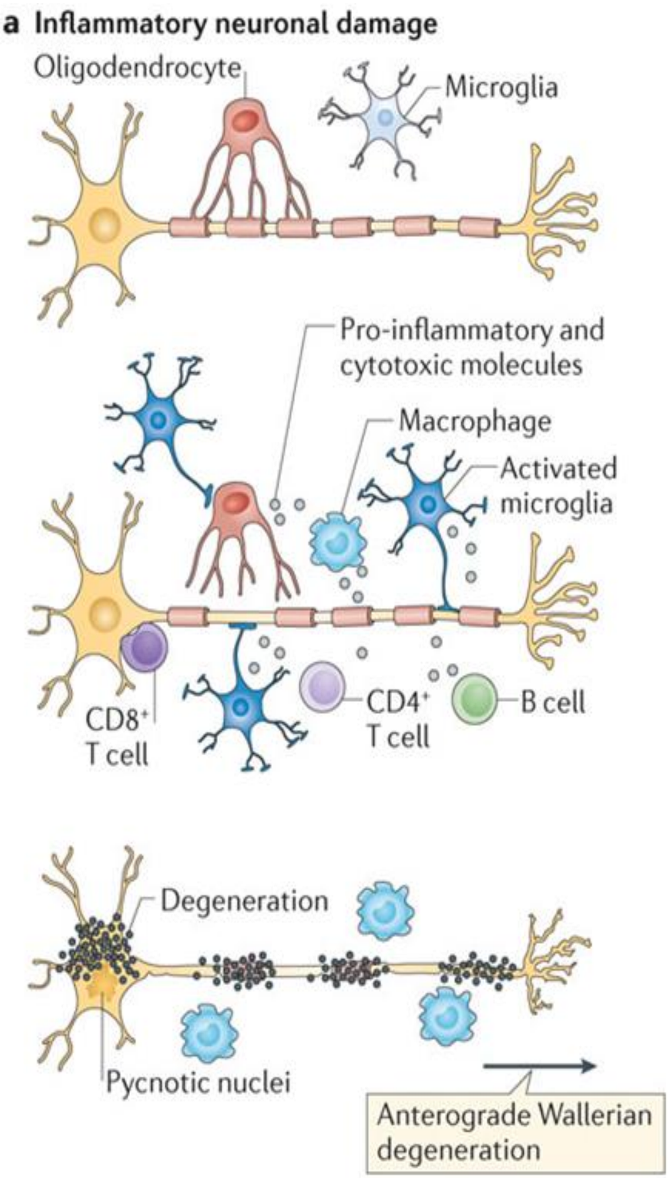


Grey matter pathology in multiple sclerosis

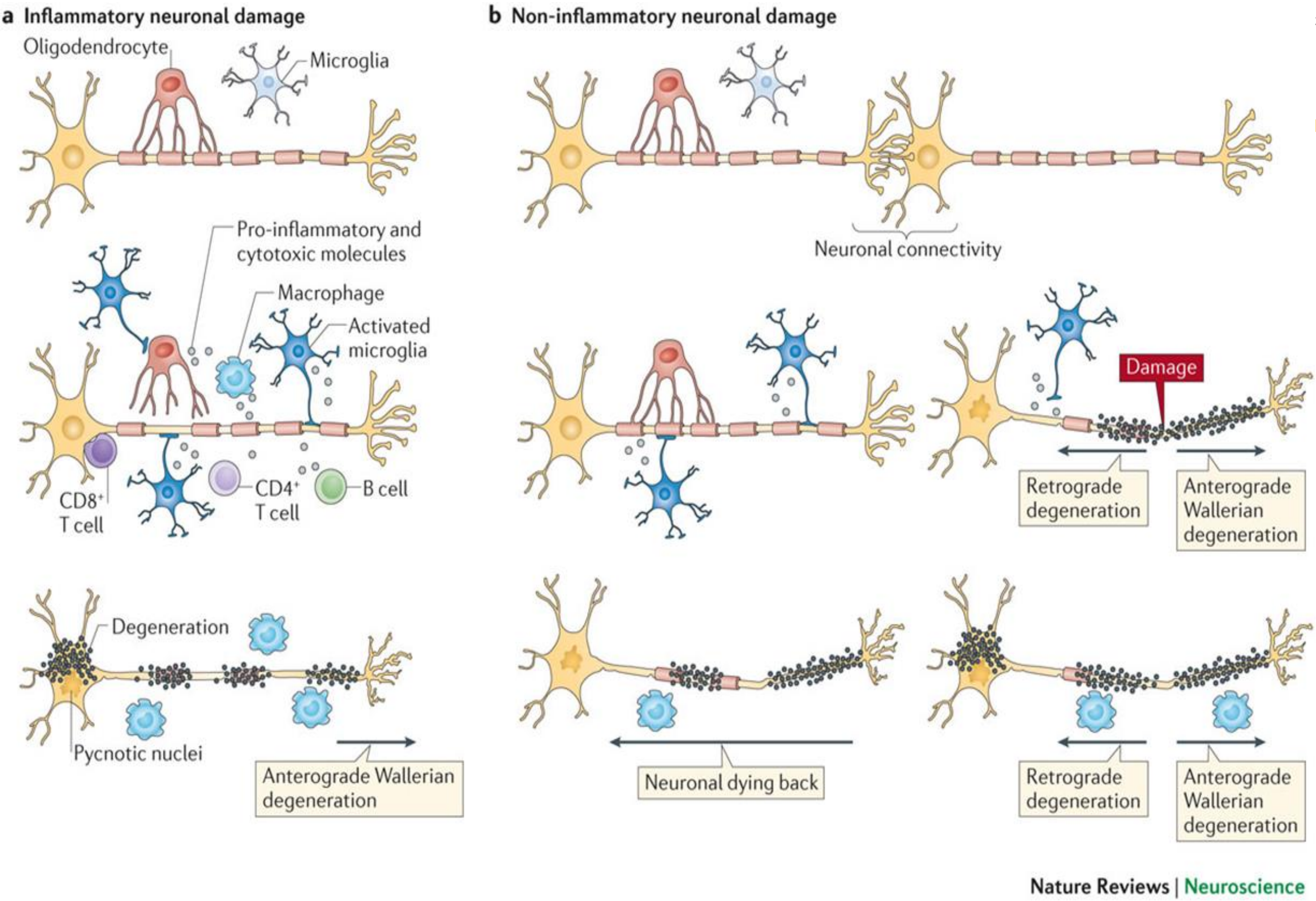




Calabrese et al, 2015. Exploring the origins of grey matter damage in multiple sclerosis. Nature reviews Neuroscience 16(3):147-58



Calabrese et al, 2015. Exploring the origins of grey matter damage in multiple sclerosis. Nature reviews Neuroscience 16(3):147-58



Calabrese et al, 2015. Exploring the origins of grey matter damage in multiple sclerosis. Nature reviews Neuroscience 16(3):147-58

Pathogenesis of GM lesions in MS

- The involvement of a T cell with specificity for both a myelin and neuronal antigen.
- A chronic **compartmentalized** inflammatory response to a self-antigen or self-antigens.

Bettelli, E. *et al*. *J. Exp. Med.* **197**, 1073–1081 (2003).
Krishnamoorthy, G. *et al*. Myelin-specific T cells also recognize neuronal autoantigen in a transgenic mouse model of multiple sclerosis. *Nature Med.* **15**, 626–632 (2009).

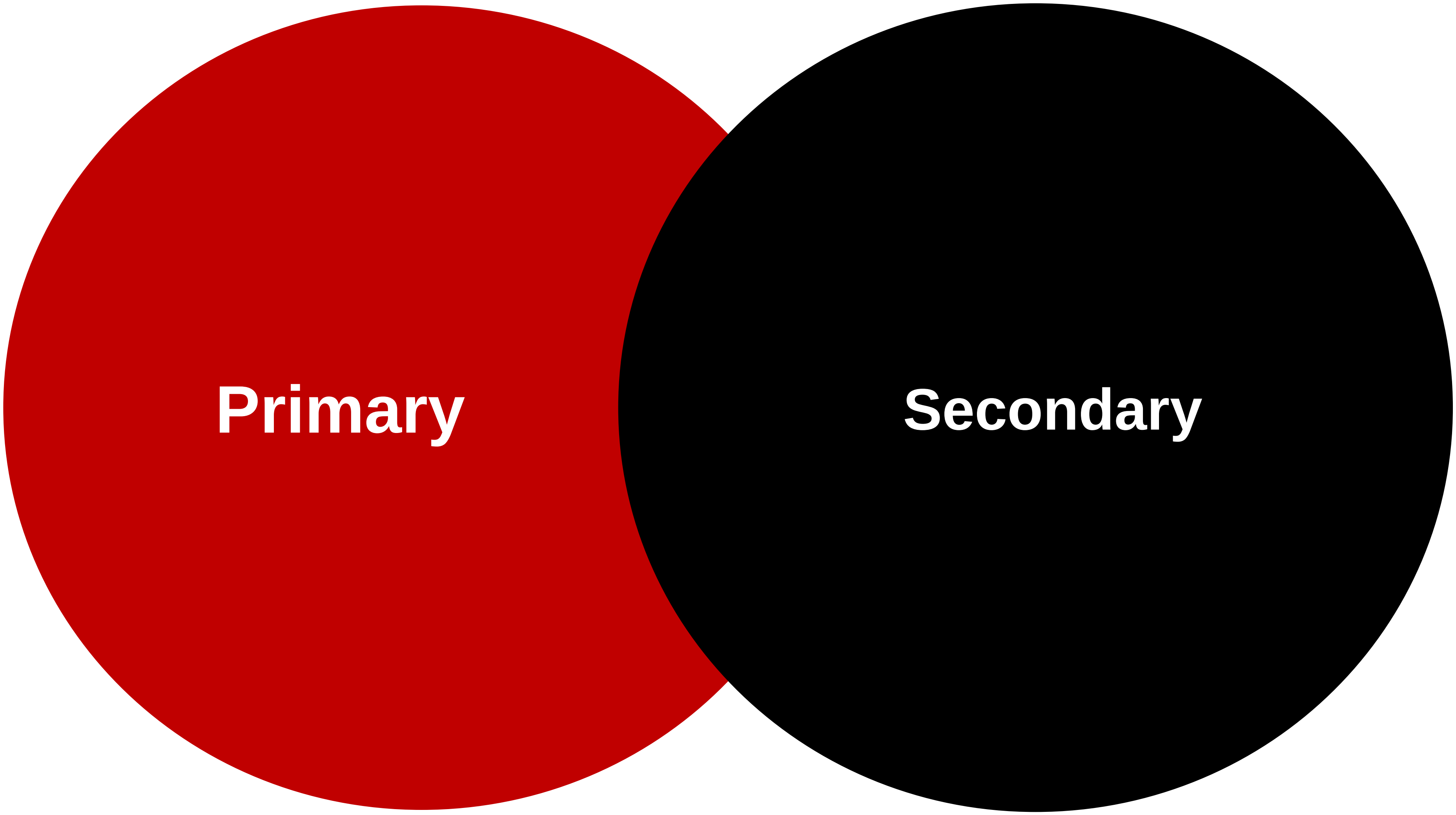
Pathogenesis of GM lesions in MS

- Cortical demyelination and neuronal loss could involve an infectious agent with **primary tropism** for oligodendrocytes and/or cortical neurons ?!

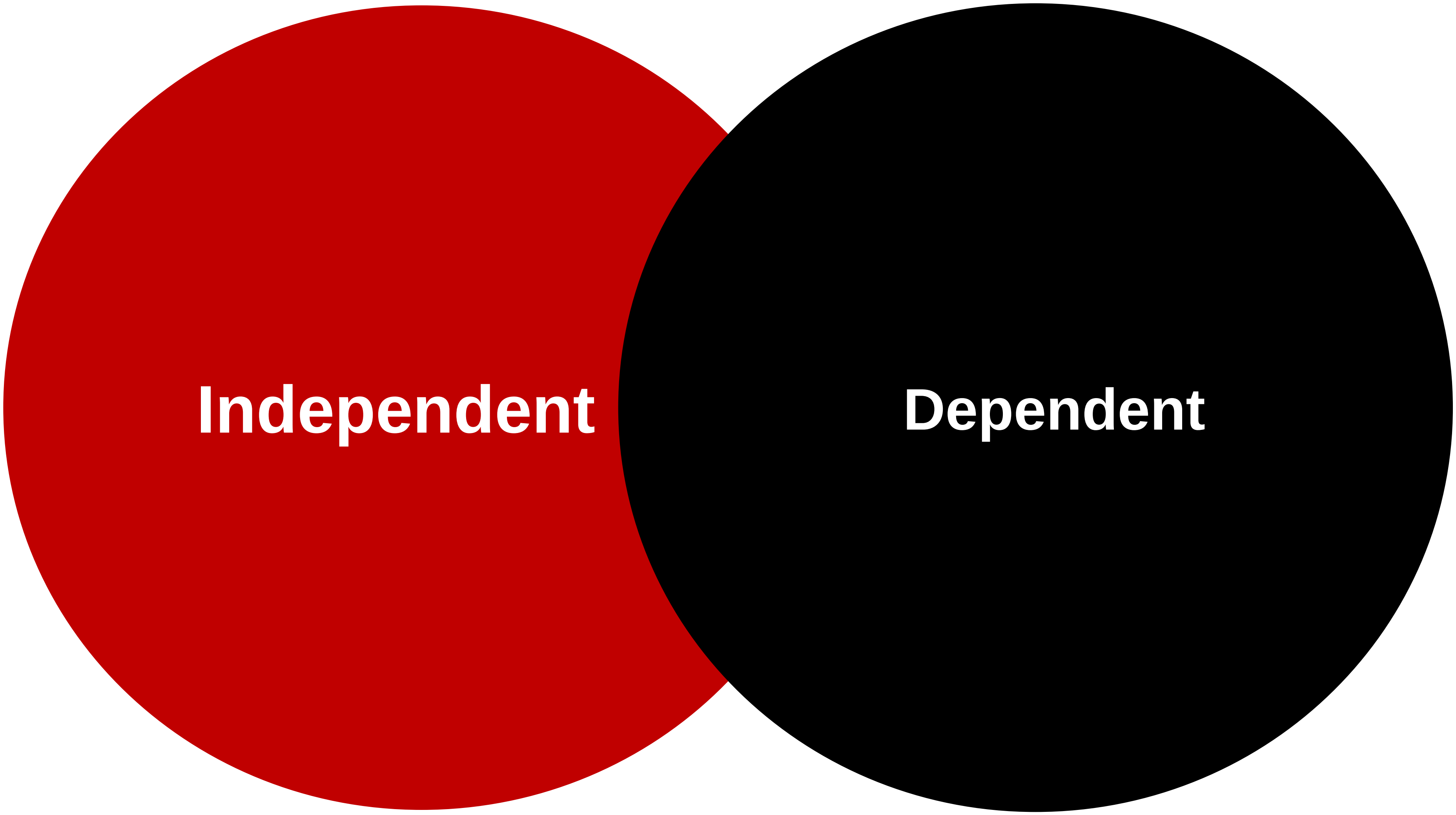
- An infectious organism located in the adjacent meninges e.g. Epstein–Barr virus (EBV)

Borkosky, S. S., Whitley, C., Kopp-Schneider, A., zur Hausen, H. & de Villiers, E. M. Epstein–Barr virus stimulates torque teno virus replication: a possible relationship to multiple sclerosis. *PLoS ONE* **7**, e32160 (2012).

Grey matter pathology in multiple sclerosis



Grey matter and white matter pathology in multiple sclerosis

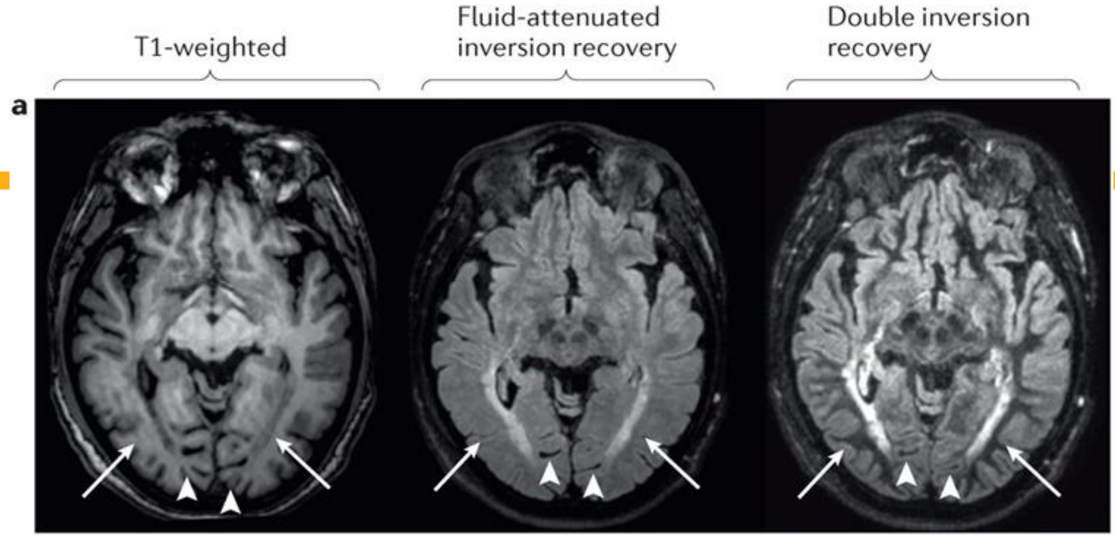


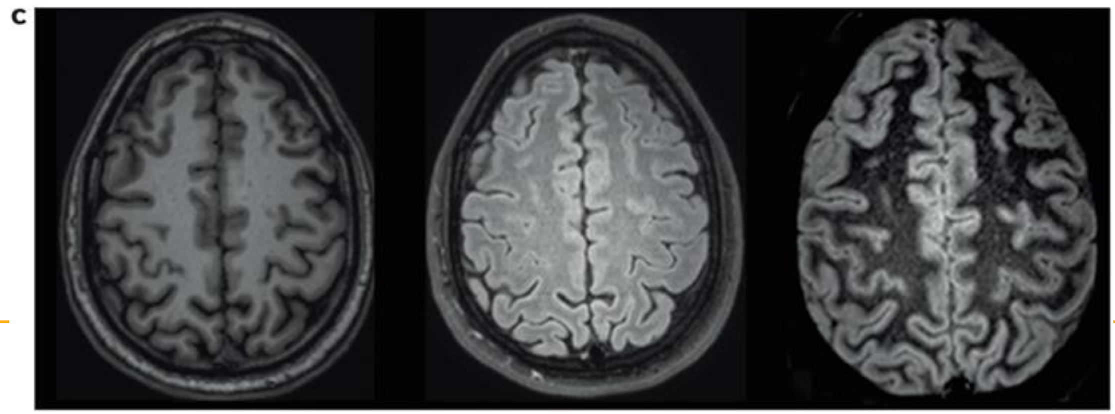
Grey matter and white matter pathology in multiple sclerosis

In vivo imaging studies confirmed the presence of grey matter lesions

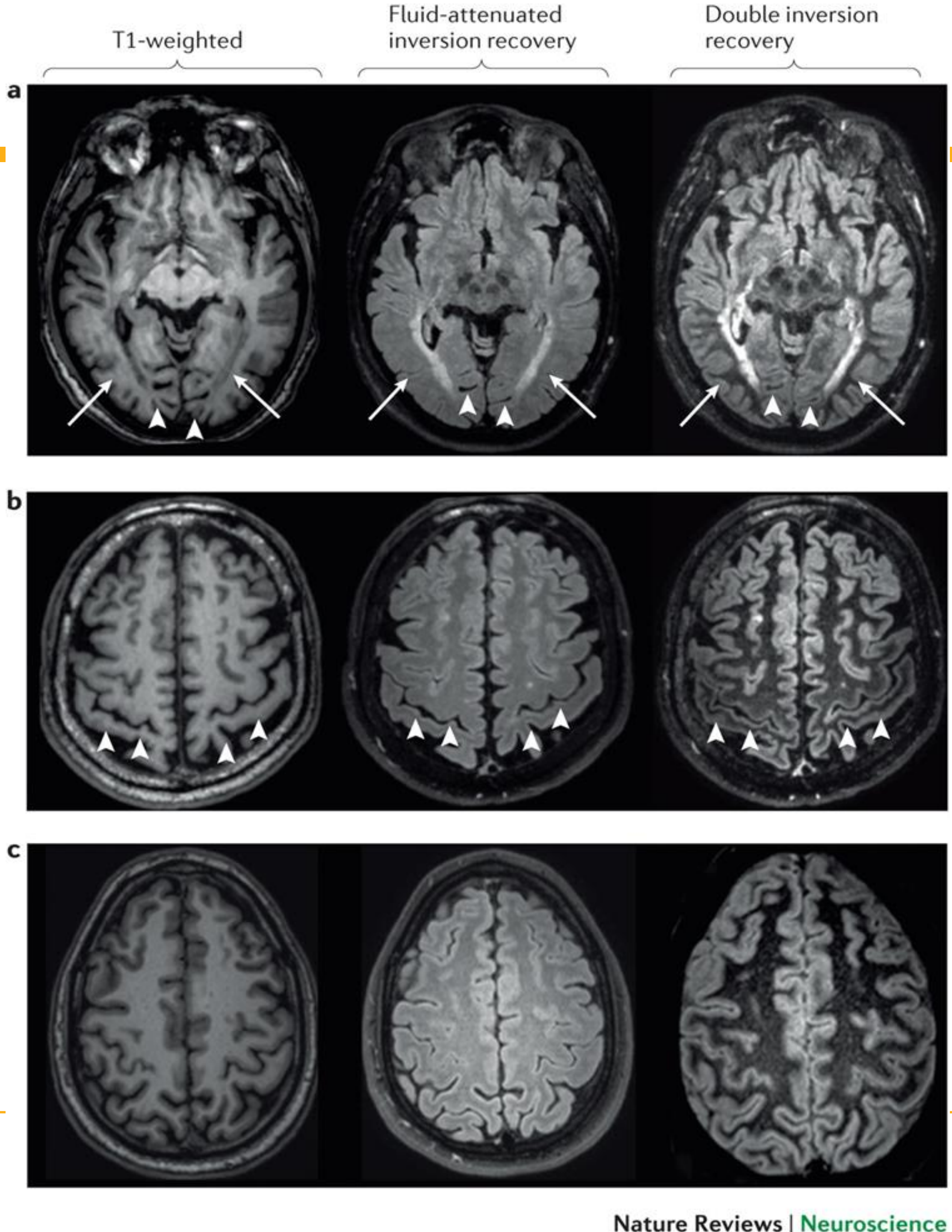
- During the earliest phases of the disease.
- In patients with very low white matter lesion volume.
- Sometimes even in patients with RIS (before any clinical symptoms are present).
- Preceding the occurrence of white matter lesions altogether.

Calabrese, M. *et al*. *Arch. Neurol.* **64**, 1416–1422 (2007).
Giorgio, A. *et al*. Cortical lesions in radiologically isolated syndrome.*Neurology* **77**, 1896–1899 (2011).
Calabrese, M. & Gallo, P. Magnetic resonance evidence of cortical onset of multiple sclerosis. *Mult. Scler.* **15**, 933–941 (2009).



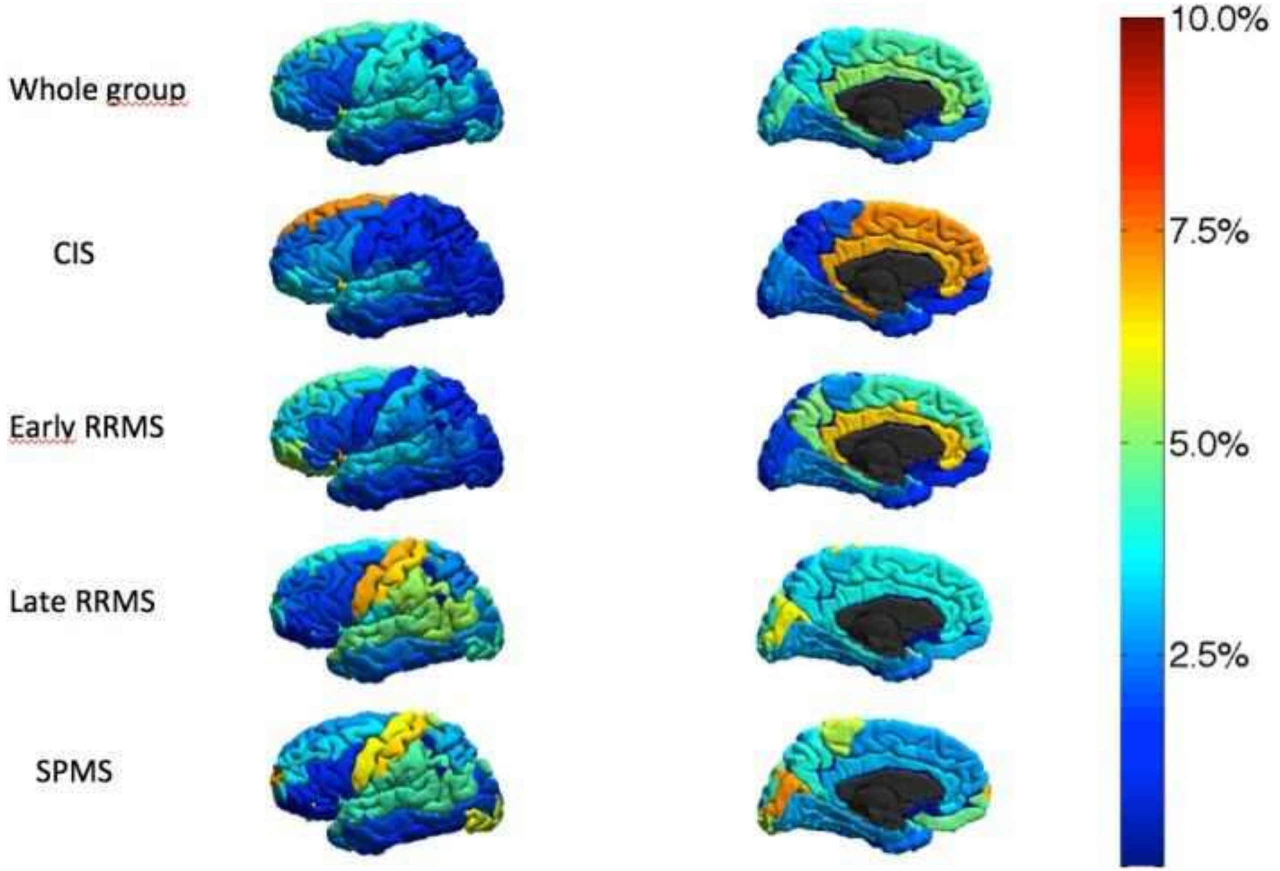


Nature Reviews | Neuroscience


T1-weighted
Fluid-attenuated inversion recovery
Double inversion recovery
a
b
c
Nature Reviews | Neuroscience

The correlation between the appearance of new cortical lesions and cortical thinning

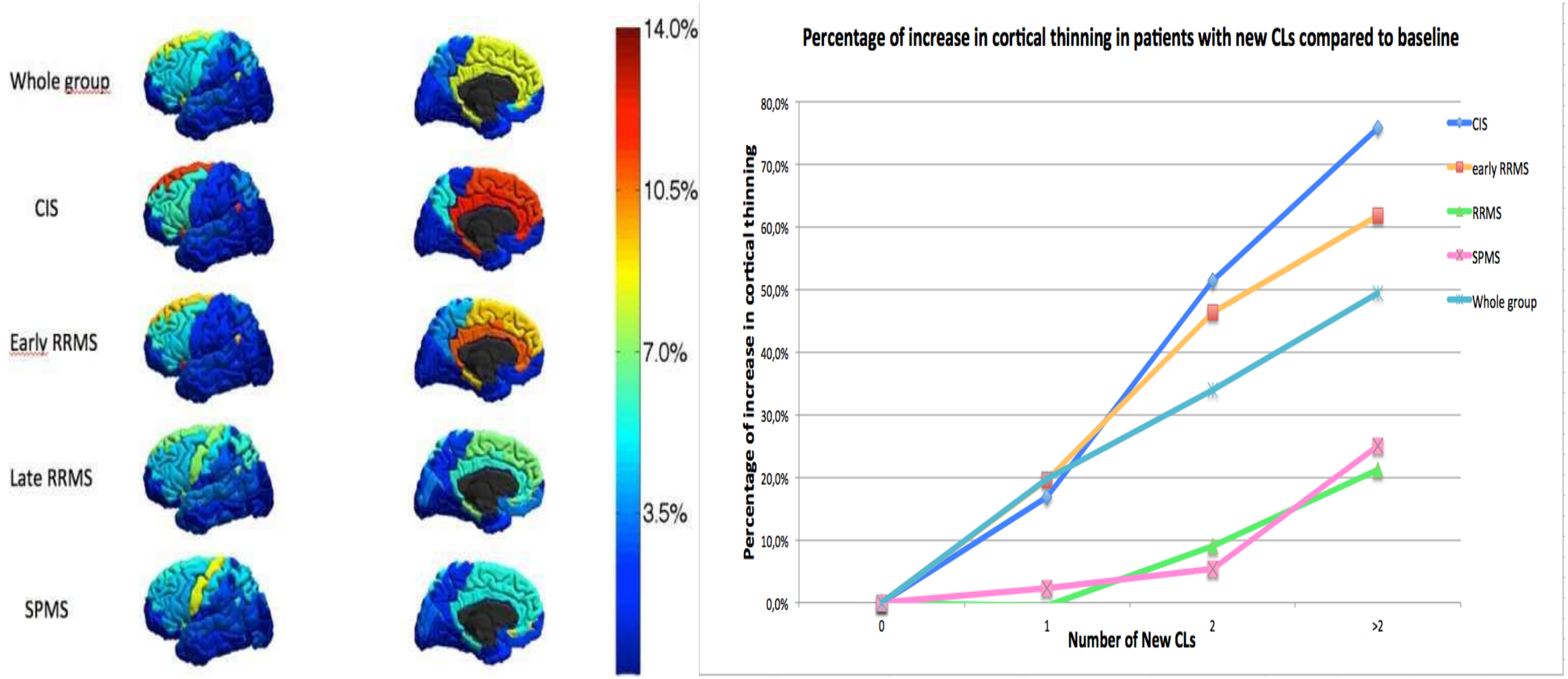
- **3D Regional map of the frequency of the appearance of new grey matter lesions during the 5-year follow up in the whole group and in the different MS subsets.**



Calabrese M, Reynolds R, Magliozzi R, Castellaro M, Morra A, et al. (2015) Regional Distribution and Evolution of Gray Matter Damage in Different Populations of Multiple Sclerosis Patients. PLOS ONE 10(8): e0135428. https://doi.org/10.1371/journal.pone.0135428

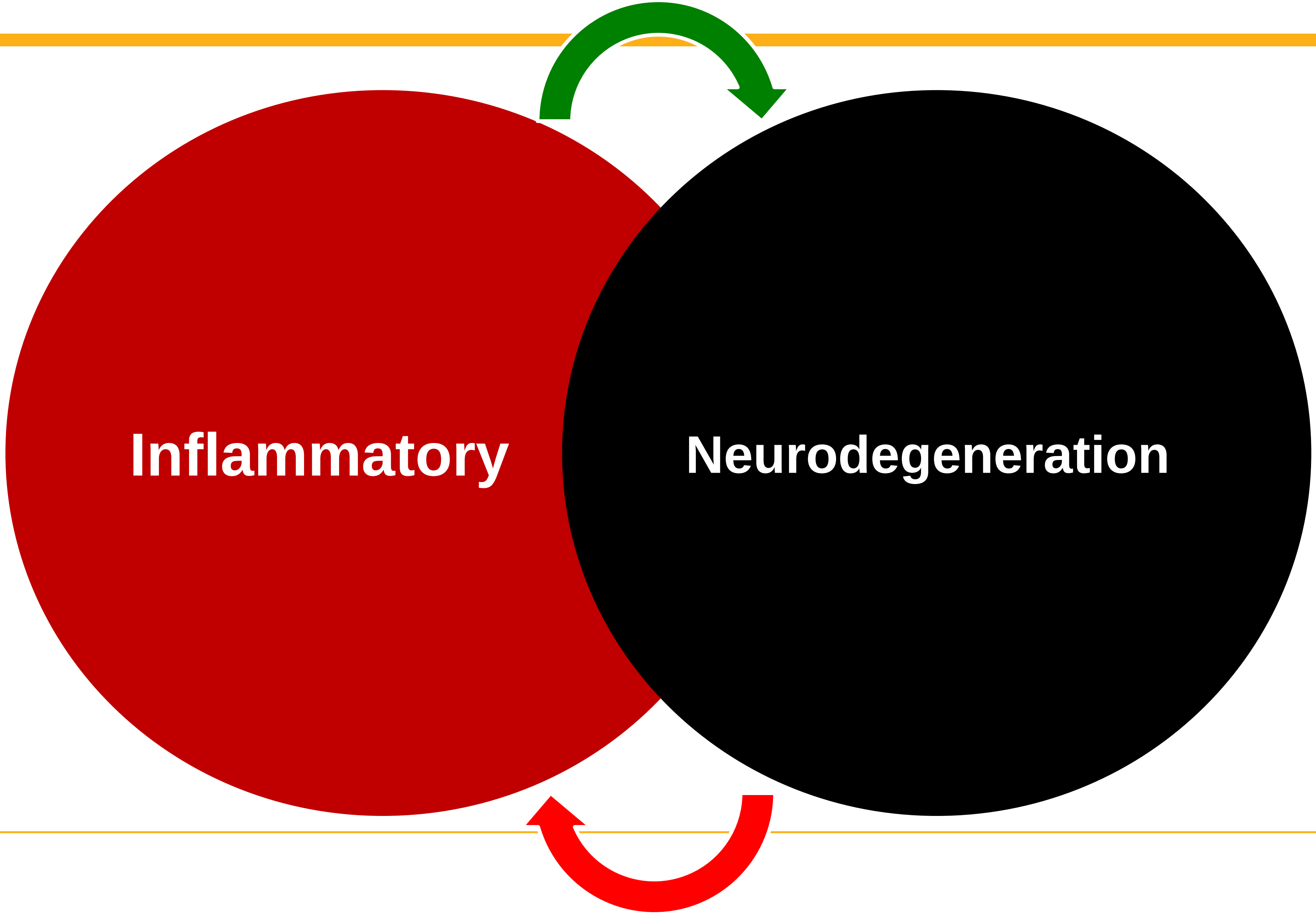
The correlation between the appearance of new cortical lesions and cortical thinning

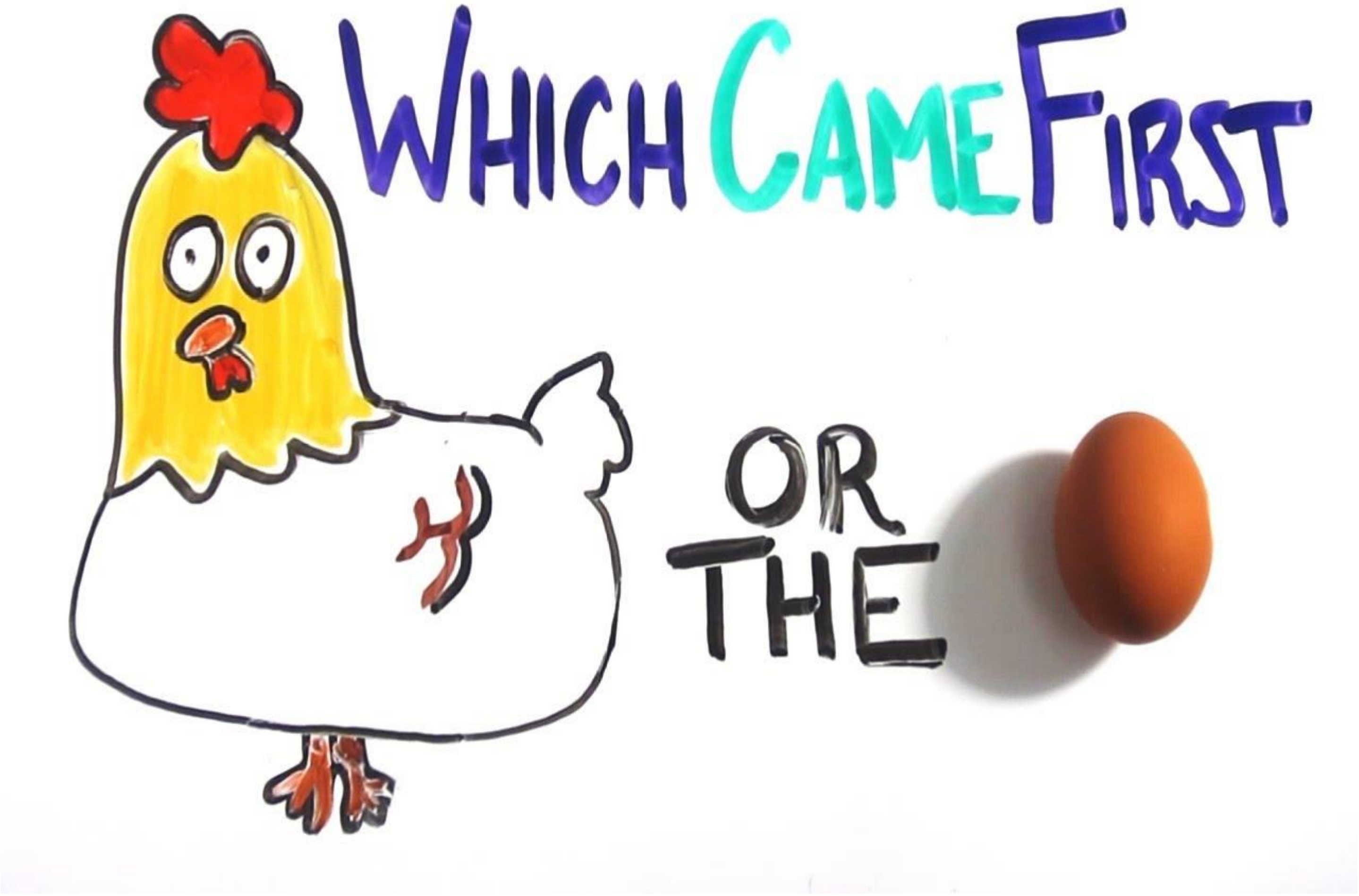
- **3D Regional map of the cortical thickness change during the 5-year follow up in the whole group and in the different MS subsets.**



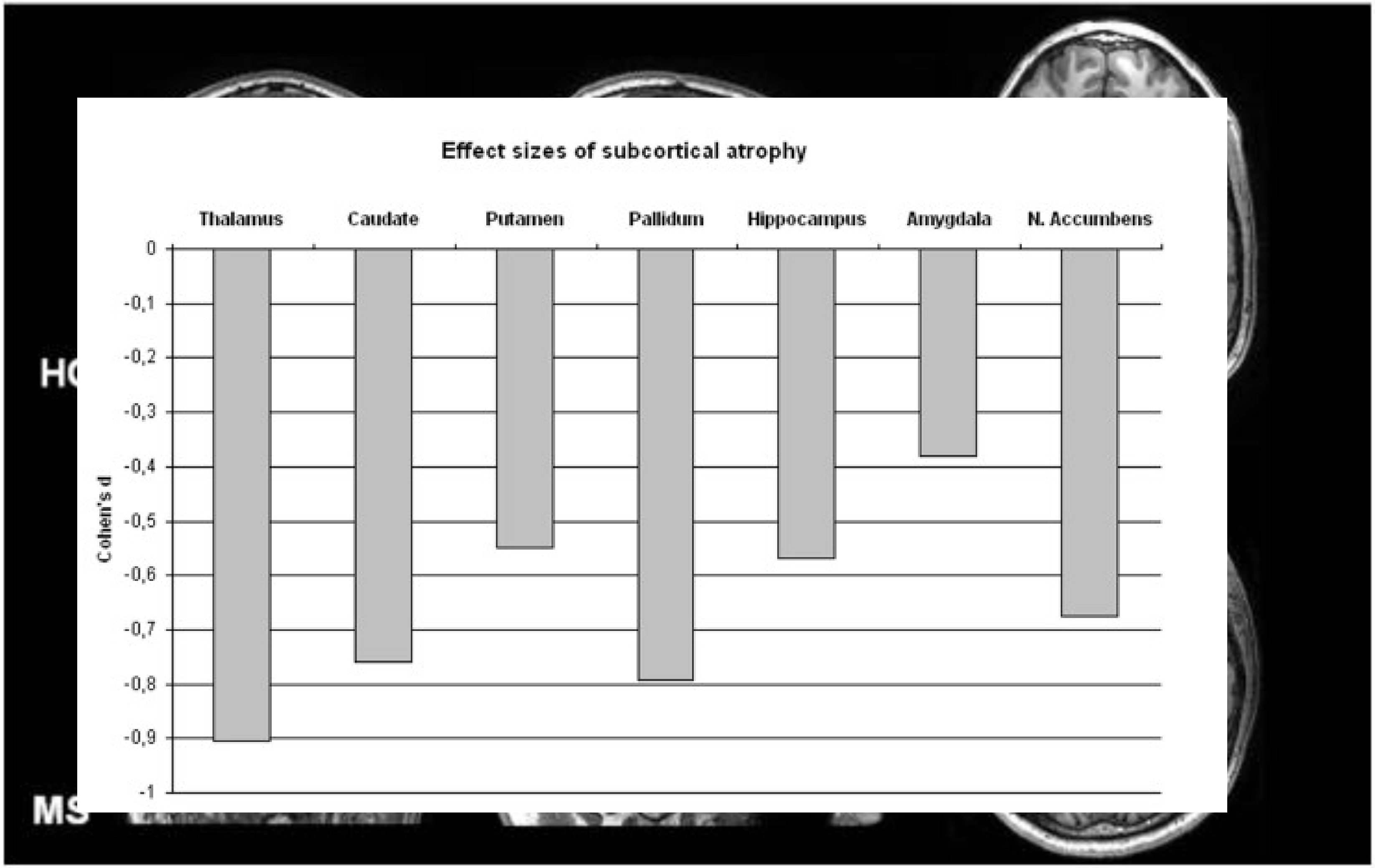
Calabrese M, Reynolds R, Magliozzi R, Castellaro M, Morra A, et al. (2015) Regional Distribution and Evolution of Gray Matter Damage in Different Populations of Multiple Sclerosis Patients. PLOS ONE 10(8): e0135428. https://doi.org/10.1371/journal.pone.0135428

Grey matter pathology in multiple sclerosis




WHICH CAME FIRST
OR THE

Subcortical grey matter

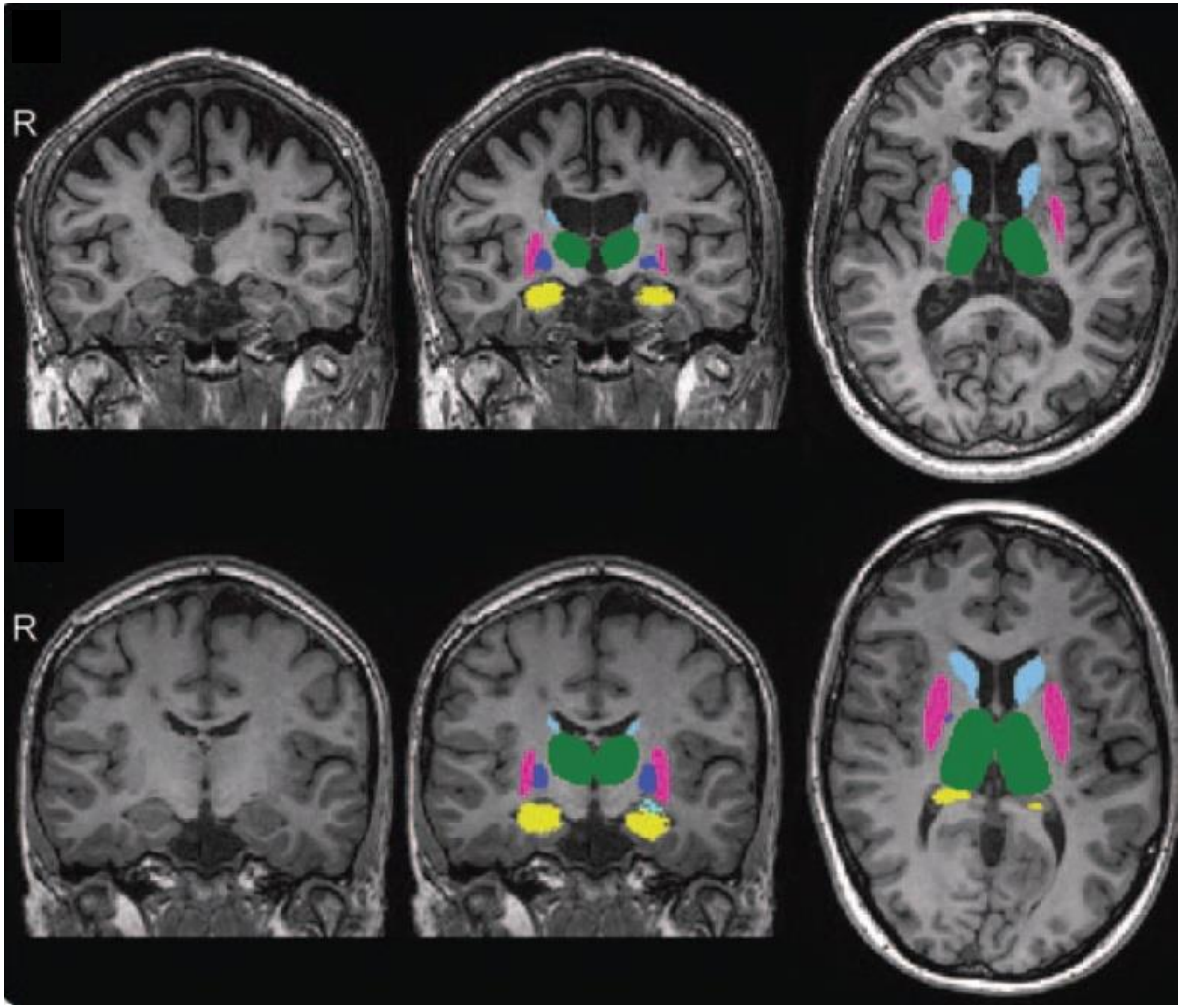


Reproduced with permission from Schoonheim M, Popescu V, Rueda Lopes FC, Wiebenga OT, Vrenken H, Douw L, Polman CH, Geurts JJG, Barkhof F. Subcortical atrophy and cognition: Sex effects in multiple sclerosis. *Neurology* 2012;79:1754-1761

Thalamic atrophy was more marked in men with MS

MS male

MS female



Reproduced with permission from Schoonheim M, Popescu V, Rueda Lopes FC, Wiebenga OT, Vrenken H, Douw L, Polman CH, Geurts JJG, Barkhof F. Subcortical atrophy and cognition: Sex effects in multiple sclerosis. *Neurology* 2012;79:1754-1761

Iron deposition in the subcortical deep gray matter (SDGM) of multiple sclerosis (MS)

Serum iron concentration is associated with subcortical deep gray matter iron levels in multiple sclerosis patients

Niels Bergsland[a,c], Simone Agostini[a], Maria M. Laganà[a], Roberta Mancuso[a], Laura Mendozzi[a], Eleonora Tavazzi[a], Pietro Cecconi[a], Mario Clerici[a,b] and Francesca Baglio[a]

Iron deposition has been noted widely in the subcortical deep gray matter (SDGM) of multiple sclerosis (MS) patients. Recent evidence suggests that serum iron may cross the blood–brain barrier and might be associated with SDGM iron deposition. The aim of the current study was to assess whether an iron-sensitive MRI measure is related to serum iron concentrations. This was a retrospective, cross-sectional study of 22 MS patients and 24 healthy controls (HCs), group matched for age and sex. Participants were imaged on a 1.5-T MRI scanner. High-resolution T1-weighted images and susceptibility-weighted images

for MS patients in the globus pallidus ($P=0.009$) only. In MS patients only, there was a significant relationship between serum iron and putaminal iron volume (partial $r=0.449$, $P=0.041$), whereas trends were evidenced for the caudate (partial $r=0.396$, $P=0.078$) and the globus pallidus (partial $r=0.410$, $P=0.065$). Serum iron content in MS patients may be related to SDGM iron content. These results warrant confirmation in a larger study of MS patients. *NeuroReport* 00:000–000

and SDGM iron content. MS patients presented with significantly smaller SDGM tissue volumes of the caudate, globus pallidus, putamen, and thalamus (all $P \leq 0.0001$). With respect to HCs, increased iron content was observed

Iron deposition in the subcortical deep gray matter (SDGM) of multiple sclerosis (MS)

Published February 23, 2017 as 10.3174/ajnr.A5109

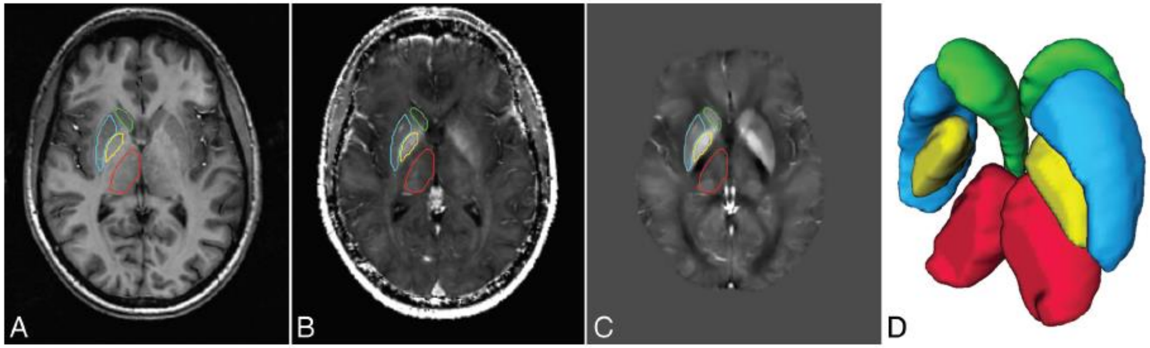
ORIGINAL RESEARCH
ADULT BRAIN

Cognitive Implications of Deep Gray Matter Iron in Multiple Sclerosis

E. Fujiwara, J.A. Kmech, D. Cobzas, H. Sun, P. Seres, G. Blevins, and A.H. Wilman

RESULTS: Compared with controls, patients showed reduced memory ($P < .001$) and processing speed ($P = .02$) and smaller putamen ($P < .001$), globus pallidus ($P = .002$), and thalamic volumes ($P < .001$). Quantitative susceptibility mapping values were increased in patients compared with controls in the putamen ($P = .003$) and globus pallidus ($P = .003$). In patients only, thalamus ($P < .001$) and putamen ($P = .04$) volumes were related to cognitive performance. After we controlled for volume effects, quantitative susceptibility mapping values in the globus pallidus ($P = .03$; trend for transverse relaxation rate, $P = .10$) were still related to cognition.

CONCLUSIONS: Quantitative susceptibility mapping was more sensitive compared with the transverse relaxation rate in detecting deep gray matter iron accumulation in the current multiple sclerosis cohort. Atrophy and iron accumulation in deep gray matter both have negative but separable relationships to cognition in multiple sclerosis.



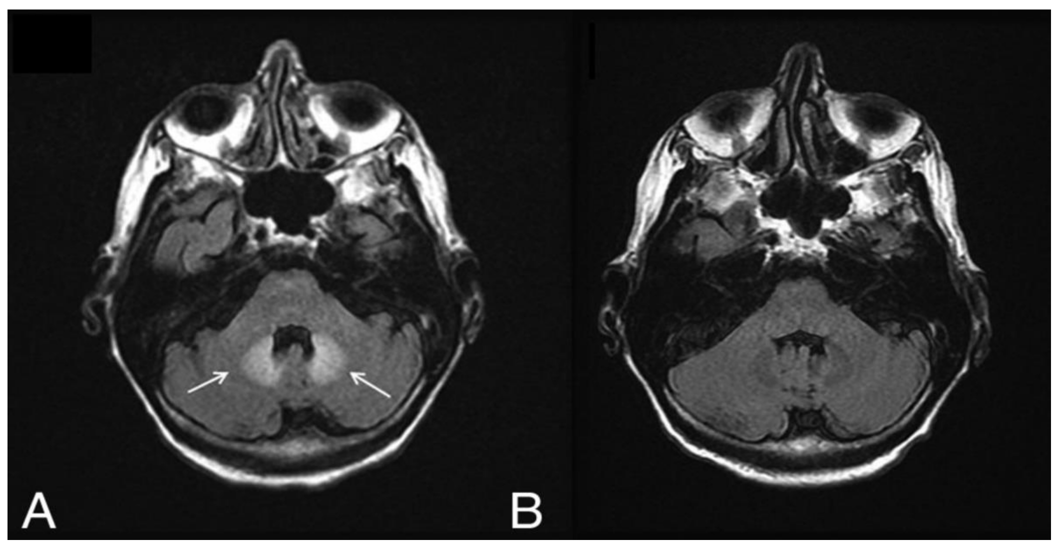
Dentate and MS

Radiology

ORIGINAL RESEARCH ■ NEURORADIOLOGY

Multiple Sclerosis: Hyperintense Dentate Nucleus on Unenhanced T1-weighted MR Images Is Associated with the Secondary Progressive Subtype[1]

Luca Roccatagliata, MD, PhD
Luisa Vuolo, MD
Laura Bonzano, PhD
Anna Pichiecchio, MD
Giovanni Luigi Mancardi, MD



Dentate and MS

ELSEVIER

Journal of the Neurological Sciences 234 (2005) 17 – 24

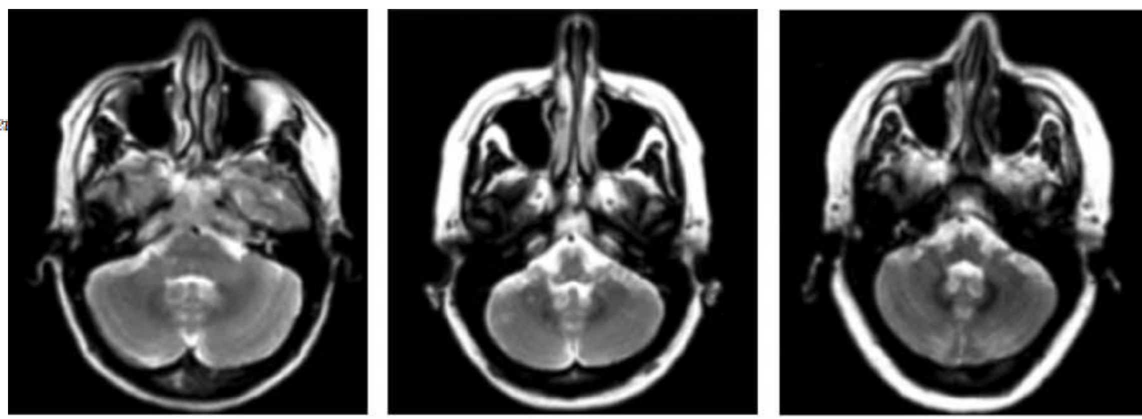
Journal of the Neurological Sciences

www.elsevier.com/locate/jns

MRI T2 hypointensity of the dentate nucleus is related to ambulatory impairment in multiple sclerosis

C.W. Tjoa[a], R.H.B. Benedict[a,b,c], B. Weinstock-Guttman[a], A.J. Fabiano[a], R. Bakshi[d,*]

[d]Departments of Ne ... ospital, Harvard



54 y.o. Normal	54 y.o. MS	53 y.o. MS
Intensity: .377	Intensity: .258	Intensity: .208
	Time 25 ft: 8.4 sec	Time 25 ft: 170 sec

Dentate and MS

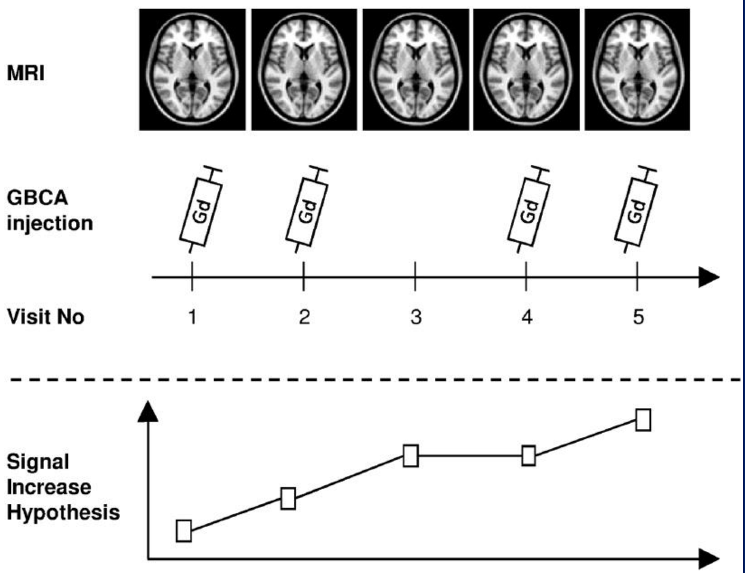
MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

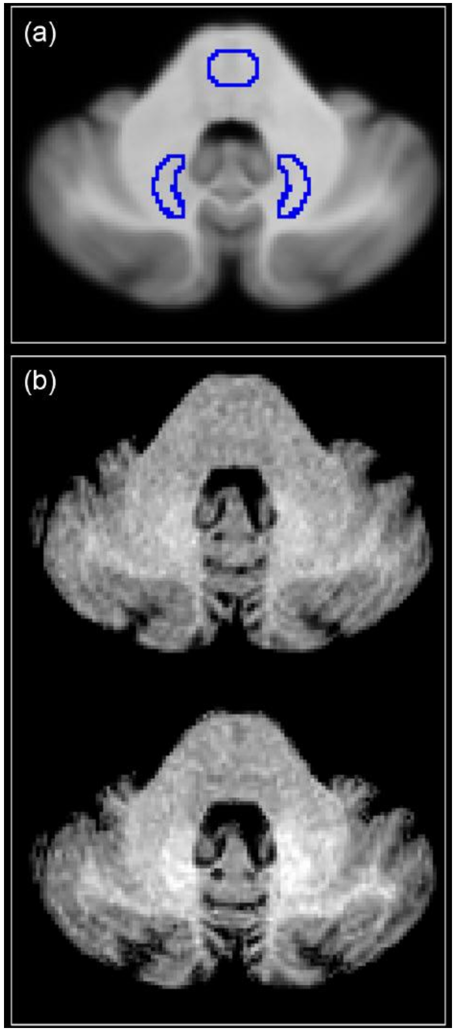
Gadopentetate but not gadobutrol accumulates in the dentate nucleus of multiple sclerosis patients

Ludwig Schlemm, Claudia Chien, Judith Bellmann-Strobl, Jan Dörr, Jens Wuerfel, Alexander U Brandt, Friedemann Paul and Michael Scheel

Multiple Sclerosis Journal
2017, Vol. 23(7) 963–972
DOI: 10.1177/1352458516670738

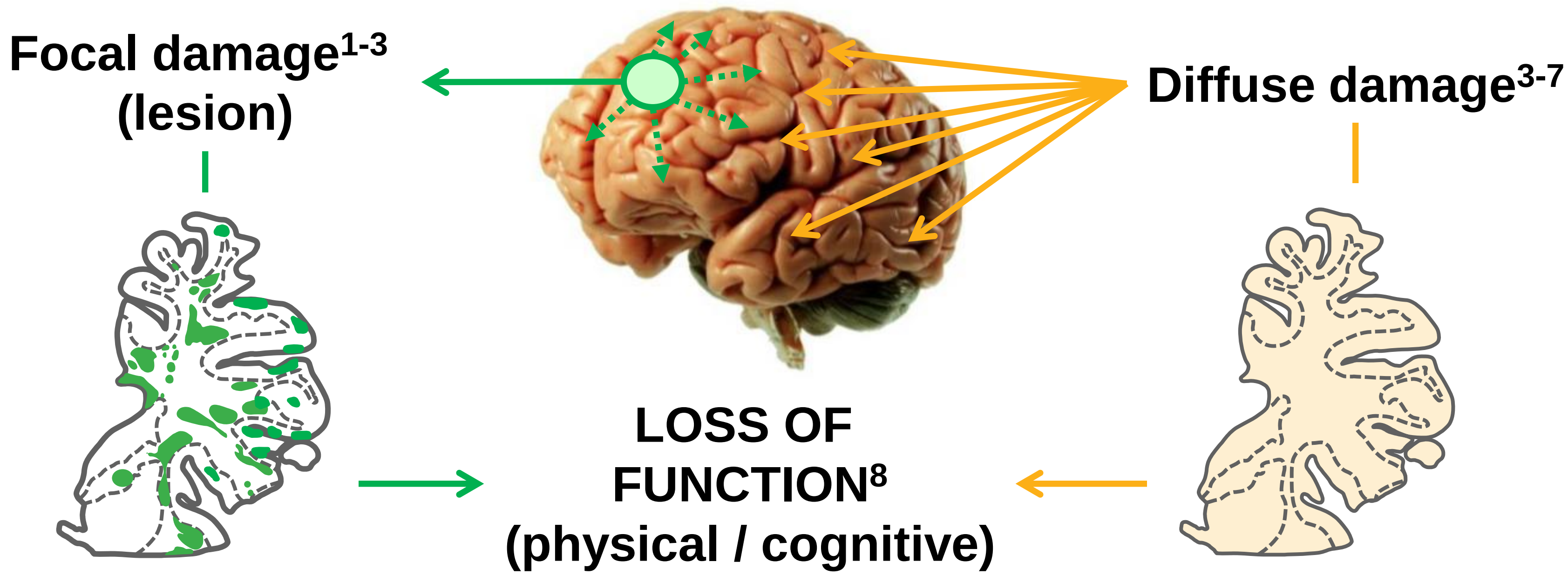


Gadopentetate dimeglumine (Gd-DTPA, Magnevist®)) being more likely to accumulate than macrocyclic agents (e.g. gadobutrol (Gd-BT-DO3A, Gadovist®)).



Our understanding of MS is changing

MS causes focal and diffuse damage to the brain



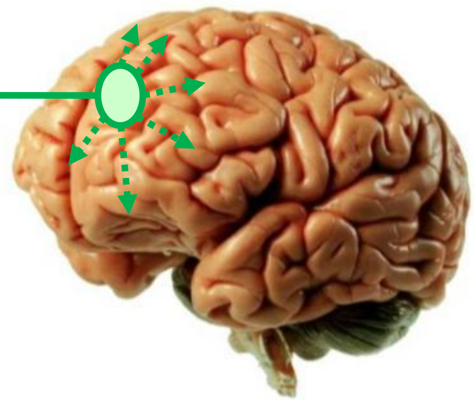
- **Focal white matter (WM) lesions are the classic hallmark of MS[1-3]**
- **It is now evident that damage also occurs in grey matter (GM) and diffusely in normal-appearing WM (NAWM)[3-7]**

1. Smirniotopoulos JG *et al. Radiographics* 2007; 2. Markovic-Plese S, McFarland HF. *Curr Neurol Neurosci Rep* 2001; 3. Kutzelnigg A and Lassmann H. *Handbook Clin Neurol* 2014; 4. Kutzelnigg A *et al. Brain* 2005; 5. Frischer JM *et al. Brain* 2009; 6. Chun J and Hartung HP. *Clin Neuropharmacol* 2010; 7. Lassmann H. *Glia* 2014; 8. Barten LJ *et al. Drug Des Devel Ther* 2010. Left and right brain images adapted with permission from Kutzelnigg A *et al.,* Cortical demyelination and diffuse white matter injury in multiple sclerosis, *Brain* 2005; 128 (Pt 11); 2705-2712 by permission of Oxford University Press

MS causes focal and diffuse damage to the brain

Focal damage[1–3] (lesion)

Diffuse damage[3–7]



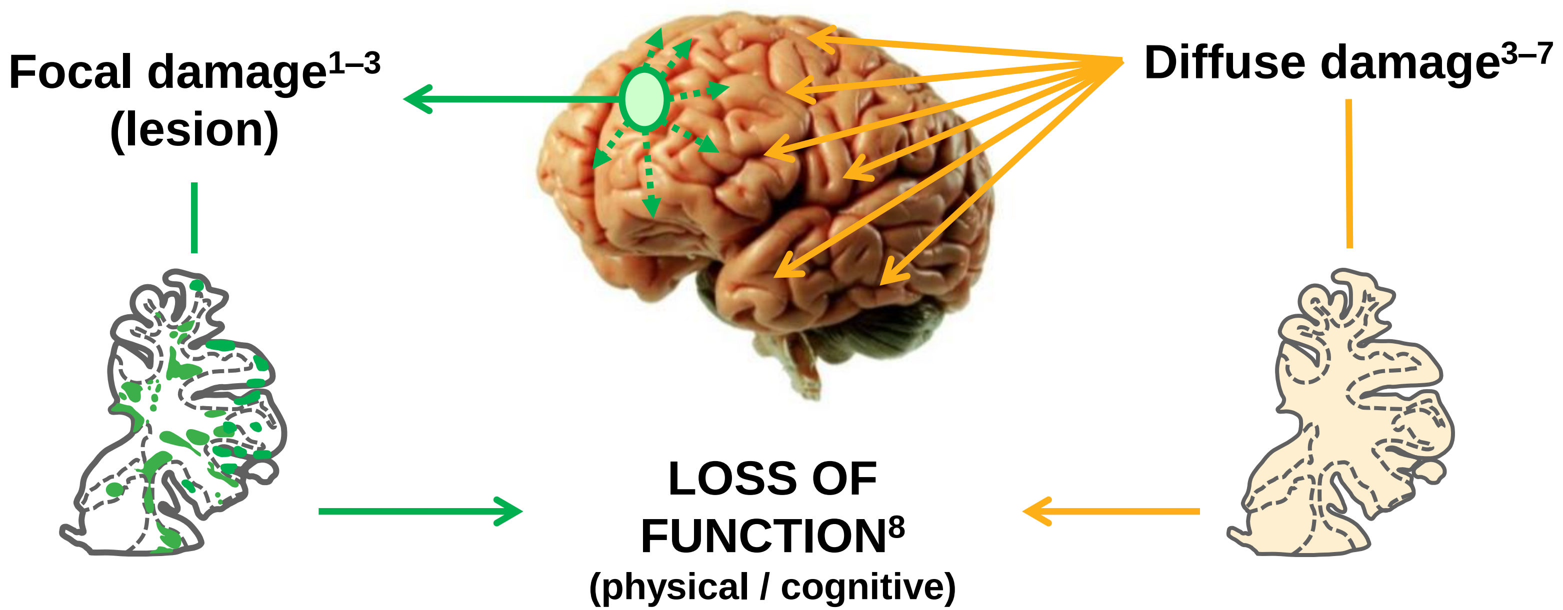
LOSS OF FUNCTION[8]

- **MRI lesions**
  T_2 / Gd^+ T_1 lesions (focal damage)
- **T_1 black holes**
  (severe localised tissue damage / destruction)

- **Brain volume loss**

*Gd^+ T_1 lesions and / or new / enlarging T_2 lesions. 1. Smirniotopoulos JG *et al. Radiographics* 2007; 2. Markovic-Plese S, McFarland HF. *Curr Neurol Neurosci Rep* 2001; 3. Kutzelnigg A, Lassmann H. *Handbook Clin Neurol* 2014; 4. Kutzelnigg A *et al. Brain* 2005; 5. Frischer JM *et al. Brain* 2009; 6. Chun J, Hartung HP. *Clin Neuropharmacol* 2010; 7. Lassmann H. *Glia* 2014; 8. Barten LJ *et al. Drug Des Devel Ther* 2010. Left and right brain images adapted from Kutzelnigg A *et al.*, Cortical demyelination and diffuse white matter injury in multiple sclerosis, *Brain* 2005; 128 (Pt 11); 2705-2712 by permission of Oxford University Press

MS causes focal and diffuse damage to the brain



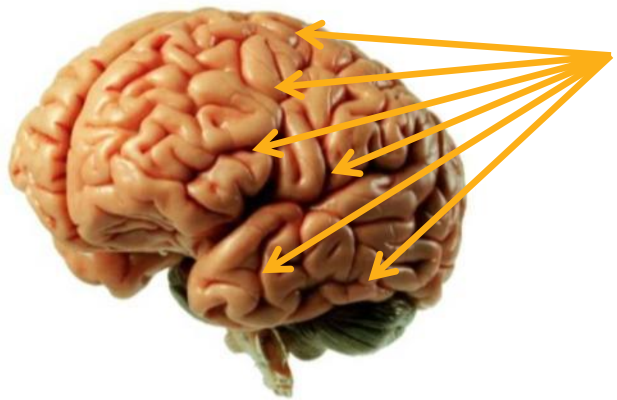
- **MRI lesions**
  T_2 / Gd^+ T_1 lesions (focal damage)
- **T_1 black holes**
  (severe localised tissue damage / destruction)

- **Brain volume loss**

*Gd^+ T_1 lesions and / or new / enlarging T_2 lesions. 1. Smirniotopoulos JG *et al. Radiographics* 2007; 2. Markovic-Plese S, McFarland HF. *Curr Neurol Neurosci Rep* 2001; 3. Kutzelnigg A, Lassmann H. *Handbook Clin Neurol* 2014; 4. Kutzelnigg A *et al. Brain* 2005; 5. Frischer JM *et al. Brain* 2009; 6. Chun J, Hartung HP. *Clin Neuropharmacol* 2010; 7. Lassmann H. *Glia* 2014; 8. Barten LJ *et al. Drug Des Devel Ther* 2010. Left and right brain images adapted from Kutzelnigg A *et al.*, Cortical demyelination and diffuse white matter injury in multiple sclerosis, *Brain* 2005; 128 (Pt 11); 2705-2712 by permission of Oxford University Press

MS causes focal and diffuse damage to the brain

Focal damage[1–3]
(lesion)



Diffuse damage[3–7]

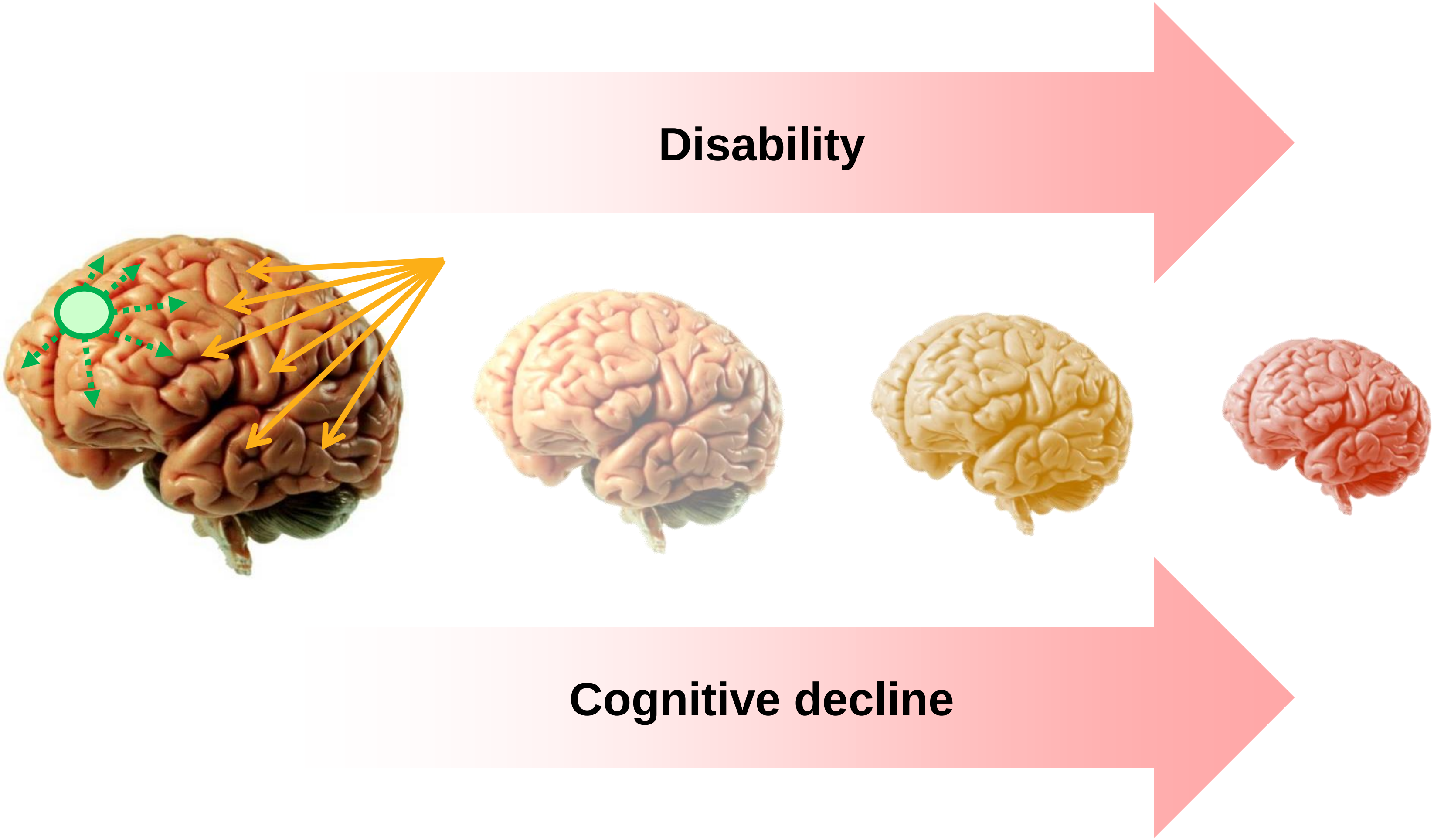
LOSS OF FUNCTION[8]

- **MRI lesions**
  T_2 / Gd^+ T_1 lesions (focal damage)
- **T_1 black holes**
  (severe localised tissue damage / destruction)

- **Brain volume loss**

*Gd^+ T_1 lesions and / or new / enlarging T_2 lesions. 1. Smirniotopoulos JG *et al. Radiographics* 2007; 2. Markovic-Plese S, McFarland HF. *Curr Neurol Neurosci Rep* 2001; 3. Kutzelnigg A, Lassmann H. *Handbook Clin Neurol* 2014; 4. Kutzelnigg A *et al. Brain* 2005; 5. Frischer JM *et al. Brain* 2009; 6. Chun J, Hartung HP. *Clin Neuropharmacol* 2010; 7. Lassmann H. *Glia* 2014; 8. Barten LJ *et al. Drug Des Devel Ther* 2010. Left and right brain images adapted from Kutzelnigg A *et al.*, Cortical demyelination and diffuse white matter injury in multiple sclerosis, *Brain* 2005; 128 (Pt 11); 2705-2712 by permission of Oxford University Press

Clinical correlates of grey matter atrophy

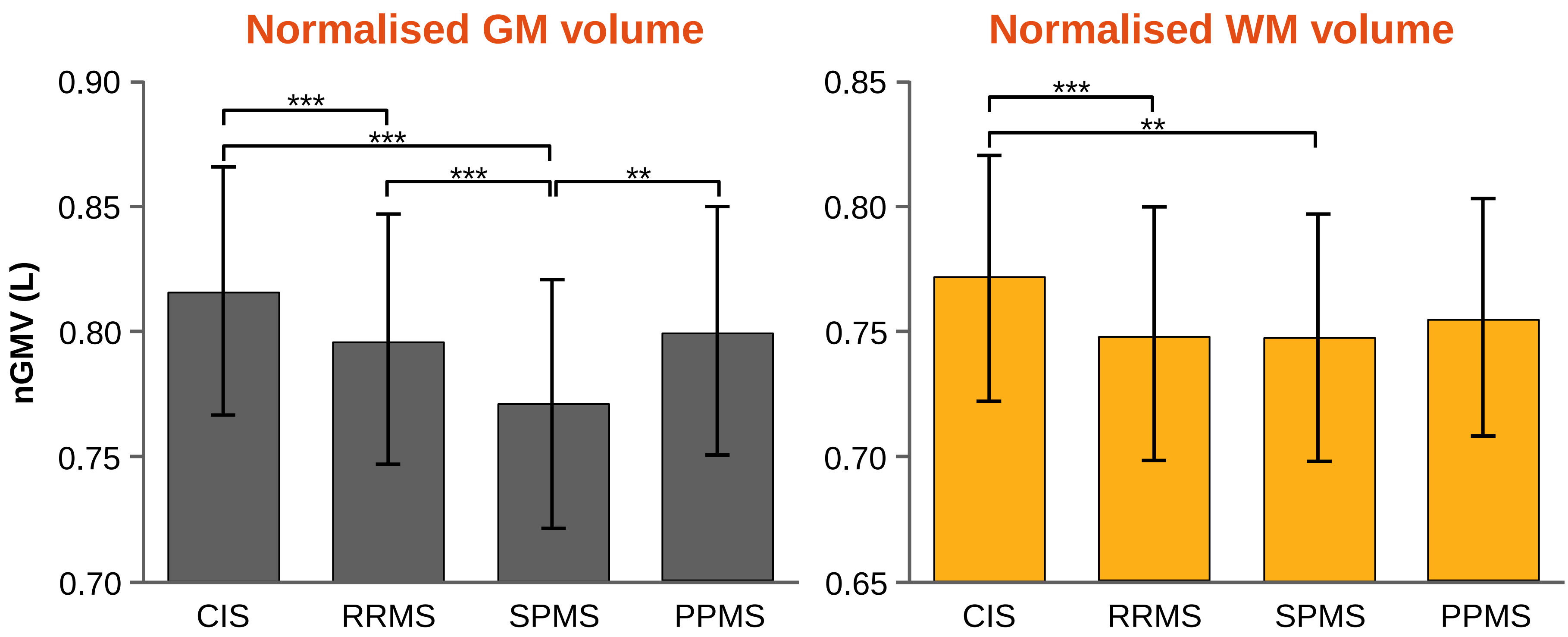


Clinical correlates of grey matter atrophy

Region	Clinical correlates
Cortex	Physical disability
Fronto-parietal cortex, striatum and thalamus	Fatigue
Dentate nucleus	Gait
Thalamus	Cognitive impairment, fatigue

Chard DT, Griffin CM, Parker GJ, Kapoor R, Thompson AJ, Miller DH: ***Brain atrophy in clinically early relapsing-remitting multiple sclerosis.*** *Brain 2002,* ***125****(Pt 2)****:****327–337.*
Niepel G, Tench Ch R, Morgan PS, Evangelou N, Auer DP, Constantinescu CS: ***Deep gray matter and fatigue in MS: a T1 relaxation time study.*** *J Neurol 2006,* ***253****(7)****:****896–902.*
Tjoa CW, Benedict RH, Weinstock-Guttman B, Fabiano AJ, Bakshi R: ***MRI T2 hypointensity of the dentate nucleus is related to ambulatory impairment in multiple sclerosis.*** *J Neurol Sci 2005,* ***234****(1–2)****:****17–24.*

GM volume changes may be more clinically relevant than WM changes



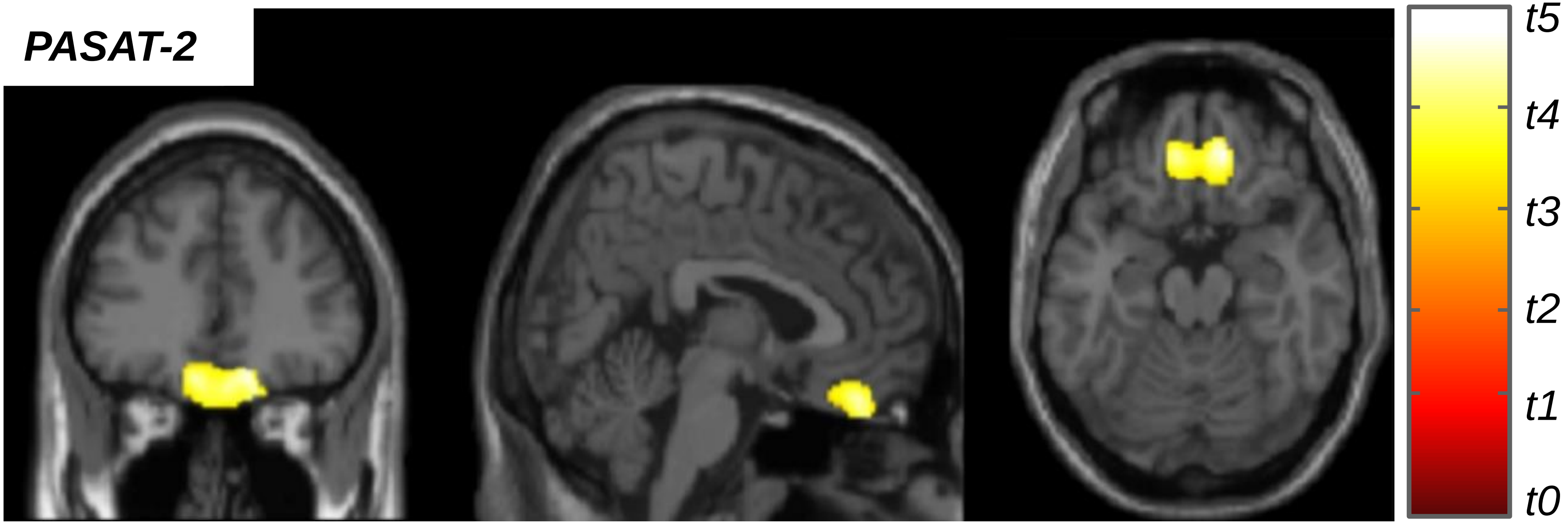
- **Multicentre study in 977 patients with MS**
- **GM but not WM volumes decreased with advancing disease stage**
- **GM volume predicted disability (EDSS) and cognitive impairment (PASAT) better than WM volume or T_2 lesion volume**

**p<0.01; ***p<0.001. PASAT, Paced Auditory Serial Addition Test

Roosendaal SD *et al. Mult Scler* 17(9) pp. 1098-1106,

Cognition and GM volume

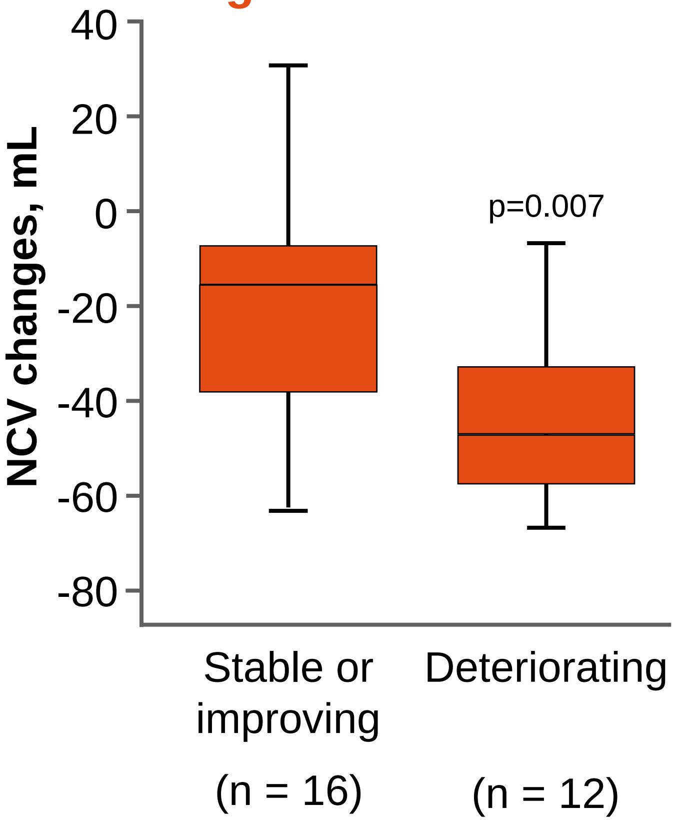
- **GM volume positively correlated with PASAT-2 at the level of the orbitofrontal cortex**
- **GM and intercranial volume ratio were closely associated with cognitive performance**



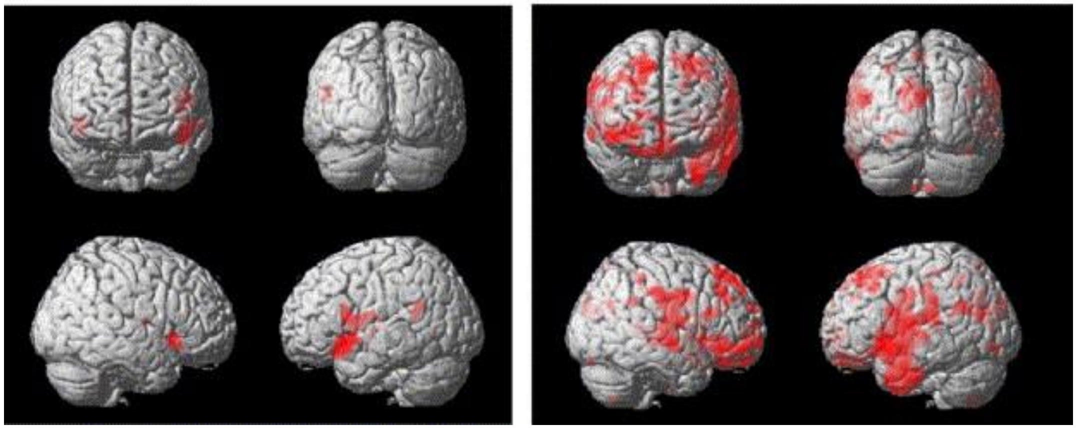
Clusters of significant correlations are superimposed on sagittal, coronal and axial slices of the single-subject T_1 template provided with Statistical Parametric Mapping 8 software. Sbardella E *et al.* (2013) Assessing the correlation between grey and white matter damage with motor and cognitive impairment in multiple sclerosis patients. *PLoS ONE* 8(5): e63250. doi:10.1371/journal.pone.0063250.

Regional brain volume loss is a marker of cognitive decline in MS

Neocortical volume loss is associated with decline on global cognition batteries[1]



Differences in regional GM volume between groups[2]



MS vs control group

MS patients with low performance vs matched control subjects

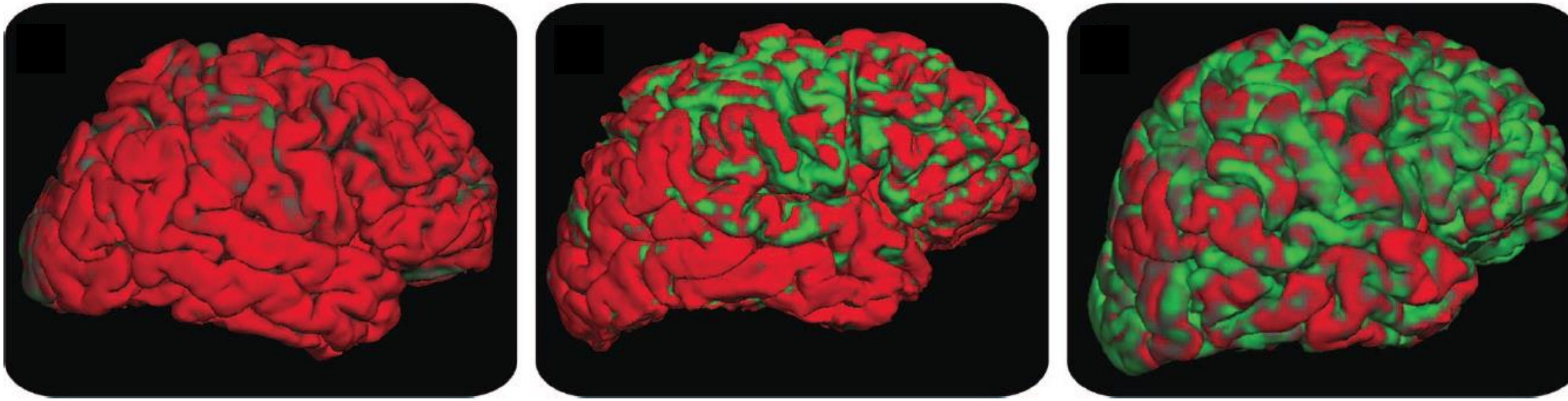
Red = area of highest difference between MS vs controls

Grey matter damage is one of the key factors associated with long-term accumulation of cognitive impairment in MS[3]

GM, grey matter, NCV, neocortical volume loss

1. Amato MP *et al. Arch Neurol.* Copyright © (2007) American Medical Association. All rights reserved; 2. Reproduced from *Neuroimage* , Vol.30. Morgen K, Sammer G, Courtney SM, Wolters T, Melchior H, Blecker CR, Oschmann P, Kaps M, Vaitl D. Evidence for a direct association between cortical atrophy and cognitive impairment in relapsing–remitting MS, p891-898. Copyright (2006), with permission from Elsevier; 3. Filippi M *et al. Neurology* 2013

Cortical thickness and cognition in MS



red = thick cortical areas (>2.0 mm), **green** = thin cortical areas (<2.0 mm)

Healthy adult	RRMS	RRMS
35 years	36 years	34 years
Cognitive impairment		
No	No	Yes (mild)
Mean cortical thickness		
2.53	**2.32**	**2.05**

Cognitive profile in MS patients

Affected

- Information processing speed
- Attention
- Executive functions
- VS functions
- Recent and long term memory

Spared

- General intelligence
- Language
- Implicit memory

Original Article

Thalamic Involvement and Its Impact on Disability and Cognition in Multiple Sclerosis: A Clinical and Diffusion Tensor Imaging Study

Ahmed T. El Ghoneimy, Amr Hassan[1], Mohamed Homos[2], Marwa Farghaly[1], Ahmed Dahshan[1]

Departments of Neurology[1], Radiodiagnosis[2], Cairo University; Egypt

Table 1. Comparison between neuropsychological tests in MS patients and control.

	MS Patients (N=31)			Healthy control (N=18)			P-value
	Min	Max	Mean ± SD	Min	Max	Mean ± SD	
MMSE	22	30	29.3±1.3	26	30	29.7±1	0.333
CVLT-II-TR	16	63	39.0±10.2	40	70	51.8±8.7	<0.001**
CVLT-II-SR	2	16	7.9±2.9	8	15	11.6±1.8	<0.001**
CVLT-II-DR	0	14	8.5±3.2	9	15	11.4±1.7	0.001**
BVMT-TR	0	36	20.0±11.0	15	35	28.8±4.6	0.008**
BVMT-DR	0	12	6.9±4.2	6	12	10.6±1.4	0.009**
PASAT	0	39	22.1±14.9	0	3	26.7±14.7	0.038*
SDMT	2	60	27.6 ±15.5	22	54	38.6± 8.2	0.003**
VF-letter	2	10	5.2 ± 2.1	9	13	10.3± 1.2	<0.001**
VF-animaL	6	23	12.8 ± 4.8	17	23	19.3± 1.5	<0.001**

BVMT-DR Brief Visuospatial Memory Test–Revised, Delayed Recall, ***BVMT-TR*** Brief Visuospatial Memory Test–Revised, Total Recall, ***CVLT-II-DR*** California Verbal Learning Test- 2nd edition- Delayed Recall, ***CVLT-II-SR*** California Verbal Learning Test- 2nd edition- Short Term Recall, ***CVLT-II-TR*** California Verbal Learning Test- 2nd edition-Total Recall, ***MS*** Multiple sclerosis, ***MMSE*** Mini-Mental State Examination, ***PASAT*** Paced Auditory Serial Addition Task, ***SDMT*** Symbol Digit Modalities Test, ***VF*** Verbal Fluency.

*Significant at P<0.05 ** Significant at P<0.01

Table 2. Comparison between radiological results in MS patients and control.

	MS Patients (N=31)	Healthy control (N=18)	P value
FA Rt. Thalamus	0.45 ± 0.03	0.39 ± 0.03	<0.001*
FA Lt Thalamus	0.45 ± 0.03	0.40 ± 0.03	<0.001*
ADC Rt. Thalamus	0.79 ± 0.04	0.71 ± 0.04	<0.001*
ADC Lt. Thalamus	0.78 ± 0.03	0.71± 0.03	<0.001*

ADC Apparent Diffusion Coefficient, ***FA*** Fractional anisotropy, ***MS*** Multiple sclerosis
*Significant at P<0.01

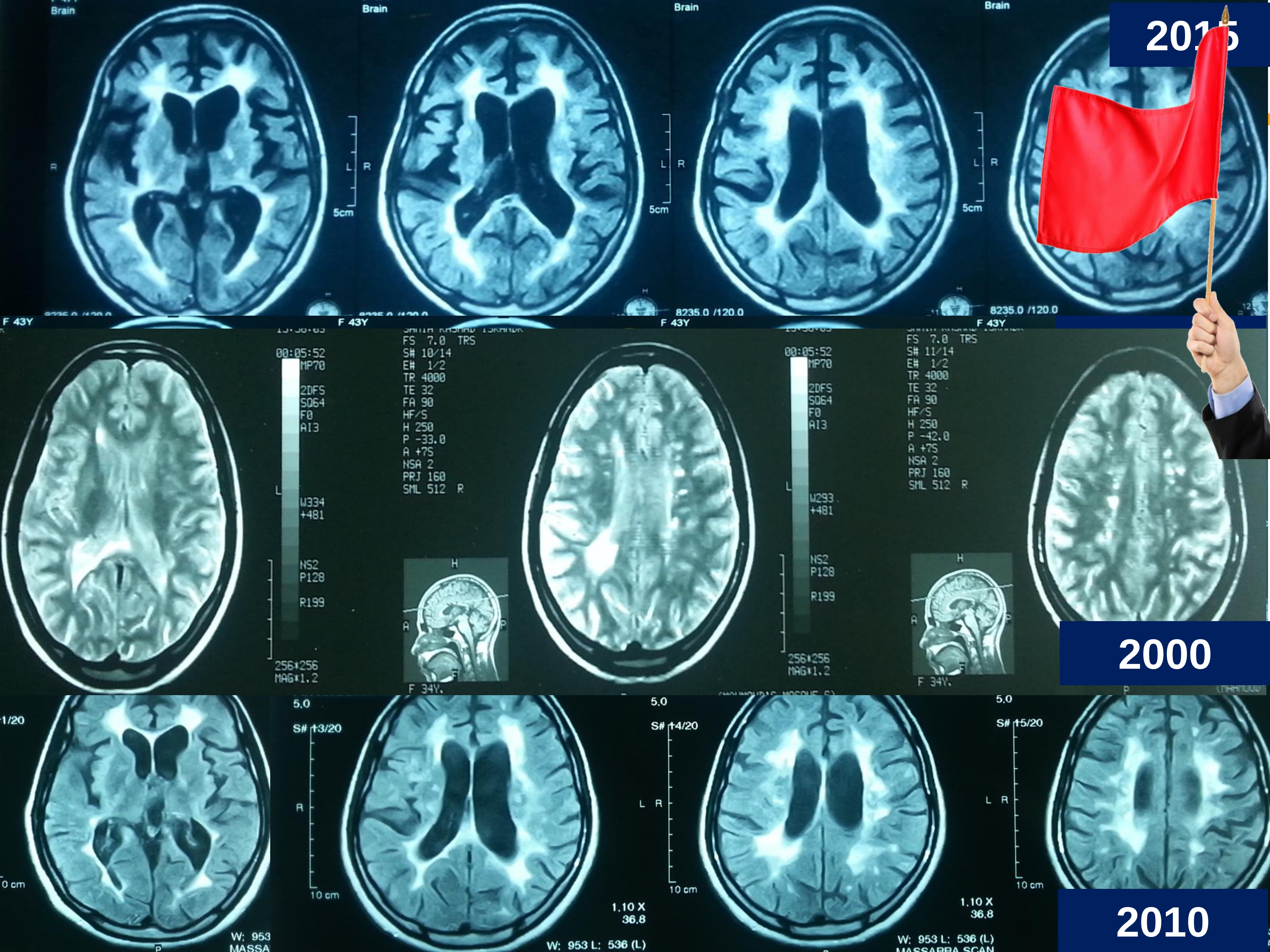
Table 3. Correlations between clinical data and neuropsychological tests.

	Duration of illness		Number of attacks		EDSS	
	r	p	r	p	r	p
CVLT-II-TR	-0.33	0.07	-0.23	0.21	-0.44	0.01**
CVLT-II-SR	-0.28	0.13	-0.17	0.35	-0.49	0.005**
CVLT-II-DR	-0.465	0.008**	-0.37	0.04*	-0.55	0.001**
BVMT-TR	-0.43	0.017*	-0.39	0.03*	-0.6	<0.001**
BVMT-DR	-0.44	0.013*	-0.38	0.034*	-0.5	0.004**
PASAT	-0.3	0.1	-0.31	0.1	-0.4	0.028*
SDMT	-0.41	0.021*	-0.22	0.23	-0.47	0.007**
VF-Letter	-0.2	0.29	-0.2	0.3	-0.43	0.02*
VF-animal	-0.29	0.12	-0.22	0.23	-0.46	0.01**

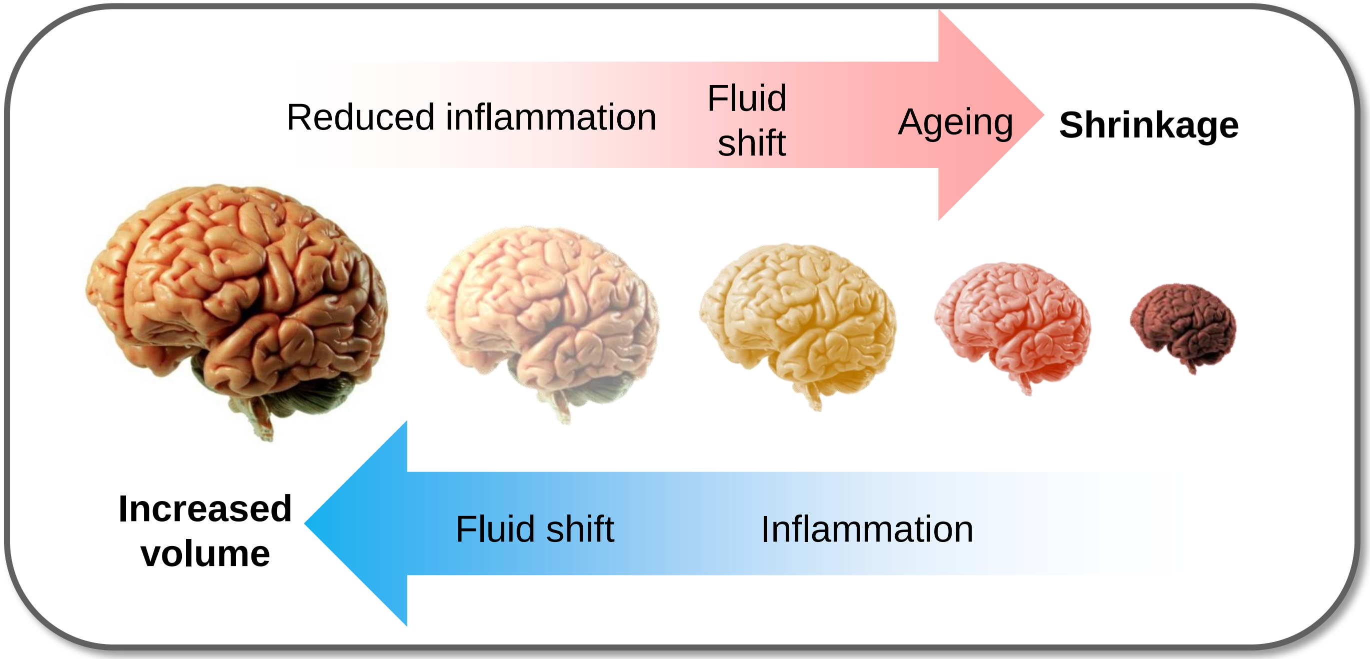
BVMT-DR Brief Visuospatial Memory Test–Revised, Delayed Recall, ***BVMT-TR*** Brief Visuospatial Memory Test–Revised, Total Recall, ***CVLT-II-DR*** California Verbal Learning Test- 2nd edition- Delayed Recall, ***CVLT-II-SR*** California Verbal Learning Test- 2nd edition- Short Term Recall, ***CVLT-II-TR*** California Verbal Learning Test- 2nd edition-Total Recall, ***EDSS*** Expanded Disability Status Scale, ***PASAT*** Paced Auditory Serial Addition Task, ***SDMT*** Symbol Digit Modalities Test, ***VF*** Verbal Fluency
*Significant at P<0.05 ** Significant at P<0.01

Case study

- 53 y old lady.
- Presented with gradual progressive dementia, quadriparesis.
- Infrequent seizures all through her illness.
- Was diagnosed at 2000 to have MS after 2 attacks of hemipresis and ataxia.


2015
2000
2010

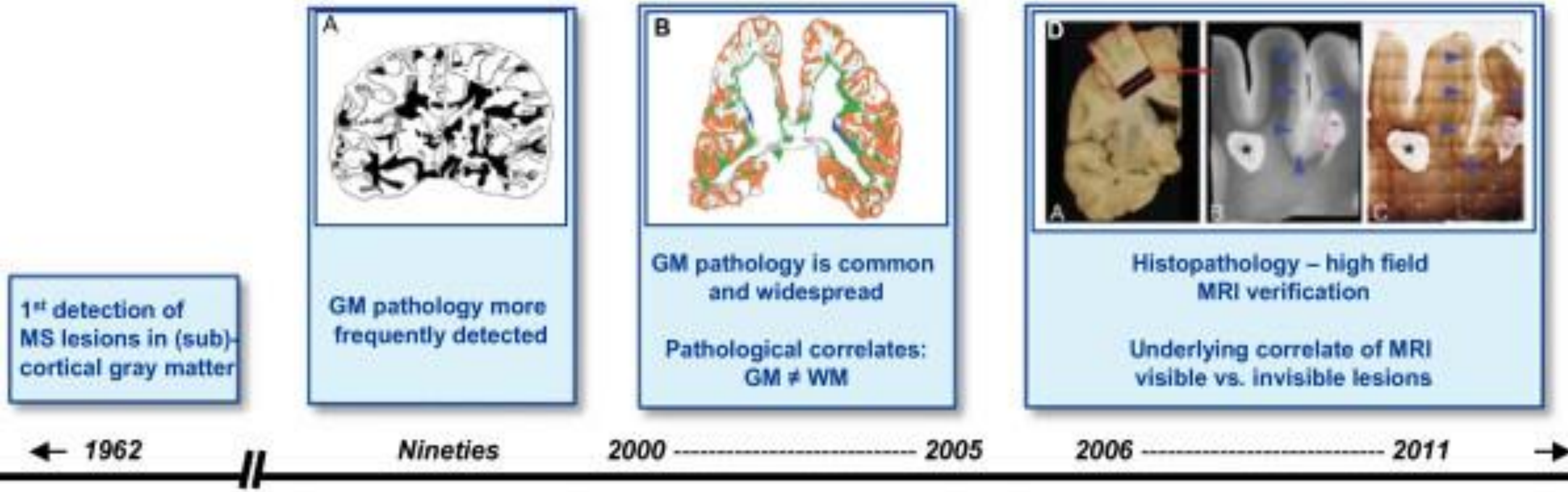
Inflammation, fluid shift and ageing affect brain volume in MS

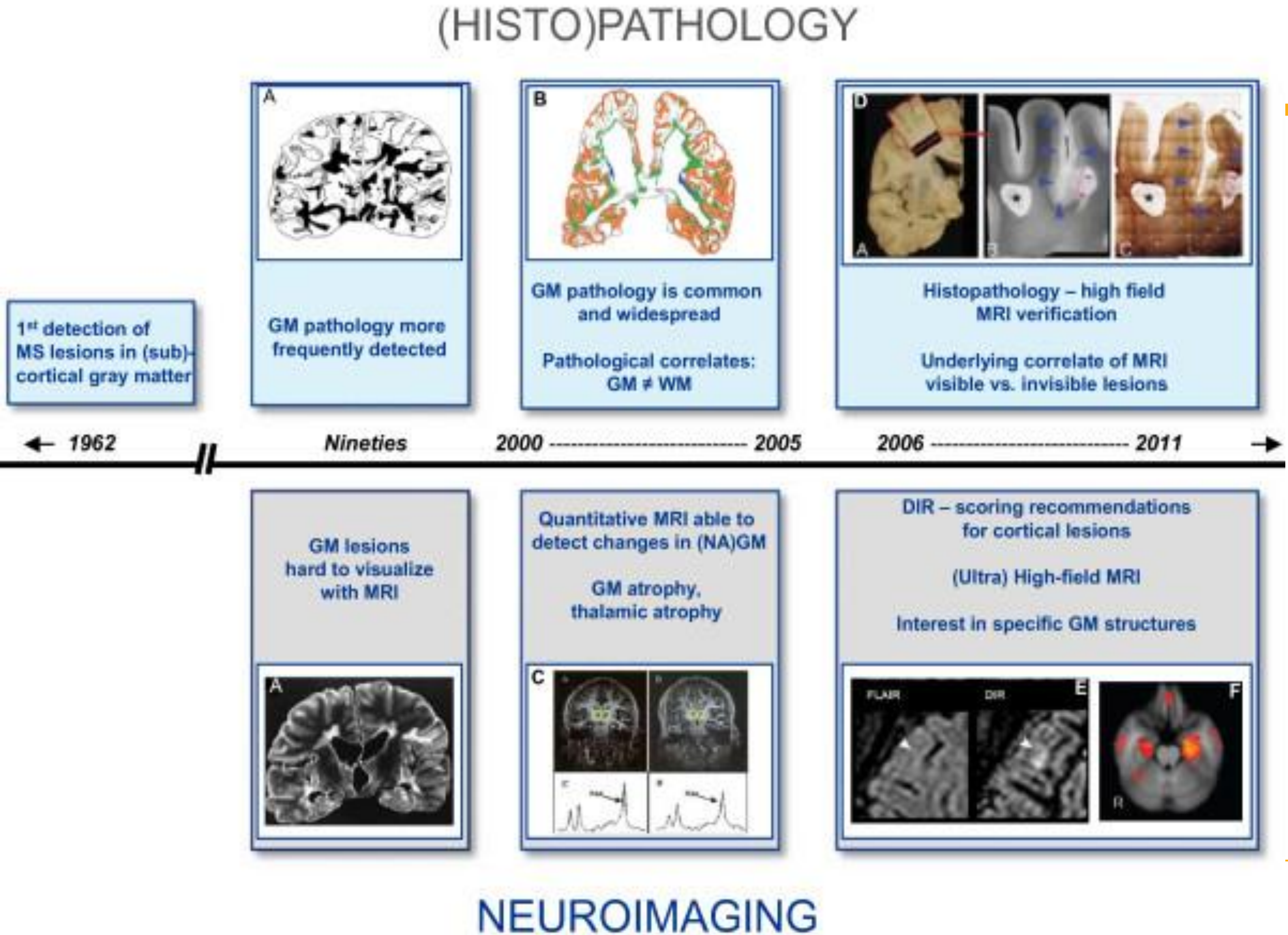


- **Neural cell changes also affect brain volume in MS**
  – microglial volume / number
  – neural tissue loss
  – gliotic scarring
  – remyelination

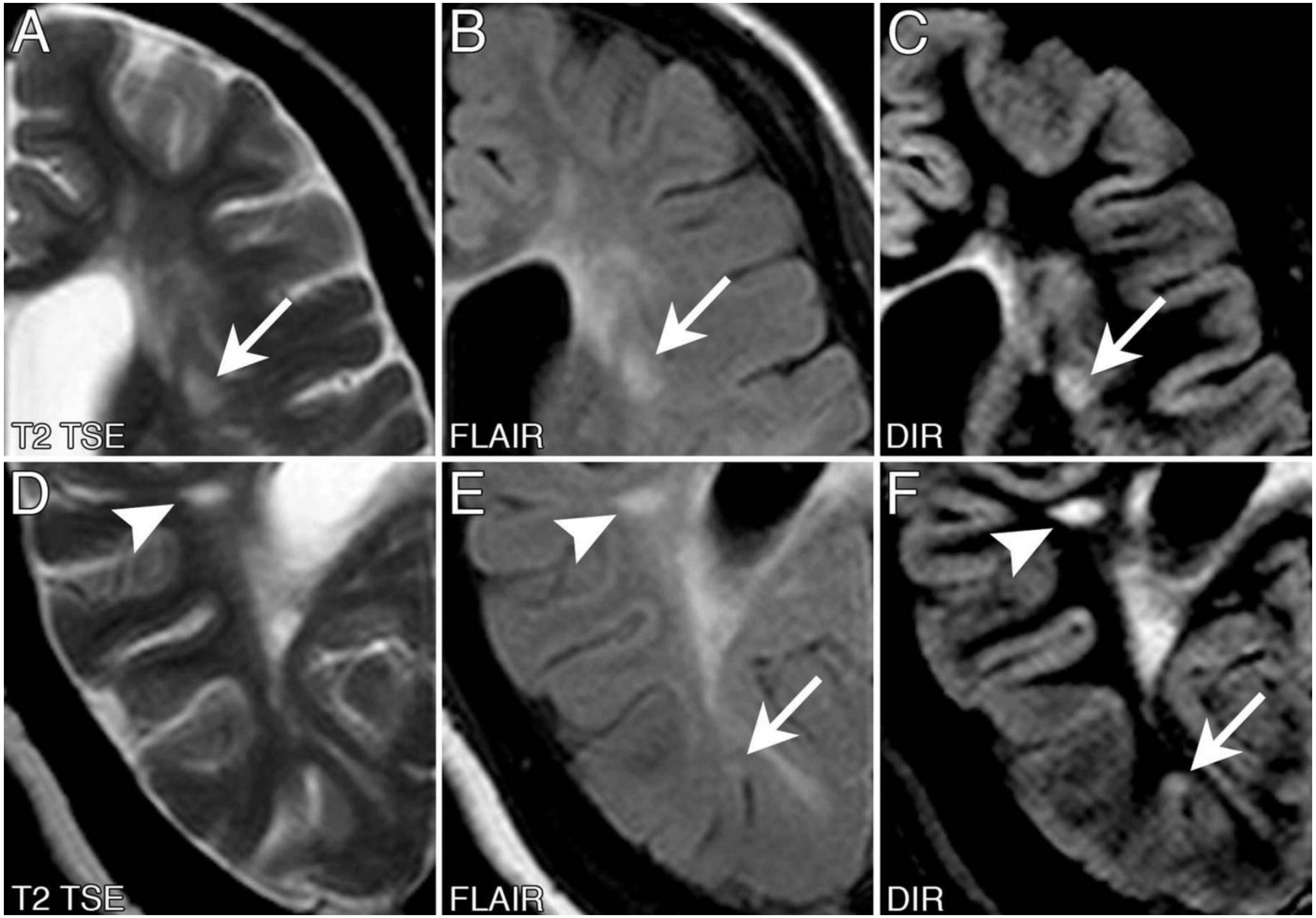
Simon JH. *Mult Scler* 2006; Barkhof F *et al. Nat Rev Neurol* 2009

(HISTO)PATHOLOGY




(HISTO)PATHOLOGY
A
B
D
A
B
C
1st detection of MS lesions in (sub)-cortical gray matter
GM pathology more frequently detected
GM pathology is common and widespread
Pathological correlates: GM ≠ WM
Histopathology – high field MRI verification
Underlying correlate of MRI visible vs. invisible lesions
1962
Nineties
2000 ------------------------------ 2005
2006 ------------------------------ 2011
GM lesions hard to visualize with MRI
Quantitative MRI able to detect changes in (NA)GM
GM atrophy, thalamic atrophy
DIR – scoring recommendations for cortical lesions
(Ultra) High-field MRI
Interest in specific GM structures
A
C
FLAIR
DIR
E
F
R
NEUROIMAGING

DIR



Pitfalls of DIR

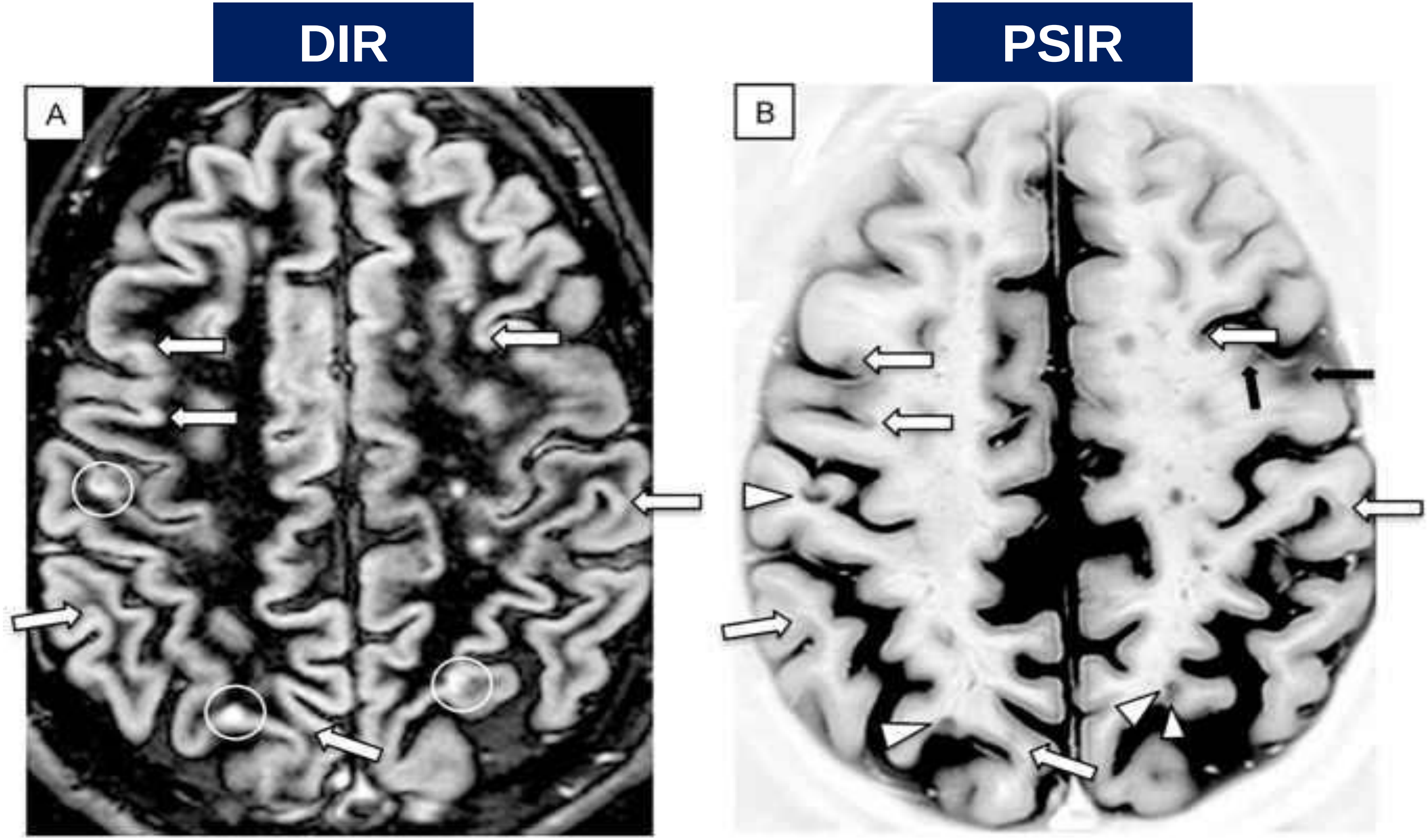
- It does not always allow a correct identification of the two main CL subtypes recognized histologically, i.e., pure intracortical (IC) and leukocortical
- Differentiation of LC lesions from juxtacortical lesions is challenging and sometimes impossible.
- Missing the identification of small oval IC lesions

J Neurol Neurosurg Psychiatry. 2012 Sep;83(9):877-82. doi: 10.1136/jnnp-2012-303023. Epub 2012 Jul 17.

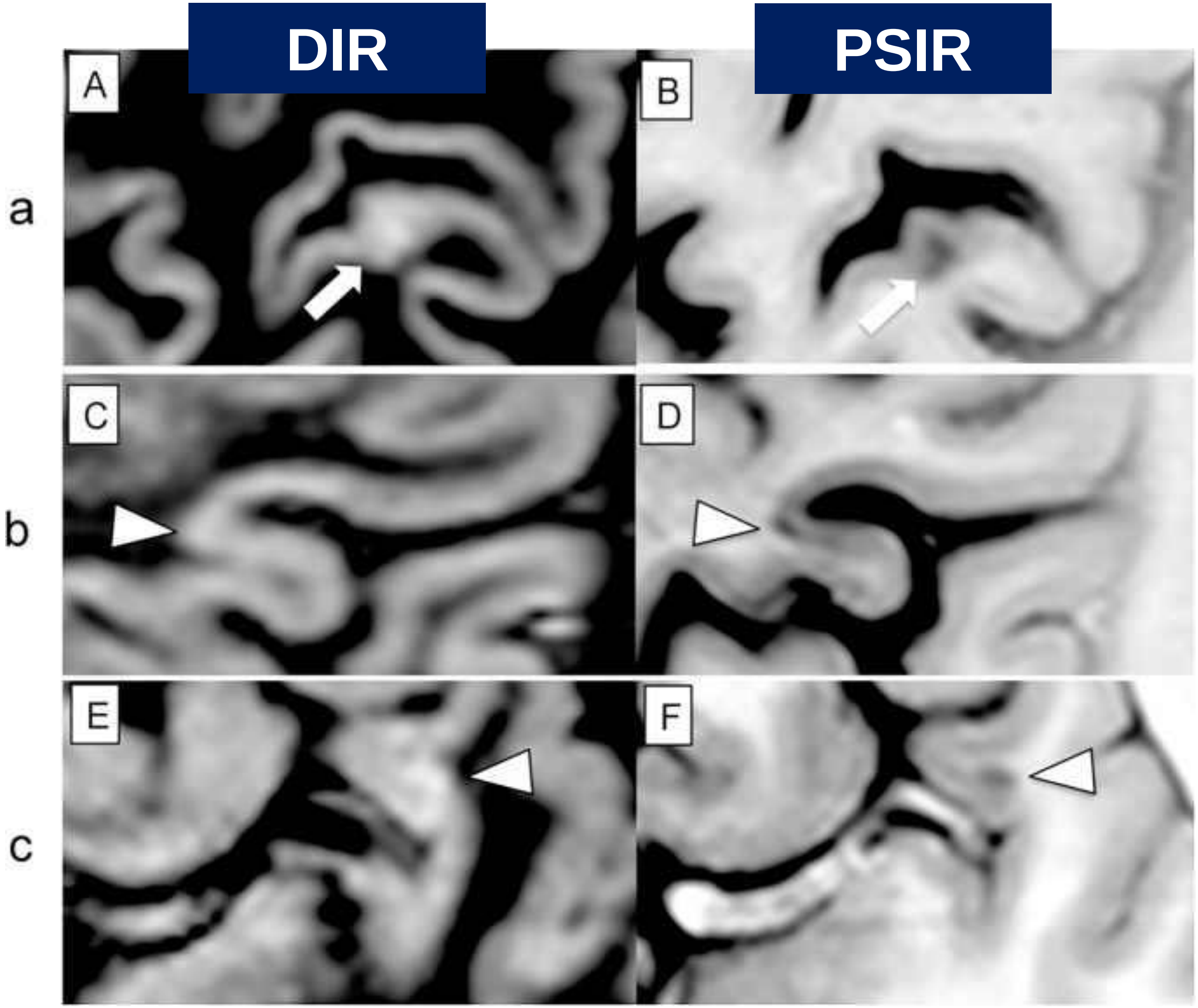
Improved detection of cortical MS lesions with phase-sensitive inversion recovery MRI.

Sethi V[1], Yousry TA, Muhlert N, Ron M, Golay X, Wheeler-Kingshott C, Miller DH, Chard DT.

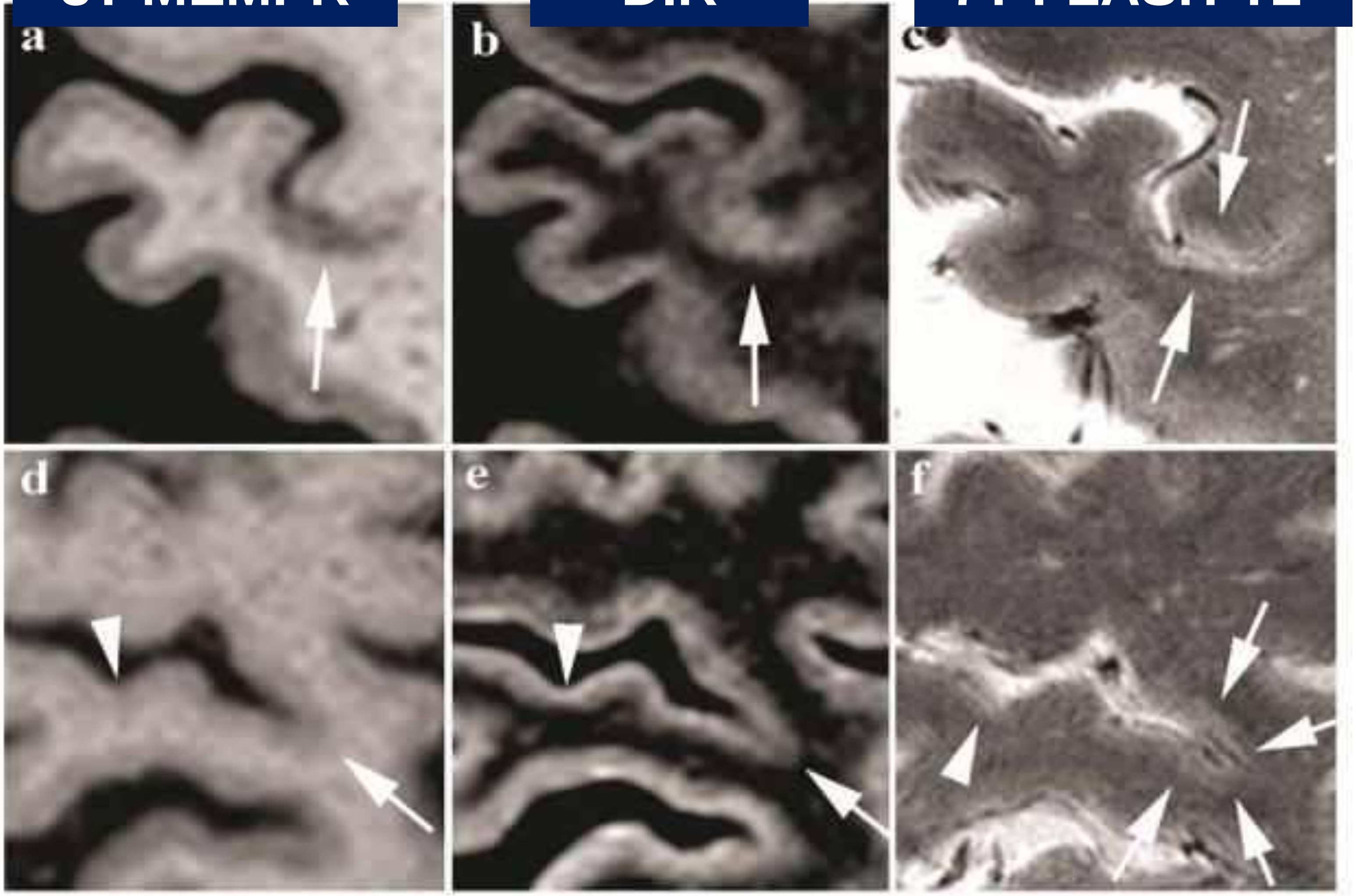
DIR Vs PSIR



DIR Vs PSIR



3T MEMPR	DIR	7T FLASH-T2*



Current Opinion in Neurology:
June 2014 - Volume 27 - Issue 3 - p 290–299
doi: 10.1097/WCO.0000000000000095
DEMYELINATING DISEASES: Edited by Hans-Peter Hartung

Magnetic resonance outcome measures in multiple sclerosis trials: time to rethink?

Filippi, Massimo; Preziosa, Paolo; Rocca, Maria A.

Measures		Pathological substrates	Clinical relevance	Sensitivity to changes	Application in clinical trials	Response to treatment
Active lesions (new T2 and Gd-enhancing)		Inflammation and demyelination	++	++	Yes	+++
Evolution of active lesions into permanent black holes		Axonal loss, demyelination, gliosis	+	++	Yes	++
Brain atrophy		Neuro-axonal loss, demyelination	+++	++	Yes	++
GM atrophy		Neuro-axonal loss, demyelination	+++	+++	Yes	++
Cervical cord atrophy		Neuro-axonal loss, demyelination	+++	++	Few, single-center, clinical trials	Undetermined
Cortical lesions		Inflammation, demyelination and axonal loss	++	++	Few, single-center, clinical trials	+
Quantitative MRI-based techniques	MT MRI	Demyelination	++	++	Yes	++
	^{1}H-MRS	Metabolic abnormalities (NAA/Cr ratio)	+	++	Yes	+
	DT MRI	Demyelination, axonal damage, gliosis	++	++	Not yet	Undetermined
Functional reorganization		Synaptic plasticity	++	++	Few, single-center studies, mainly on the	+

McDonlad's Criteria 2017

THE LANCET Neurology

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Position Paper

Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

Prof Alan J Thompson, MD, Prof Brenda L Banwell, MD, Prof Frederik Barkhof, MD, Prof William M Carroll, MD, Timothy Coetzee, PhD, Prof Giancarlo Comi, MD, Prof Jorge Correale, MD, Prof Franz Fazekas, MD, Prof Massimo Filippi, MD, Prof Mark S Freedman, MD, Prof Kazuo Fujihara, MD, Prof Steven L Galetta, MD, Prof Hans Peter Hartung, MD, Prof Ludwig Kappos, MD, Prof Fred D Lublin, MD, Prof Ruth Ann Marrie, MD, Prof Aaron E Miller, MD, Prof David H Miller, MD, Prof

ECTRIMS European Committee for Treatment and Research in Multiple Sclerosis

actrims Americas Committee for Treatment and Research in Multiple Sclerosis

MSPARIS2017

7TH JOINT ECTRIMS – ACTRIMS MEETING
25–28 OCTOBER 2017, PARIS, FRANCE

3. Cortical and juxtacortical lesions can be used in fulfilling MRI criteria for DIS
   - *In the 2010 McDonald Criteria, cortical lesions could not be used in fulfilling MRI criteria for DIS*

Conclusions

- GM damage in MS is common and widespread, especially in chronic MS.

- GM atrophy correlated more strongly than WM atrophy with disability and cognitive impairment.

- Cortical lesions have been difficult to visualize with conventional MRI, but due to newer imaging techniques (like DIR, PSIR and (Ultra) high-field MRI) lesion detection improved.




THANK YOU

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