Cognitive functions and inflammation in multiple sclerosis: mechanisms and concepts

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Service de Neurologie CHU de Bordeaux

EAE and neuroimmunology

OBSERVATIONS ON ATTEMPTS TO PRODUCE ACUTE DISSEMINATED ENCEPHALOMYELITIS IN MONKEYS

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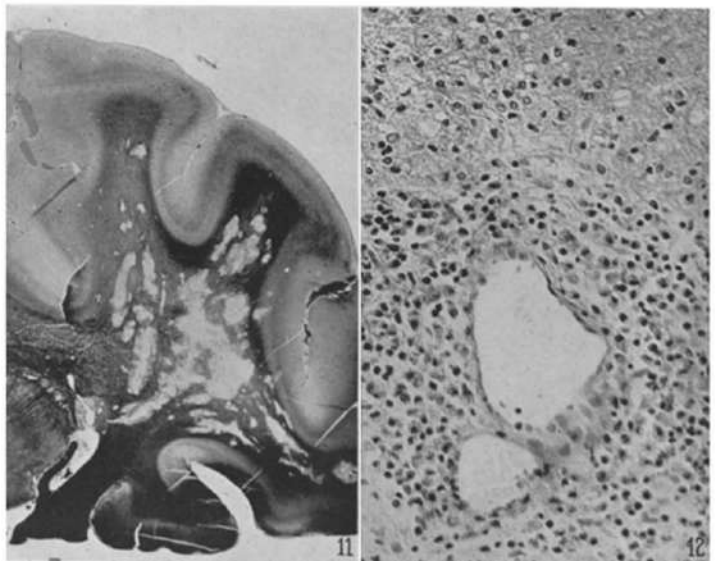
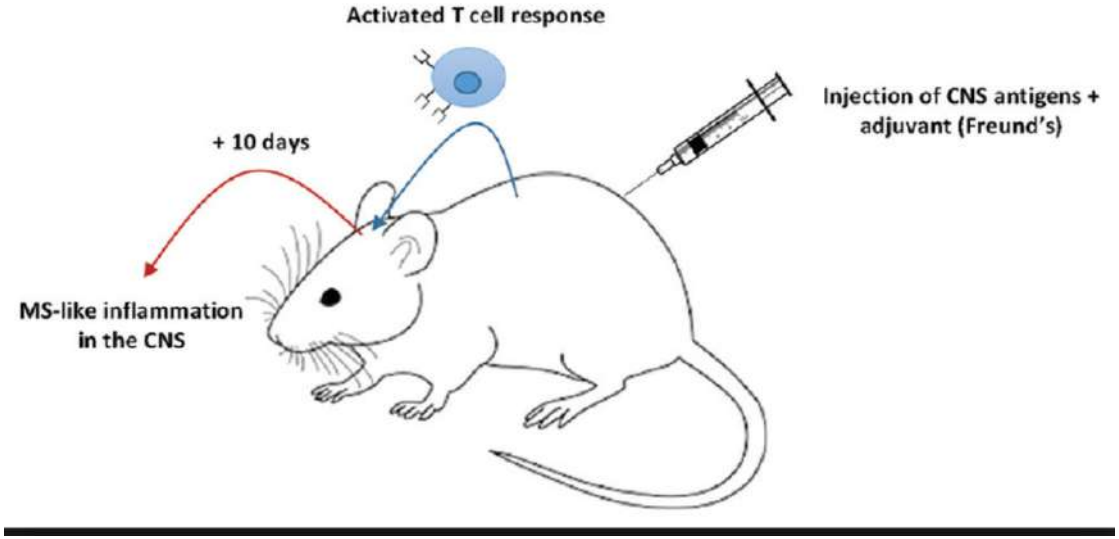
(From the Hospital of The Rockefeller Institute for Medical Research)

PLATES 1 TO 3

(Received for publication, February 21, 1933)





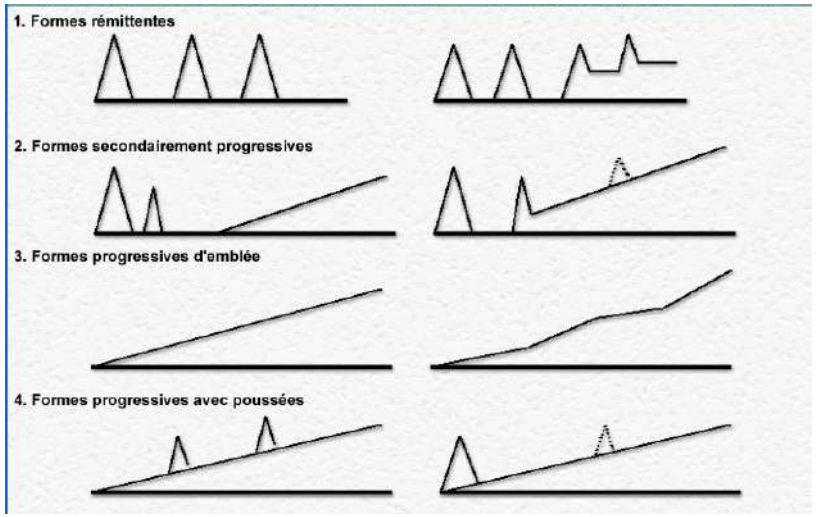
How to define multiple sclerosis?

- First cause of neurological disability in young adults

(100 000 patients in France, onset usually 15-35)

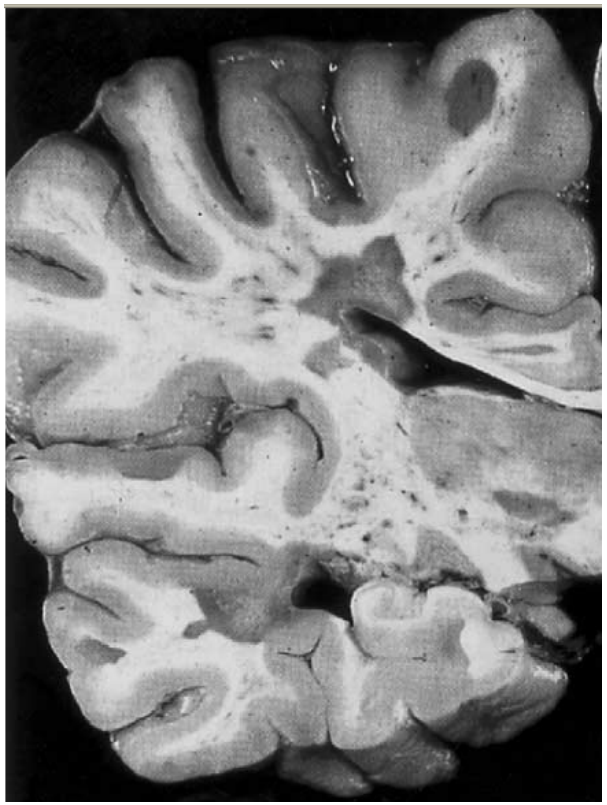
Motor disability (pyramidal, cerebellar)
Sensory disturbances(vision, sensitive…)
Vegetative symptoms
Fatigue, pain
Cognitive impairment

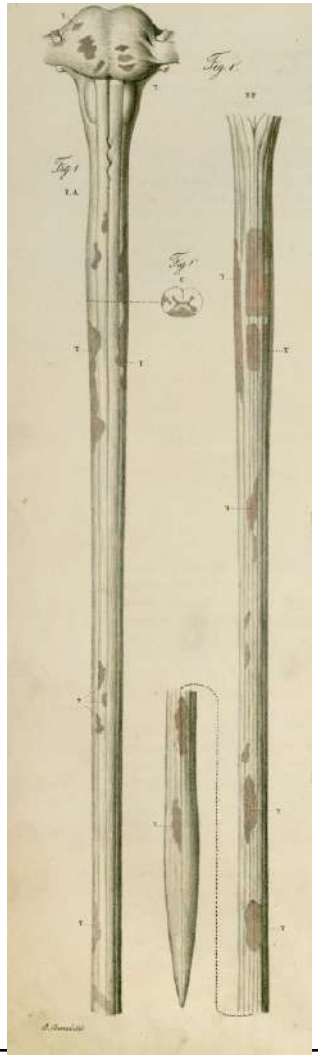
2 main clinical phenotypes
- Relapsing-remitting
- Progressive



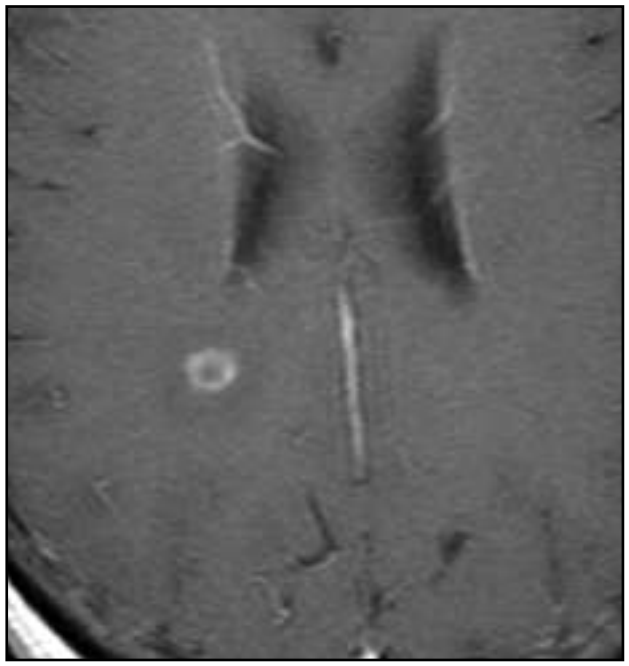
How to define multiple sclerosis?

- Multifocal inflammatory demyelinating disease of the central nervous system



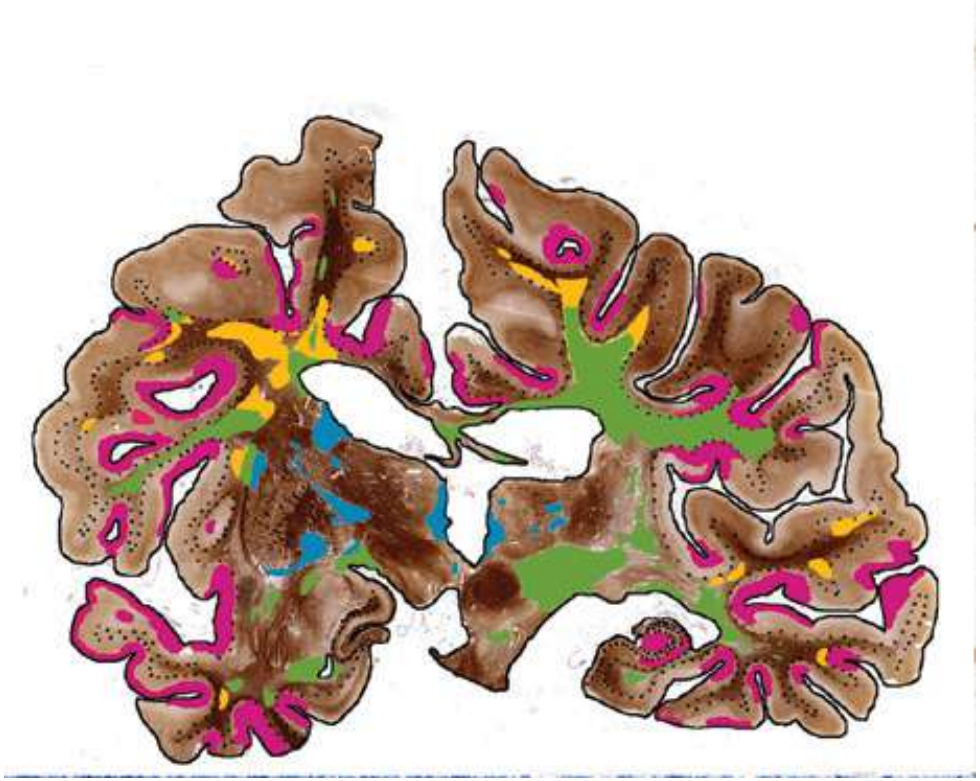


Focal inflammatory lesions associated with clinical relapses



How to define multiple sclerosis?

- Neurodegenerative disease characterized by progressive brain and spinal cord atrophy

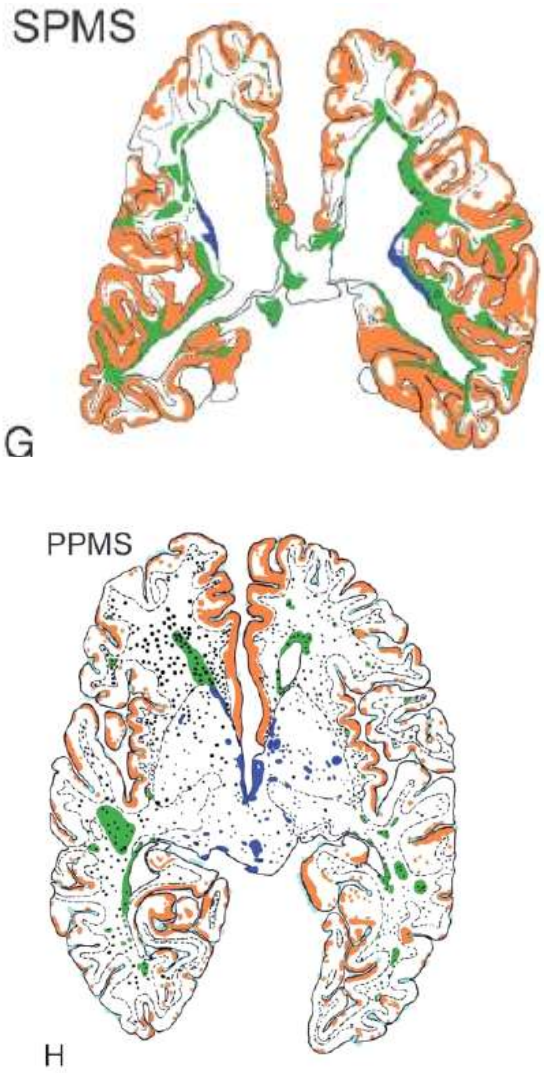


Lassmann, 2012
SPMS
Marked atrophy with dilatation of cerebral ventricles and outer cerebrospinal fluid spaces

MS pathology

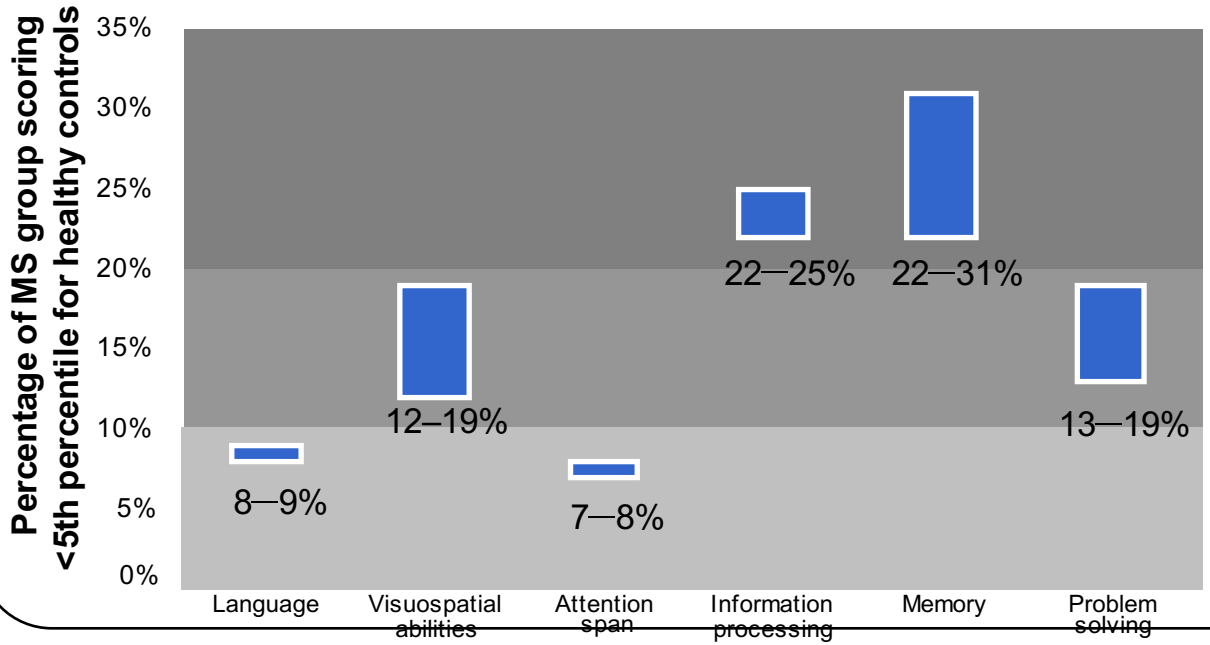
- Focal lesions
  - axonal degeneration
    Diffuse WM injury)
- Cortical demyelination and deep GM injury

→ Atrophy



Main cognitive functions affected in MS

- **Information processing speed (IPS)**
- **Learning/Memory**
- Attention, working memory
- Executive functions, Verbal fluency
- Reasoning, conceptualisation



Rao et al., 1991

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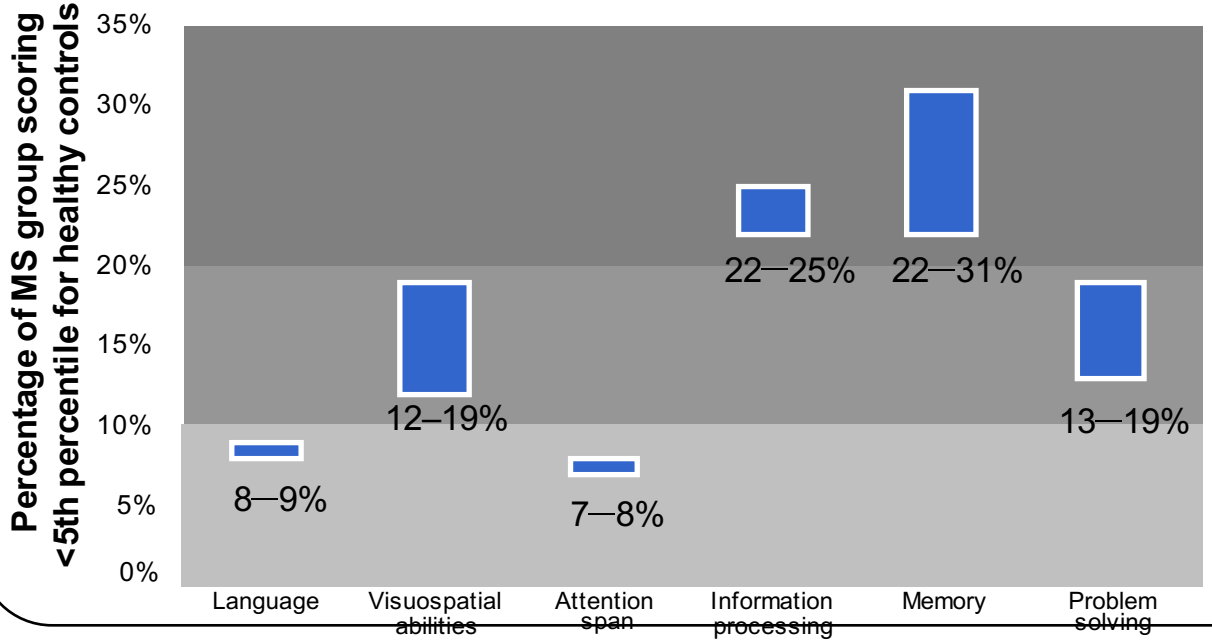


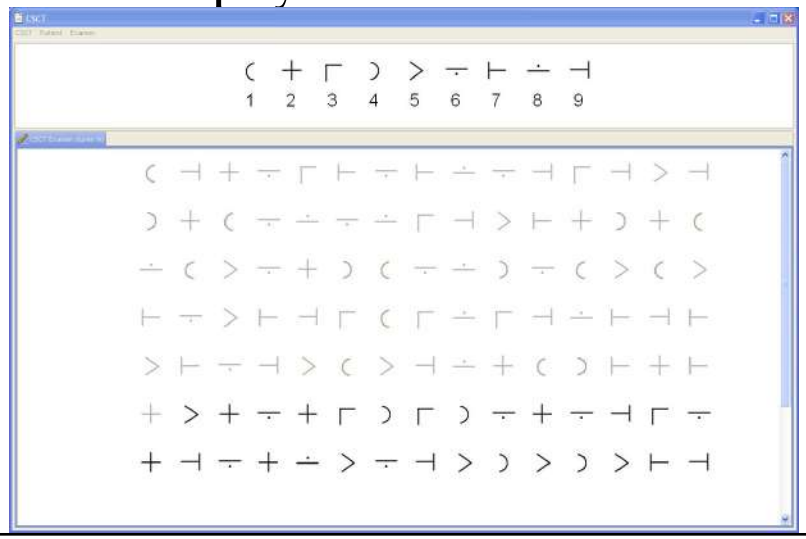
Role of inflammation and neurodegenerescence in cognitive impairment in MS?

Rao et al., 1991

Mechanisms of CI in MS

IPS

- Early symptom
- Main CI in RRMS
- Associated with diffuse white matter injury, focal inflammation and brain atrophy

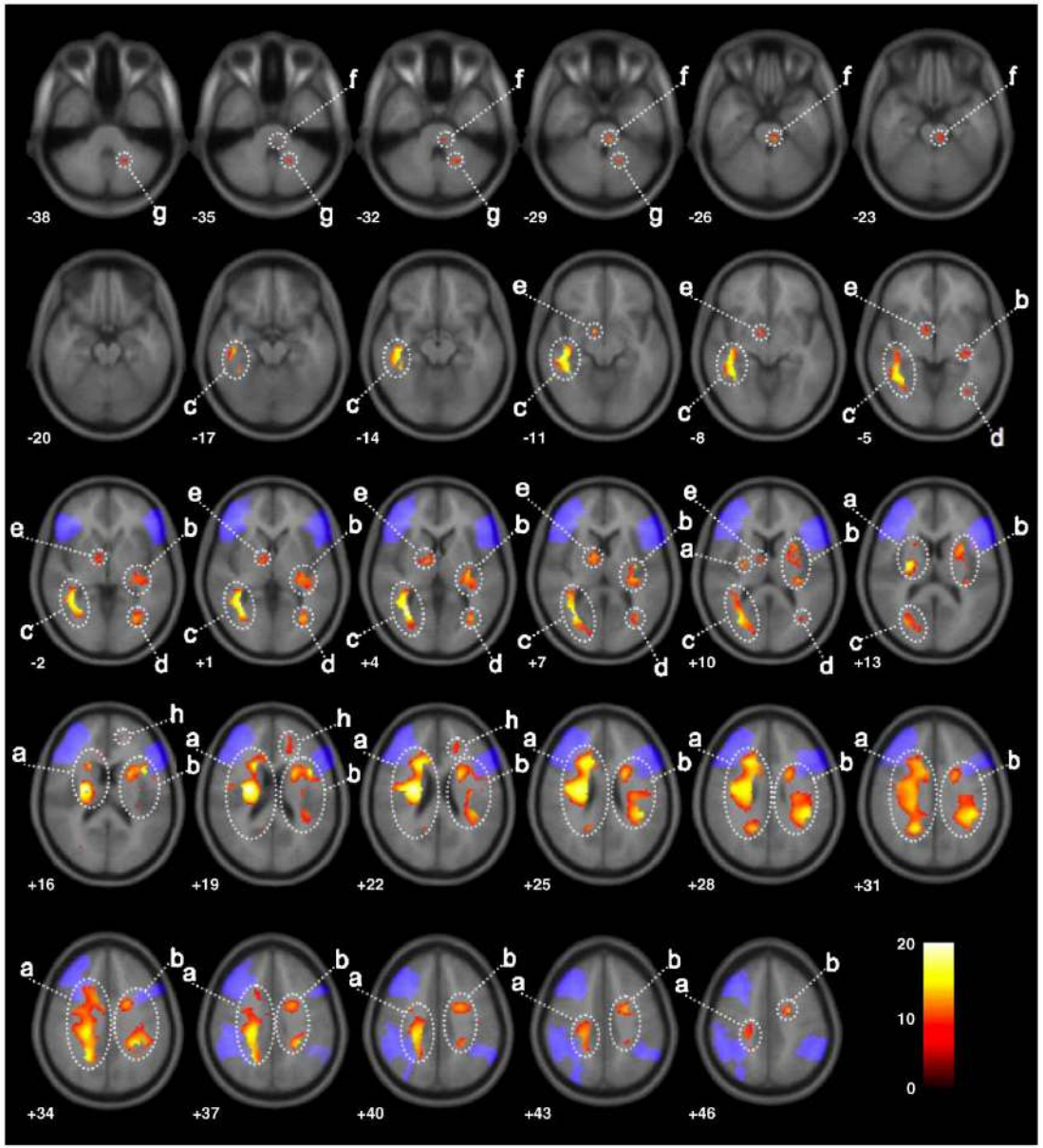


Memory

- Early symptom
- More severe in PMS
- Hippocampal atrophy

Ruet, 2013 Benedict, 2005

Contribution of lesions to IPS deficit



Voxelwise analysis of lesions probability maps (T2)

Lesions located in the cingulum, parieto-frontal pathways and thalamo-cortical projections, with a left-sided predominance, as well as the right cerebellar white matter correlated moderately with NP test performances

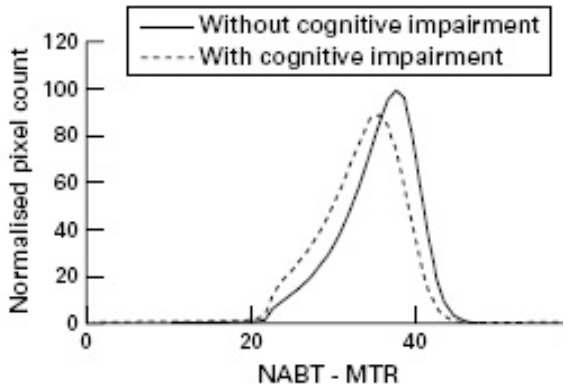
Sepulcre et al. Neuroimage, 2009

Contribution of normal appearing brain tissue pathology to IPS deficits

Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis

M S A Deloire, E Salort, M Bonnet, Y Arimone, M Boudineau, H Amieva, B Barroso, J-C Ouallet, C Pachai, E Galliaud, K G Petry, V Dousset, C Fabrigoule, B Brochet

J Neurol Neurosurg Psychiatry 2005;76:519–526. doi: 10.1136/jnnp.2004.045872



MT histograms of the normal appearing brain tissue (NABT) in patients with multiple sclerosis with and without cognitive impairment.

56 early RRMS

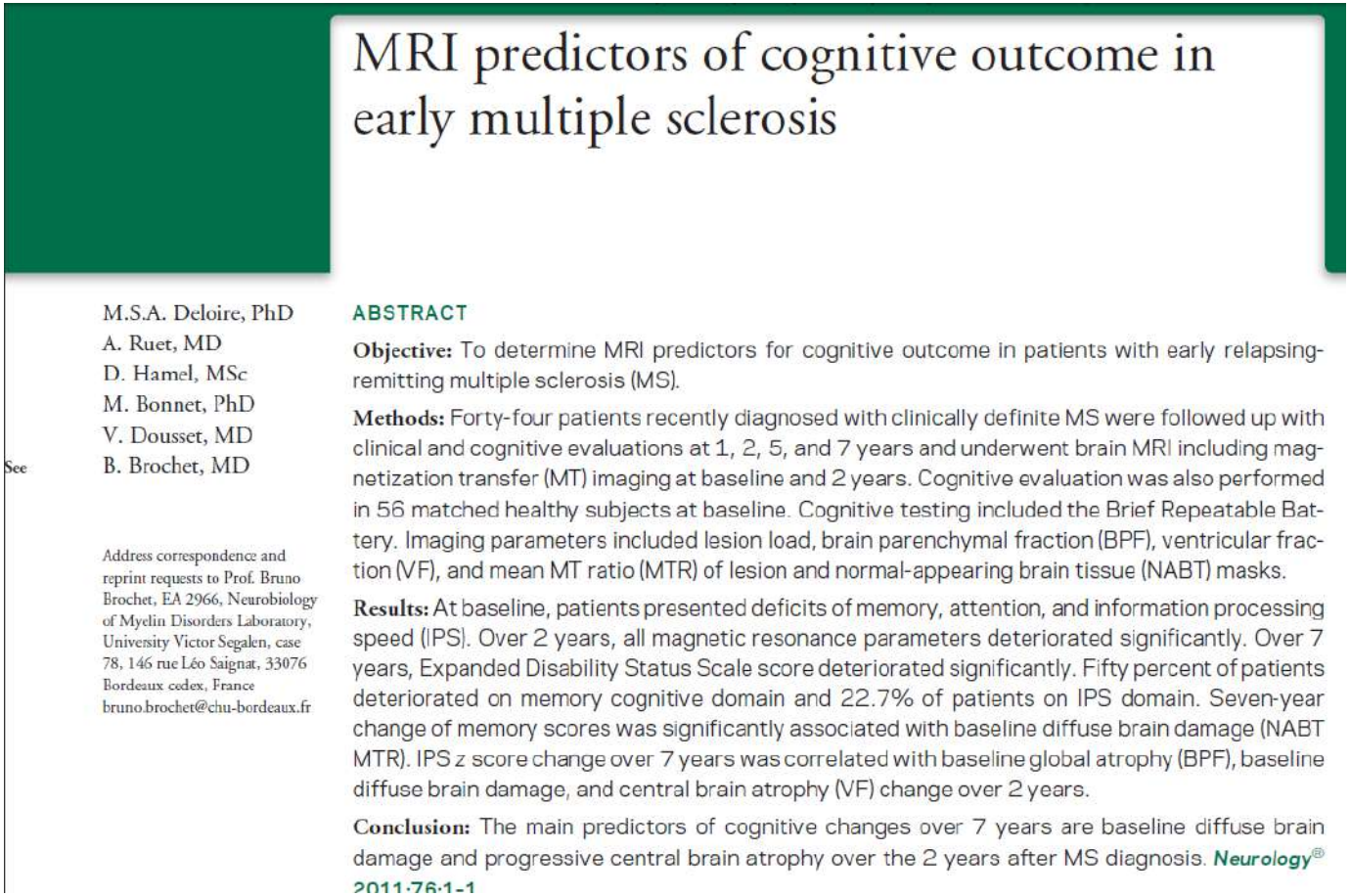
IPS vs lesion volume, brain atrophy or magnetization transfer ratio of normal appearing brain tissue (outside lesions) (reflecting axonal pathology)

Multivariate analysis:

Correlation of magnetization transfer ratio in normal appearing brain parenchyma with NP test

Contribution of normal appearing brain tissue pathology

NABT MTR in patients with early RRMS (2 years) predicts the progression of cognitive impairment during the subsequent **seven year** period (*Deloire et al, Neurology 2011*)



MRI predictors of cognitive outcome in early multiple sclerosis

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See

ABSTRACT

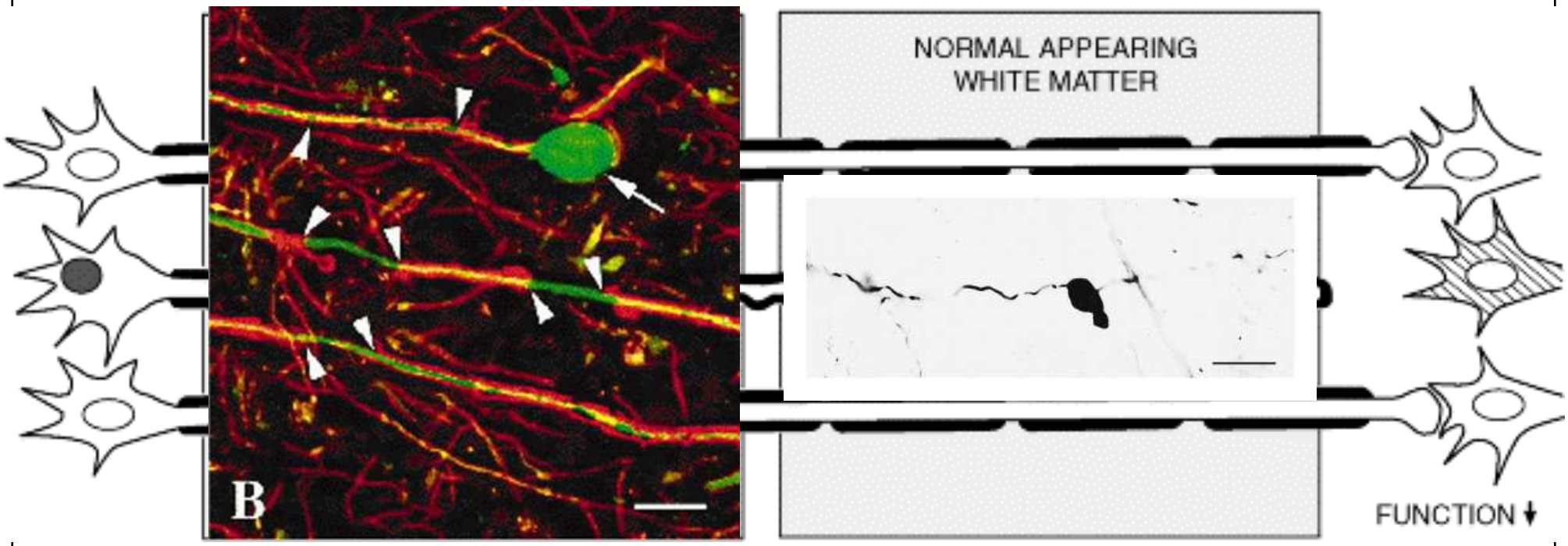
Objective: To determine MRI predictors for cognitive outcome in patients with early relapsing-remitting multiple sclerosis (MS).

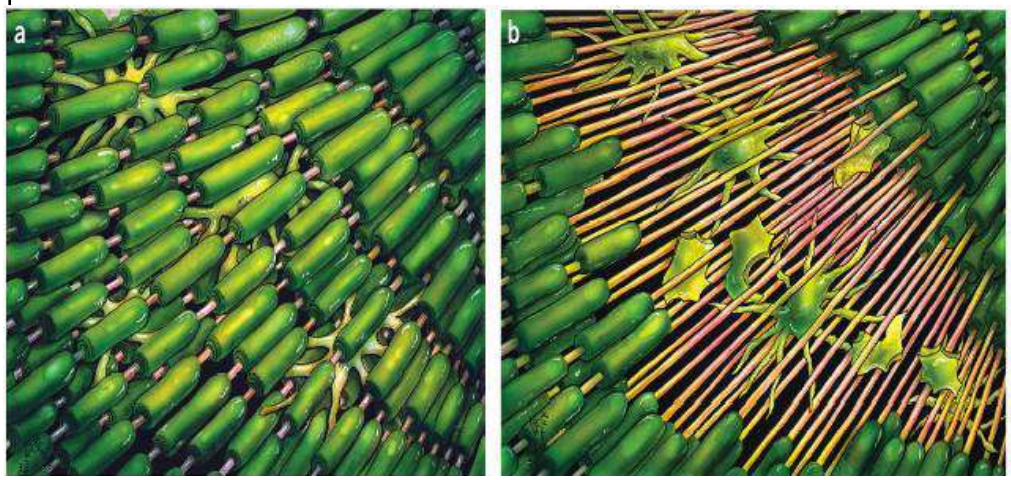
Methods: Forty-four patients recently diagnosed with clinically definite MS were followed up with clinical and cognitive evaluations at 1, 2, 5, and 7 years and underwent brain MRI including magnetization transfer (MT) imaging at baseline and 2 years. Cognitive evaluation was also performed in 56 matched healthy subjects at baseline. Cognitive testing included the Brief Repeatable Battery. Imaging parameters included lesion load, brain parenchymal fraction (BPF), ventricular fraction (VF), and mean MT ratio (MTR) of lesion and normal-appearing brain tissue (NABT) masks.

Results: At baseline, patients presented deficits of memory, attention, and information processing speed (IPS). Over 2 years, all magnetic resonance parameters deteriorated significantly. Over 7 years, Expanded Disability Status Scale score deteriorated significantly. Fifty percent of patients deteriorated on memory cognitive domain and 22.7% of patients on IPS domain. Seven-year change of memory scores was significantly associated with baseline diffuse brain damage (NABT MTR). IPS z score change over 7 years was correlated with baseline global atrophy (BPF), baseline diffuse brain damage, and central brain atrophy (VF) change over 2 years.

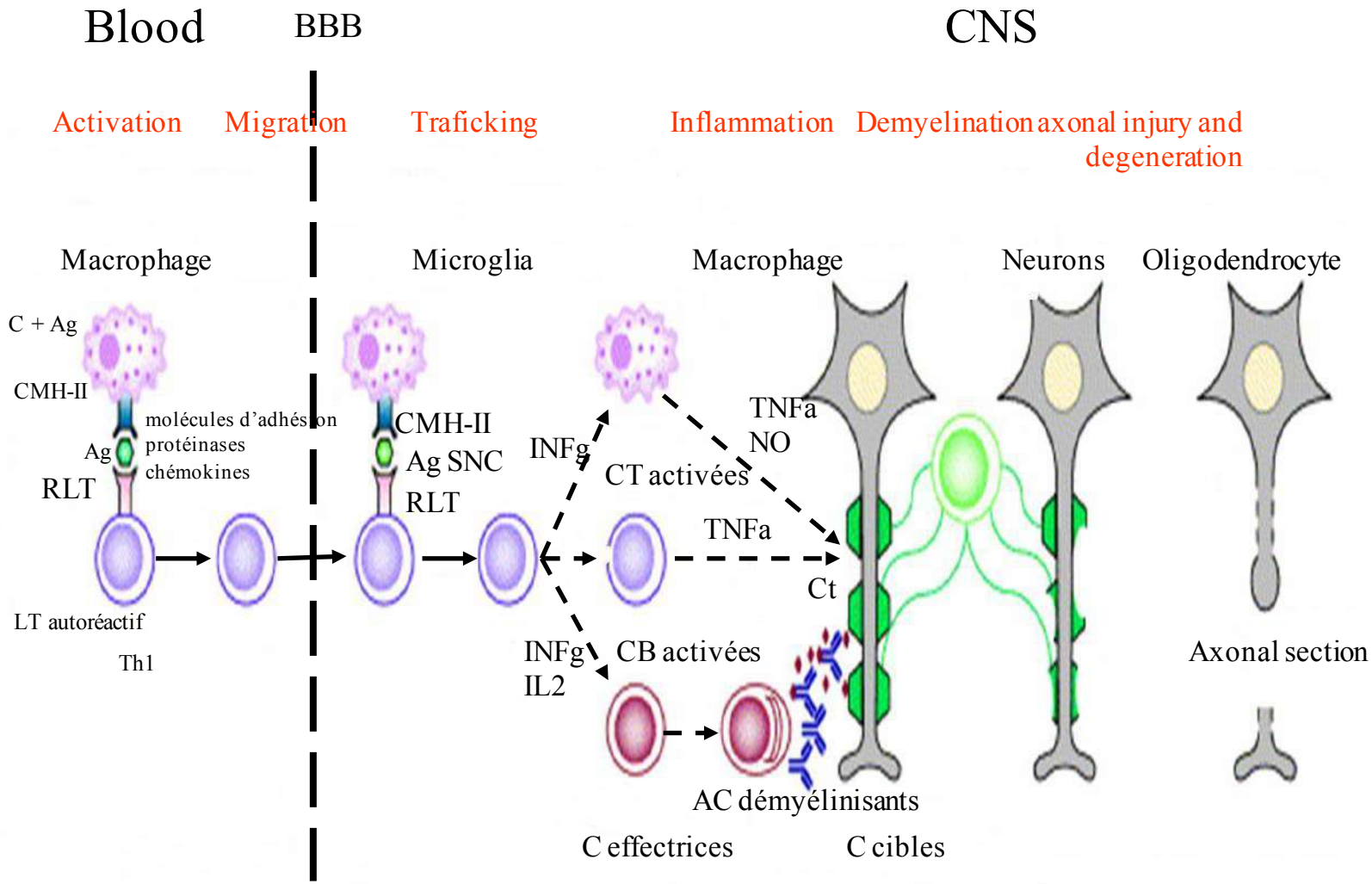
Conclusion: The main predictors of cognitive changes over 7 years are baseline diffuse brain damage and progressive central brain atrophy over the 2 years after MS diagnosis. *Neurology*®
2011;76:1-1

Mechanisms of neurodegeneration in WM



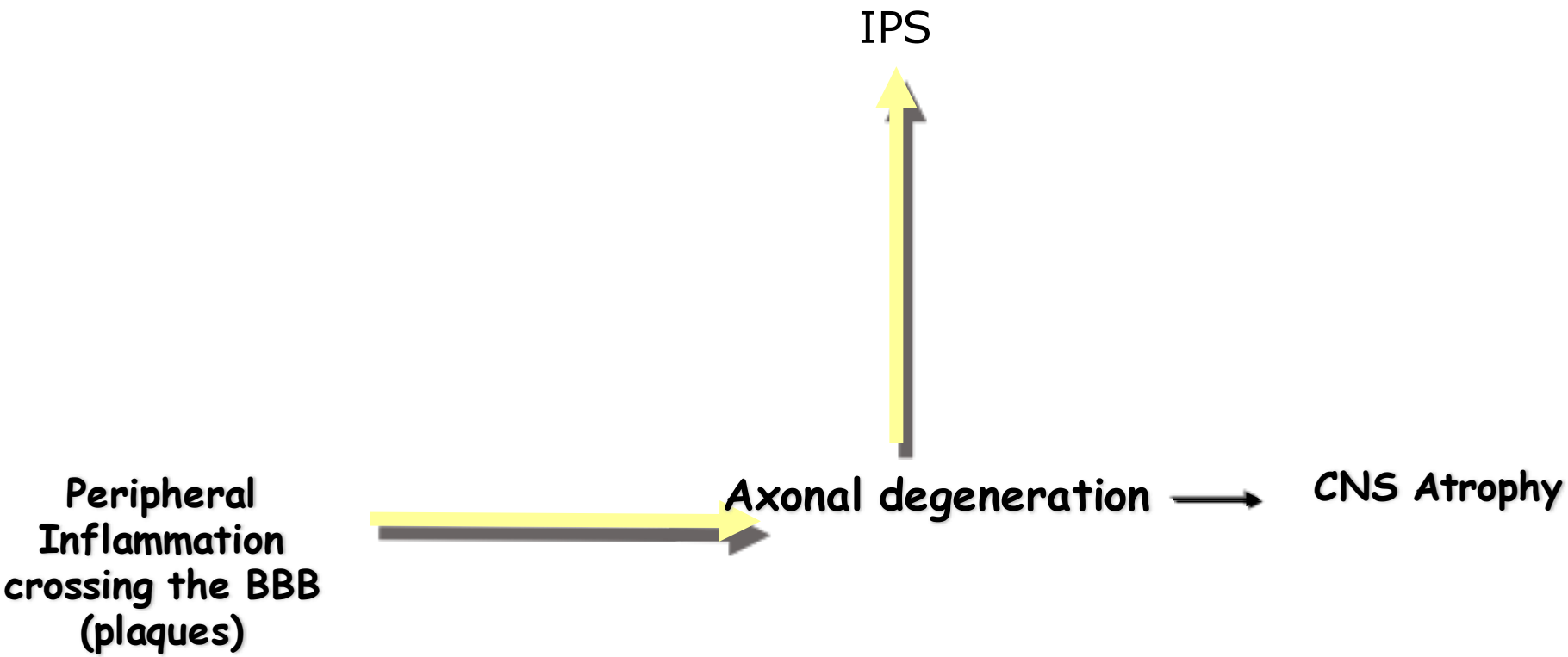


Trapp et al. NEJM 1998



(Pelletier , 2006)

Mechanisms of IPS slowness



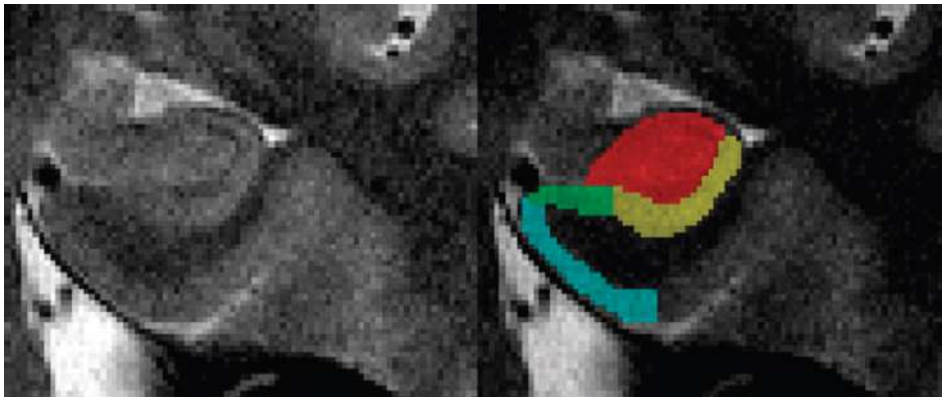
Hippocampus and memory deficits in MS

Correlation between **hippocampal atrophy** and memory

Table 2 Correlation between total and subregional hippocampal volumes and cognitive test performance

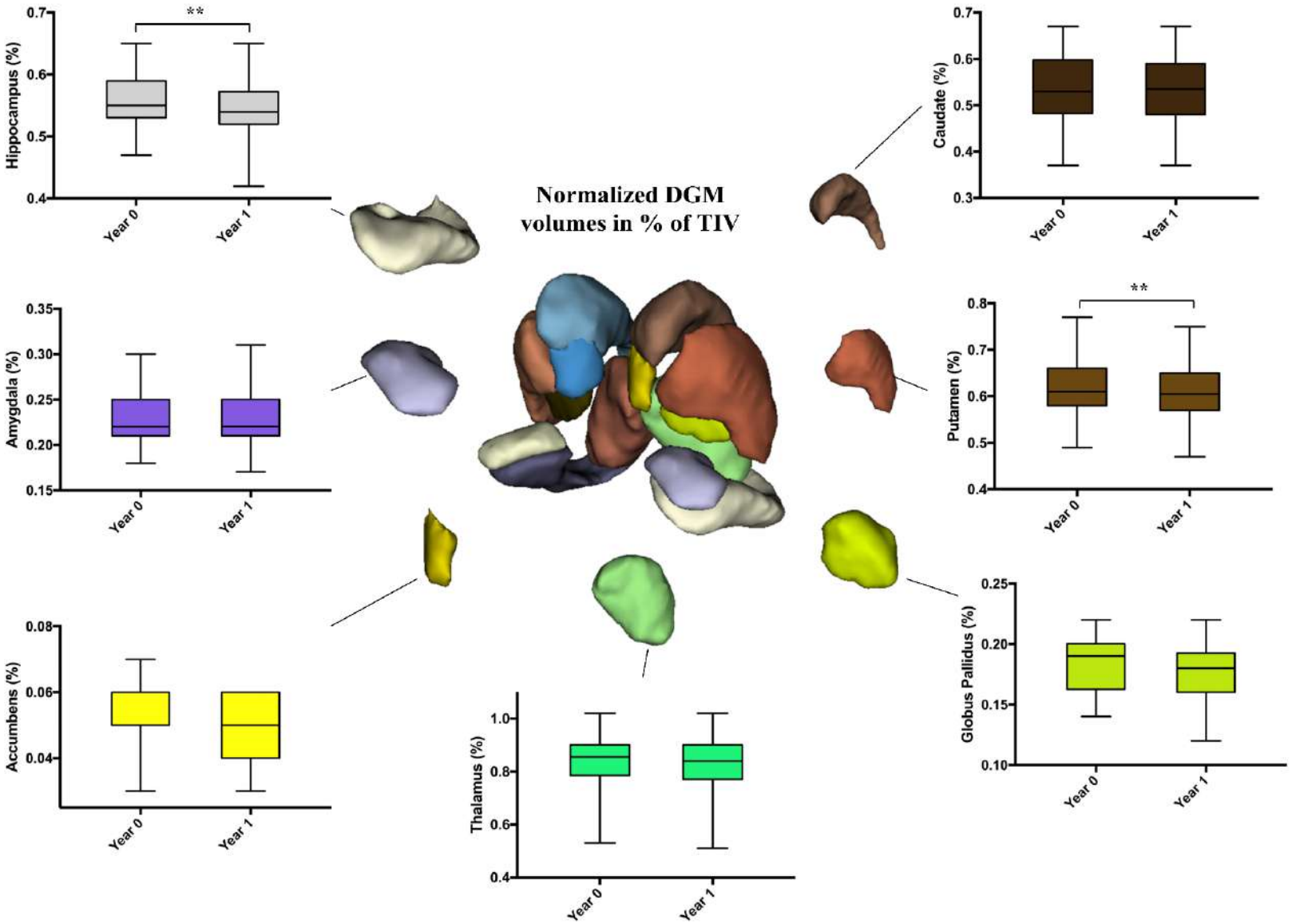
Hippocampal region	Spearman's rank correlation coefficient			
	PASAT	Significance	Word list learning	Significance
Left and right				
CA1	0.19	NS	−0.39	$P = 0.0224$
CA23DG	0.06	NS	−0.30	NS
SUB	0.02	NS	−0.42	$P = 0.0143$
ERC	0.01	NS	−0.28	NS
Total	0.15	NS	−0.48	$P = 0.0038$
Right				
CA1	−0.17	NS	−0.27	NS
CA23DG	0.05	NS	−0.24	NS
SUB	−0.05	NS	−0.34	NS
ERC	−0.03	NS	−0.28	NS
Total	0.04	NS	−0.38	$P = 0.0266$
Left				
CA1	0.23	NS	−0.44	$P = 0.0087$
CA23DG	0.08	NS	−0.33	NS
SUB	0.04	NS	−0.45	$P = 0.0072$
ERC	0.05	NS	−0.34	NS
Total	0.16	NS	−0.49	$P = 0.0029$

Results shown are for RRMS and SPMS patients combined.
NS = not significant.



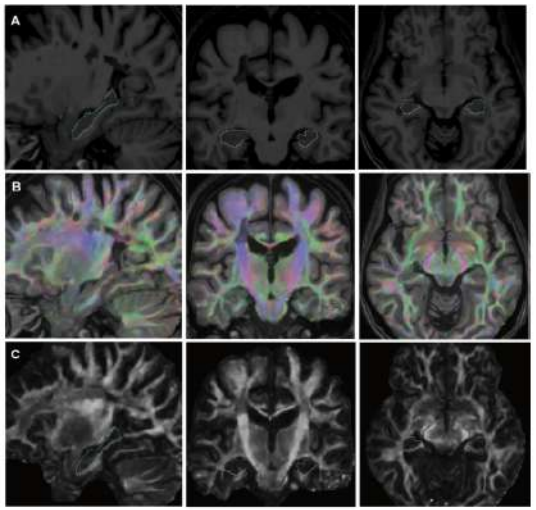
RRMS (DD=3.5) and SPMS (DD=13)

Sicotte et al. Brain, 2008



Koubiyr et al., ECTRIMS 2017: GM atrophy in CIS

Memory and hippocampal microstructure in early MS

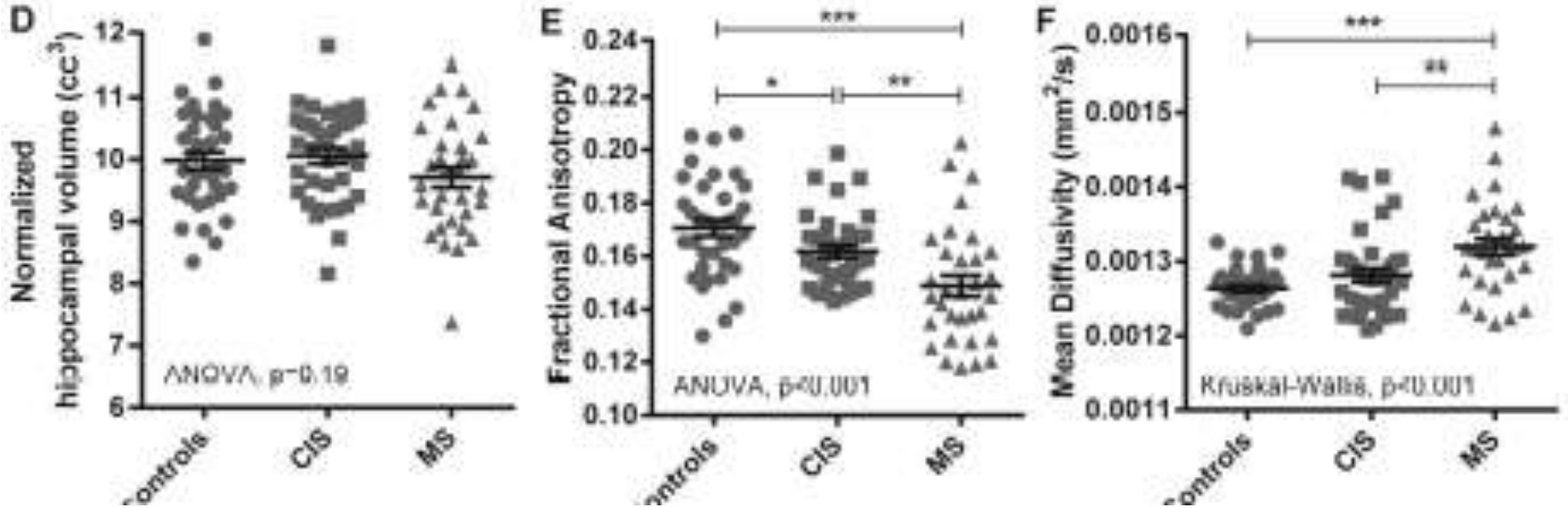


hippocampal masks

Diffusion tensor imahing MAPS

Planche et al; MSJ 2016

FA maps registered in the MNI space with hippocampal masks.



Correlation microstructural abnormalities (DTI)/memory

CIS (n=37)	T2-LL	NHV	FA	MD
Information processing speed	r=-0.13, p=0.45[a]	r=0.04, p=0.84[a]	r=0.10 p=0.54[a]	r=-0.23, p=0.18[a]
Working memory	r=-0.16, p=0.36[a]	r=-0.11, p=0.53[a]	r=-0.17, p=0.31[a]	r=-0.01, p=0.98[a]
Episodic verbal memory (learning trials)	r=-0.24, p=0.14[a]	r=0.02, p=0.93[a]	r=-0.07, p=0.67[a]	r=-0.29, p=0.08[a]
Episodic verbal memory (long term recall)	r=-0.07, p=0.68[a]	r=0.02, p=0.89[a]	r=0.01, p=0.96[a]	r=-0.57, p=0.0002[a]

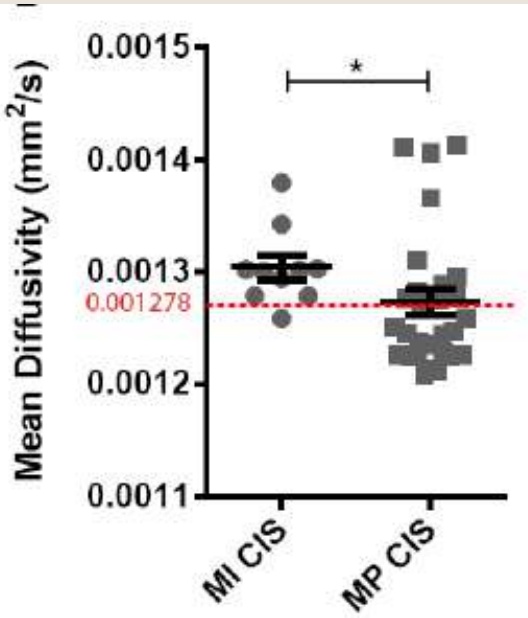
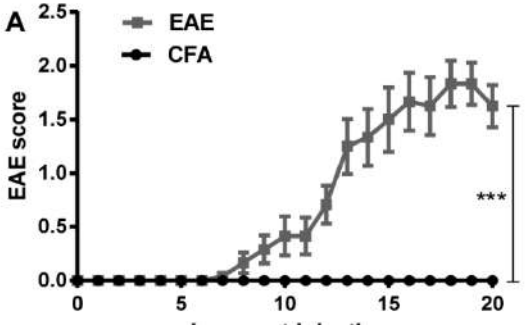
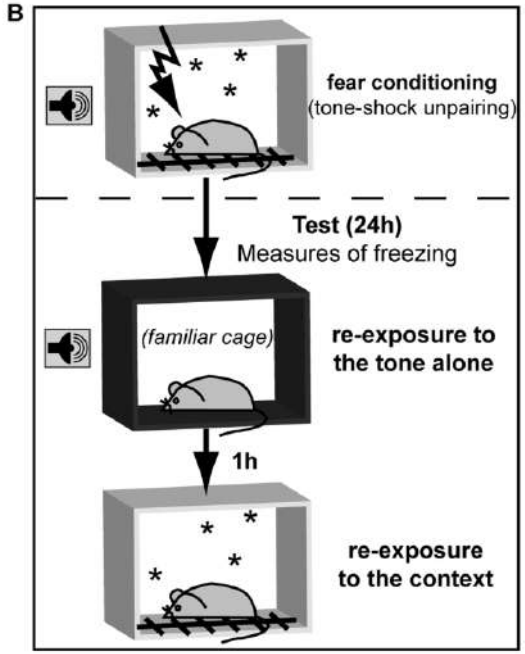


Planche et al; MSJ 2016

Experimental Autoimmune Encephalomyelitis
Model: fear conditionning



Contextual fear conditionning
(A Desmedt)



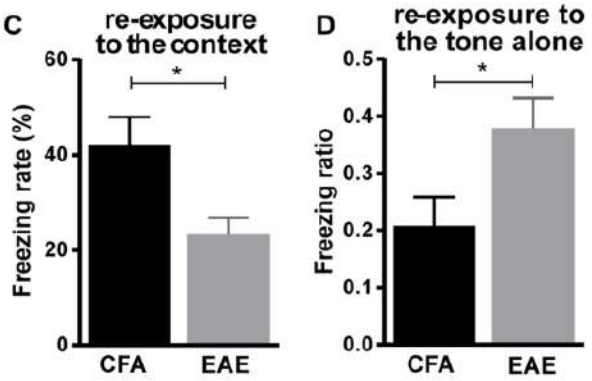
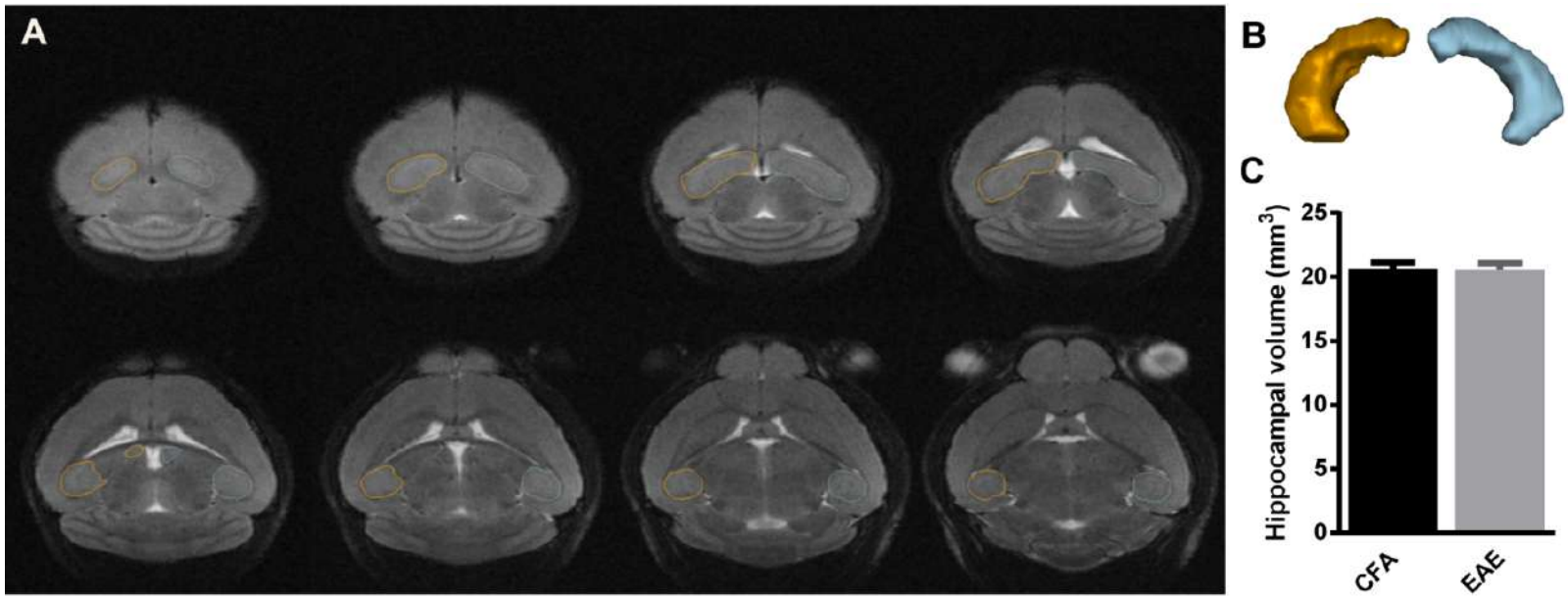


Planche et al., Brain Behav Immun. 2017

EAE-mice showed an early hippocampal-dependent memory deficit

Hippocampal volume

Planche et al., Brain Behav Immun. 2017



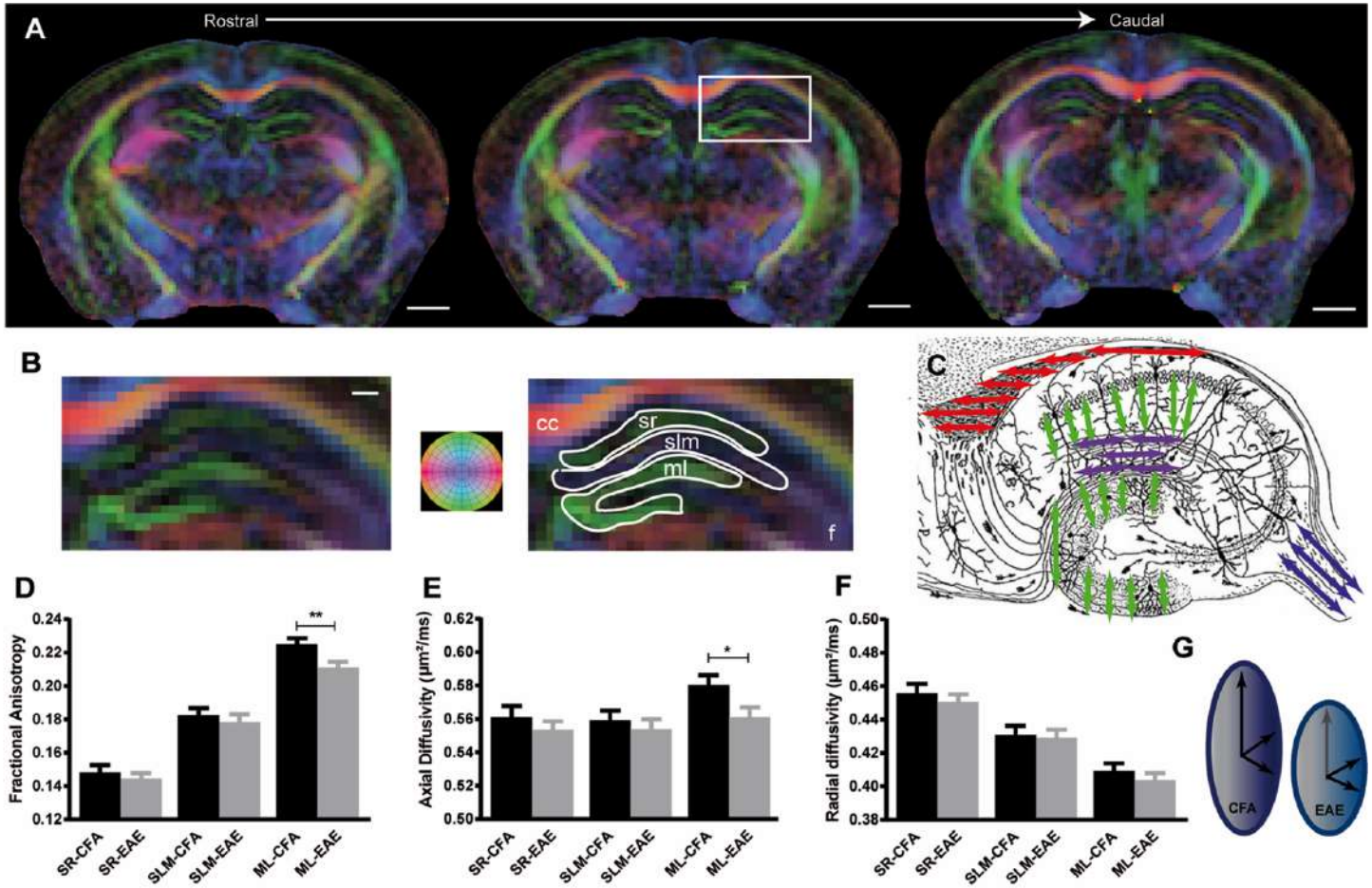
4.7T scanner

no difference between EAE and CFA-mice 20 d.p.i.
20.58mm^3 vs 20.67mm^3, p=0.90,

No atrophy

Diffusion tensor imaging: microstructural injury in hippocampus

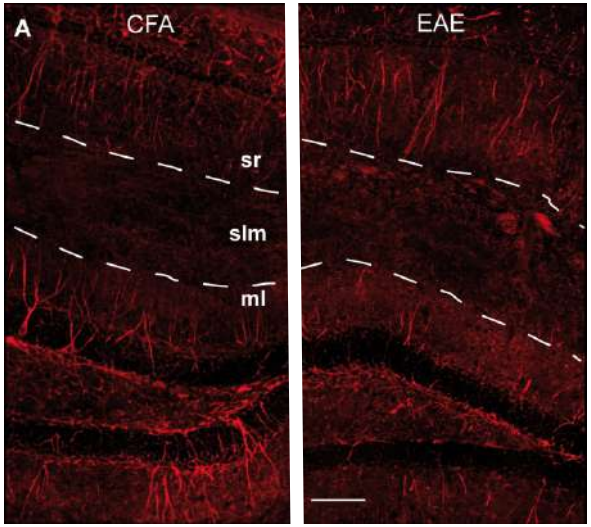
Planche et al., Brain Behav Immun. 2017

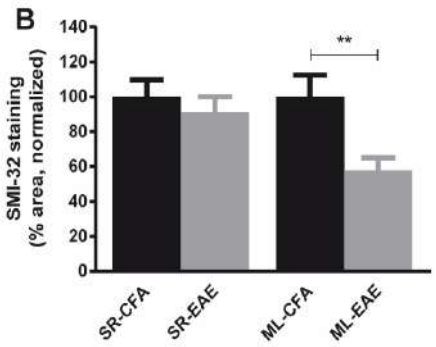


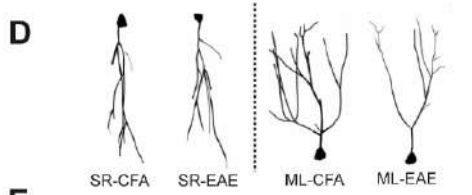
***In vivo* DTI revealed selective microstructural modifications in the molecular layer of the dentate gyrus of EAE-mice**

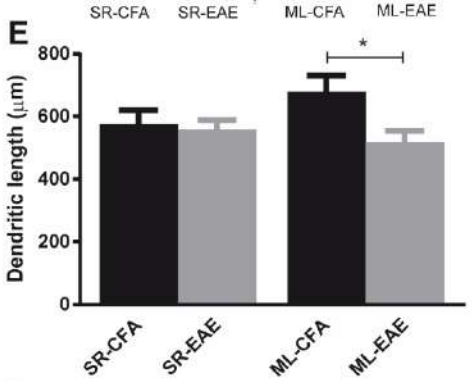
Planche et al., Brain Behav Immun. 2017

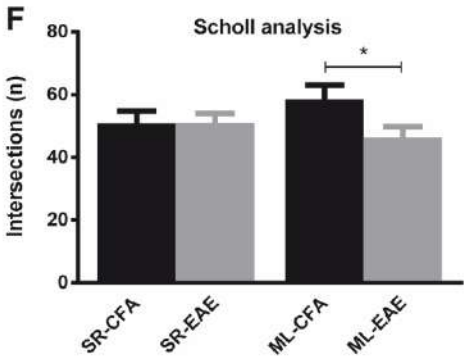
Histology





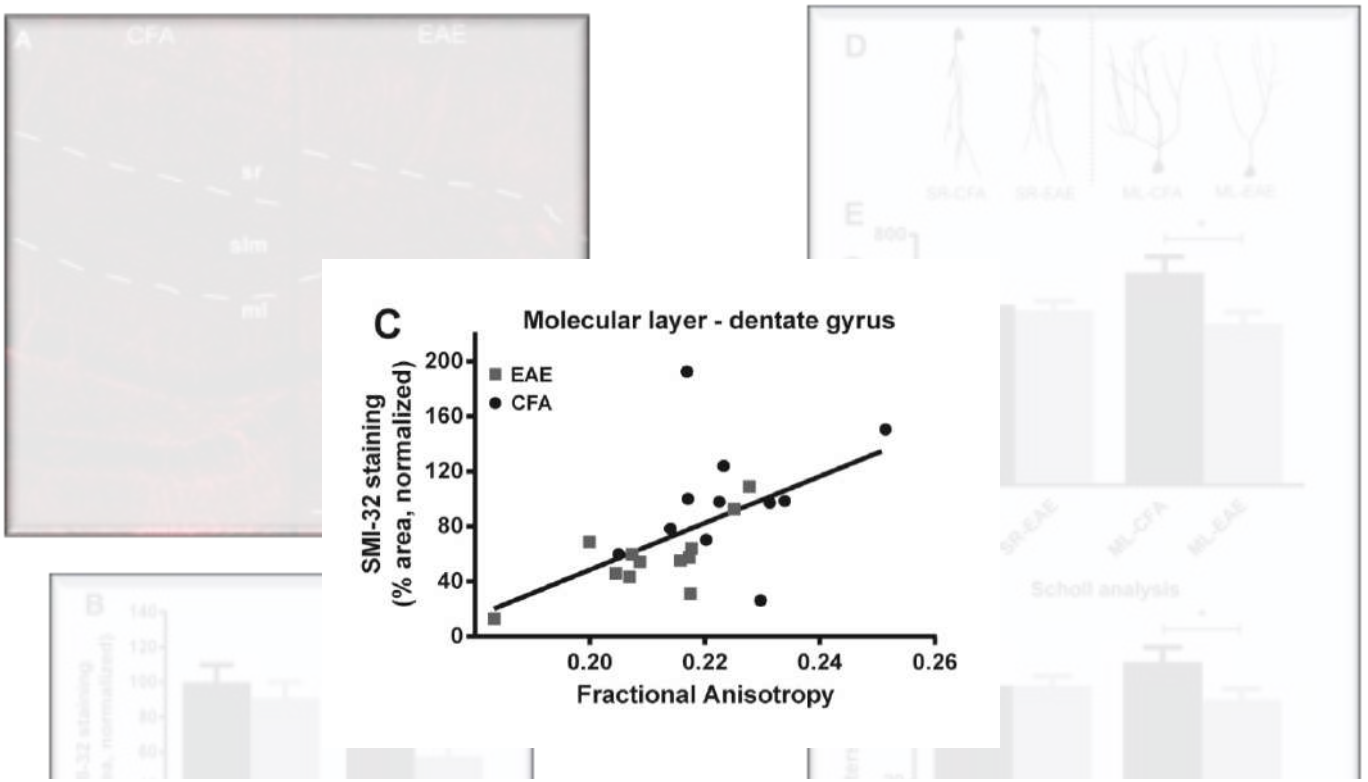






EAE-mice showed a selective and early neurodegenerative process in the dentate gyrus

Planche et al., Brain Behav Immun. 2017



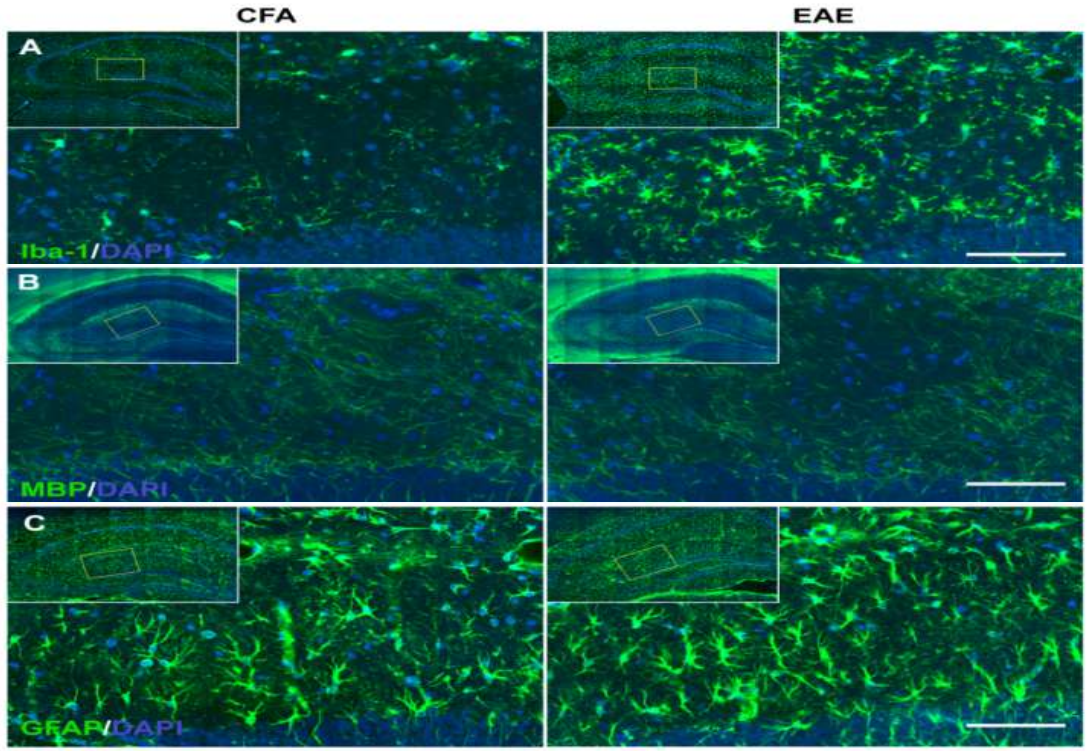
The loss of neurites was correlated with FA and AD in the molecular layer of the dentate gyrus

EAE-mice showed a selective and early neurodegenerative process in the dentate gyrus

Planche et al., Brain Behav Immun. 2017

Microglial activation in hippocampus

- Activated microglia (without neither lymphocyte infiltrates nor demyelination)
- Minocycline (systemic or in situ) prevent memory deficit, DTI abnormalities and pathological lesions by stopping microglial activation.

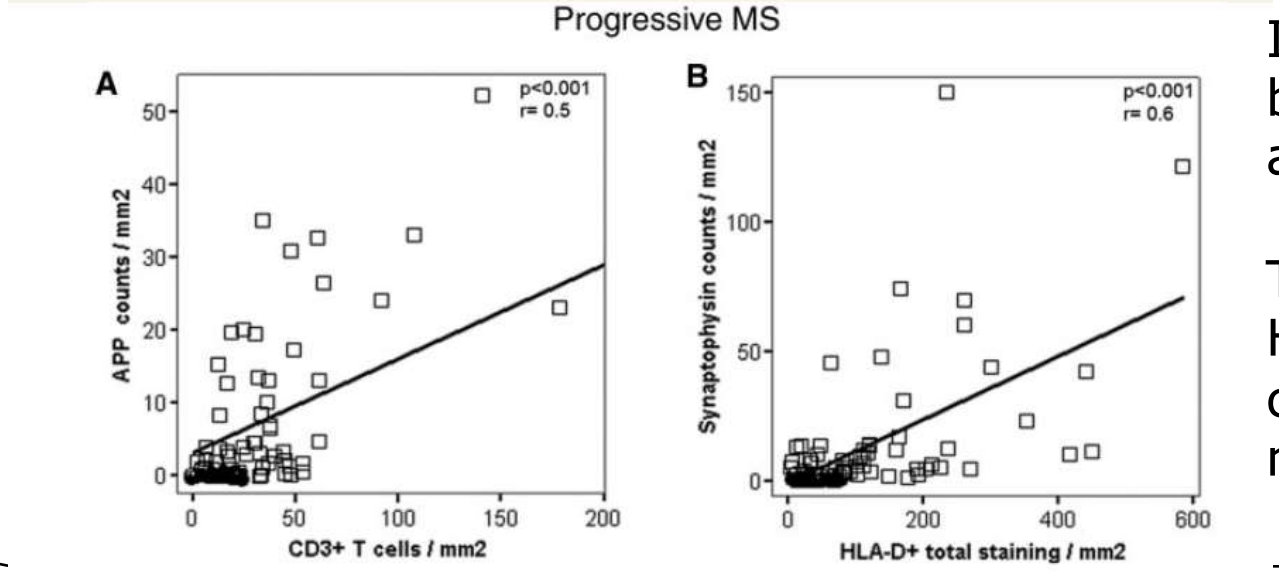


doi:10.1093/brain/awp070 Brain 2009: 132; 1175–1189 | 1175

BRAIN
A JOURNAL OF NEUROLOGY

The relation between inflammation and neurodegeneration in multiple sclerosis brains

Josa M. Frischer,[1,*] Stephan Bramow,[2,*] Assunta Dal-Bianco,[1] Claudia F. Lucchinetti,[3] Helmut Rauschka,[4] Manfred Schmidbauer,[4] Henning Laursen,[5] Per Soelberg Sorensen[2] and Hans Lassmann[1]



Inflammation in the brain is linked to axonal injury

T cells
HLAD+ microglial cells and macrophages

Lymphoïd folicles in meninges

Maggliozzi et al.,
Brain 2007: 130;
1089-1104

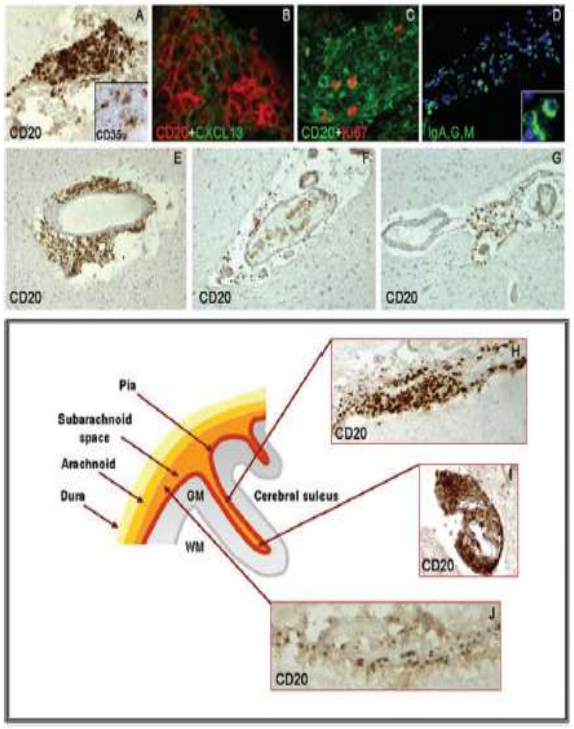
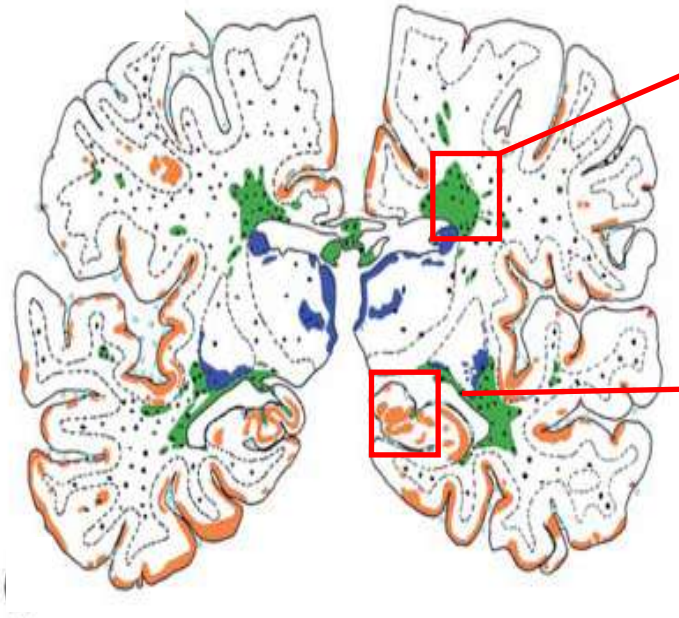
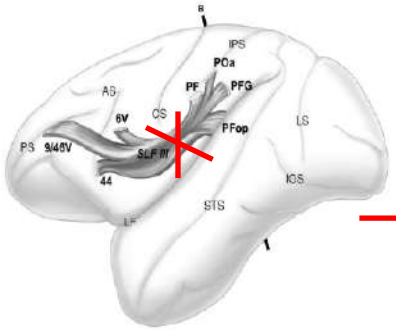


Fig. 1 Characterization of ectopic B-cell follicles and inflammatory cell infiltrates in post-mortem brain tissue from cases with SPMS and PPMS. Immunostainings of serial brain sections from a F+ SPMS case (**A–D**) shows an intrameningeal ectopic B-cell follicle in a cerebral sulcus containing CD20+ B cells (**A**), ramified stromal cells/FDC expressing CD35 (inset in **A**) and CXCL13 (**B**, double immunofluorescence staining with monoclonal anti-CD20 (red) and polyclonal anti-CXCL13 (green) antibodies], proliferating B cells (**C**, double immunofluorescence staining with monoclonal anti-CD20 (green) and polyclonal anti-Ki67 (red) antibodies] and plasmablasts/plasma cells stained with an anti-Ig-G, -A, -M polyclonal antibody (**D**; the inset shows two intrafollicular plasma cells at high-power magnification). Panel **E** shows prominent perivascular accumulation of CD20+ B cells in a periventricular WML from a F+ SPMS case. Several scattered CD20+ B cells are present in the scarcely inflamed meninges entering a cerebral sulcus in a F– SPMS case (**F**) and in a PPMS case (**G**). The lower, composite panel illustrates the localization of ectopic B-cell follicles in the multiple sclerosis brain. The schematic drawing shows that ectopic B-cell follicles develop along (**H**) and in the depth (**I**) of the cerebral sulci, whereas scattered B lymphocytes (**J**) are detected in the meninges covering the external brain surface. The micrographs in panels **H–J** show representative fields from a F+ SPMS case out of the 12 examined. Original magnifications: **E–G** = 100 ×; **A**, **D**, **H–J** = 200×, **B**, **C** and insets in **A** and **D** = 400×.

Conclusion

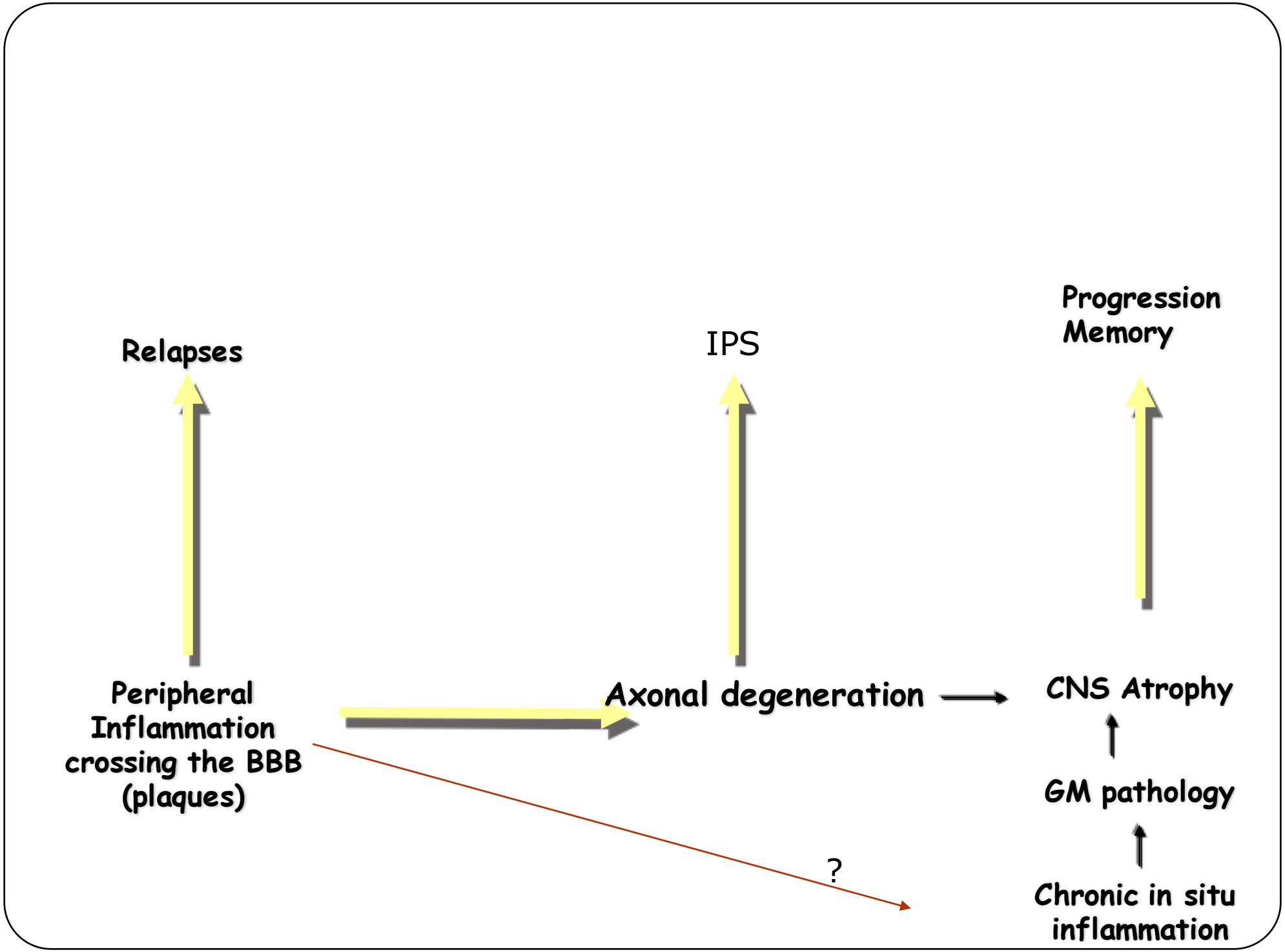




Deficit of speed of information processing

Early connectivity disturbance
Diffuse and focal (WM)

Gray matter injury → Memory impairment,


Relapses
IPS
Progression
Memory
Peripheral
Inflammation
crossing the BBB
(plaques)
Axonal degeneration
CNS Atrophy
GM pathology
?
Chronic in situ
inflammation