CENTRO ANALISI MONZA

CORSO ECM

SCLEROSI MULTIPLA:
dalla chiarezza diagnostica all'efficacia terapeutica

Dall'attacco immunitario al sintomo clinico: note di fisiopatologia

Dr. Paolo Confalonieri
Centro Sclerosi Multipla
Istituto Neurologico "Carlo Besta", Milano

FONDAZIONE I.R.C.C.S.
ISTITUTO NEUROLOGICO CARLO BESTA

Sistema Sanitario Regione Lombardia

La Sclerosi Multipla è una malattia

del sistema nervoso centrale, con una

componente infiammatoria demielinizzante

immunomediata ed

una componente degenerativa assonale

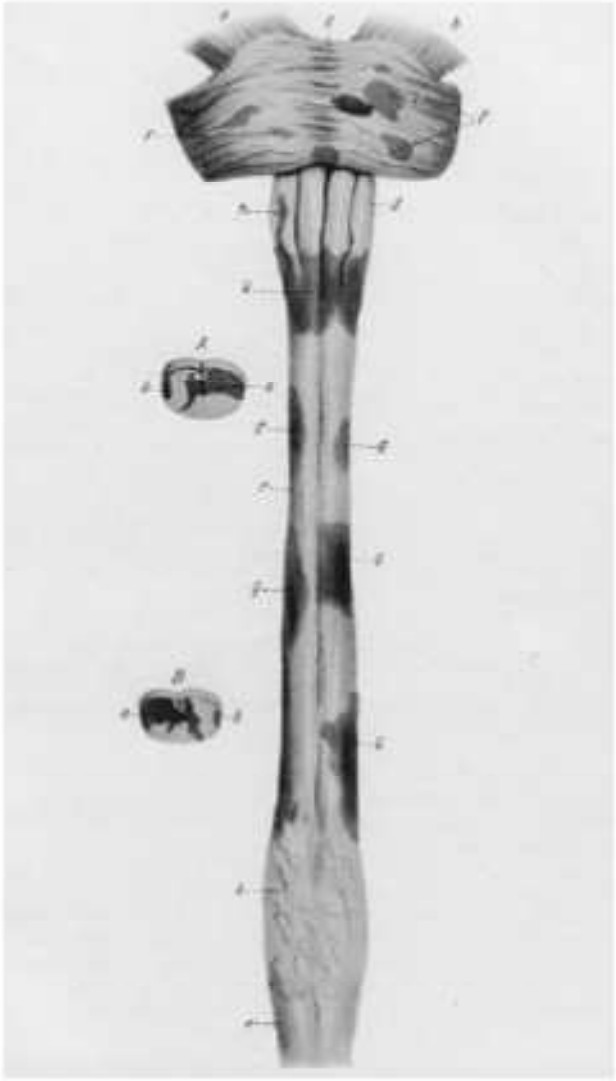
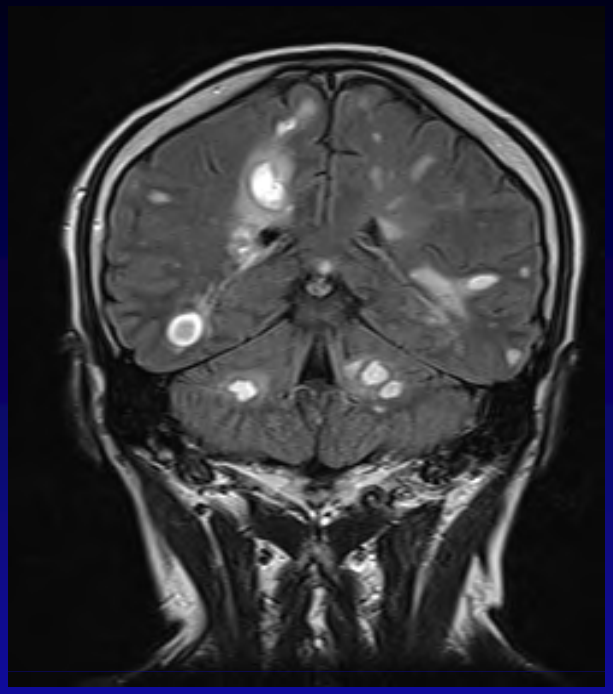
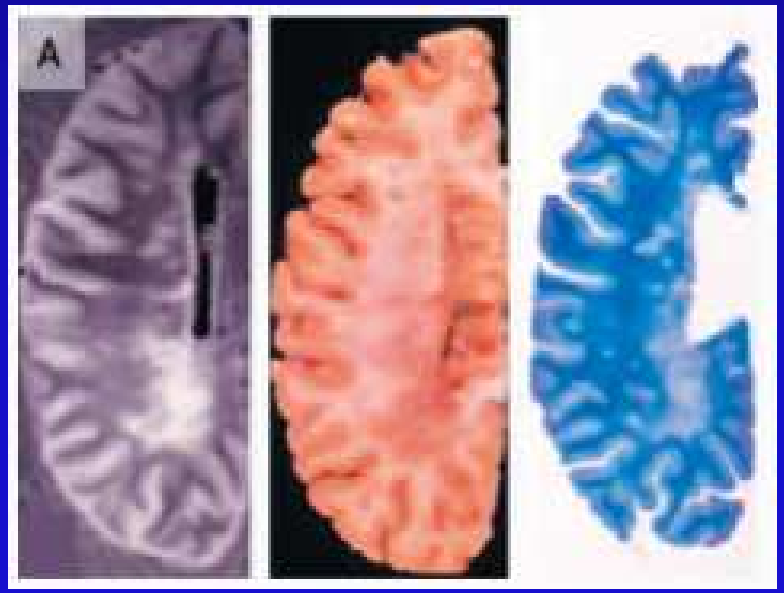
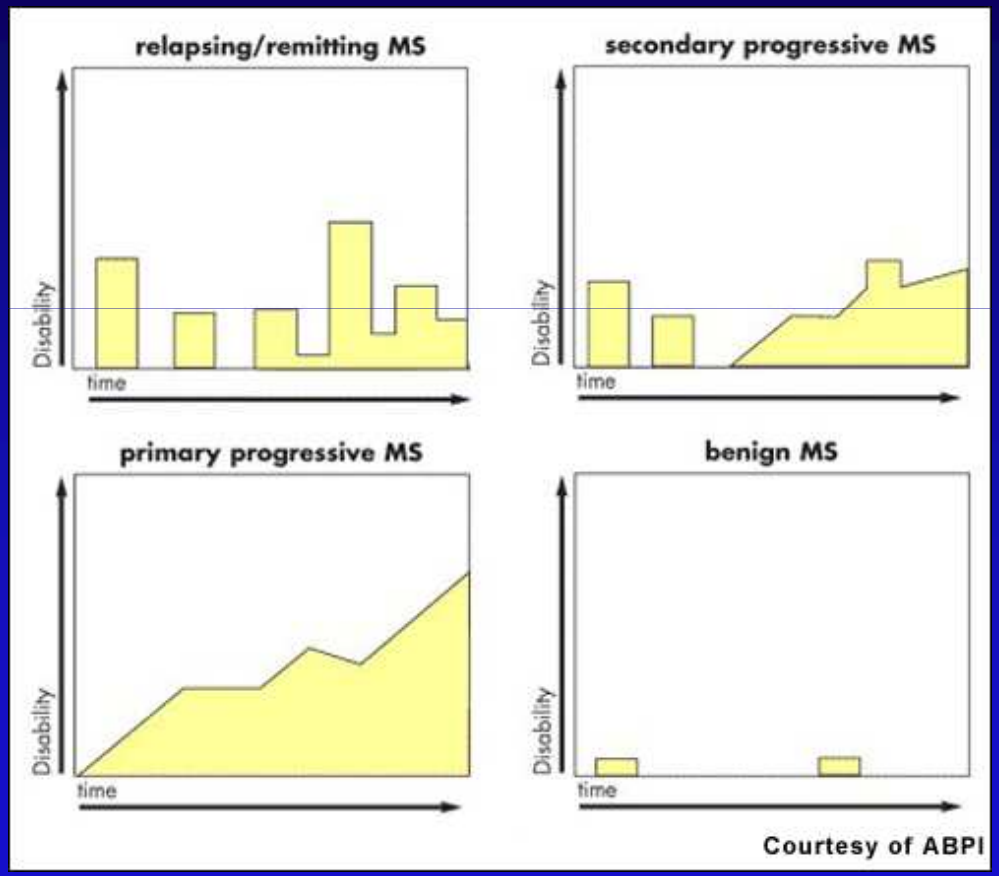


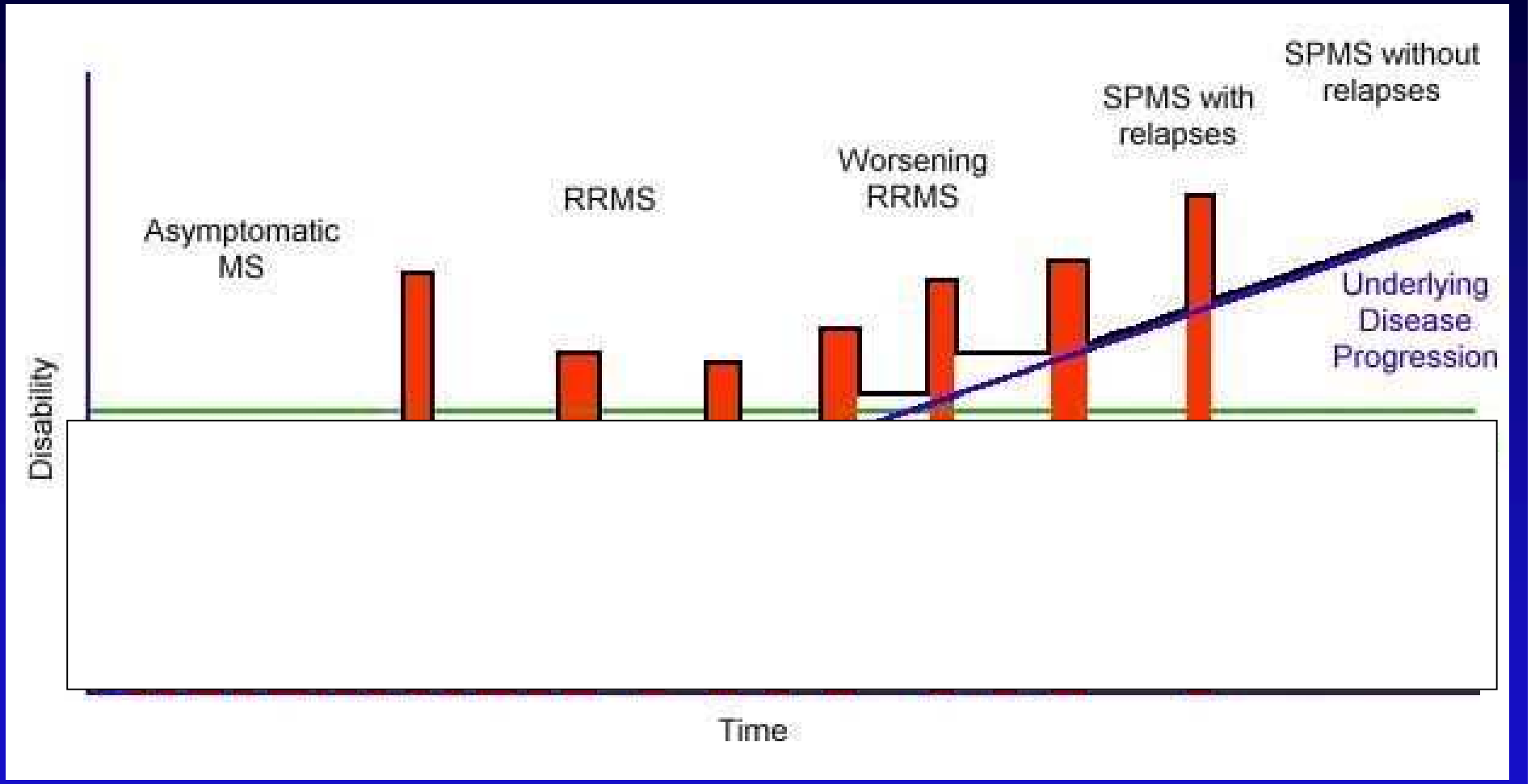
Fig. 3 Medulla spinalis with sclerotic parts, from Carswell's pathological anatomy (1838)



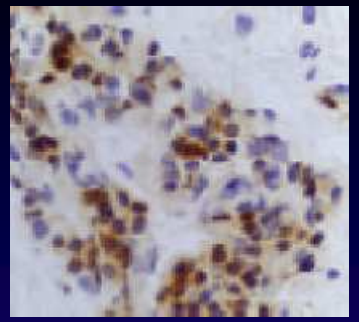


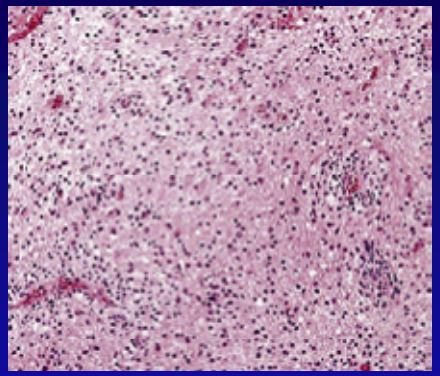
Sclerosi Multipla:
diverse forme di malattia definite dall'andamento clinico




SPMS without relapses
SPMS with relapses
Worsening RRMS
RRMS
Asymptomatic MS
Underlying Disease Progression
Disability
Time

Primo episodio di malattia
(Sindrome Clinica Isolata: CIS):





-Fattori predisponenti

-Possibili trigger

-Attivazione immunitaria:

- attivazione linfociti autoreattivi
- aderenza e fuoriuscita dai vasi sanguigni con attraversamento barriera ematoencefalica
- coinvolgimento linfociti T e linfociti B
- attivazione di agenti tossici
- azione lesiva su mielina e assoni

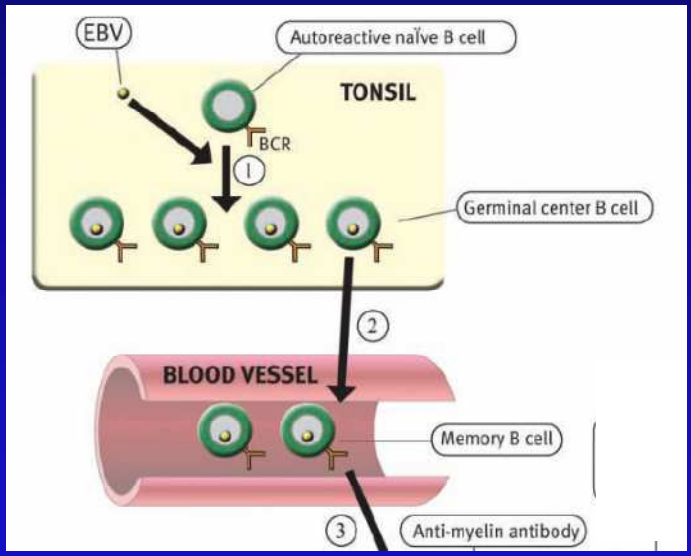
Trigger?

Hypothesis

The Essential Role of Epstein-Barr Virus in the Pathogenesis of Multiple Sclerosis

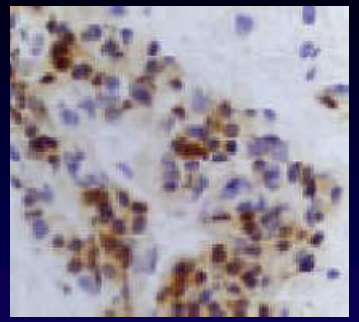
The Neuroscientist
17(4) 351–367

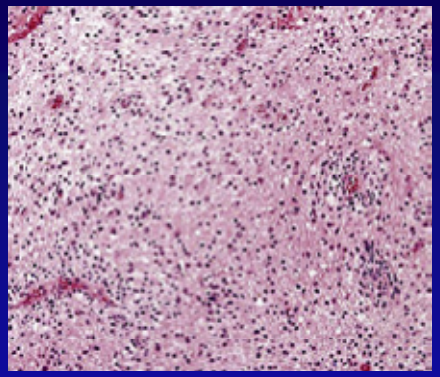
DOI: 10.1177/1073858410381531
http://nro.sagepub.com
SAGE



There is increasing evidence that infection with the Epstein-Barr virus (EBV) plays a role in the development of multiple sclerosis (MS), a chronic inflammatory demyelinating disease of the CNS. This article provides a four-tier hypothesis proposing (1) EBV infection is essential for the development of MS; (2) EBV causes MS in genetically susceptible individuals by infecting autoreactive B cells, which seed the CNS where they produce pathogenic autoantibodies and provide costimulatory survival signals to autoreactive T cells that would otherwise die in the CNS by apoptosis;

Primo episodio di malattia
(Sindrome Clinica Isolata: CIS):





-Fattori predisponenti

-Possibili trigger

-**Attivazione immunitaria**:

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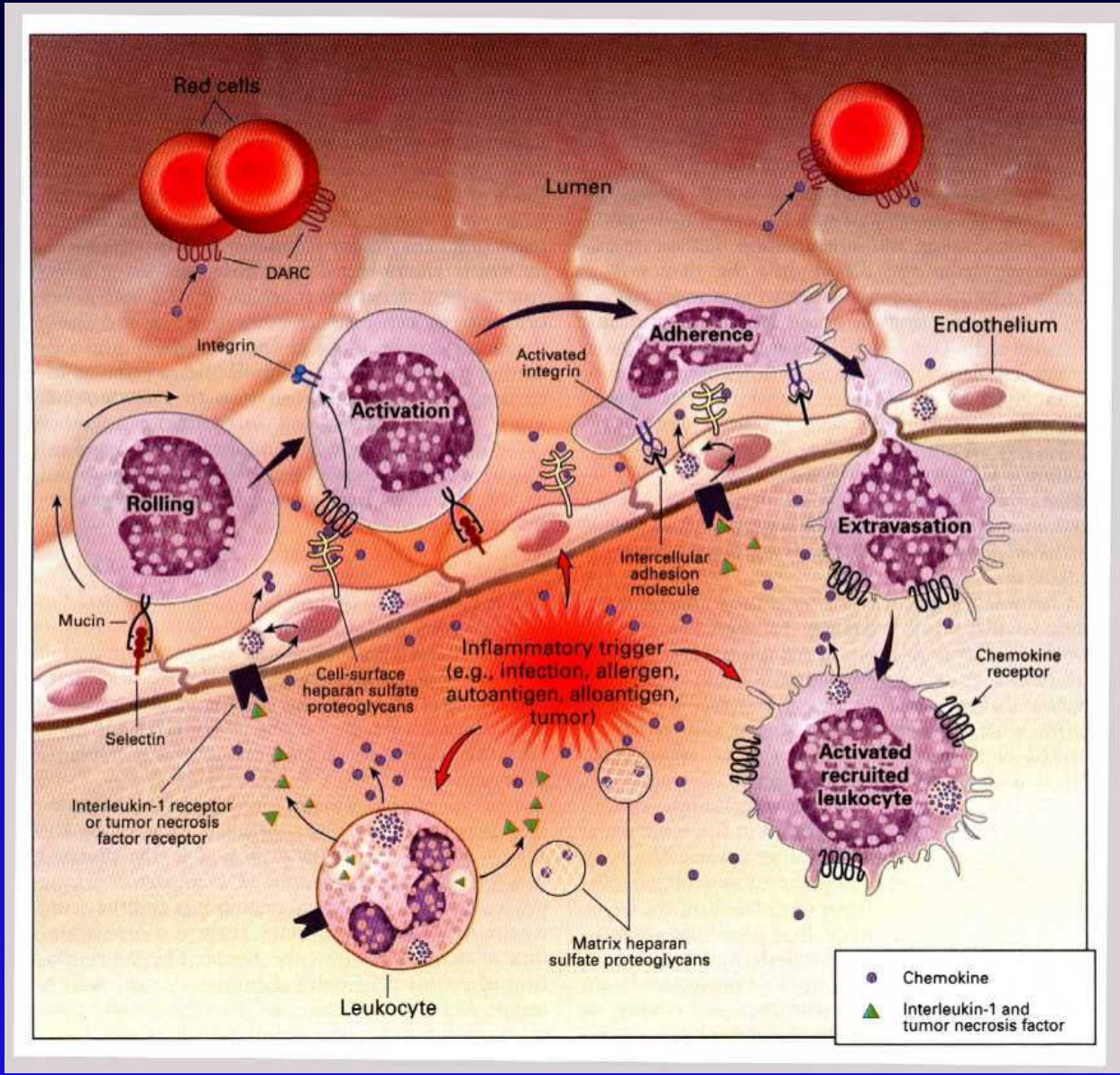
- coinvolgimento linfociti T e linfociti B
- attivazione di agenti tossici
- azione lesiva su mielina e assoni

Leucociti attivati, fuoriuscita dai vasi ematici:

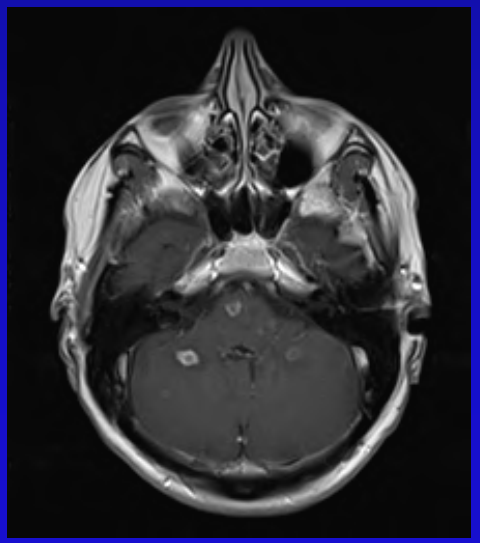


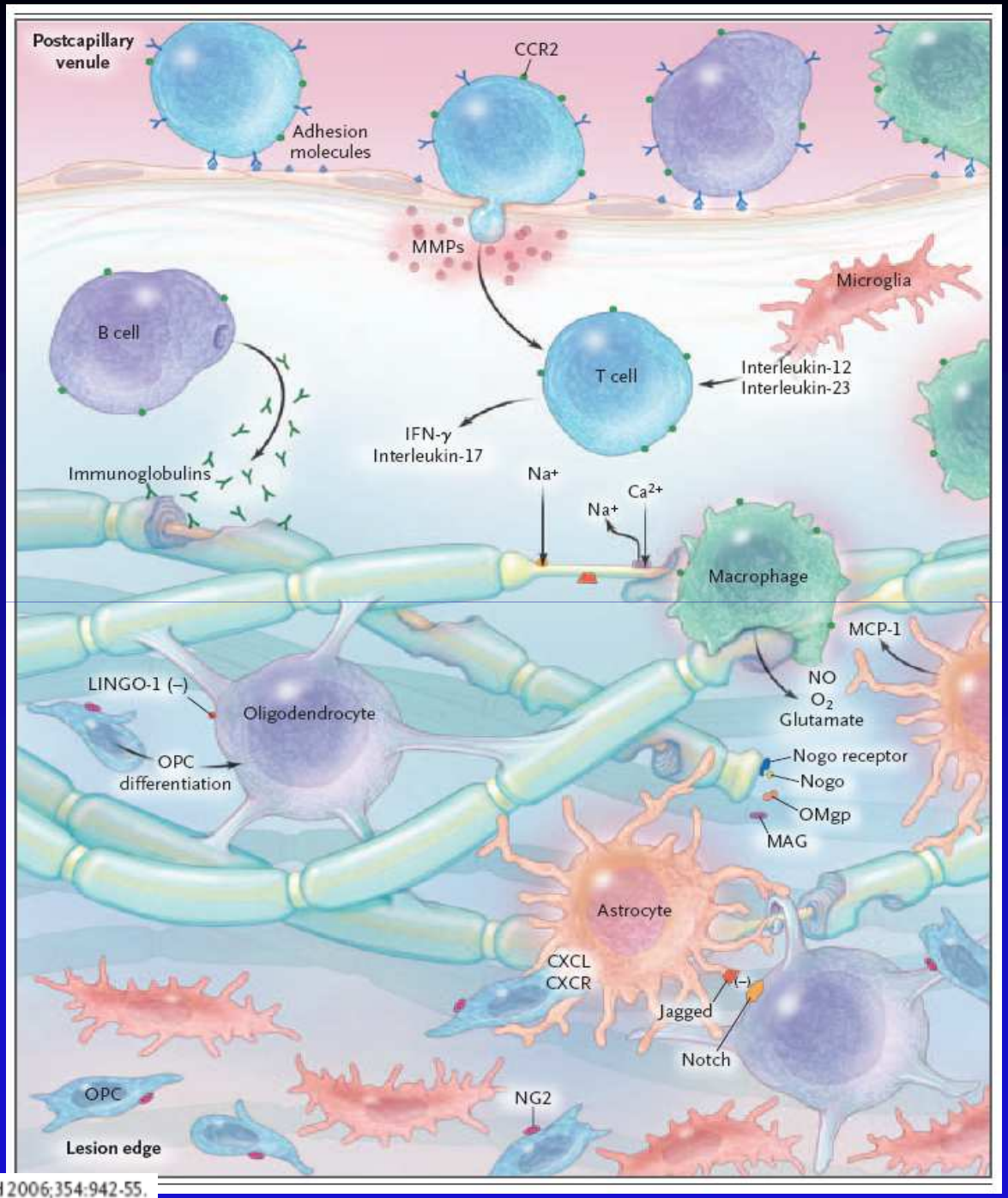
Interazione Leucociti-endotelio

Migrazione Transendoteliale

Integrine

Chemochine e recettori





N Engl J Med 2006;354:942-55.

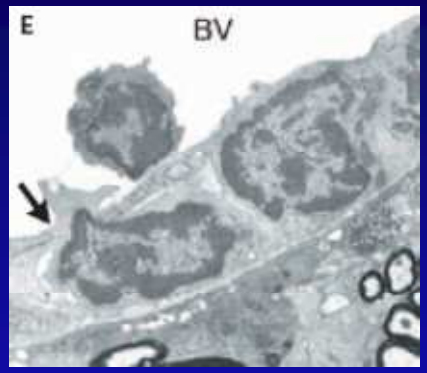
Linfociti T
Linfociti B
Macrofagi
Astrociti
Cellule gliali
Oligodendrociti

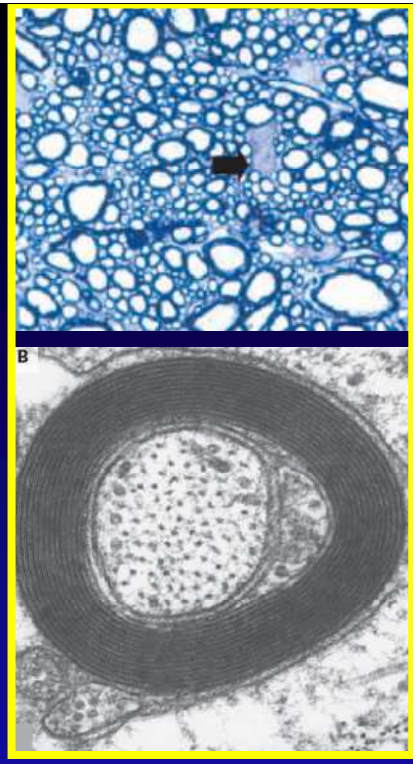
Citochine
Recettori

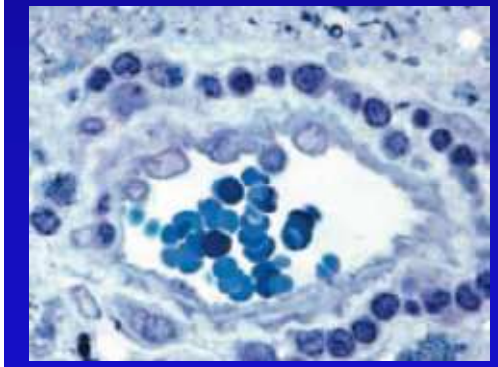
Plasmacellule
Anticorpi
Complemento

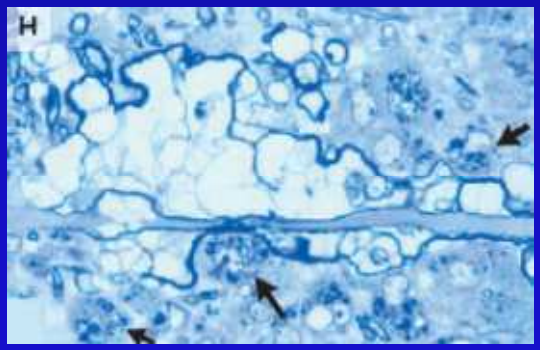
Infiammazione
Demielinizzazione
Danno assonale

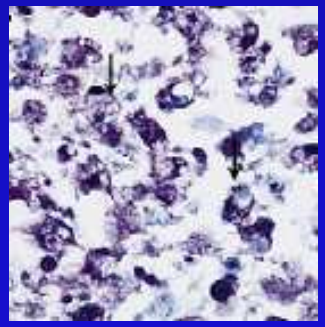
SM Recidivante-Remittente: infiammazione e lesioni della sostanza bianca **Demielinizzazione**

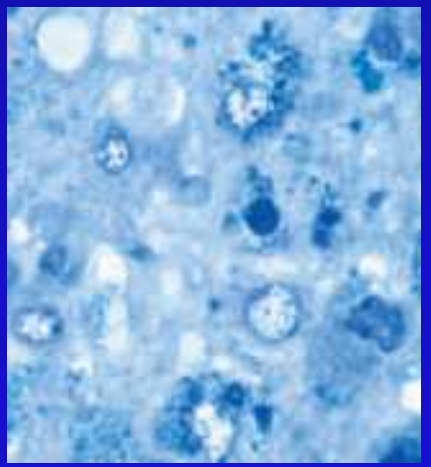






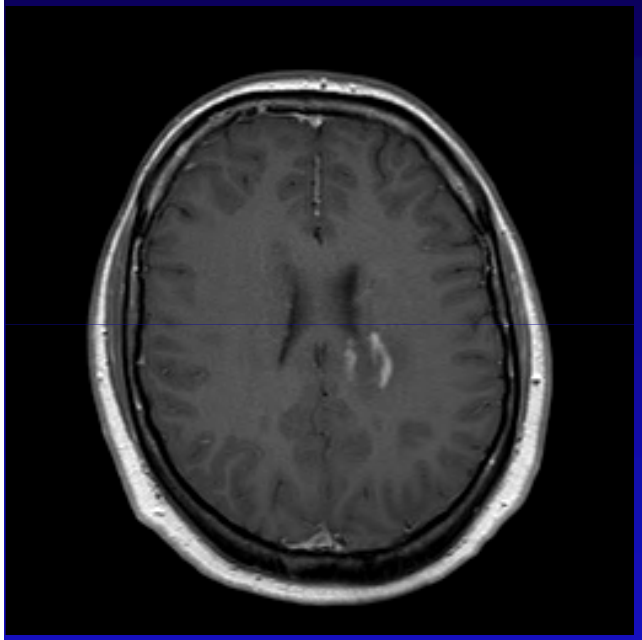


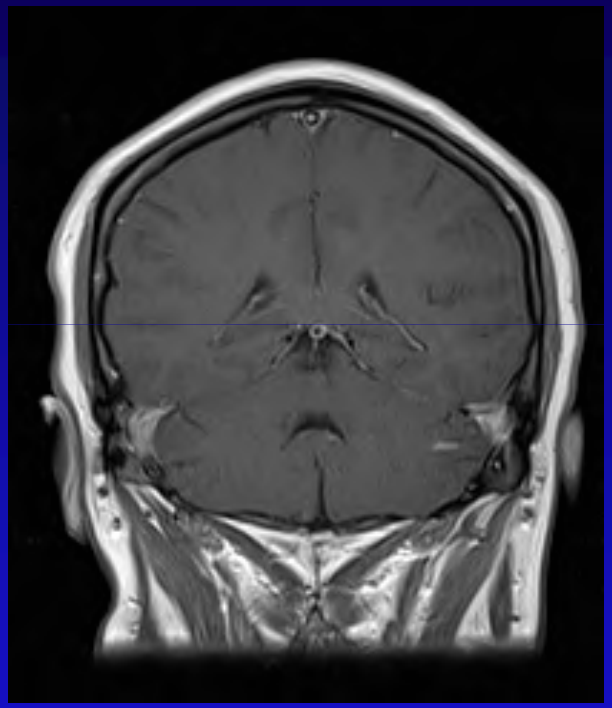


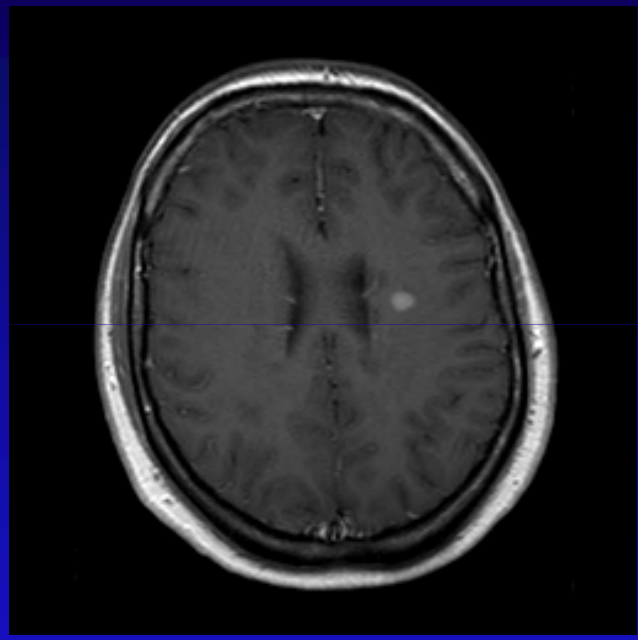


N Engl J Med 2006;354:942-55.

Paziente DMP



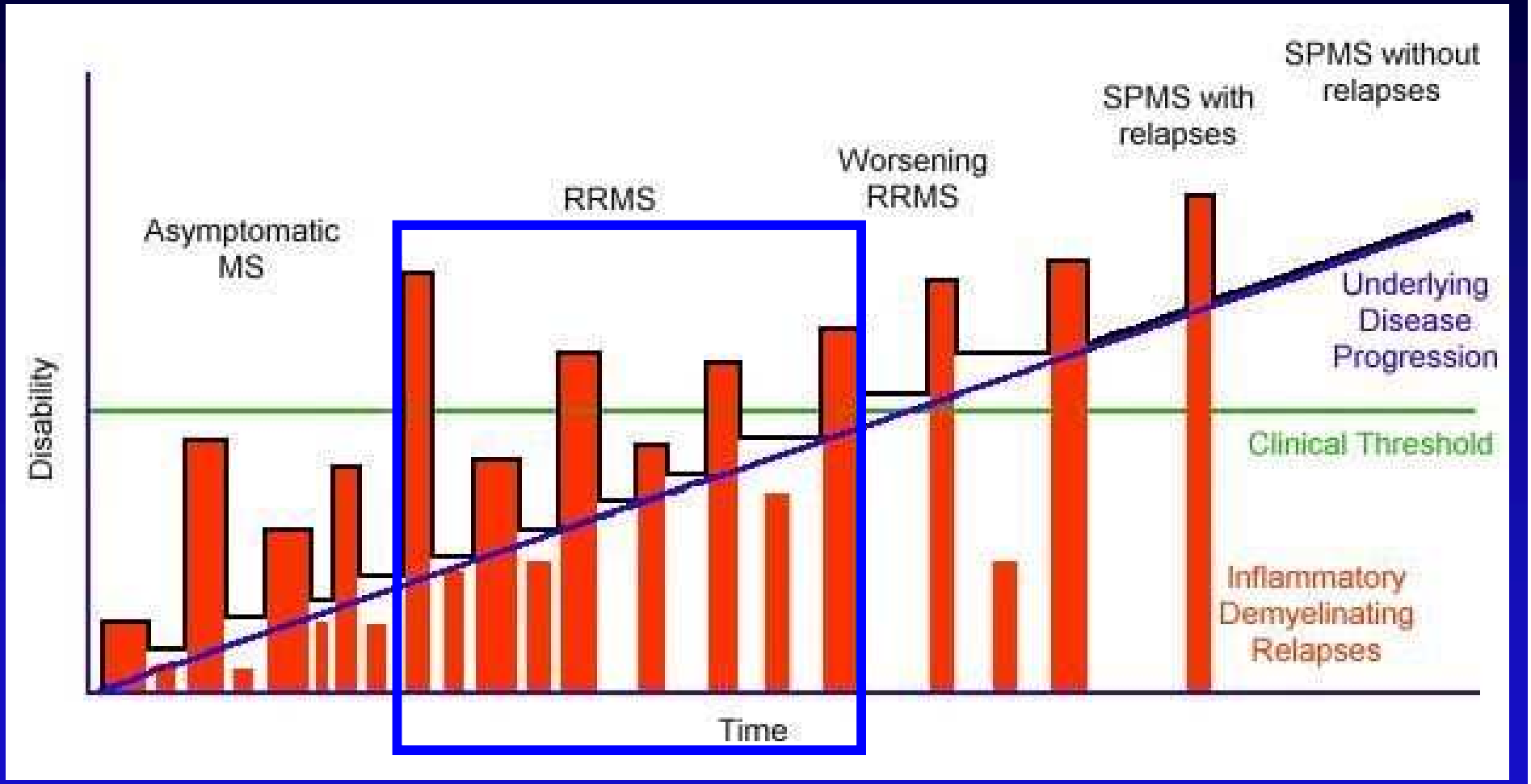




Maggio 2011

agosto 2011

ottobre 2011


SPMS without relapses
SPMS with relapses
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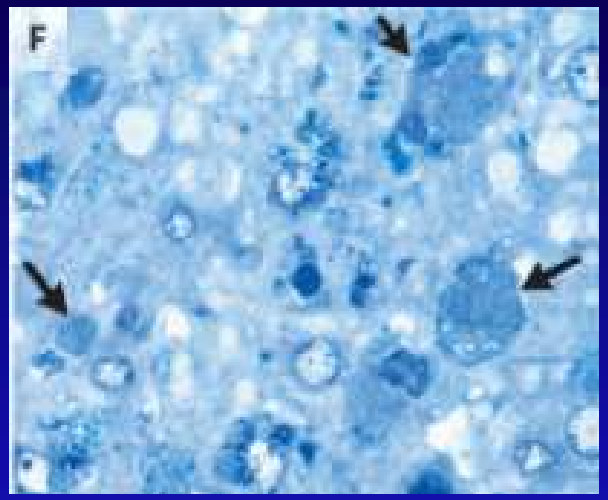
Disability
Time

SM Recidivante-Remittente: infiammazione e lesioni della sostanza bianca

Danno assonale precoce



N Engl J Med 2006;354:942-55.

Brain (1997), **120**, 393–399

Axonal damage in acute multiple sclerosis lesions

B. Ferguson,[1,2] M. K. Matyszak,[1] M. M. Esiri[2] and V. H. Perry[1]

The New England Journal of Medicine

AXONAL TRANSECTION IN THE LESIONS OF MULTIPLE SCLEROSIS

Bruce D. Trapp, Ph.D., John Peterson, B.S., Richard M. Ransohoff, M.D., Richard Rudick, M.D., Sverre Mörk, M.D., Ph.D., and Lars Bö, M.D.

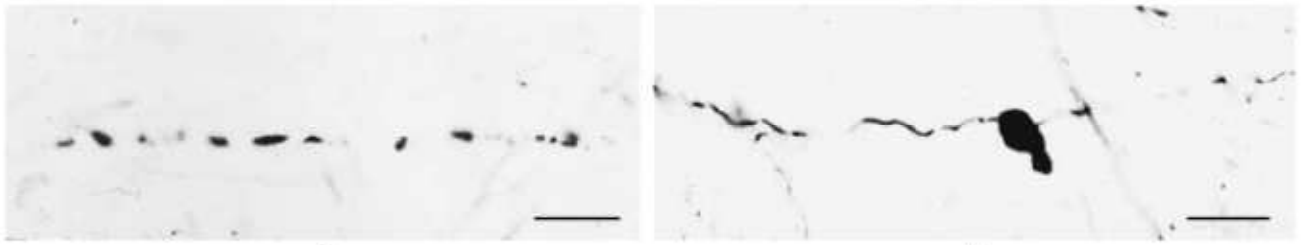


Figure 2. Patterns of Axonal Pathologic Changes in Multiple-Sclerosis Lesions.

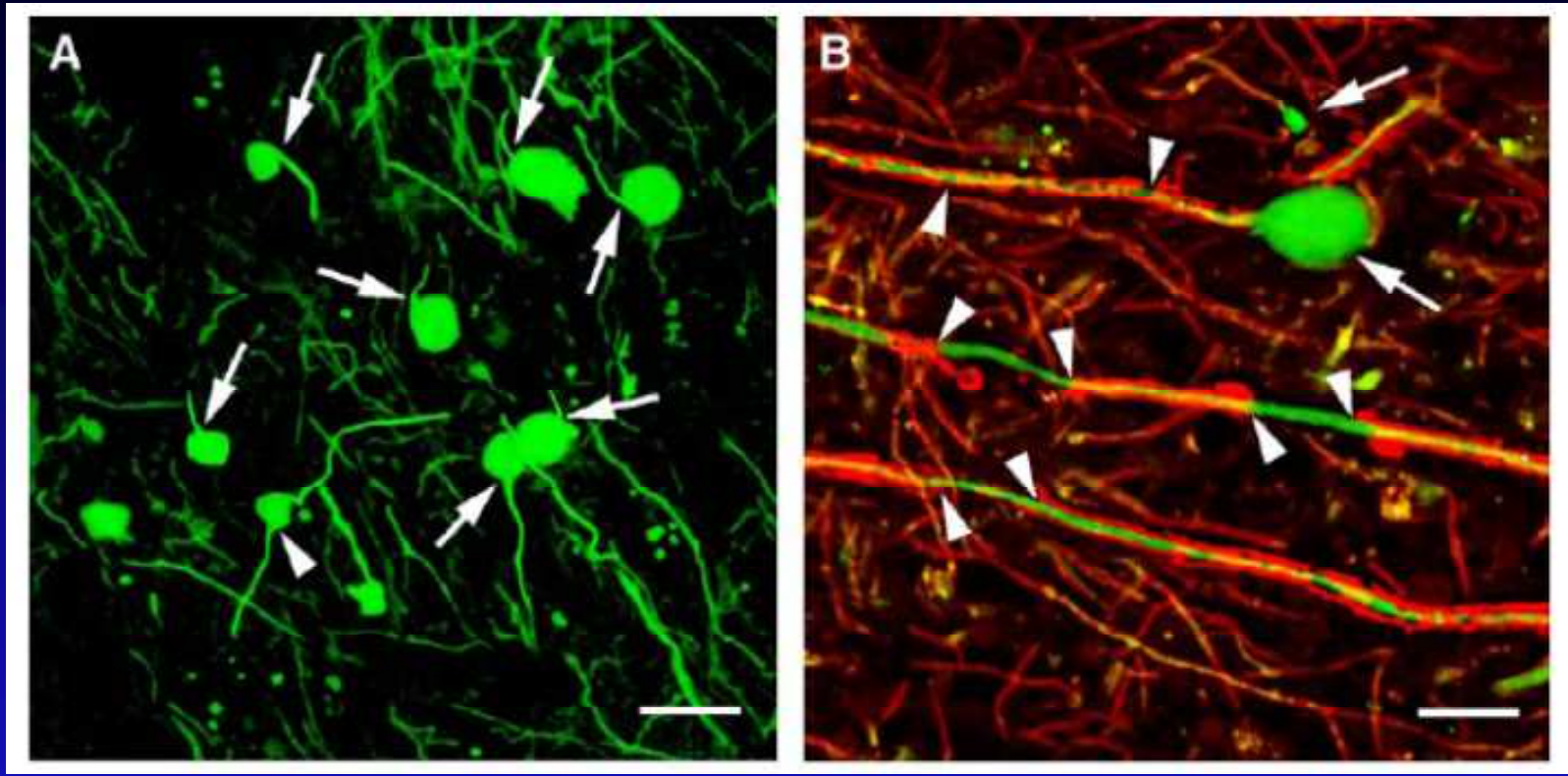
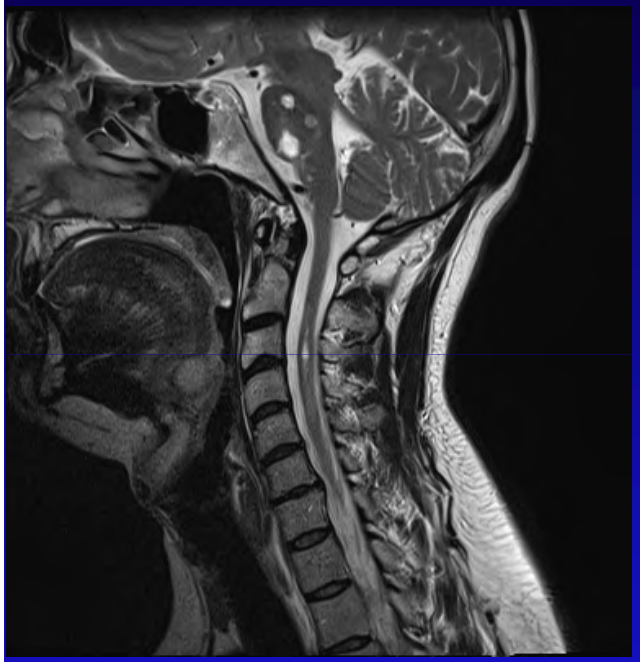
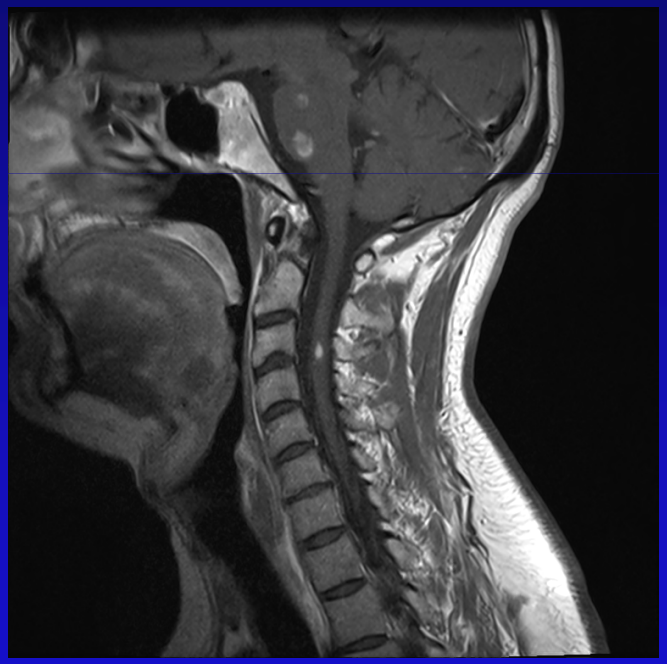


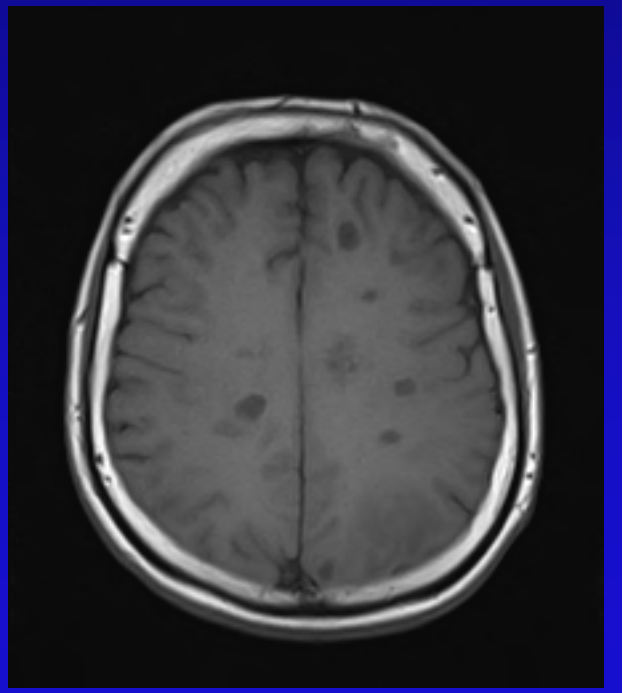
Fig. 3. Confocal analysis of axonal ovoids confirmed transection of axons in MS lesions. (*A*) Most axonal ovoids had single axonal connections indicative of axonal transection (*arrows*), some had two axonal connections (*arrowhead*), indicating the axons had not undergone transection. (*B*) Nonphosphorylated neurofilament-positive axons (green) undergoing demyelination at the border of a chronic active lesion (*arrowheads*; red is myelin basic protein). Two of the axons end in terminal ovoids (*arrows*). Macrophages and microglia associate with transected axons (green) in active MS lesions.

(*Adapted from* Trapp BD, Peterson J, Ransohoff RM, et al. Axonal transection in the lesions of multiple sclerosis. N Engl J Med 1998;338:278–85; with permission.)

SM Recidivante-Remittente:
infiammazione e lesioni della sostanza bianca.
Risonanza Magnetica con demielinizzazione e danno assonale







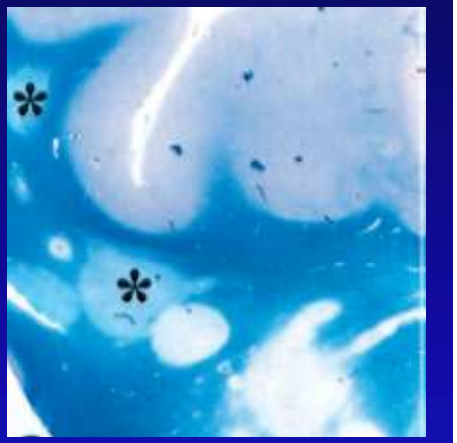
Hyperintensity on T2-WI of MS lesions is related primarily to increased water content, and thus cannot distinguish between inflammation, edema, demyelination, Wallerian degeneration, and axonal loss.

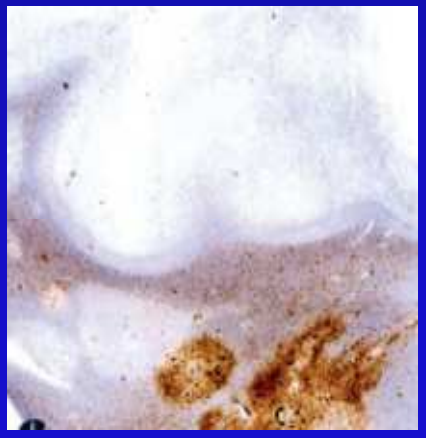
Heterogeneity of Multiple Sclerosis Lesions: Implications for the Pathogenesis of Demyelination

Claudia Lucchinetti, MD,* Wolfgang Brück, MD,† Joseph Parisi, MD,‡ Bernd Scheithauer, MD,§ Moses Rodriguez, MD,* and Hans Lassmann, MD#

Table 3. Structural and Immunological Features of Different Patterns of Active Multiple Sclerosis Lesions

Feature	Pattern I	Pattern II	Pattern III	Pattern IV
Inflammation				
Composition of Infiltrates				
CD3 T cells	197 ± 68	133 ± 18	145 ± 23	134 ± 71
Plasma cells	5.9 ± 1.9	9.3 ± 2.1	5.4 ± 1.6	3.8
Macrophages	1,158 ± 105	931 ± 71	842 ± 91	1,650 ± 30
C9neo	−	++	−	−
Demyelination				
Perivenous pattern	+	+	−	±
Lesion edge	Sharp	Sharp	Ill-defined	Sharp
Concentric pattern	0/10	0/45	8/25	0/3
Oligodendrocytes				
#OG in DM	295 ± 73	249 ± 30	51 ± 24	55 ± 55
DNA frag in OG	±	±	++APO	++PPWM
OG apoptosis	−	−	14–37%	−
Myelin protein loss	Even	Even	MAG ≫ Others	Even
Remyelination				
Shadow plaques	++	++	−	−

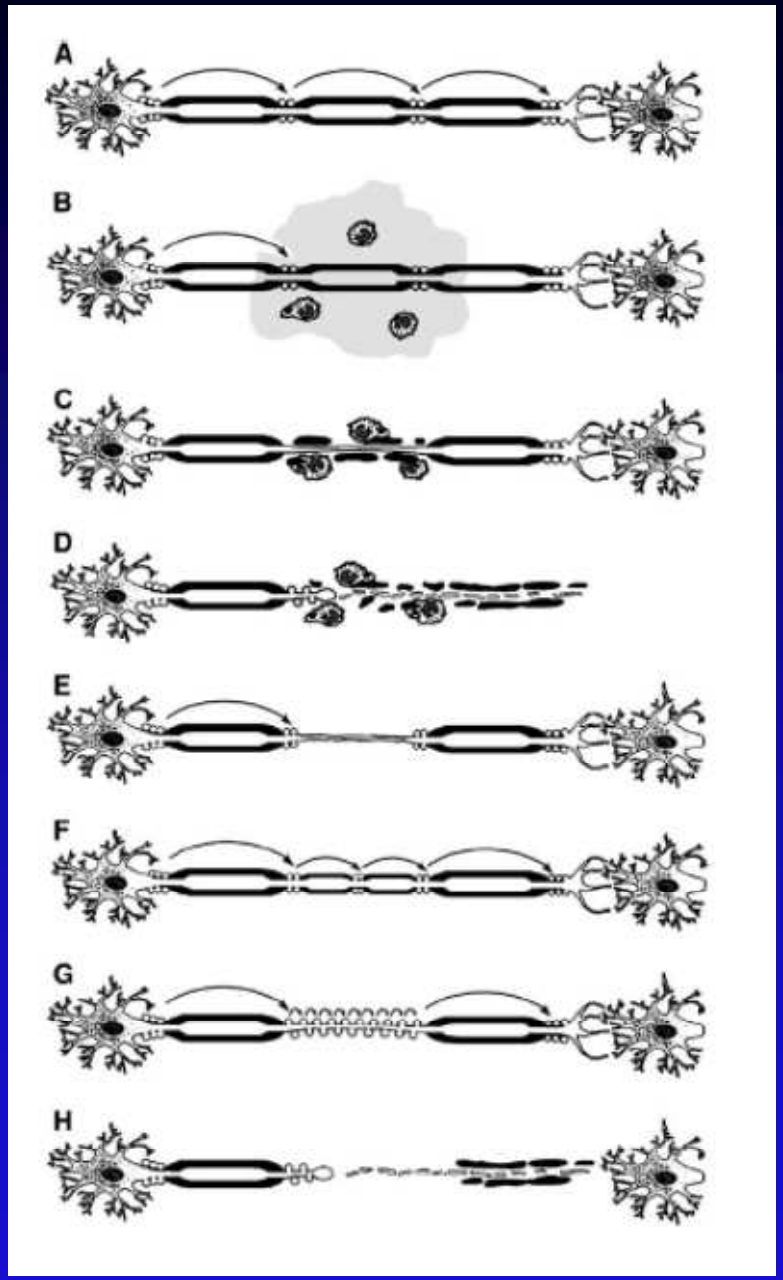




Discussion

This study demonstrates a pronounced heterogeneity in the immunopathological profiles of lesions between different MS patients.

Ann Neurol 2000;47:707–717



Conduzione saltatoria da nodo a nodo

Edema e infiammazione: blocco conduzione

Demielinizzazione

Lesione assonale in corso di infiammazione

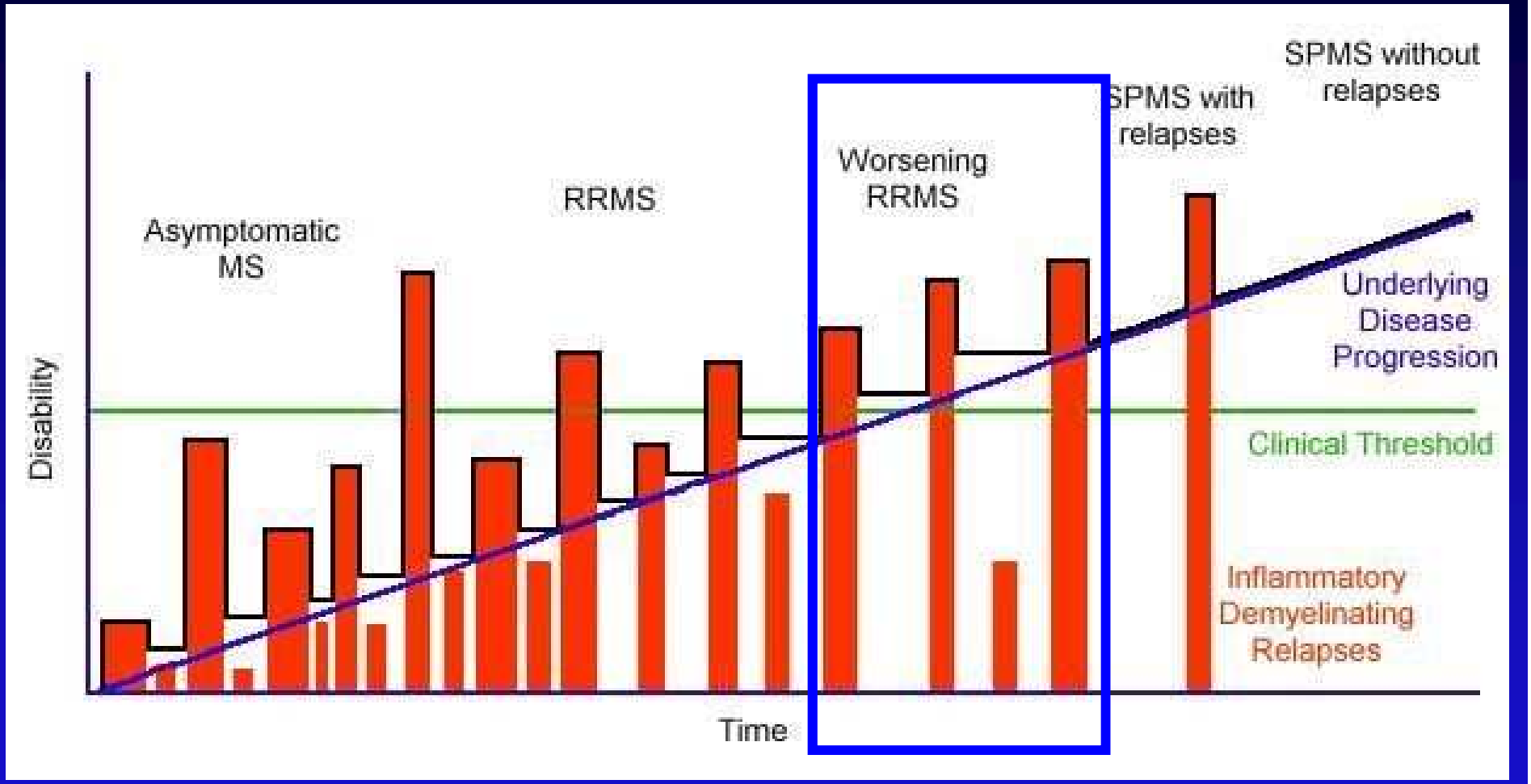
Blocco di conduzione persistente

Rimielinizzazione e riattivazione conduzione

Ridistribuzione dei canali per il sodio

Degenerazione assoni demielinizzati

Neurol Clin 23 (2005) 107–129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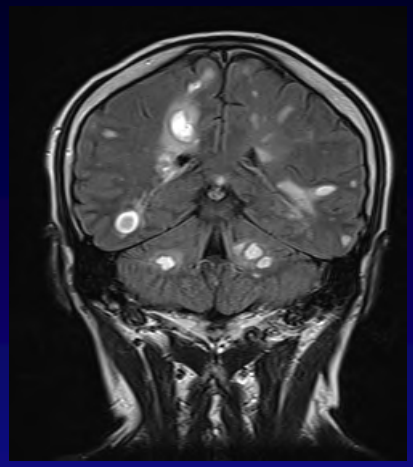


“La Sclerosi Multipla e’ una malattia caratterizzata da lesioni focali della sostanza bianca”

ma…

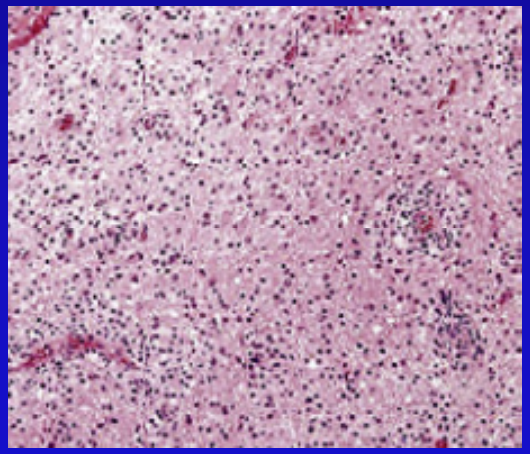
Progressive multiple sclerosis is associated with diffuse injury in the NAWM

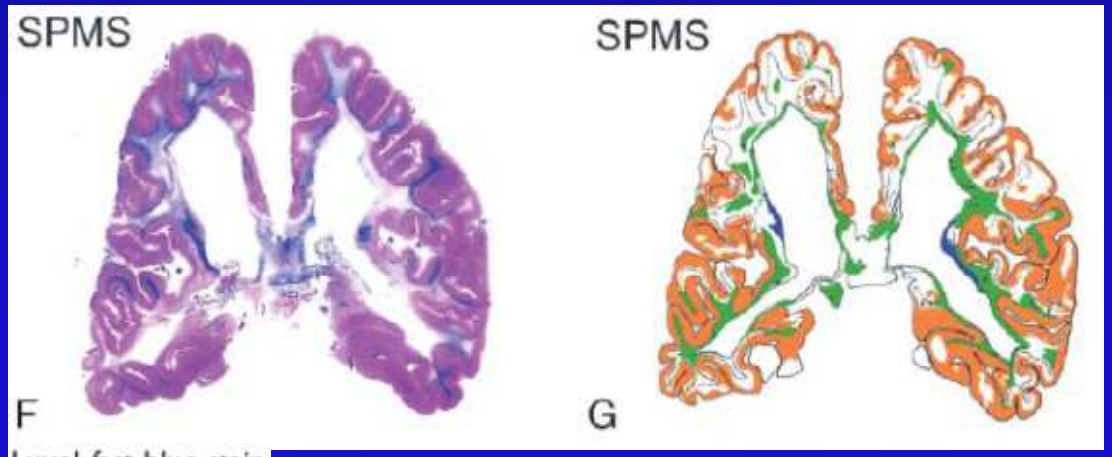
Widespread and diffuse injury was present in the NAWM in patients with SPMS and PPMS (Fig. 1). This was most clearly evident when whole hemispheric or double hemispheric sections were analysed, and consisted of a global reduction in the intensity of myelin staining due to decreased fibre density (axons and myelin), doi:10.1093/brain/awh641

Brain (2005), **128**, 2705–2712

Cortical demyelination and diffuse white matter injury in multiple sclerosis

Alexandra Kutzelnigg,[1] Claudia F. Lucchinetti,[3] Christine Stadelmann,[5] Wolfgang Brück,[5,6] Helmut Rauschka,[2] Markus Bergmann,[7] Manfred Schmidbauer,[2] Joseph E. Parisi[4] and Hans Lassmann[1]





Luxol fast blue stain

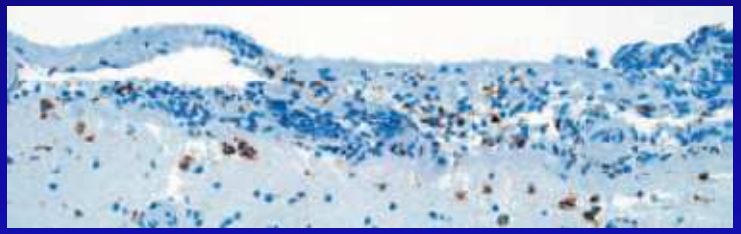
The NEW ENGLAND JOURNAL of MEDICINE

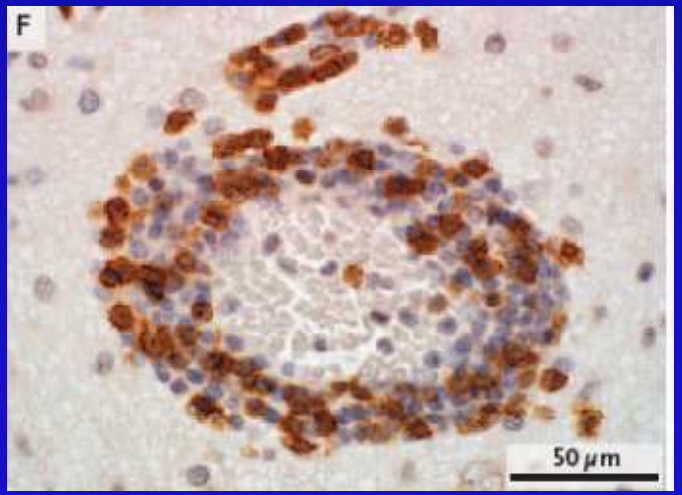
ORIGINAL ARTICLE

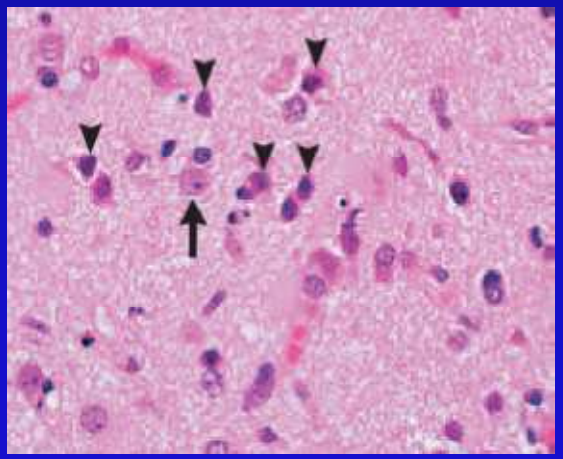
Inflammatory Cortical Demyelination in Early Multiple Sclerosis

Claudia F. Lucchinetti, M.D., Bogdan F.G. Popescu, M.D., Ph.D.,

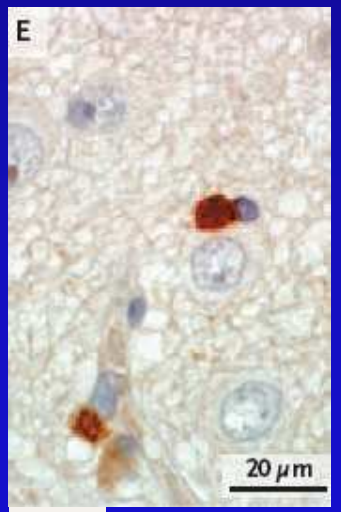
N Engl J Med 2011;365:2188-97.







neuronal injury



T cells
are close to oligodendrocytes.

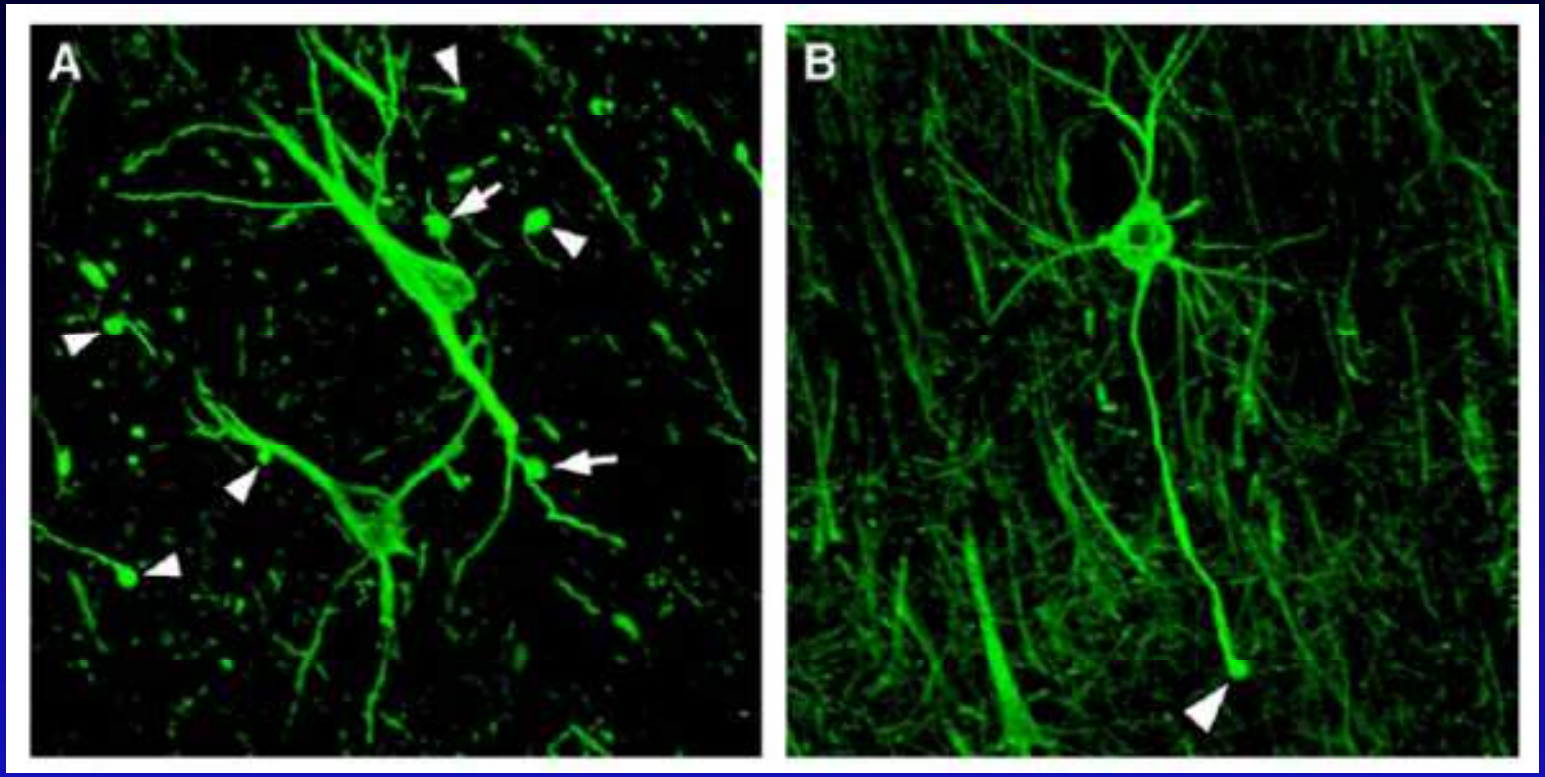


Fig. 5. Neuronal pathology in cortical lesions. (*A, B*) Nonphosphorylated neurofilament-positive ovoids are abundant in cortical lesions (green). Confocal microscopy confirmed most of these ovoids as terminal ends of neurites (*A*, *arrowheads*) and some as "en passant" swellings (*A*,

(*Adapted from* Peterson JW, Bo L, Mork S, et al. Transected neurites, apoptotic neurons and reduced inflammation in cortical multiple sclerosis lesions. Ann Neurol 2001;50:389–400; with permission.)

Cortical pathology and cognitive impairment in multiple sclerosis

Expert Rev. Neurother. 11(3), 425–432 (2011)

Massimiliano Calabrese[†1], Francesca Rinaldi[1], Paola Grossi[1] and Paolo Gallo[1]

[1]Multiple Sclerosis Centre of Veneto Region, First Neurology Clinic, Department of Neurosciences, University Hospital of Padova, Via Giustiniani 5, Padova, 35128, Italy
[†]Author for correspondence:
Tel.: +39 049 821 3615
Fax: +39 049 821 2574
calabresem@hotmail.it

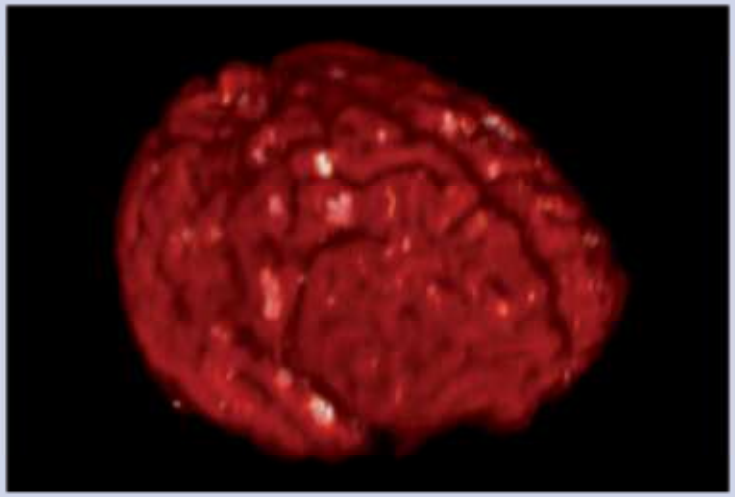


Figure 1. Cortical lesions (white spots) identified using 3D double inversion recovery imaging in a relapsing–remitting multiple sclerosis patients with cognitive impairment. A 3D reconstruction of the cortex was obtained by means of Medical Image Processing, Analysis and Visualization [101].

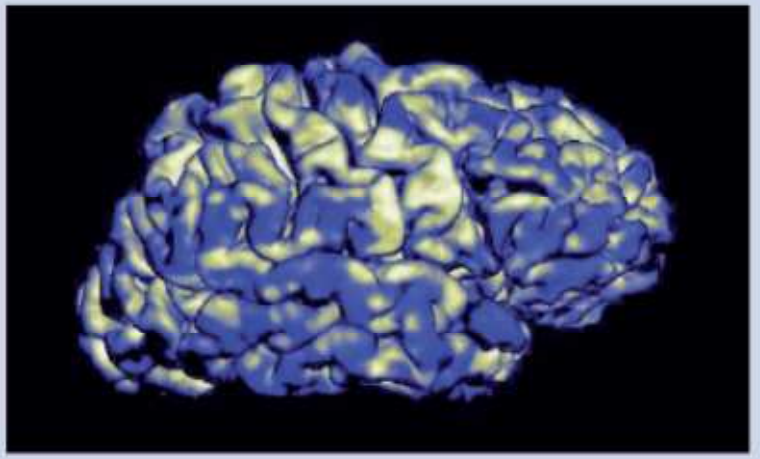


Figure 2. Lateral view of the pial surface 3D representation with cortical thickness map overlaid in a blue/light yellow color scale of a 31-year-old cognitive impaired relapsing–remitting multiple sclerosis man having 5 years of disease duration, mean CTh = 2.05 ± 0.47. Cortical areas thinner that 2.0 mm are represented in light yellow, while cortical areas thicker than 2.0 mm are in blue.

Cortical pathology and cognitive impairment in multiple sclerosis

Expert Rev. Neurother. 11(3), 425–432 (2011)

Massimiliano Calabrese[†1], Francesca Rinaldi[1], Paola Grossi[1] and Paolo Gallo[1]

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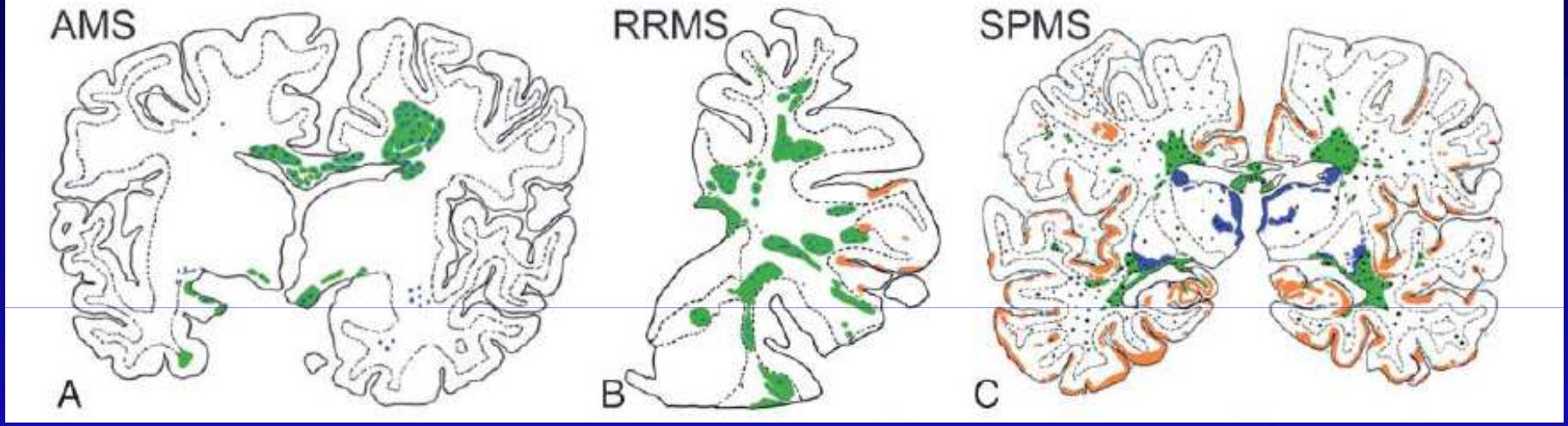
"*le lesioni corticali rappresentano probabilmente la causa principale della sofferenza cognitiva, in aggiunta alle alterazioni della sostanza bianca apparentemente normale…*"

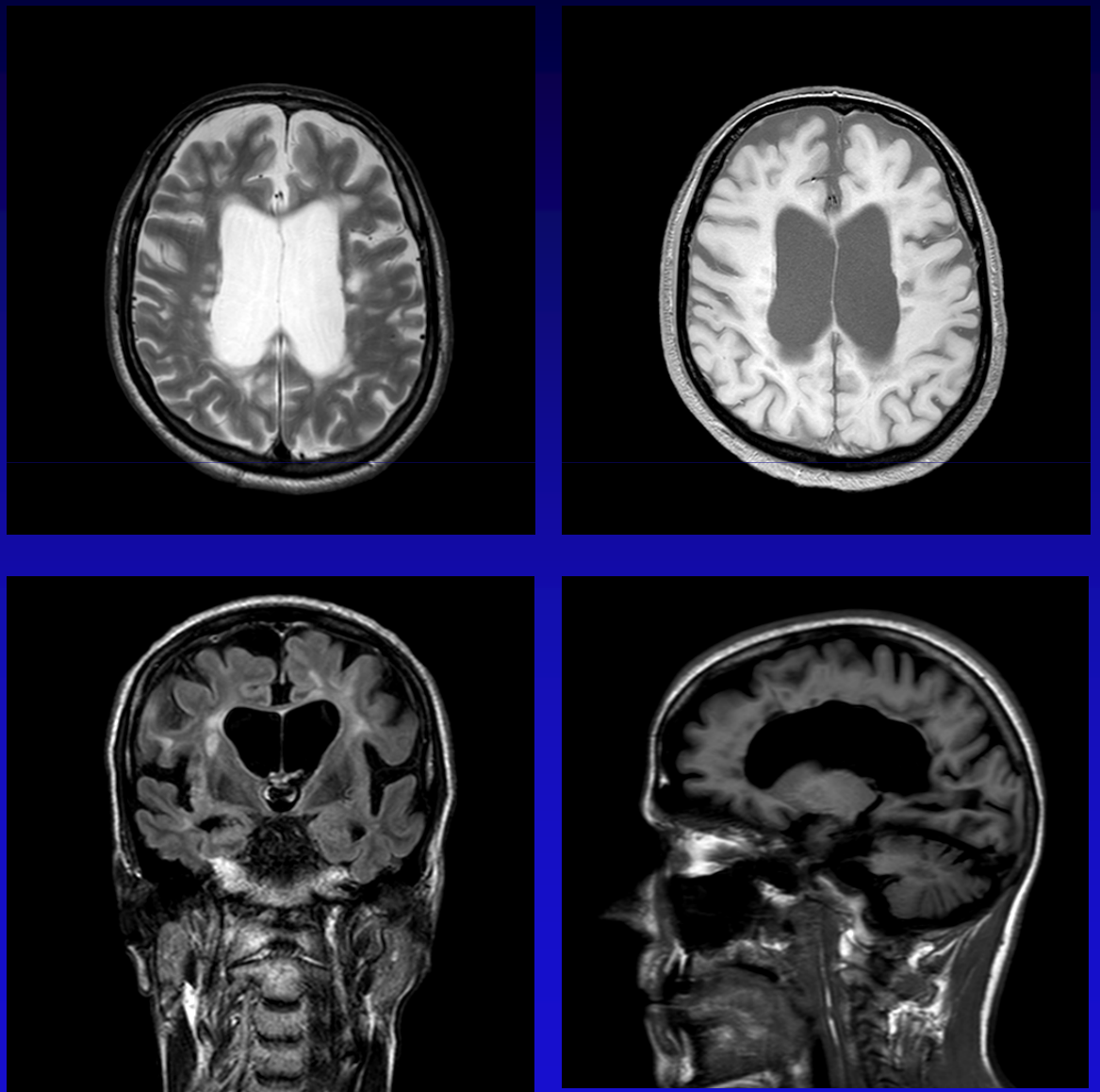
"*lesioni corticali ed atrofia corticale sono comuni già nelle prime fasi di malattia, e contribuiscono al precoce fallimento dei meccanismi compensatori corticali…*"



Durata malattia:

45 giorni 3 anni 16 anni

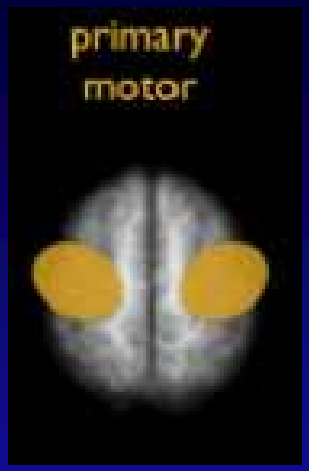
Paziente FD, 50 anni, 25 anni di malattia

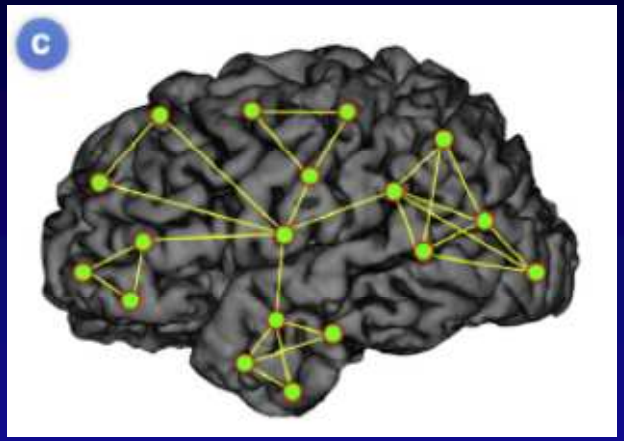


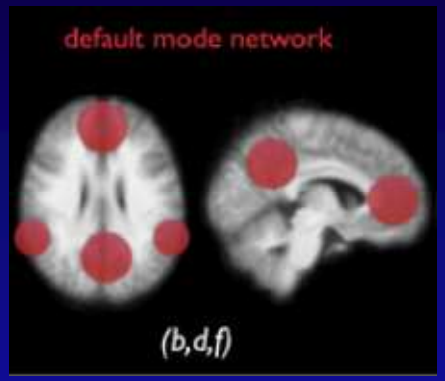
REVIEW

Exploring the brain network:

Functional connectivity







Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis

Increased functional connectivity indicates the severity of cognitive impairment in multiple sclerosis

David J. Hawellek[a,1], Joerg F. Hipp[a,b], Christopher M. Lewis[c,d,e], Maurizio Corbetta[d,e,f], and Andreas K. Engel[a]

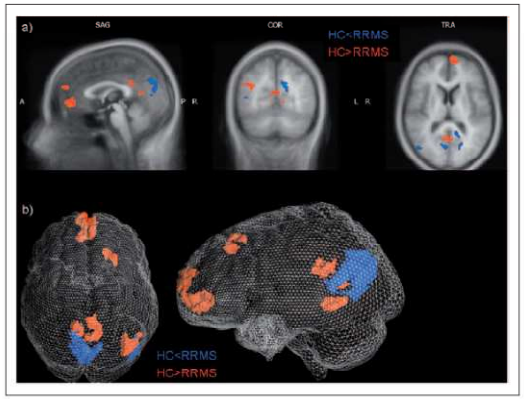


Figure 2. Statistical comparison between patient groups.
Two-group statistical comparison between the entire group of RRMS patients and HCs. The clusters of significant activity are displayed as statistical maps overlaid on three orthogonal slices of the averaged normalized anatomy (a), as well as through reconstruction as 3D volumes (b). HCs: healthy controls, RRMS, relapsing–remitting multiple sclerosis.

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
17(4) 411–422

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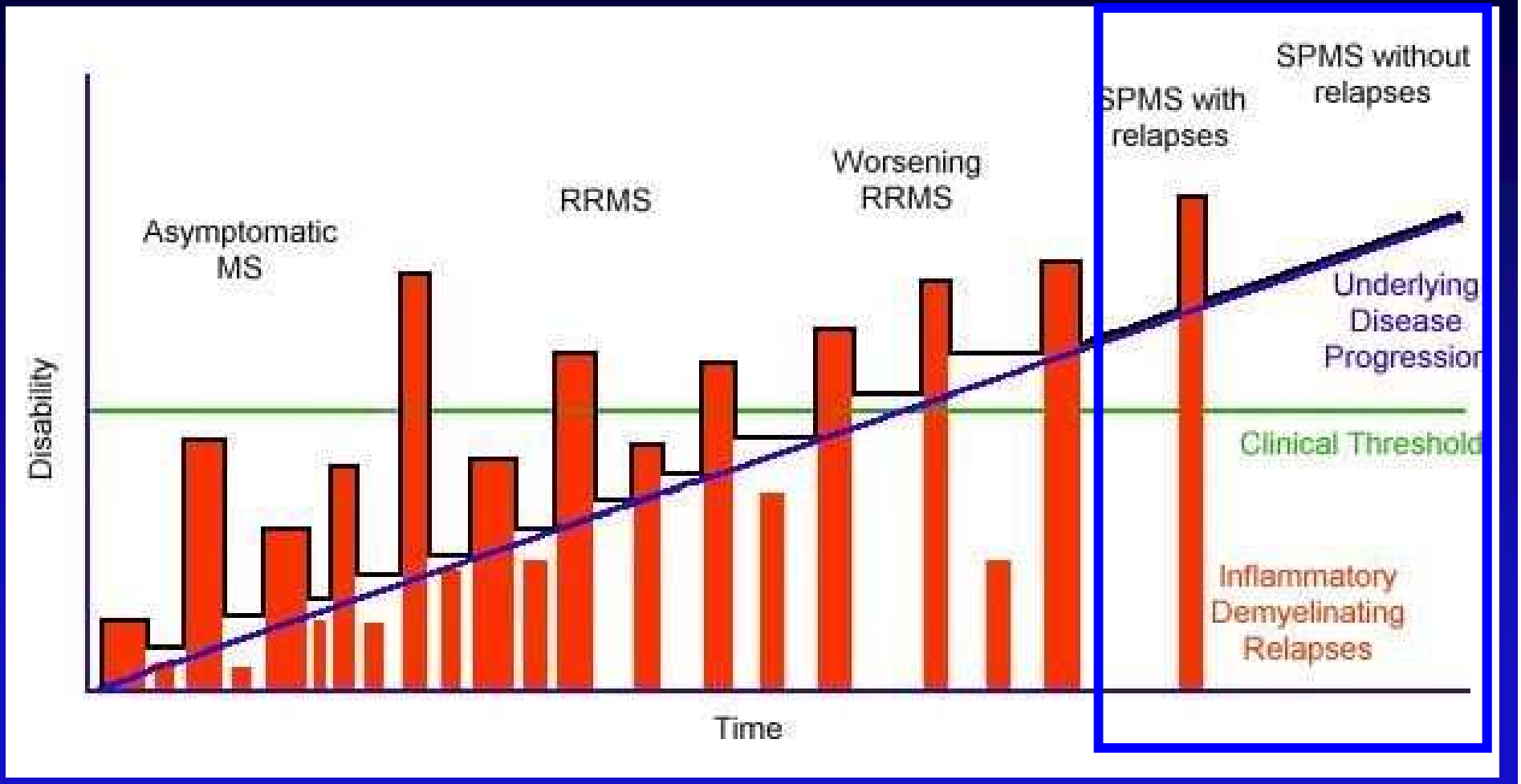
Distributed changes in default-mode resting-state connectivity in multiple sclerosis

Simona Bonavita[1,2,*], Antonio Gallo[1,2], Rosaria Sacco[1], Marida Della Corte[1], Alvino Bisecco[1], Renato Docimo[1], Luigi Lavorgna[1], Daniele Corbo[1], Alfonso Di Costanzo[6], Fabio Tortora[1], Mario Cirillo[1], Fabrizio Esposito[2,4,5] and Gioacchino Tedeschi[1,2,3]


SPMS without relapses
SPMS with relapses
Worsening RRMS
RRMS
Asymptomatic MS
Underlying Disease Progression
Clinical Threshold
Inflammatory Demyelinating Relapses
Disability
Time

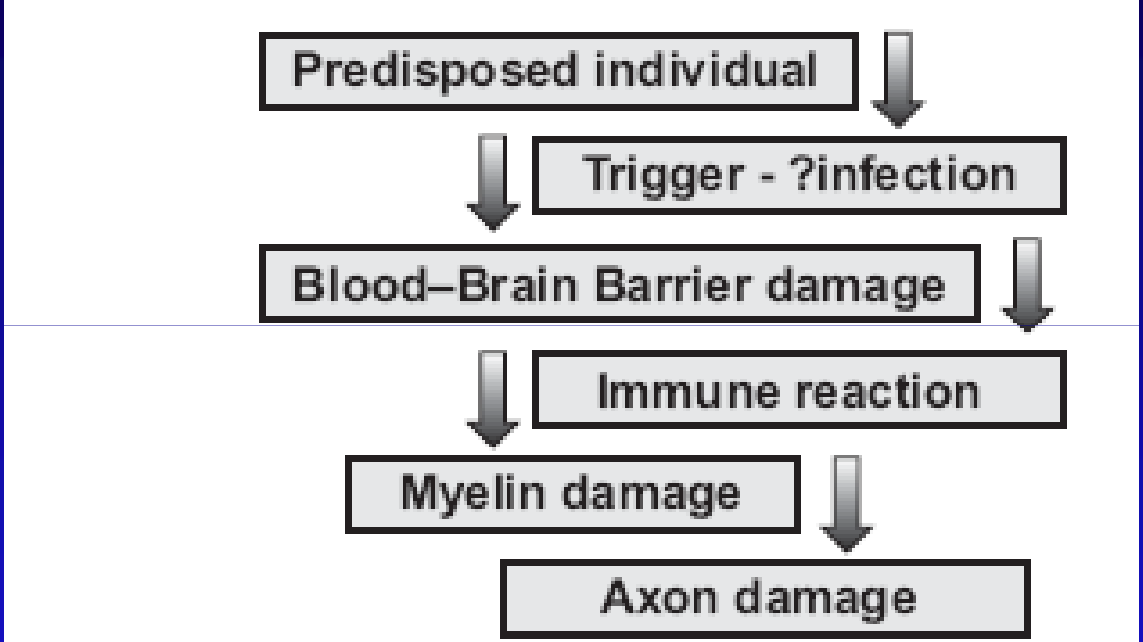


Fig. 2 – Current picture of the disease process in multiple sclerosis.

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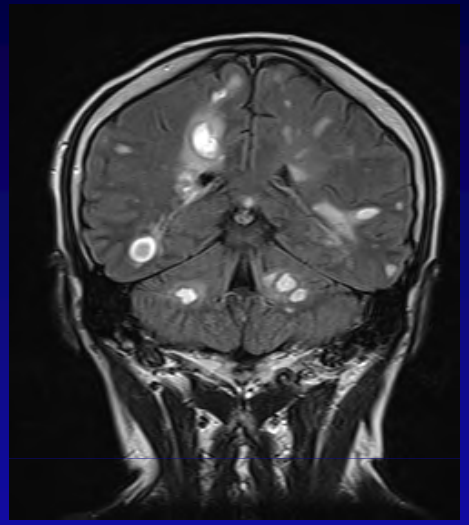
SM, cosa abbiamo visto:



- Infiammazione della sostanza bianca
- demielinizzazione
- danno assonale
- eterogeneità fisiopatologica fra i pazienti e nel singolo paziente
- coinvolgimento sostanza bianca apparentemente normale
- coinvolgimento corticale
- alterazioni della connettività nei network funzionali