Neuropathology in MS

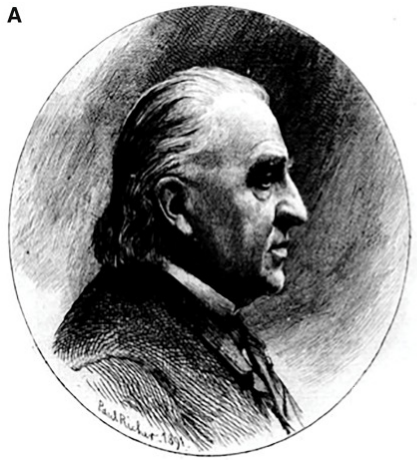
Oranuch Chuapakdee, MD

Historical Perspective

- Scle´rose en Plaques
- First Description by, Jean-Martin Charcot (1825–93)
  - The name "multiple sclerosis" is short for

  multiple cerebrospinal sclerosis, due to numerous glial scars (or sclerae – essentially plaques or lesions) that develop on the white matter of the brain and spinal cord".
- Definition of MS
  - Inflammatory demyelinating disease of CNS, affected myelin, neuron, oligodendrocyte and axon

A

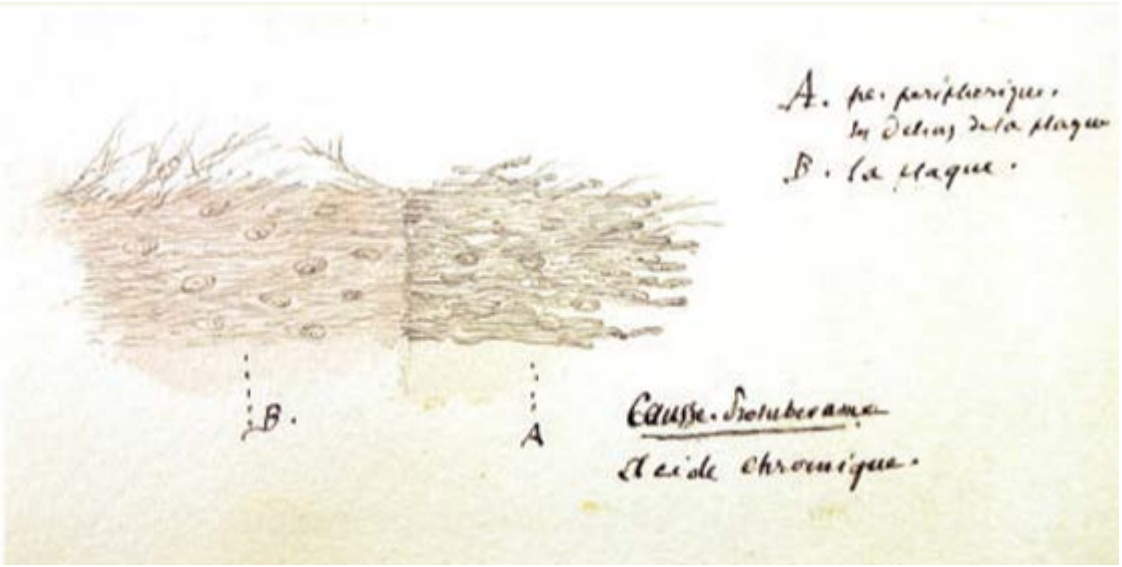


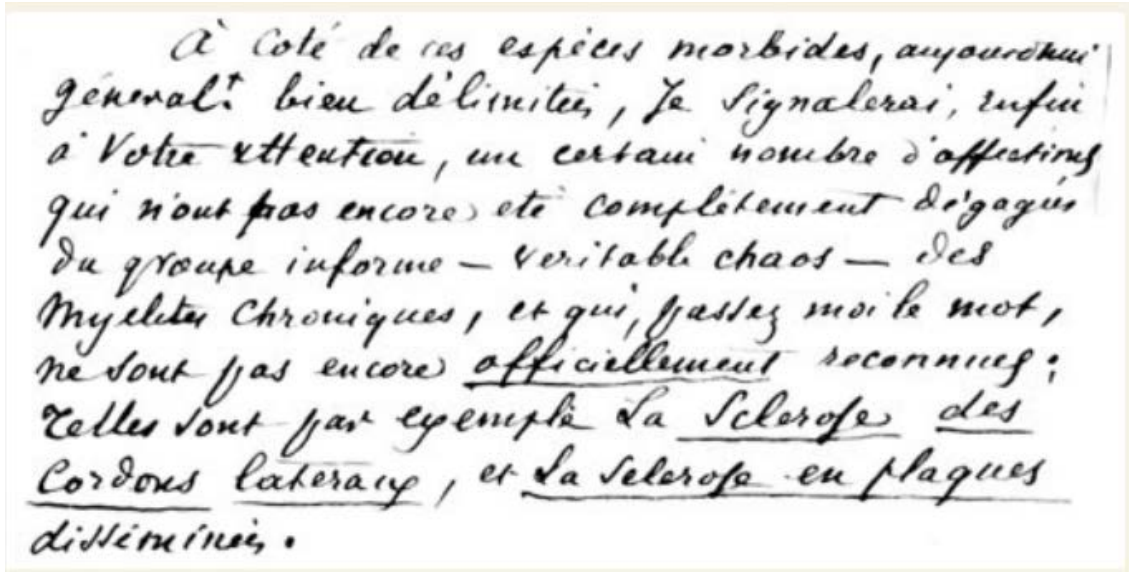
B

C

Zalc B. One hundred and fifty years ago Charcot reported multiple sclerosis as a new neurological disease. Brain. 2018;141(12):3482-8.

Historical Perspective



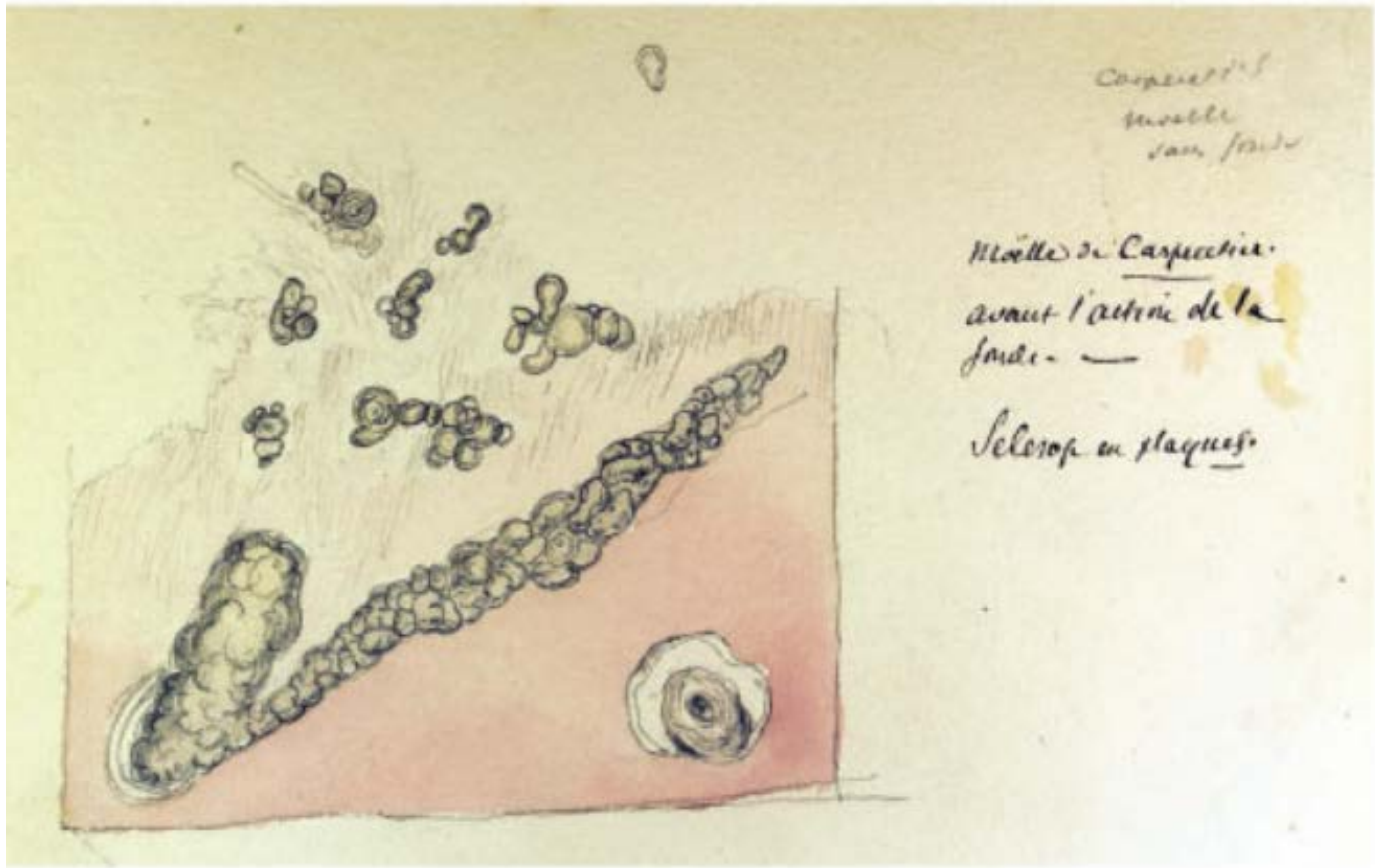


- A. periphery outside the plaque
- B. the plaque
- Bottom: Causse[patient'sname], Protuberance

'Beside these morbid symptoms usually well defined, I will, finally, point your attention to a certain number of diseases, which have not yet been completely cleared from the shapeless group – real chaos- of chronic myelitis, and which, pardon me the word, are not yet officially recognized; such are for example the sclerosis of lateral bundles and multiple sclerosis.

Zalc B. One hundred and fifty years ago Charcot reported multiple sclerosis as a new neurological disease. Brain. 2018;141(12):3482-8.

Historical Perspective

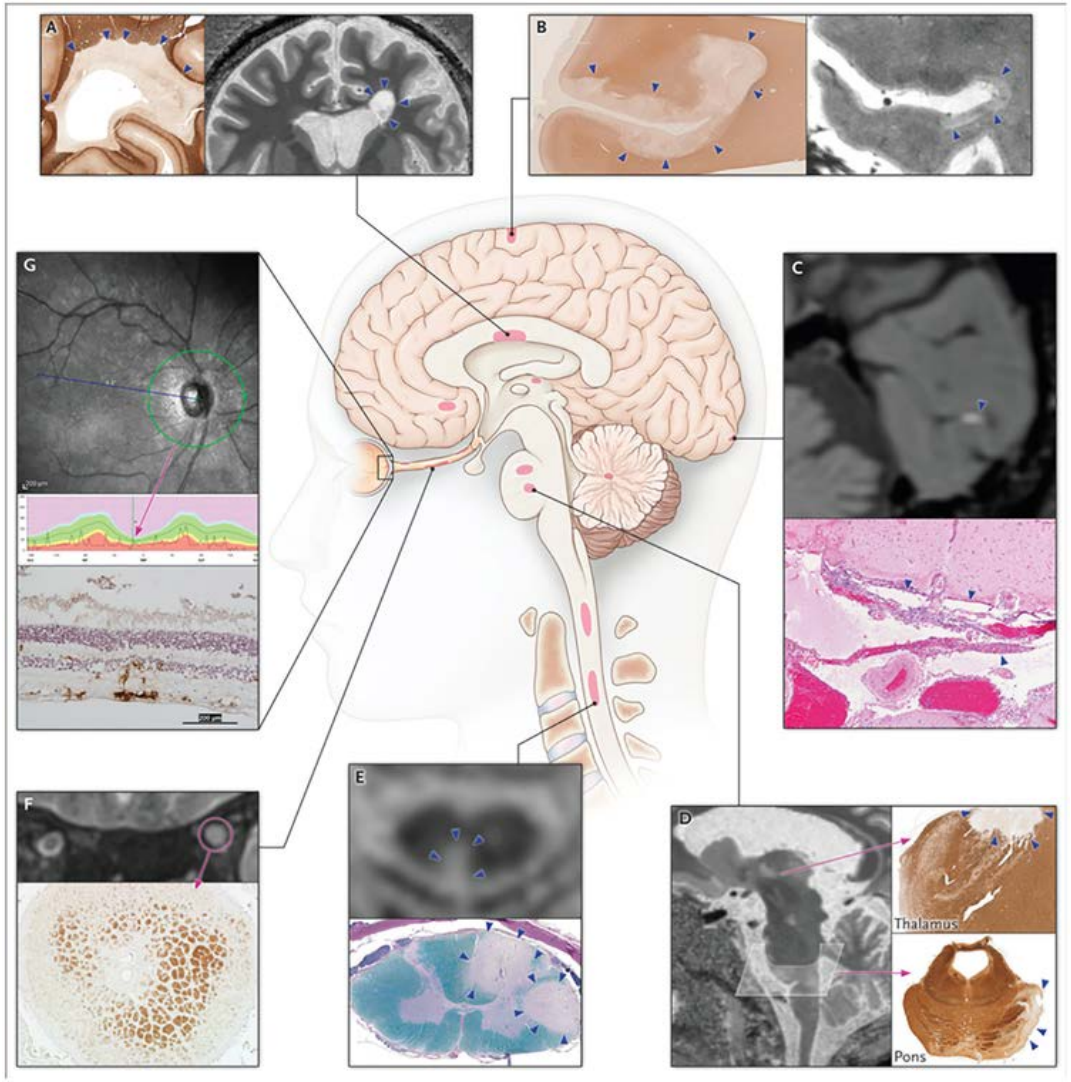


- The demyelinated axons and the rare faction of axons (due to axonal degeneration)
- The presence of myelin debris (greasy droplets)

Zalc B. One hundred and fifty years ago Charcot reported multiple sclerosis as a new neurological disease. Brain. 2018;141(12):3482-8.

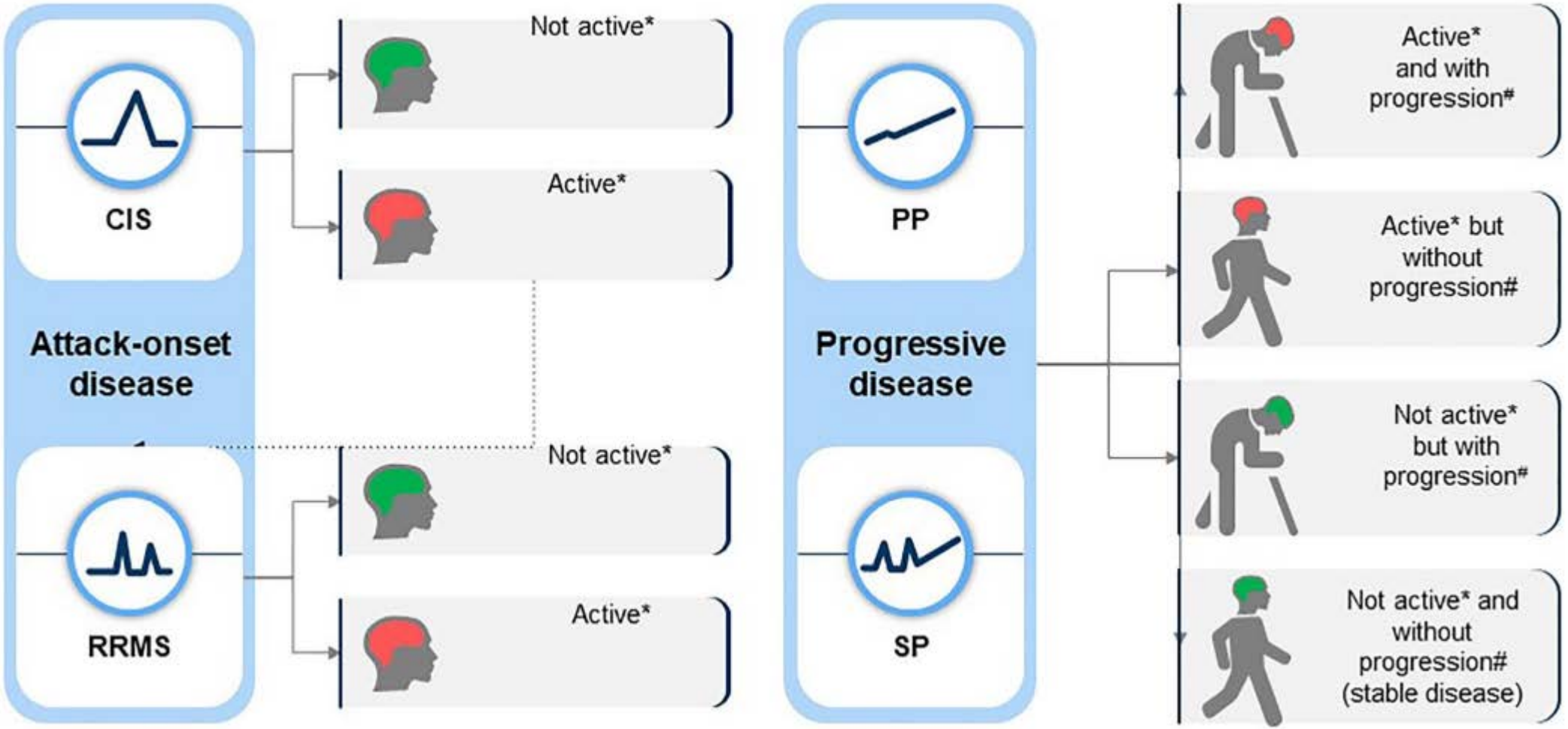
Topography of MS

- Predilection site
  - Optic nerve, periventricular WM, subpial cortical area, spinal cord, brainstem- MCP, cerebellum
- MS not involve only white matter lesion, also meninges, cortical and deep gray matter e.g. thalamus and pons
- Pathological hallmark
  - Sharply demarcated focal lesions
  - Primary demyelination
  - Variable axonal loss
  - Reactive gliosis in white and grey matter



Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. New England Journal of Medicine. 2018;378(2):169-80.

Lublin 2013 multiple sclerosis phenotype

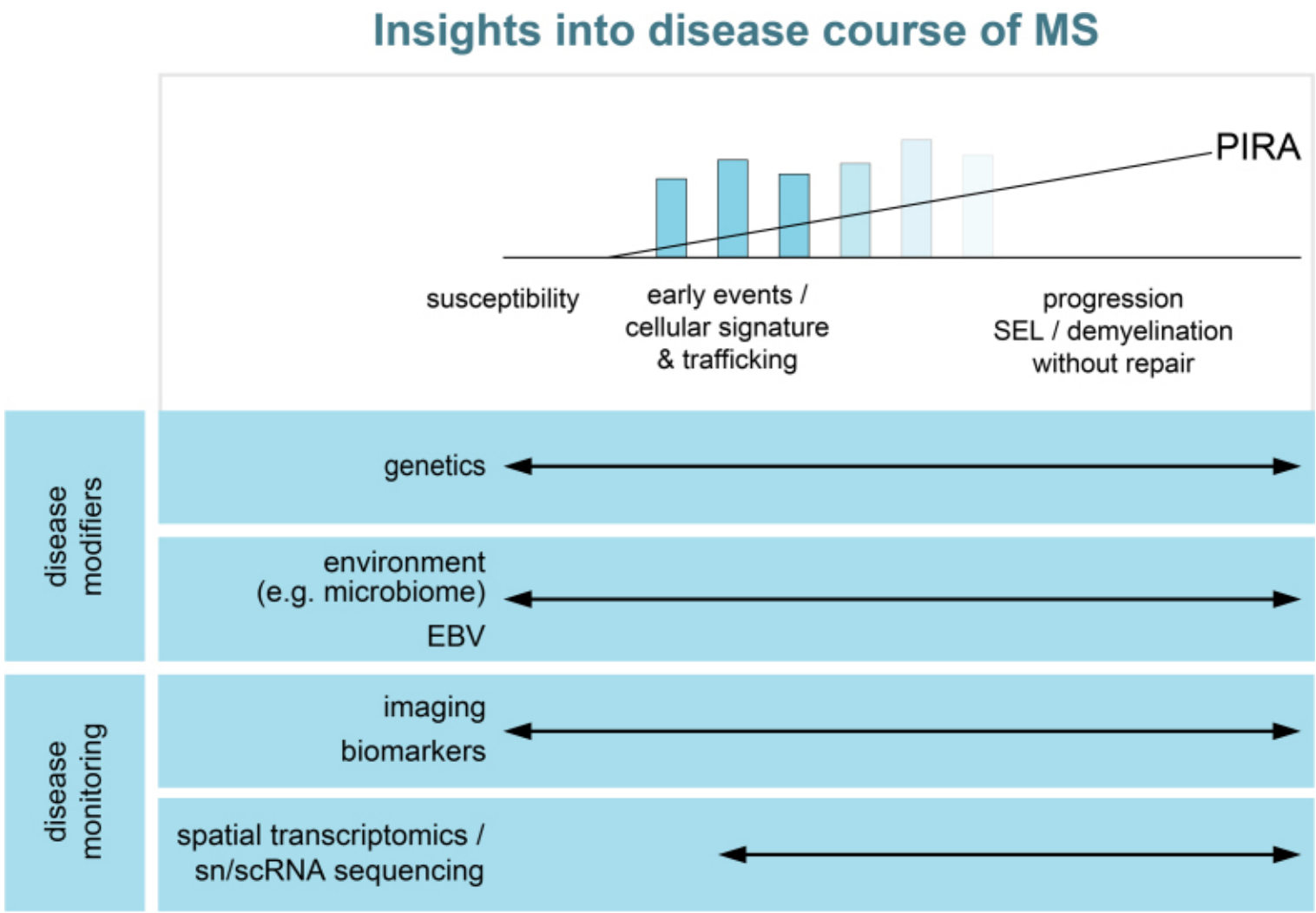


Lublin 2013 multiple sclerosis defintion

Term	Definition	Recommended time frame for evaluation
Active disease	Clinical: relapses, acute or subacute episodes of new or increasing neurologic dysfunction, followed by full or partial recovery, in the absence of fever or infection	Annually (but can be another time frame, as long as it is specified)
	and/or	
	Imaging: gadolinium-enhancing lesions or new or unequivocally enlarging T2 lesions	Annually (but can be another time frame, as long as it is specified)
Progressing disease or disease progression	Accrual of disability, independent of any relapse activity, during the progressive phase of MS (PPMS or SPMS)	Annually by clinical assessment (but can be another time frame, as long as it is specified)
Worsening disease	Any increase in impairment/disability irrespective of whether it has resulted from residual deficits following a relapse or (increasing) progressive disability during the progressive phase of the illness	Not required

LublinFD,ReingoldSC,CohenJA, et al.Definingtheclinical courseofmultiple sclerosis: the2013revisions.Neurology2014;83:278–286

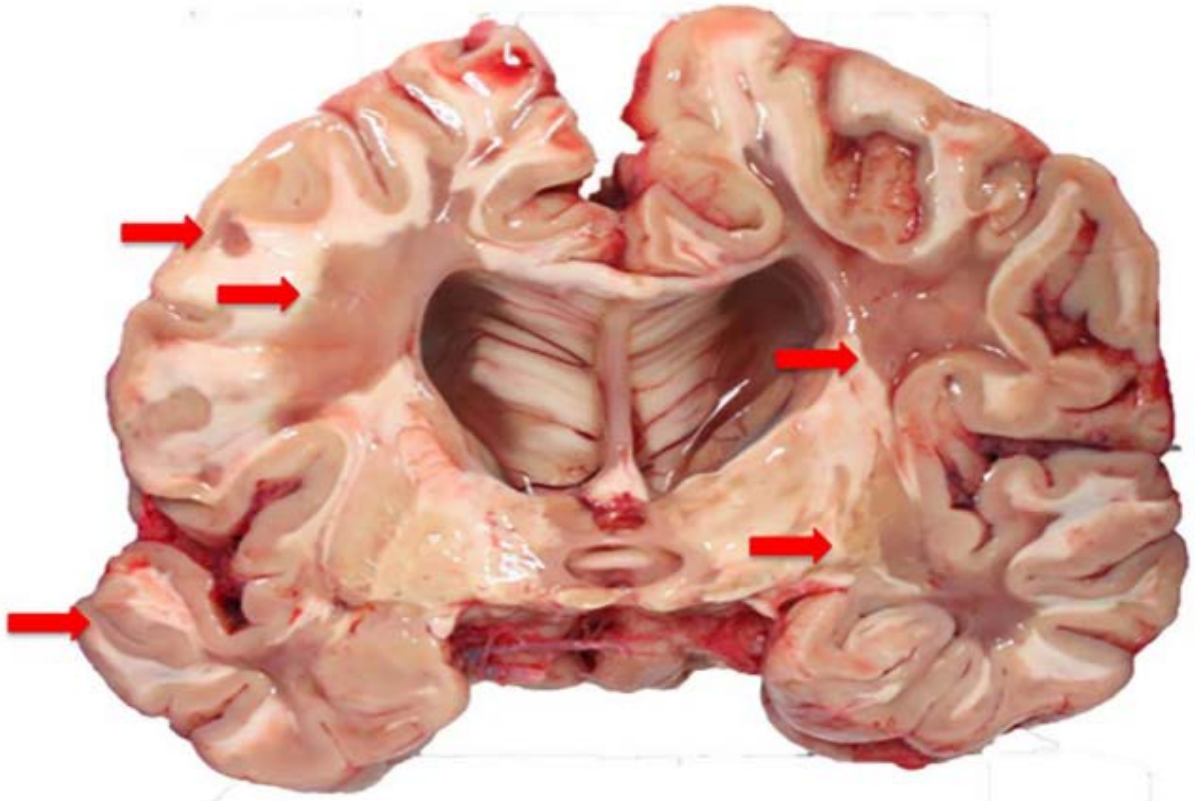
MS Progression



- Potential mechanisms driving disease progression include
- Persistent focal inflammation resulting in slowly expanding lesions
- Meningeal inflammation causing cortical demyelination and neuronal injury
- Inflammation induced diffuse changes in white matter (WM)
- Compensatory mechanism, such as remyelination and brain plasticity

Kuhlmann T, Antel J. Multiple sclerosis: 2023 update. *Free Neuropathol*. 2023;4:4-3

MS Plaque – Gross Pathology



- Plaques in MS evolve asynchronously, show different stages of inflammation and heterogeneity of tissue response
- Axons are often swollen in active plaques and some (typically a smaller proportion) are transected
- Hallmarks of white matter MS plaques
  - Myelin loss
  - A sharp margin
  - Veins at the centers of lesions
  - The presence of lymphocytes, microglia, myelin-laden macrophages and reactive astrocytes
  - Disruption of vessel walls.

Matthews PM, et al. Pract Neurol 2016;16:279–287

1994 -Staging of MS white matter lesions

ELSEVIER

Journal of Neuroimmunology 51 (1994) 135–146

Journal of Neuroimmunology

Detection of MHC class II-antigens on macrophages and microglia, but not on astrocytes and endothelia in active multiple sclerosis lesions

Lars Bö [1,a], Sverre Mörk [b], Pei Ann Kong [a], Harald Nyland [c], Carlos A. Pardo [d], Bruce D. Trapp *,[a]

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[d] *Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA*

(Received 22 September 1993; revision received and accepted 21 January 1994)

- 1. Active – hypercellular
- 2. Chronic active – hypocellular center with hypercellular rim
- 3. Chronic inactive - hypocellular

1996 – Classification of demyelinating activity

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CLASSIFICATION OF DEMYELINATING ACTIVITY IN MS LESIONS ON THE BASIS OF MYELIN DEGRADATION PRODUCTS AND MACROPHAGE ACTIVATION

Stage	MOG	PLP	LFB	PAS	Vacuoles	Macrophage marker	Remyel
Early active	+++	++	++	-	-	MRP14	-
Late active	+	+++	++	-	-	27E10	-
Inactive	-	-	-	+/-	+/-	-	-
Early remyel	-	+/-	+/-	+	+	-	++
Late remyel	-	-	-	+/-	+/-	-	+++

Table 2. Staging is based on the presence of immunocytochemical or histochemical reactivity of macrophage degradation products and macrophage activation antigens in the lesions. MOG: Myelin oligodendrocyte glycoprotein; PLP: Proteolipid protein; LFB: Luxol fast blue; PAS: periodic acid Schiff reaction; Vacuoles: empty vacuoles (neutral lipids).

Brain Pathology 6: 259-274 (1996)

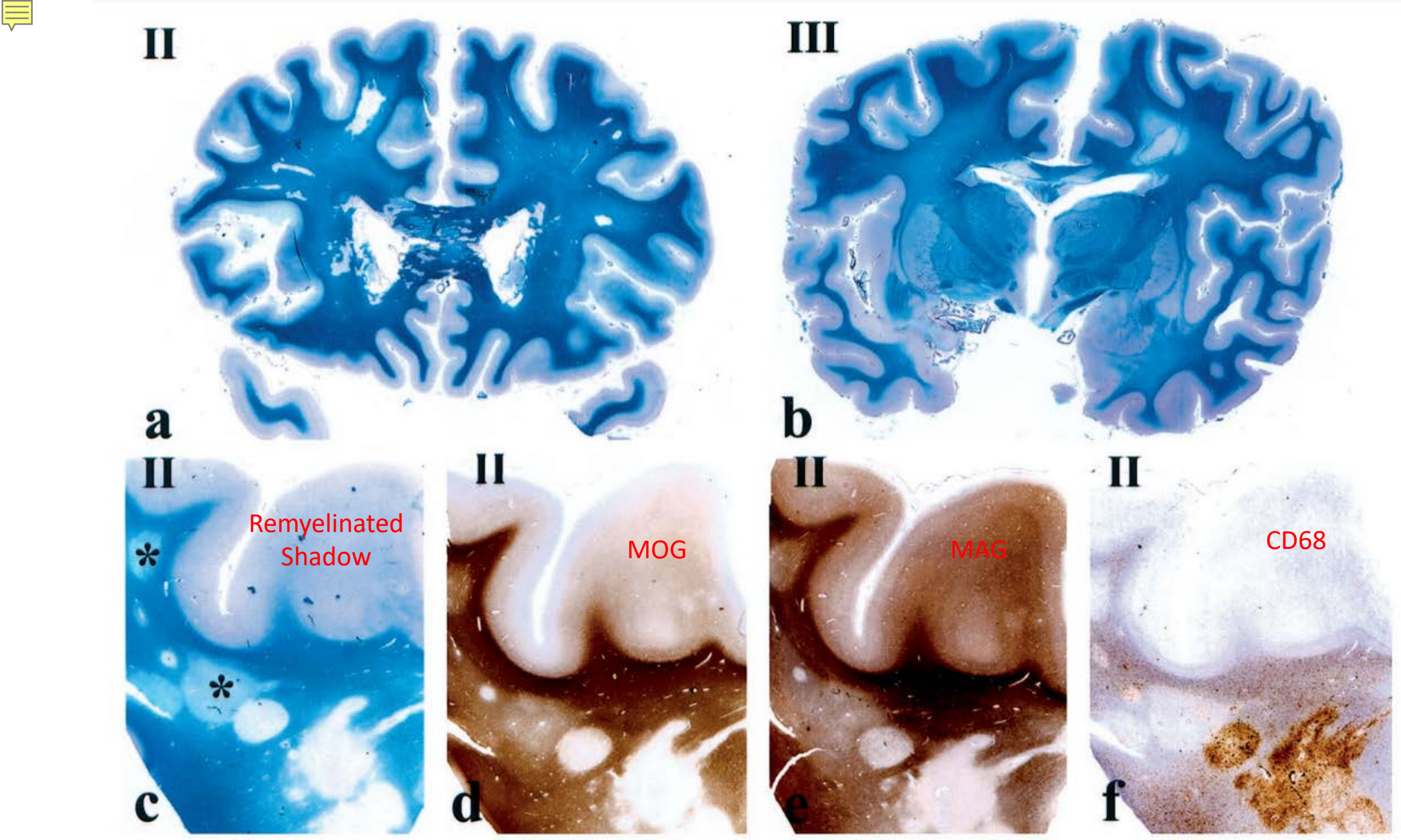
2000 - Staging of MS white matter lesions

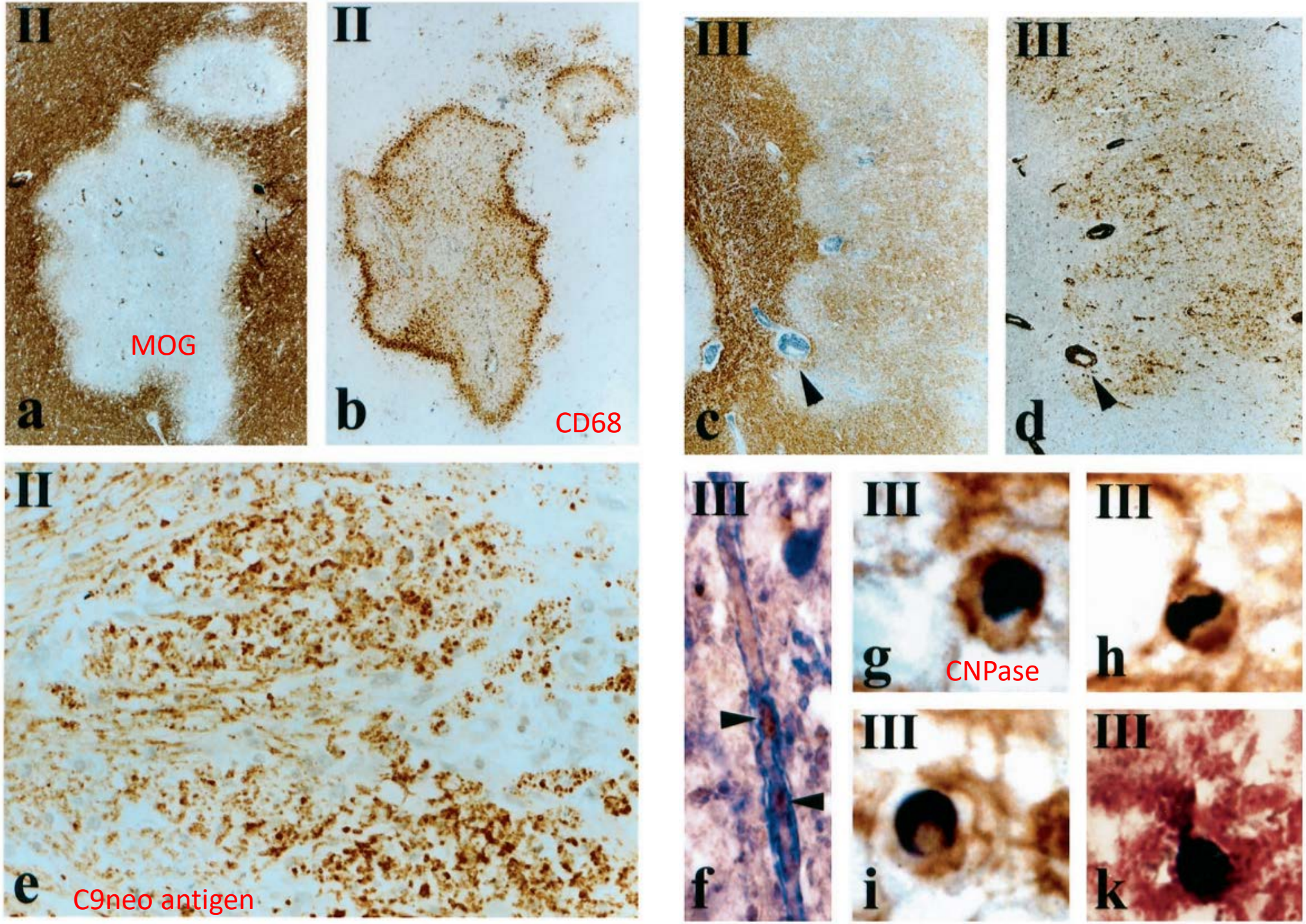
Table 2. Antibodies Used for Immunocytochemistry

Antigen	Antibody Type	Target	Source
CD3	mAb	T cells	Dako, Glostrup, Denmark
L-26	mAb	B cells	
human IgG	mAb	B cells, plasma cells	
KiM1P	mAb	Monocytes, microglia	Radzun et al[42]
CD68	mAb	Macrophages	Dako, Glostrup, Denmark
27E10	mAb	Activated macrophages	BMA Biomedicals, Augst, Switzerland
MRP 14	mAb	Activated macrophages	
C9neo	mAb	Activated terminal compl	Storch et al[15]
C9neo	polyAb	Activated terminal compl	
MBP	mAb	Myelin	Boehringer, Mannheim, Germany
GFAP	mAB	Astrocytes	
PLP	mAb	Myelin	Serotec, Oxford, UK
MAG B11F7	mAb	Myelin	Doberson et al[43]
MAG D7E10	mAb	Myelin	
MAG	polyAb	Myelin	Matthieu et al[44]
MOG 8-18C5	mAb	Myelin/oligodendrocytes	Piddlesden et al[45]
MOG Y10	mAb	Myelin/oligodendrocytes	
MOG Z12	mAb	Myelin/oligodendrocytes	
CNPase	mAB	Myelin/oligodendrocytes	Affinity Res Prod, UK

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	++	++	−	−

Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol. 2000;47(6):707-17.


II
III
a
b
II
Remyelinated
Shadow
*
*
c
II
MOG
d
II
MAG
e
II
CD68
f



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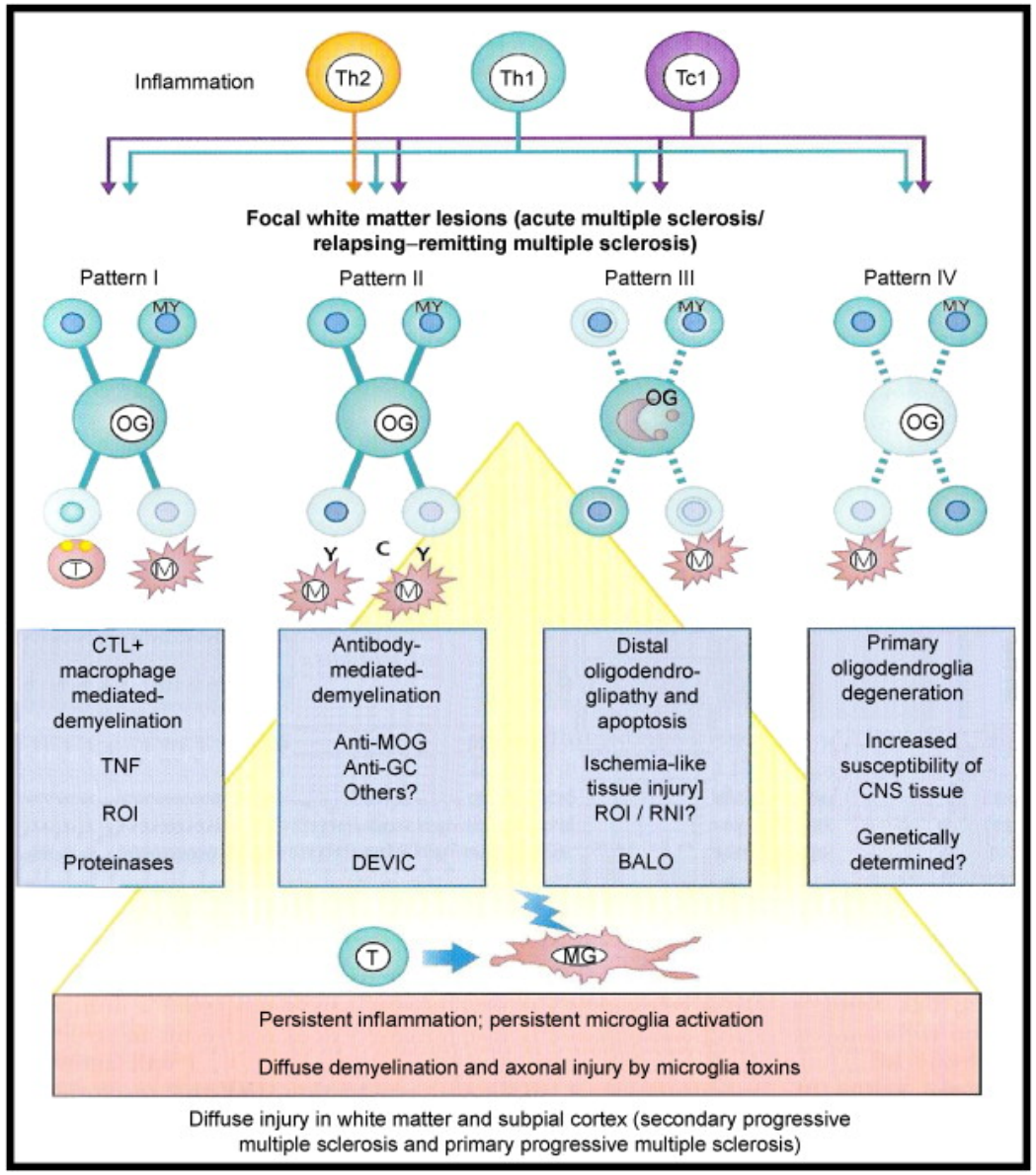


- Pattern I — T cell/macrophage → TNF-alpha, NO mediate demyelination
  Pattern II— antibodies → complement activation mediated demyelination
- Pattern III— distal oligodendrogliopathy (dying back) → loss of MAG and CNPase due to metabolic and hypoxia, apoptosis
- Pattern IV— Primary oligodendroglia degeneration (PPMS – 1%)

CurrentDiagnosticPathology(2007)13,193–202

Pattern I	• Present in approximately 15% of patients with MS • Characterized by sharp demarcated perivascular lesions, active demyelination, lack of immunoglobulin deposition, and lack of complement activation on a T lymphocyte • Damage to myelin may be caused by toxic factors produced by macrophages.
Pattern II	• Present in approximately 58% of patients with MS • Characterized by sharp demarcated edges, active demyelination with equal loss of myelin components, loss of oligodendrocytes at the active border • Demyelination triggered via direct damage on the myelin sheaths/antibody and other mediated mechanisms
Pattern III	• Present in approximately 26% of patients with MS • Characterized by poorly defined lesions, demyelination with oligodendrocyte apoptosis • Oligodendrocyte apoptosis may be driven by other metabolic process (ie, mitochondrial dysfunction)
Pattern IV	• Present in just 1% of patients • Characterized by significant nonapoptotic death of oligodendrocytes in periplaque WM, infiltrating T cells, activated microglia/macrophages

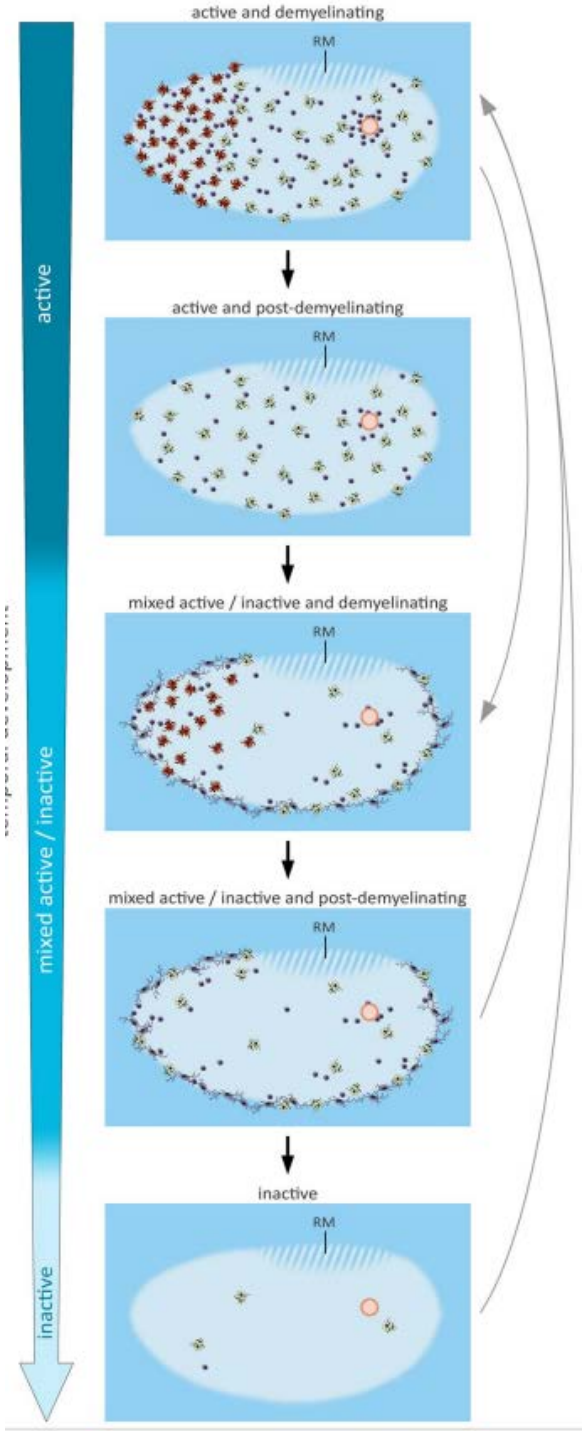
Popescu BF, Pirko I, Lucchinetti CF. Pathology of multiple sclerosis: where do we stand? *Continuum (Minneap Minn)*. 2013;19(4 Multiple Sclerosis):901-921
Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol. 2000;47(6):707-17.

2017 – Histological Classification

An updated histological classification system for multiple sclerosis lesions

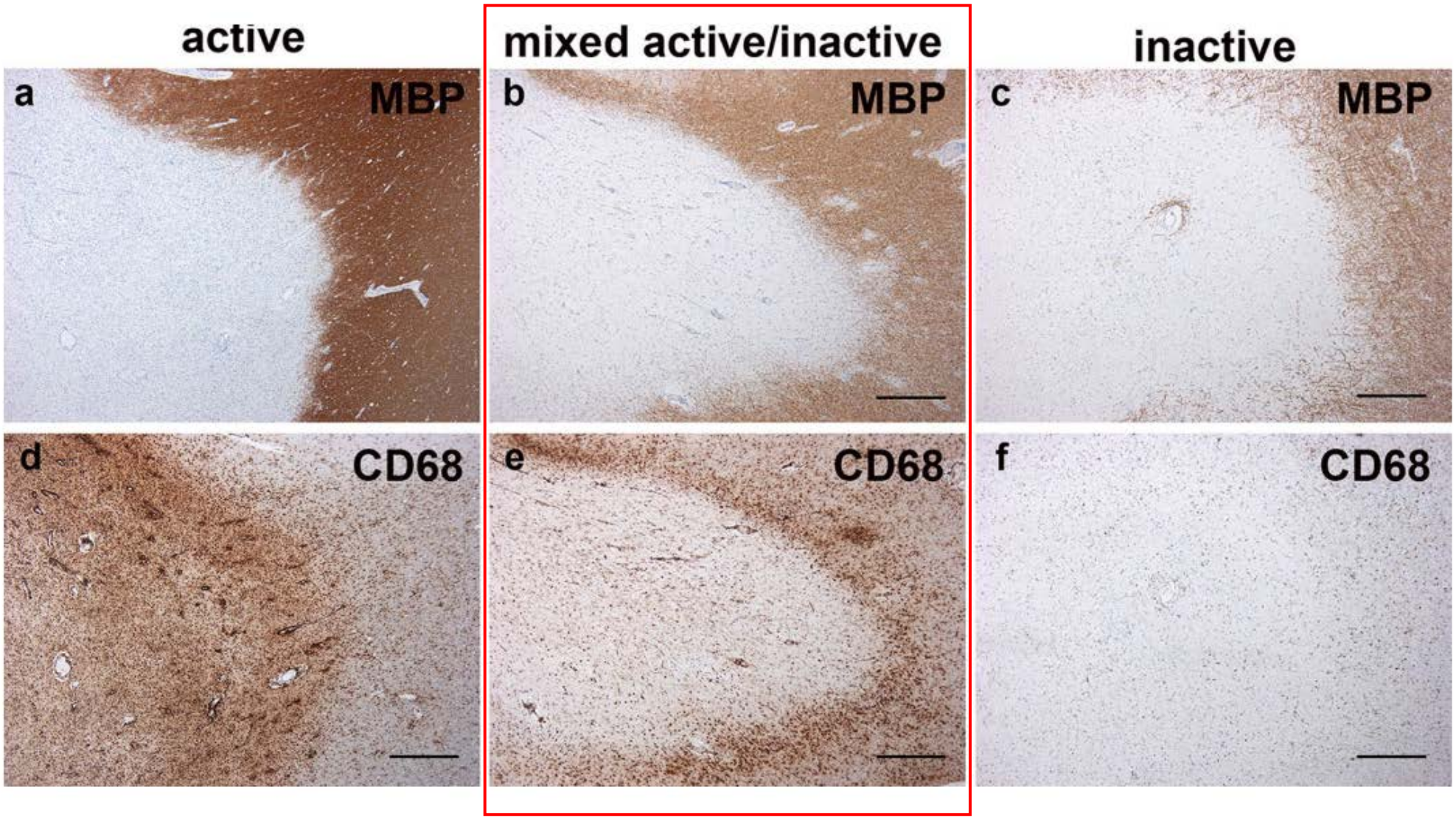
Tanja Kuhlmann[1] · Samuel Ludwin[2,4] · Alexandre Prat[3] · Jack Antel[4] · Wolfgang Brück[5] · Hans Lassmann[6]

- Active and early demyelinating: Microglia/Macrophages throughout containing myelin degradation products (MOG+/MBP+/PLP+..)
- Active and Late demyelinating: Microglia/Macrophages containing myelin degradation products (MOG+/MBP+/PLP+..)
- Active and post demyelinating: Foamy lipid laden Microglia/Macrophages lacking myelin products
- Mixed active/inactive and demyelinating: Microglia/Macrophages rim with hypocellular center and Microglia/Macrophages with myelin products
- Mixed active/inactive and post demyelinating: Microglia/Macrophages devoid of myelin products
- Inactive: sharply demarcated hypocellular lesion with sparse Microglia/Macrophages



Kuhlmann T, Ludwin S, Prat A, Antel J, Brück W, Lassmann H. An updated histological classification system for multiple sclerosis lesions. Acta Neuropathol. 2017;133(1):13-24.

MS lesions with different disease activities



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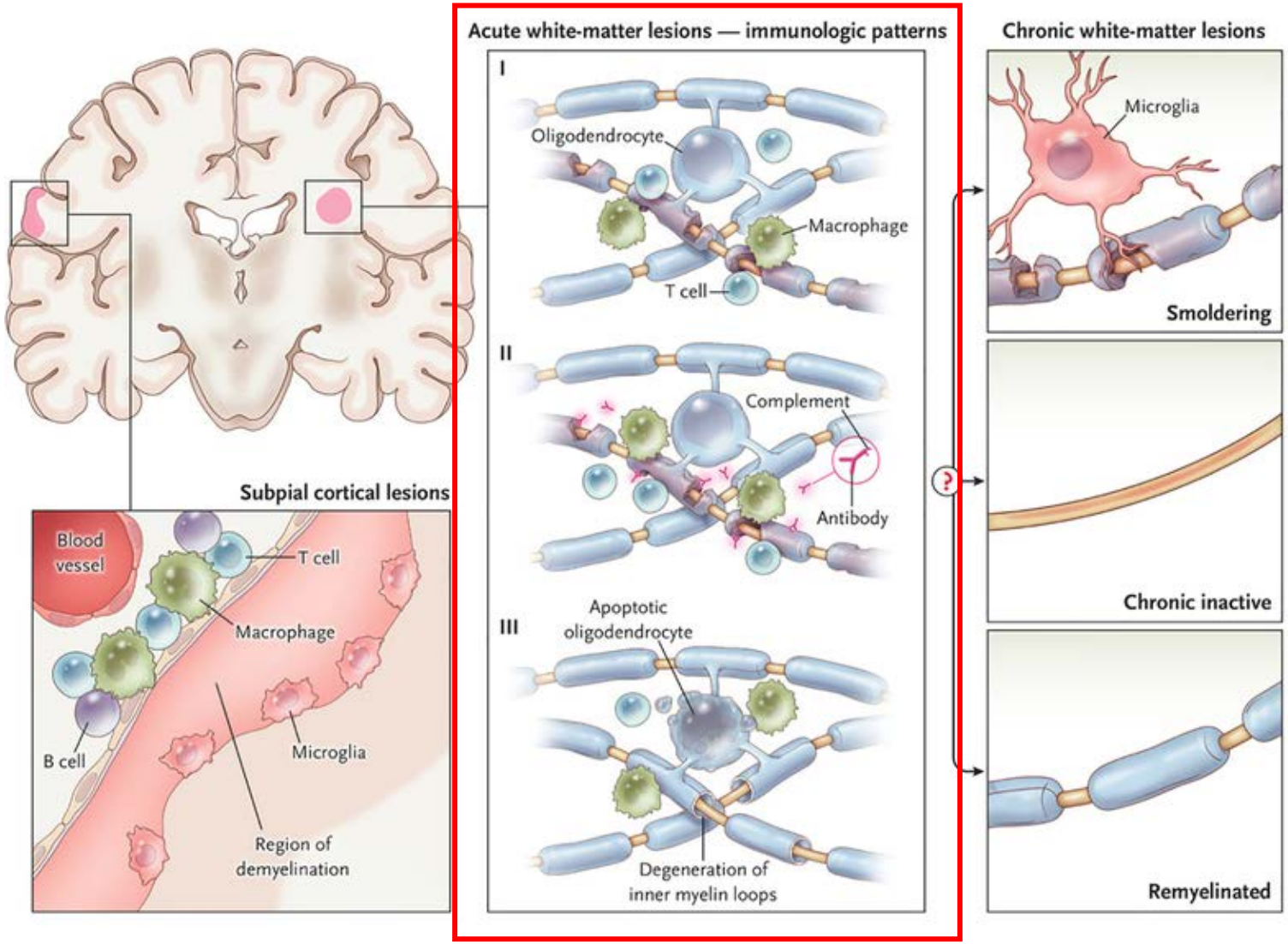
2018 - Pathology of MS

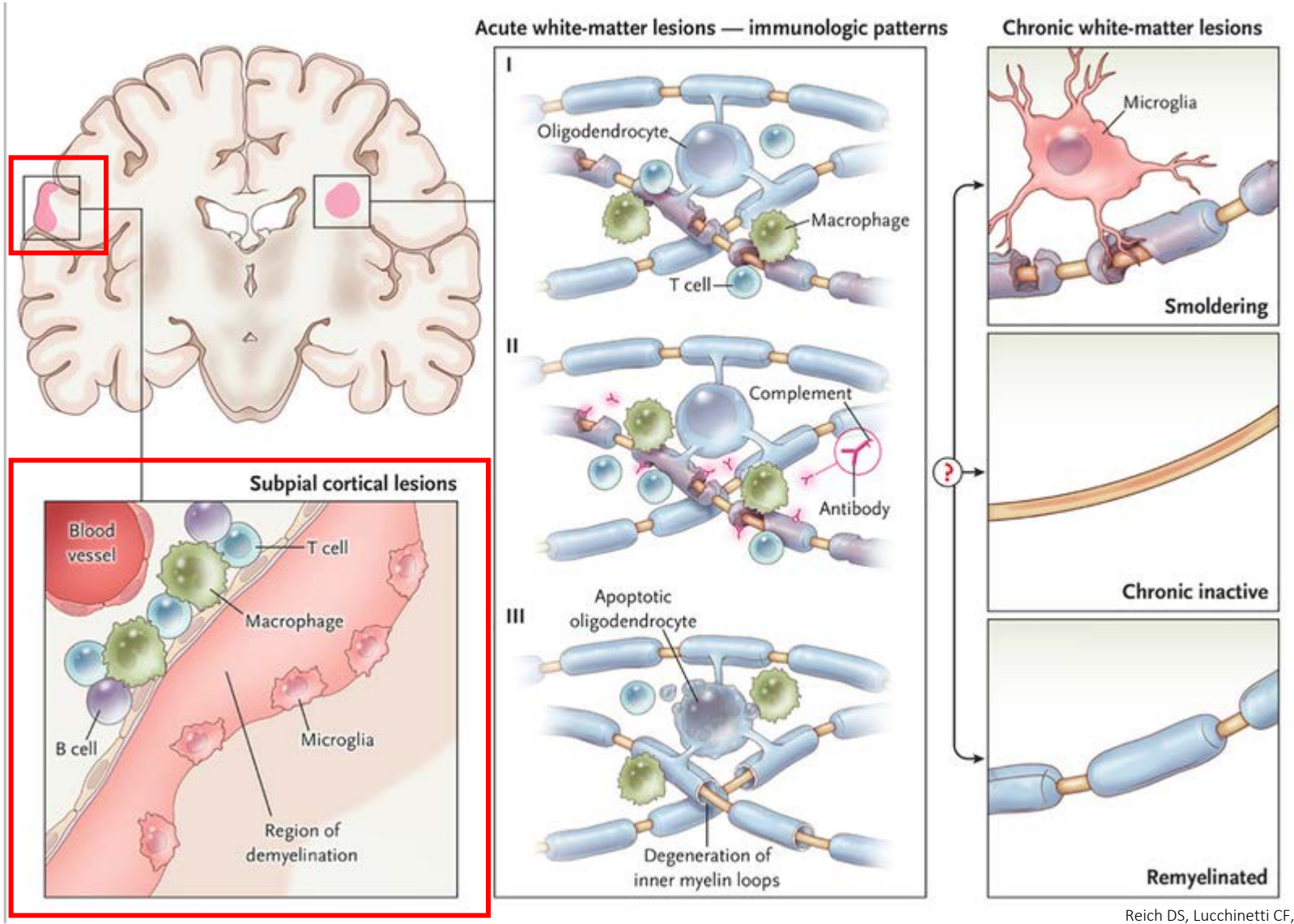


Acute active white matter demyelination

- Pattern I :mononuclear phagocytes with perivascular and parenchymal T-cell infiltration
- Pattern II :Immunoglobulin, complement deposition
- Pattern III :oligodendrocyte apoptosis with “dying back” oligodendrogliopathy
- Common pattern I&II

Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. New England Journal of Medicine. 2018;378(2):169-80.

Pathology of MS

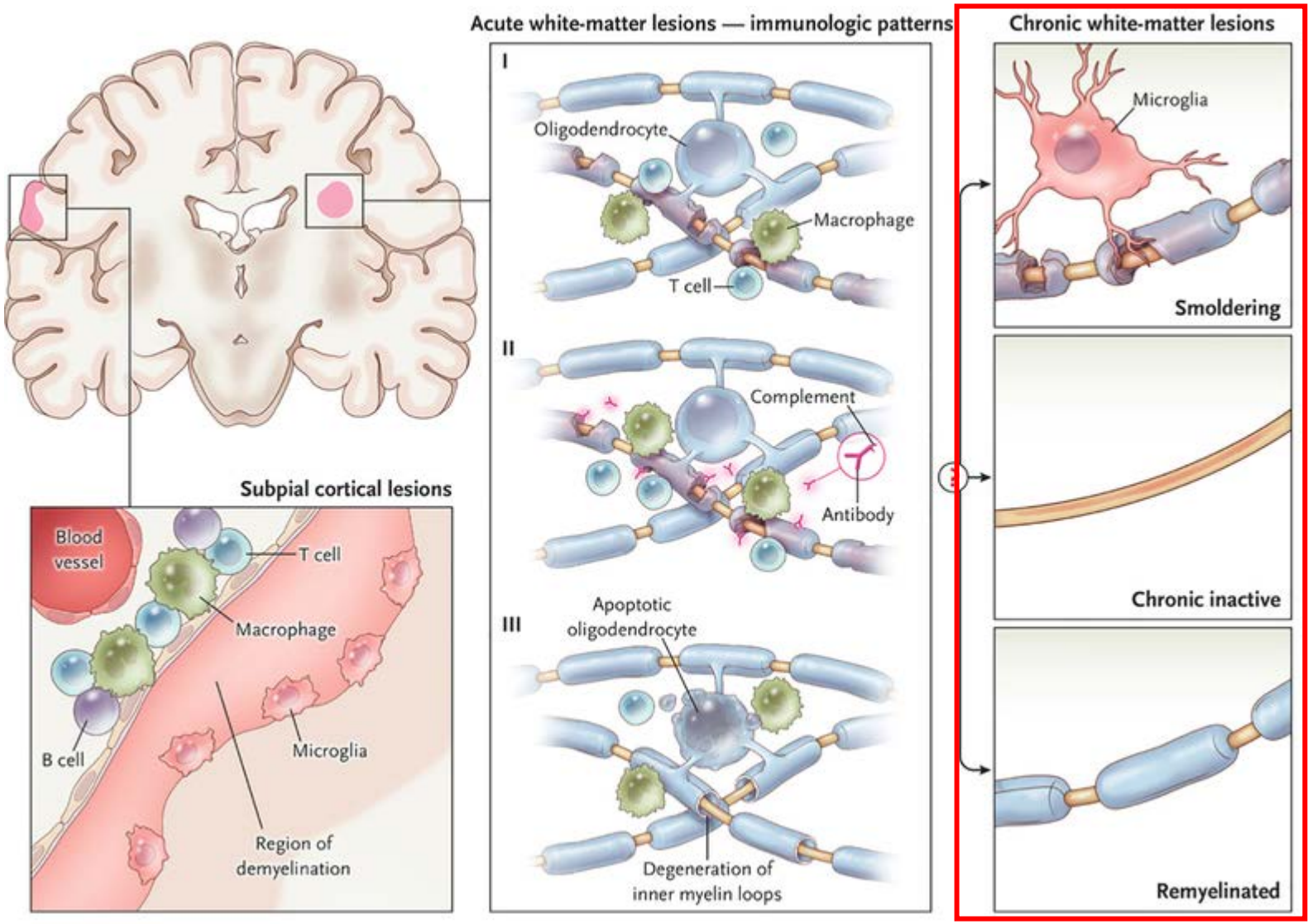


Subpial cortical lesion

- common in progressive multiple sclerosis
- demyelination of the superficial cortex
- Adjacent to diffuse and focal leptomeningeal inflammatory aggregates
- Self-sustaining structures of leptomeningeal inflammation (tertiary lymphoid follicles).

Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. New England Journal of Medicine. 2018;378(2):169-80.

Pathology of MS



Chronic white matter lesion

- Chronic active
  - inflammation and slow myelin degeneration persist (smoldering).
  - Smoldering lesions are most common in progressive multiple sclerosis.
- Chronic inactive
  - inflammation resolves without remyelination

Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. New England Journal of Medicine. 2018;378(2):169-80.

1. Active Demyelination Lesion

- Frequently detected at autopsy in patients who died during the acute or relapsing–remitting stages of MS
- Highly inflammatory: contain densely packed macrophages either throughout the lesion (acute plaques) or at the periphery (chronic active plaques)
- Complex architecture: a zone of initial tissue injury (prephagocytic areas) surrounds a zone of initial myelin phagocytosis (early active)
- A zone of advanced myelin digestion (late active) and an inactive central area, which frequently shows early remyelination.
- Remyelination seems to be unstable as long as inflammation is active

Lassmann, H. et al. Nat. Rev. Neurol. 8, 647–656 (2012)

2. Chronic Active Demyelination

- Slowly expanding lesions
- Account for approximately half of lesions in progressive MS
- Inactive lesion center is generally devoid of myelin, lacks signs of remyelination, and shows profound axonal loss; demyelinated axons are embedded in astrocytic scar tissue
- Contain small numbers of lymphocytes and microglia;55 lesion edge includes a small rim of activated microglia with intermingled macrophages, a few of which contain early myelin degradation products
- Surrounded by a zone of microglial activation and initial tissue injury.
- Pronounced and diffuse microglial activation in surrounding normal-appearing white matter

Lassmann, H. et al. Nat. Rev. Neurol. 8, 647–656 (2012)

Chronic active lesions in progressive MS brains

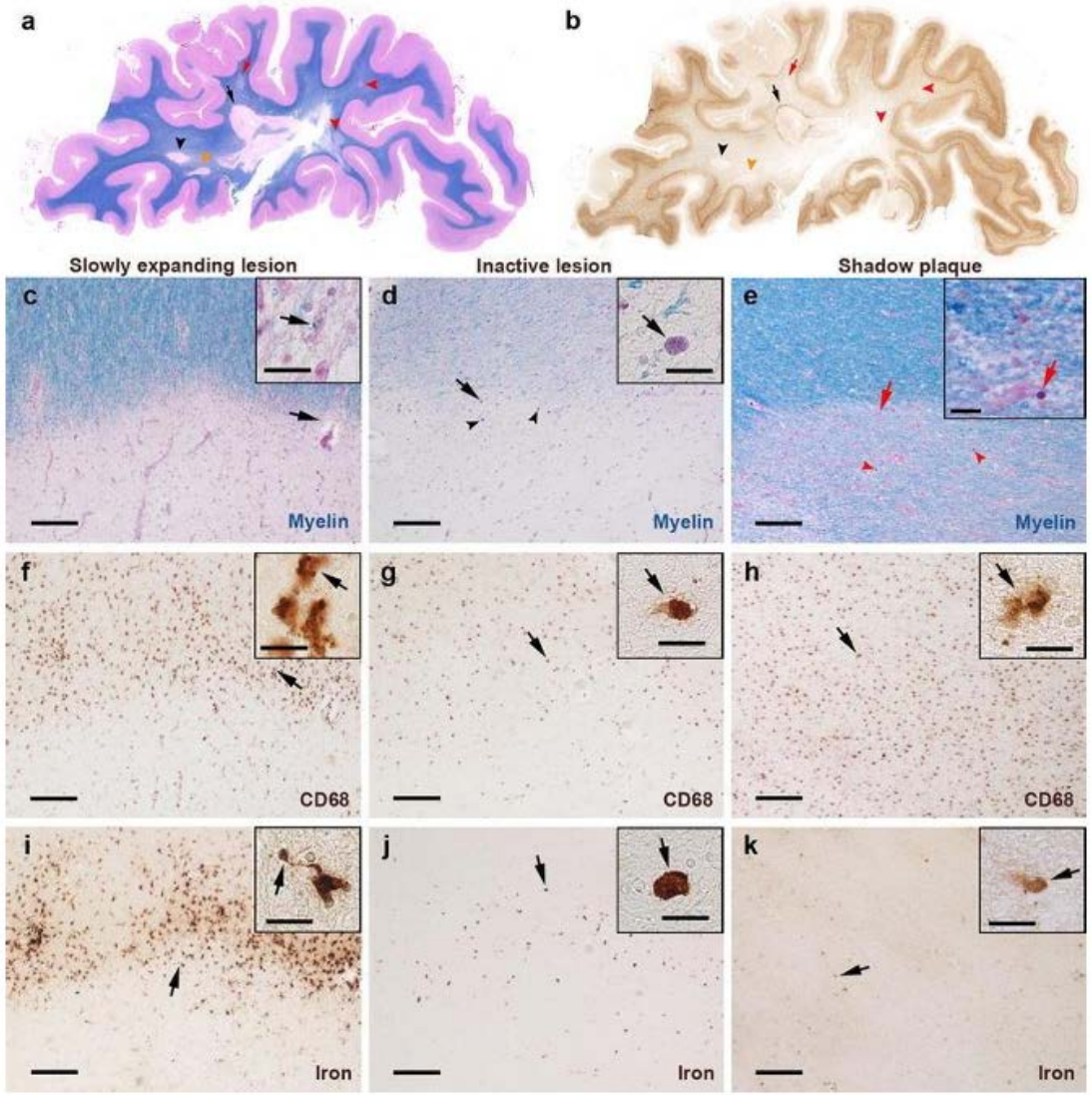
Acta Neuropathol (2017) 133:25–42
DOI 10.1007/s00401-016-1636-z

ORIGINAL PAPER

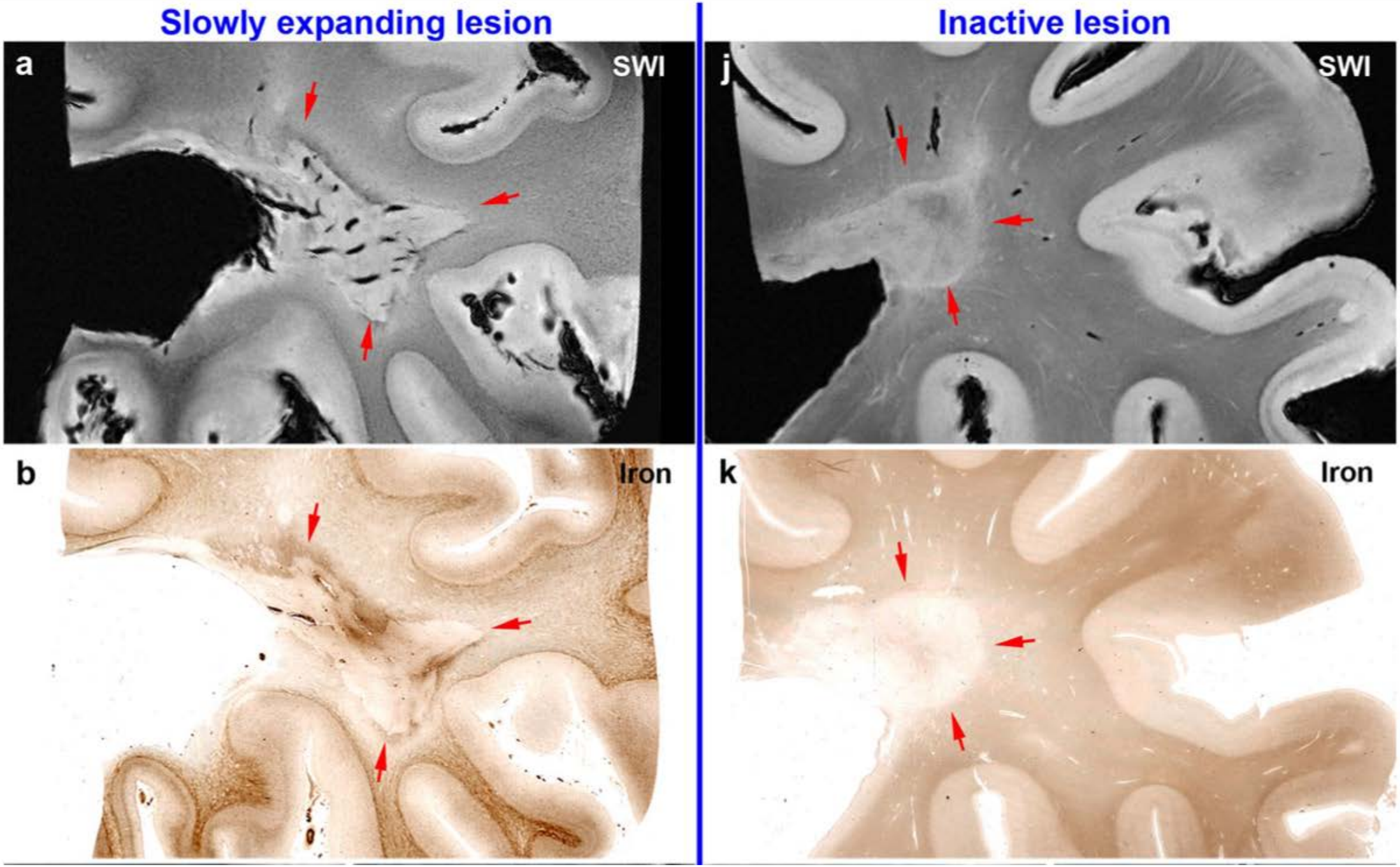
Slow expansion of multiple sclerosis iron rim lesions: pathology and 7 T magnetic resonance imaging

Assunta Dal-Bianco[1] · Günther Grabner[2,3] · Claudia Kronnerwetter[3] · Michael Weber[3] · Romana Höftberger[4] · Thomas Berger[5] · Eduard Auff[1] · Fritz Leutmezer[1] · Siegfried Trattnig[3] · Hans Lassmann[6] · Francesca Bagnato[7] · Simon Hametner[6]

- Iron accumulates inside activated microglia/macrophages at edges of some chronic demyelinated lesions, forming rims.
- Iron rims around slowly expanding and some inactive lesions but hardly around remyelinated shadow plaques



Dal-Bianco A, Grabner G, Kronnerwetter C, Weber M, Höftberger R, Berger T, et al. Slow expansion of multiple sclerosis iron rim lesions: pathology and 7 T magnetic resonance imaging. Acta Neuropathol. 2017;133(1):25-42.



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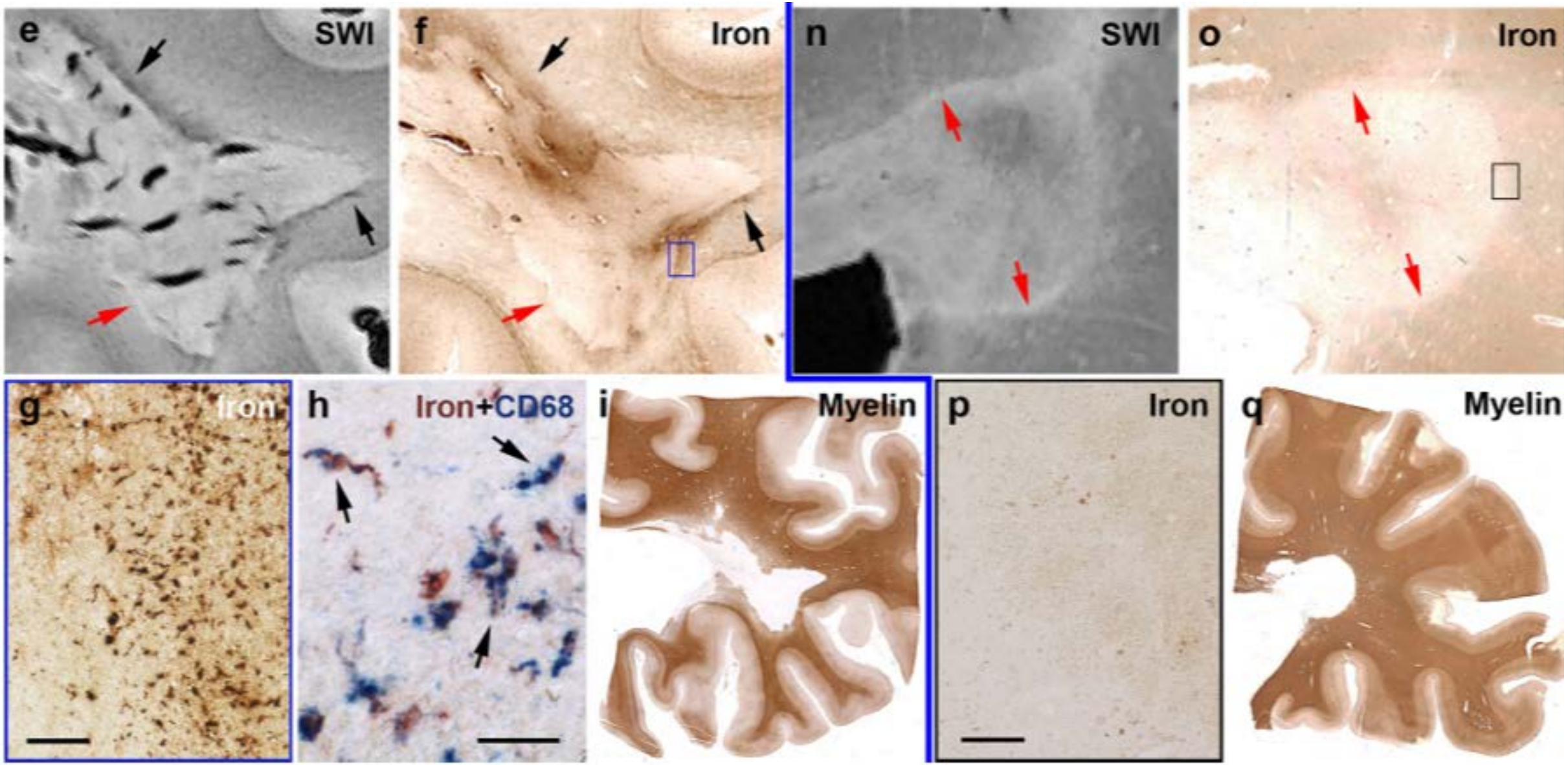

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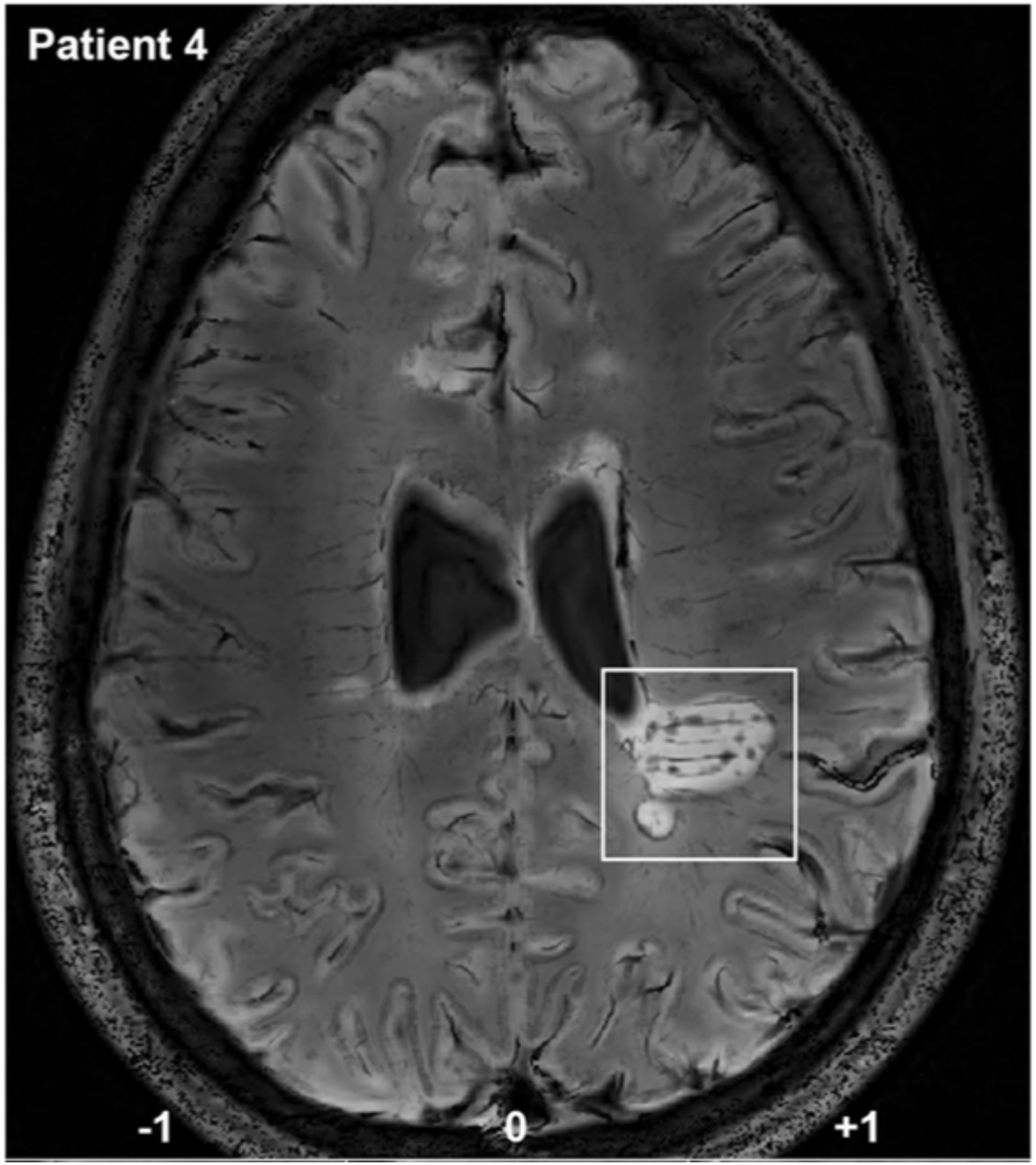

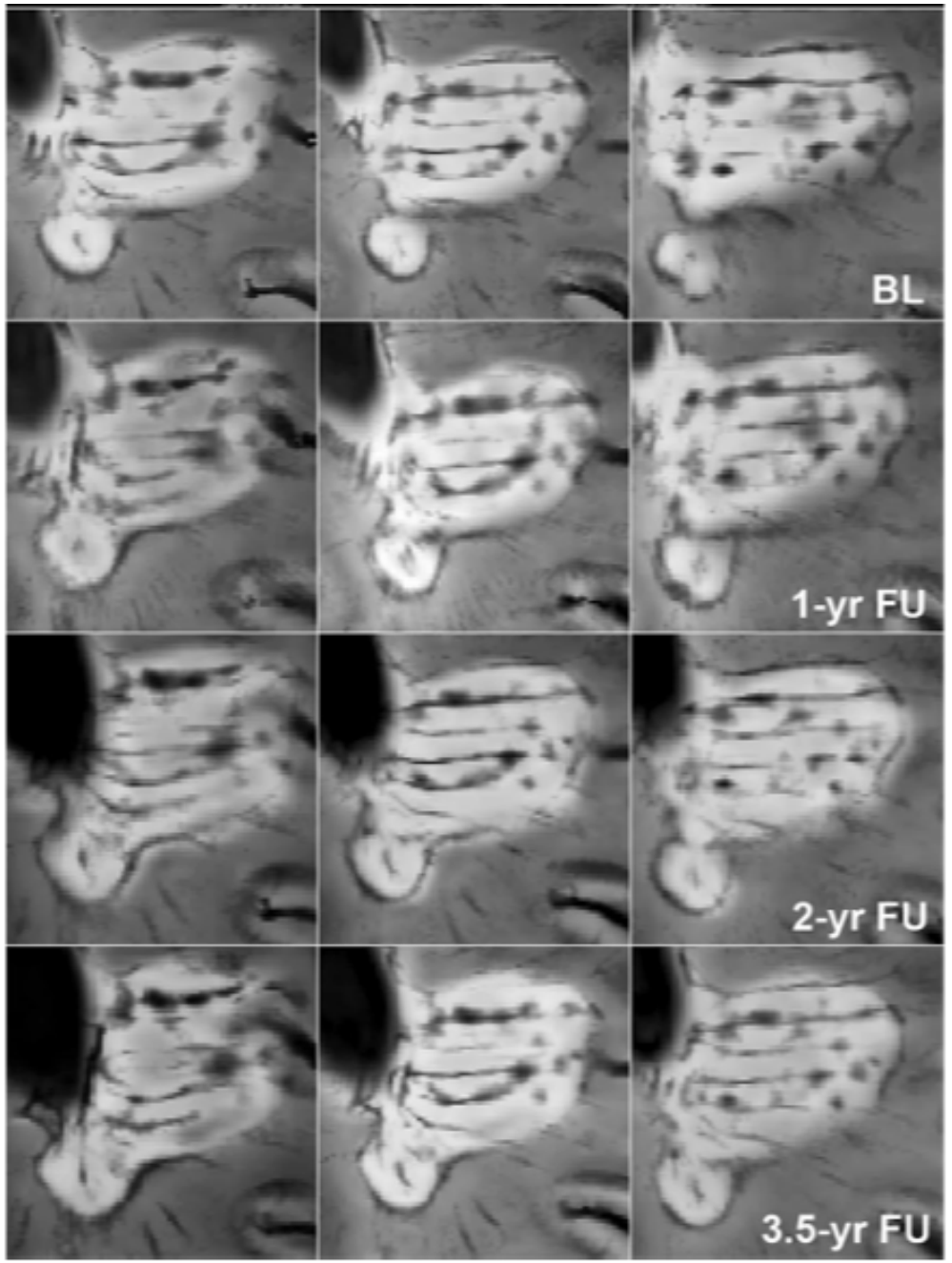

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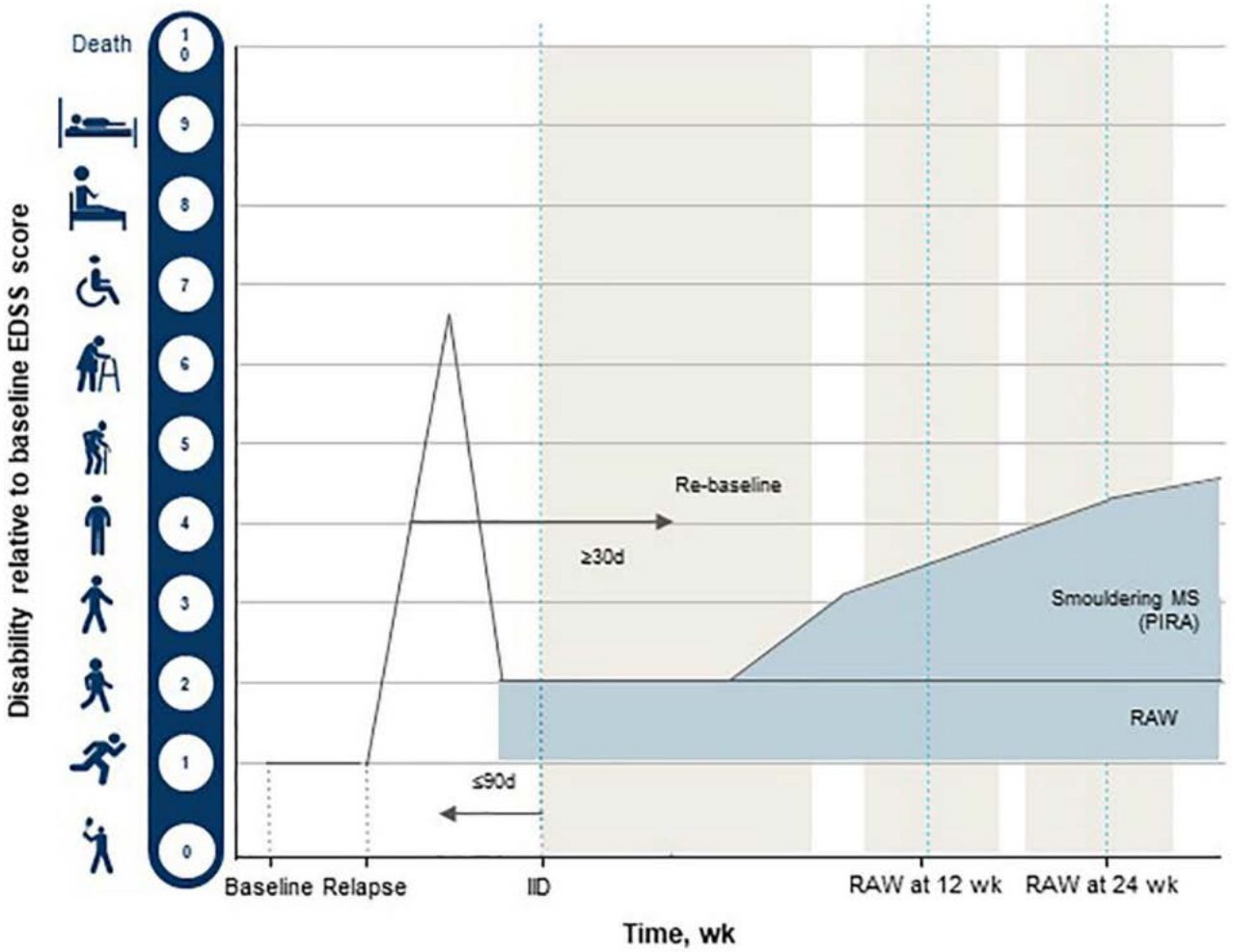
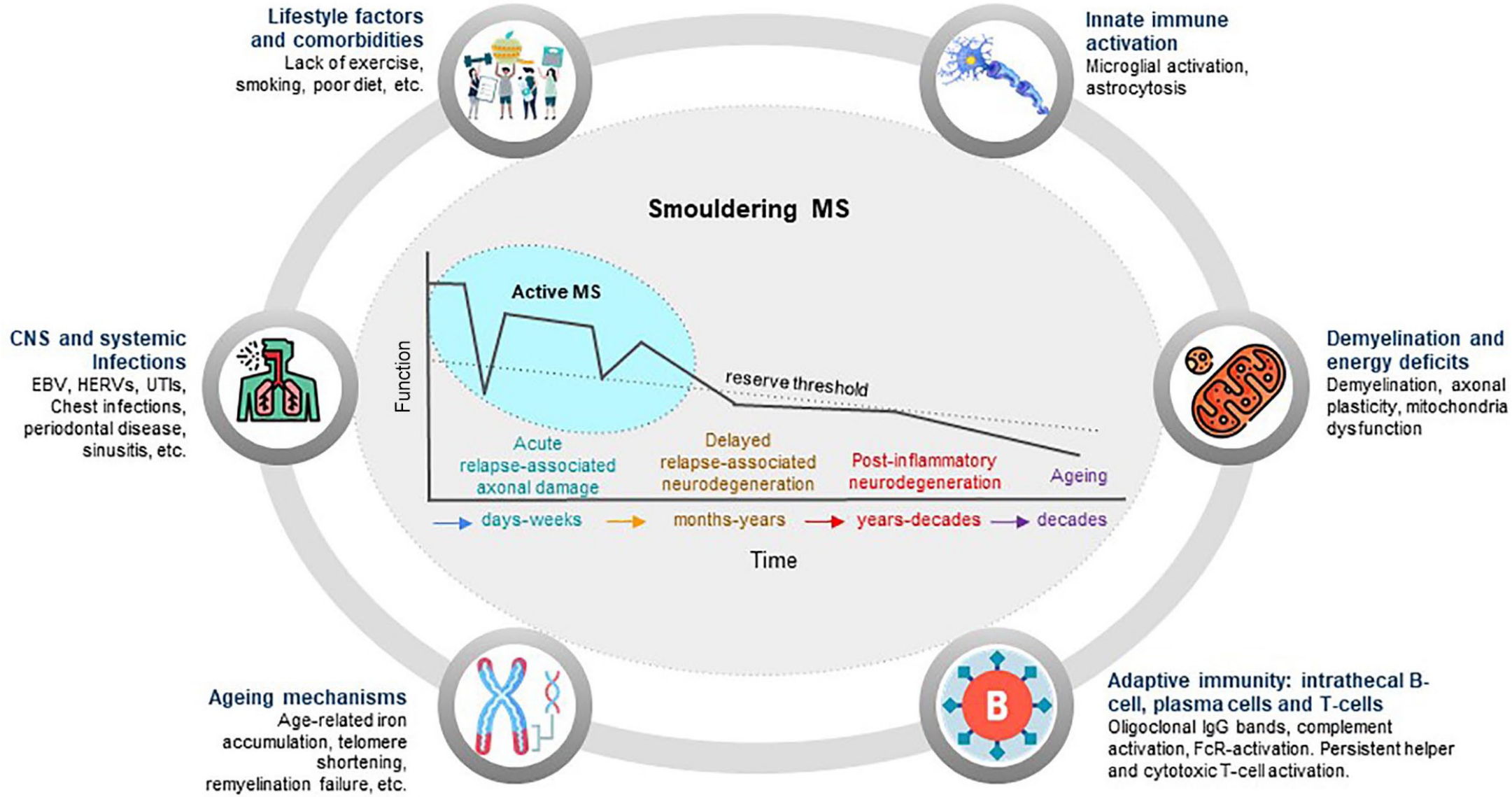
Smoldering MS



- Relapse and new MRI lesion correlate modestly with disability progression
- Primary smoldering process accompanied by a superimposed inflammatory activity
- Delayed time-dependent processes that are responsible for smoldering MS.
- Progressive MS equal inflammatory infiltrate, axonal loss, disability accumulation
- Ongoing inflammation and demyelination has been observed in end-stage MS
- Demyelination and energy deficits are responsible for delayed worsening, which occurs over weeks to months

Giovannoni G, Popescu V, Wuerfel J, Hellwig K, Iacobaeus E, Jensen MB, et al. Smouldering multiple sclerosis: the 'real MS'. Therapeutic Advances in Neurological Disorders. 2022;15:17562864211066751.

Smoldering MS



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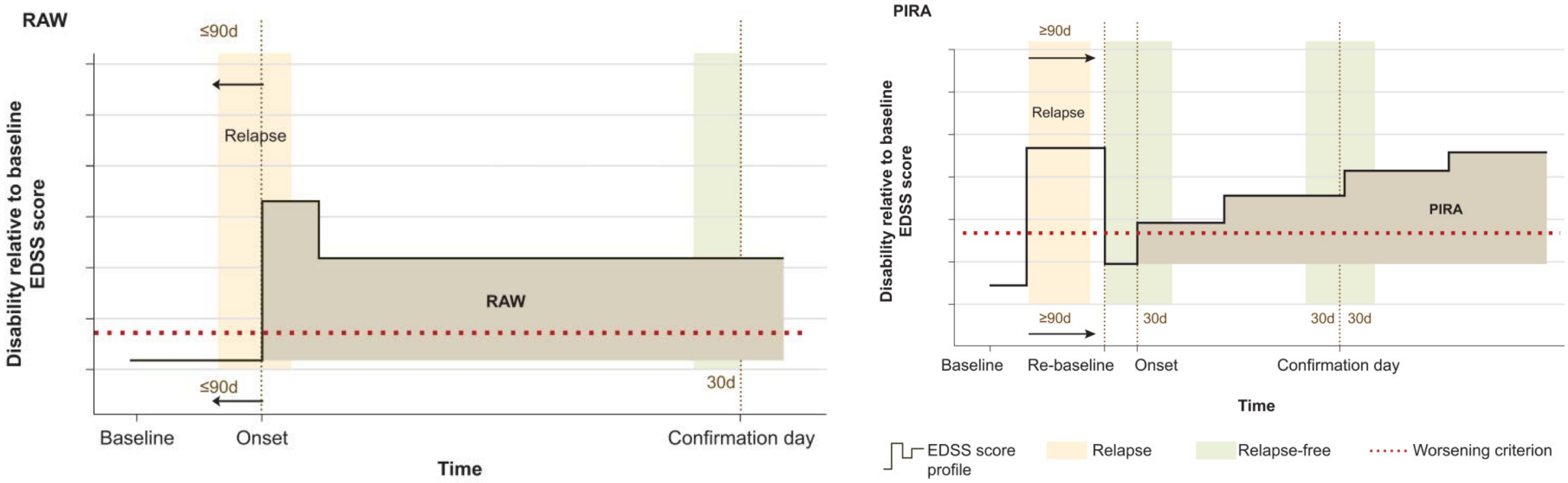
Biological Driver of Smoldering MS

- Non–relapse biological: inside-out
  - Compartmentalization
  - Smoldering, subpial cortical injury → demyelination along cortical ribbon → similar pattern of injury in thalamus and periventricular
  - Inflammation in meninges and ependyma → presence of immune cell associated with neuronal loss and microglial activation → associate with disability
- Relapse biological: outside–in
  - Activated periphery immune cell → focal inflammation in CNS
  - Subset of inactive lesion → actively inactive lesion → SELs
  - Activated microglia are seen in chronic active lesions in “inactive” progressive MS

Giovannoni G, Popescu V, Wuerfel J, Hellwig K, Iacobaeus E, Jensen MB, et al. Smouldering multiple sclerosis: the ‘real MS’. Therapeutic Advances in Neurological Disorders. 2022;15:17562864211066751.

PIRA
(Progression Independent of Relapse Activity)



Concept of PIRA

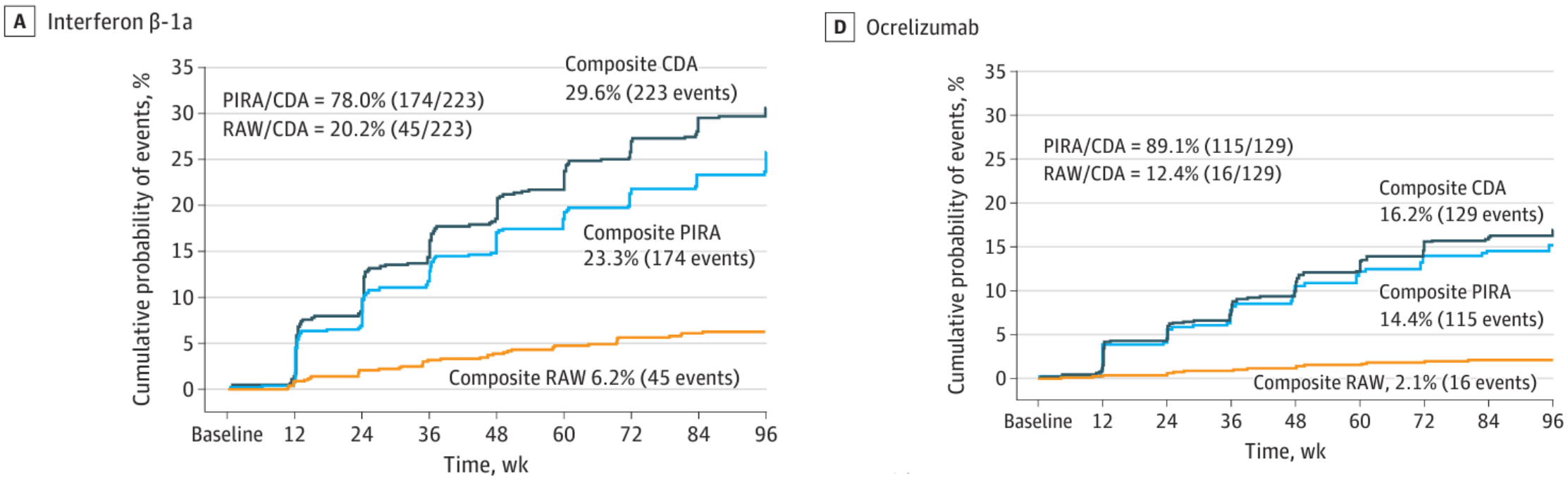
- a signal of disability progression is evident in early relapsing multiple sclerosis, independent of relapses.
- all multiple sclerosis, to a lesser or greater extent, has a signal of progression evident from early disease

Lublin FD, Häring DA, Ganjgahi H, Ocampo A, Hatami F, Čuklina J, et al. How patients with multiple sclerosis acquire disability. Brain. 2022;145(9):3147-61.

JAMA Neurology | Original Investigation

Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials

Ludwig Kappos, MD; Jerry S. Wolinsky, MD; Gavin Giovannoni, PhD; Douglas L. Arnold, MD; Qing Wang, PhD; Corrado Bernasconi, PhD; Fabian Model, PhD; Harold Koendgen, MD; Marianna Manfrini, MD; Shibeshih Belachew, MD; Stephen L. Hauser, MD



PIRA
(Progression Independent of Relapse Activity)

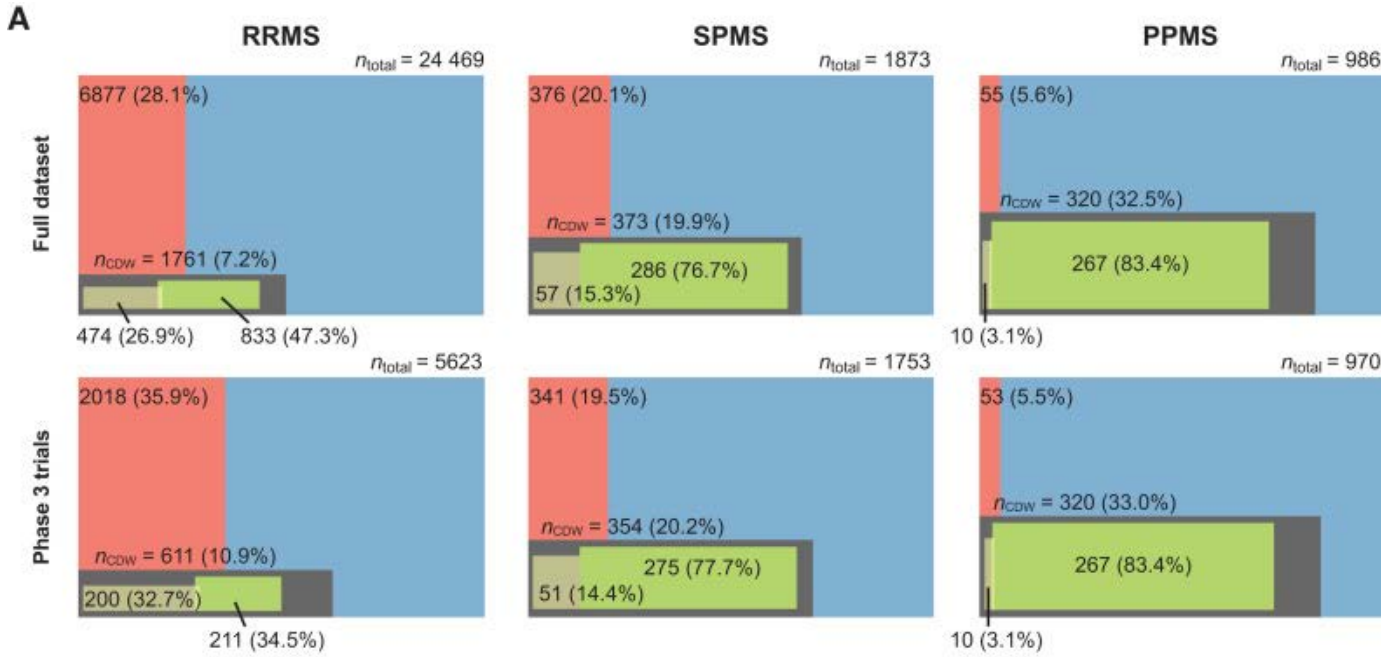
Proposed clinical definition of PIRA.

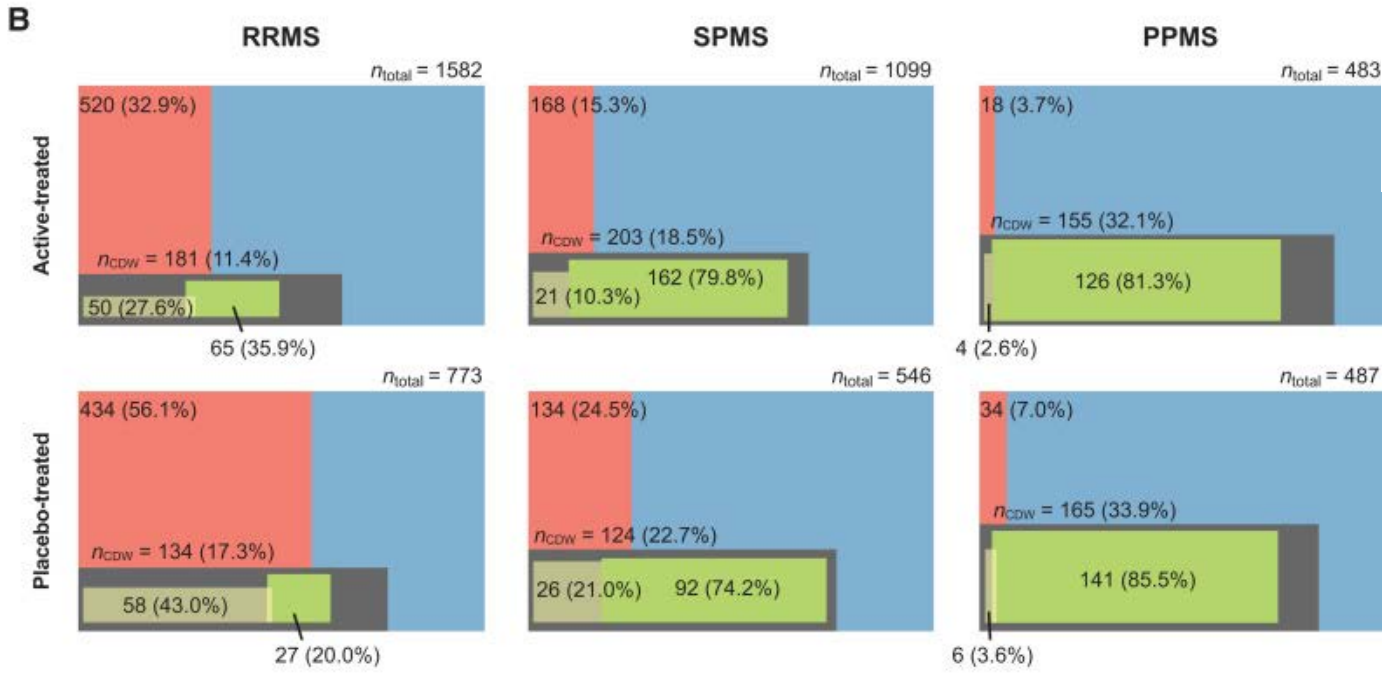
Component	Criterion
Diagnosis and baseline EDSS	Relapsing MS patients with EDSS $\leq$ 4.5, to reduce likelihood of inclusion of patients with established SPMS
DMT status	Treatment naïve or treated with disease modifying therapy
EDSS change	EDSS change required: $\geq$ 1.5 ΔEDSS for baseline EDSS 0 and $\geq$ 1 ΔEDSS for EDSS $\geq$ 1 and $\leq$ 4.5
Time to confirm PIRA	Time to confirm PIRA event as confirmed disability progression at 12/52 and 24/52
PIRA registration	Undertake the analysis with respect to registration of a PIRA event relative to relapse at > 30 days before a relapse and *both* 30 and 90 days following a relapse

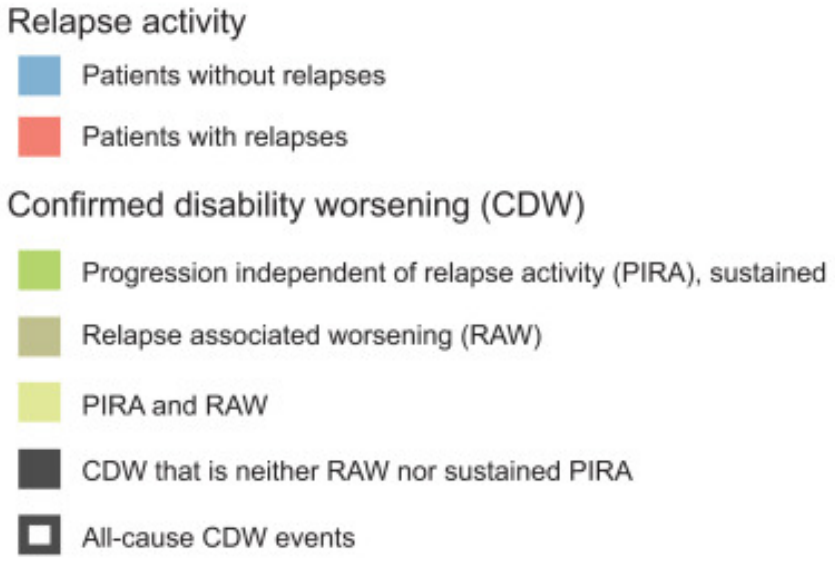
How patients with multiple sclerosis acquire disability

Fred D. Lublin,[1,†] Dieter A. Häring,[2,†] Habib Ganjgahi,[3] Alex Ocampo,[2] Farhad Hatami,[3] Jelena Čuklina,[2] Piet Aarden,[2] Frank Dahlke,[2] Douglas L. Arnold,[4] Heinz Wiendl,[5] Tanuja Chitnis,[6] Thomas E. Nichols,[3] Bernd C. Kieseier[2] and Robert A. Bermel[7]

Sharrad D, Chugh P, Slee M, Bacchi S. Defining progression independent of relapse activity (PIRA) in adult patients with relapsing multiple sclerosis: A systematic review☆. Multiple Sclerosis and Related Disorders. 2023;78:104899



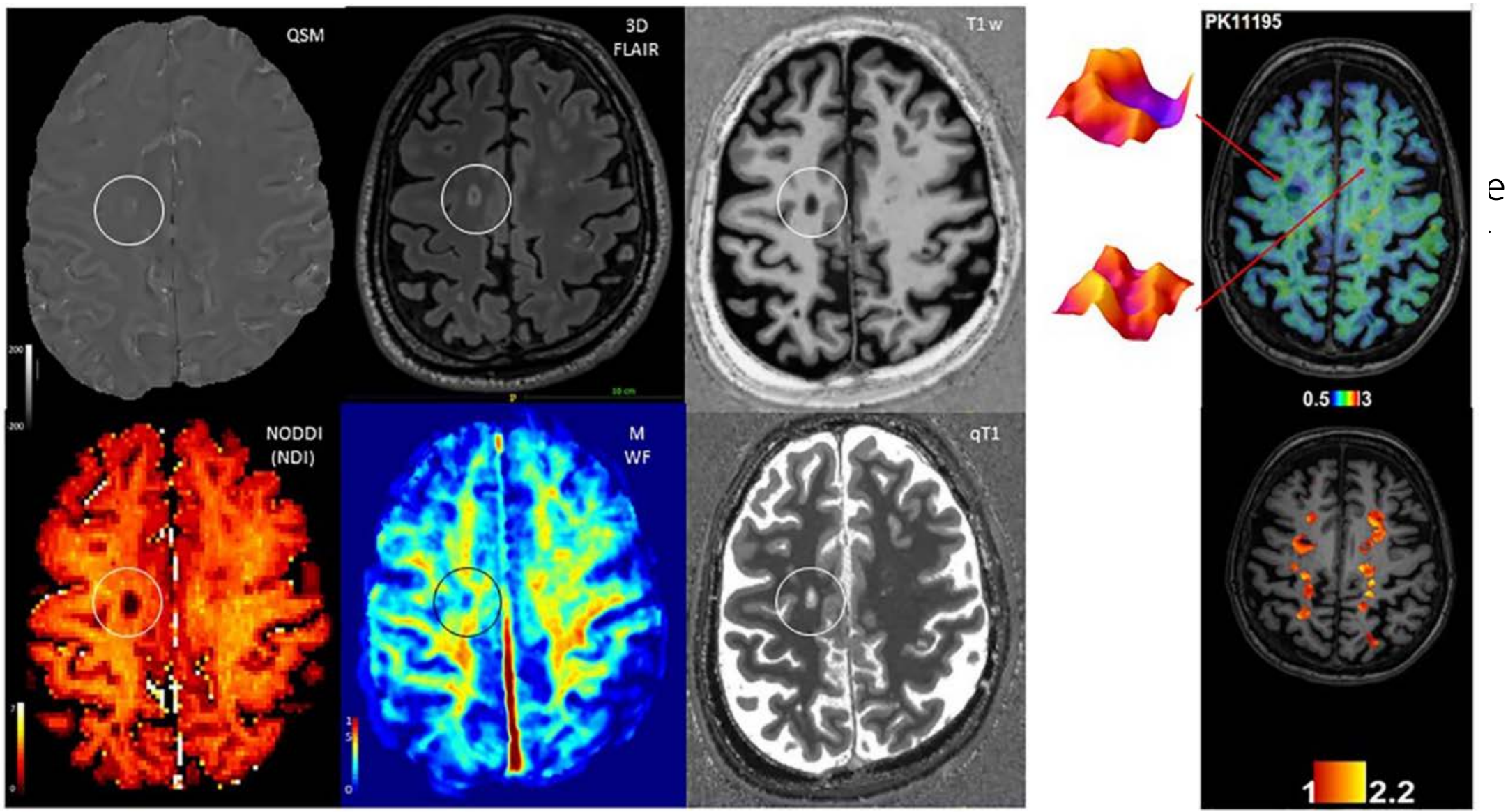




- PIRA was seen across all phenotypes, lower frequency in RRMS
- Up to 50% of the disability accumulation in adult patients with RRMS is not associated with overt relapses.
- RAW and PIRA contributed to the accumulation of disability in RRMS
- SPMS and PPMS, PIRA was the dominant driver of disease worsening.

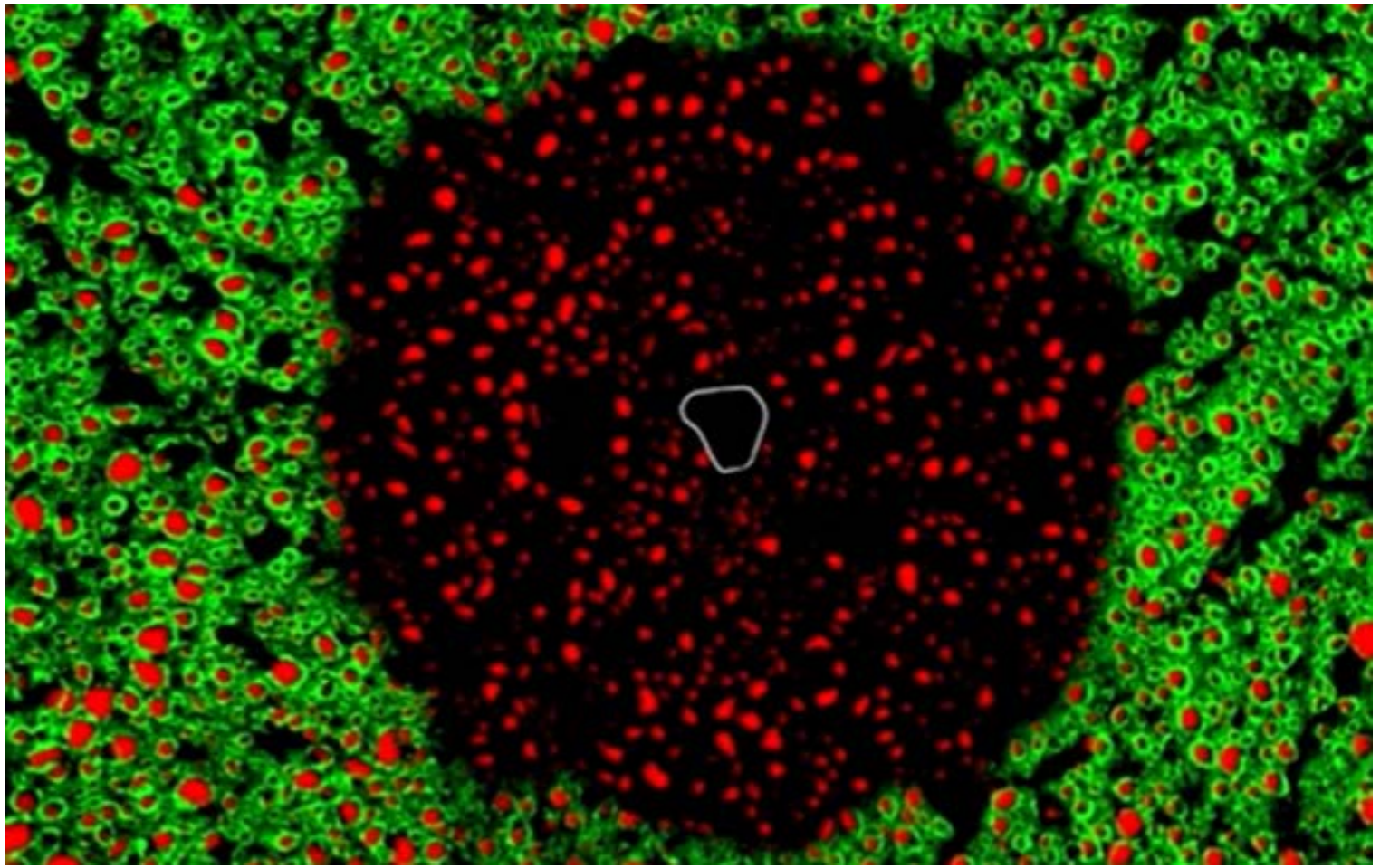
Lublin FD, Häring DA, Ganjgahi H, Ocampo A, Hatami F, Čuklina J, et al. How patients with multiple sclerosis acquire disability. Brain. 2022;145(9):3147-61.

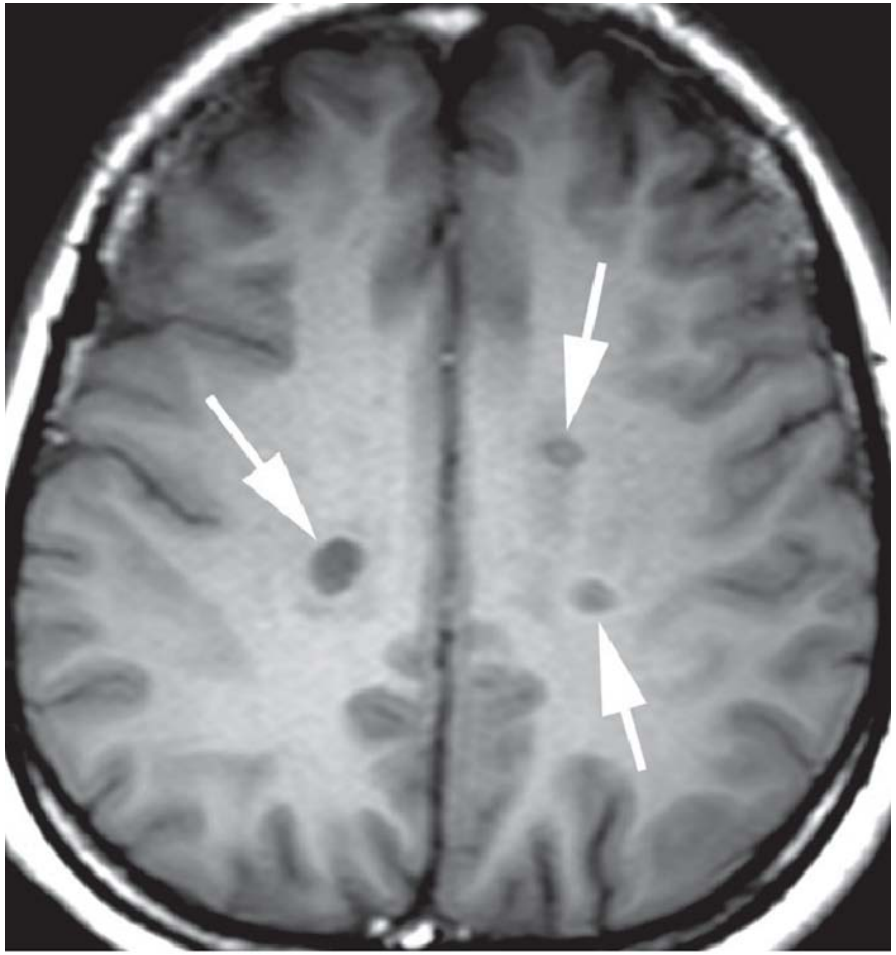
Advanced imaging in smoldering MS



Giovannoni G, Popescu V, Wuerfel J, Hellwig K, Iacobaeus E, Jensen MB, et al. Smouldering multiple sclerosis: the 'real MS'. Therapeutic Advances in Neurological Disorders. 2022;15:17562864211066751.

Chronic Inactive Lesion





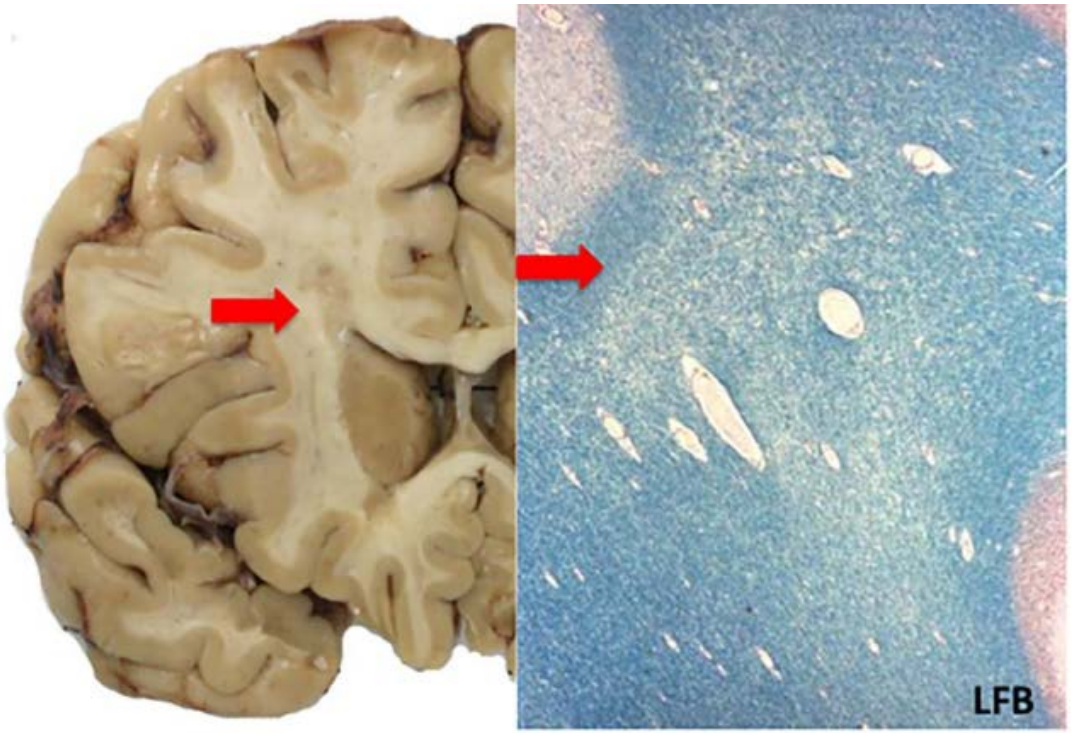
3. Chronic Inactive Lesion

- The most frequent lesion type in all stages of MS; most abundant in patients with long-standing disease
- Devoid of myelin, lack signs of remyelination, profound axonal loss; demyelinated axons are embedded in astrocytic scar tissue
- Infiltrates of T or B lymphocytes are rare, microglial density within the lesion generally lower than in surrounding normal-appearing tissue
- Clearly demarcated from the surrounding normal appearing white matter; no demyelinating or neurodegenerative activity at the lesion border

Lassmann, H. et al. Nat. Rev. Neurol. 8, 647–656 (2012)

Remyelination

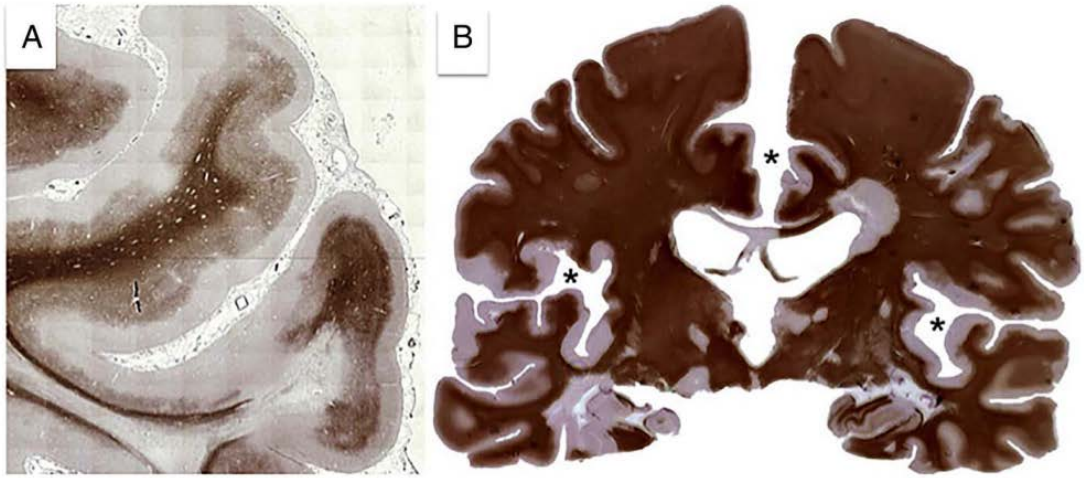
- Demyelinated plaques can undergo spontaneous repair
- Oligodendrocyte progenitor cells (OPC) → mature oligodendrocyte → Remyelination
- Shadow Plaque
- vessels in ‘shadow plaques’ almost invariably show dissection and fibrosis of their walls and an enlarged perivascular space
- Partially remyelinated areas are often seen at the edges of late active, chronic active and chronic inactive lesions



Lassmann, H. et al. Nat. Rev. Neurol. 8, 647–656 (2012)
Matthews PM, et al. Pract Neurol 2016;16:279–287

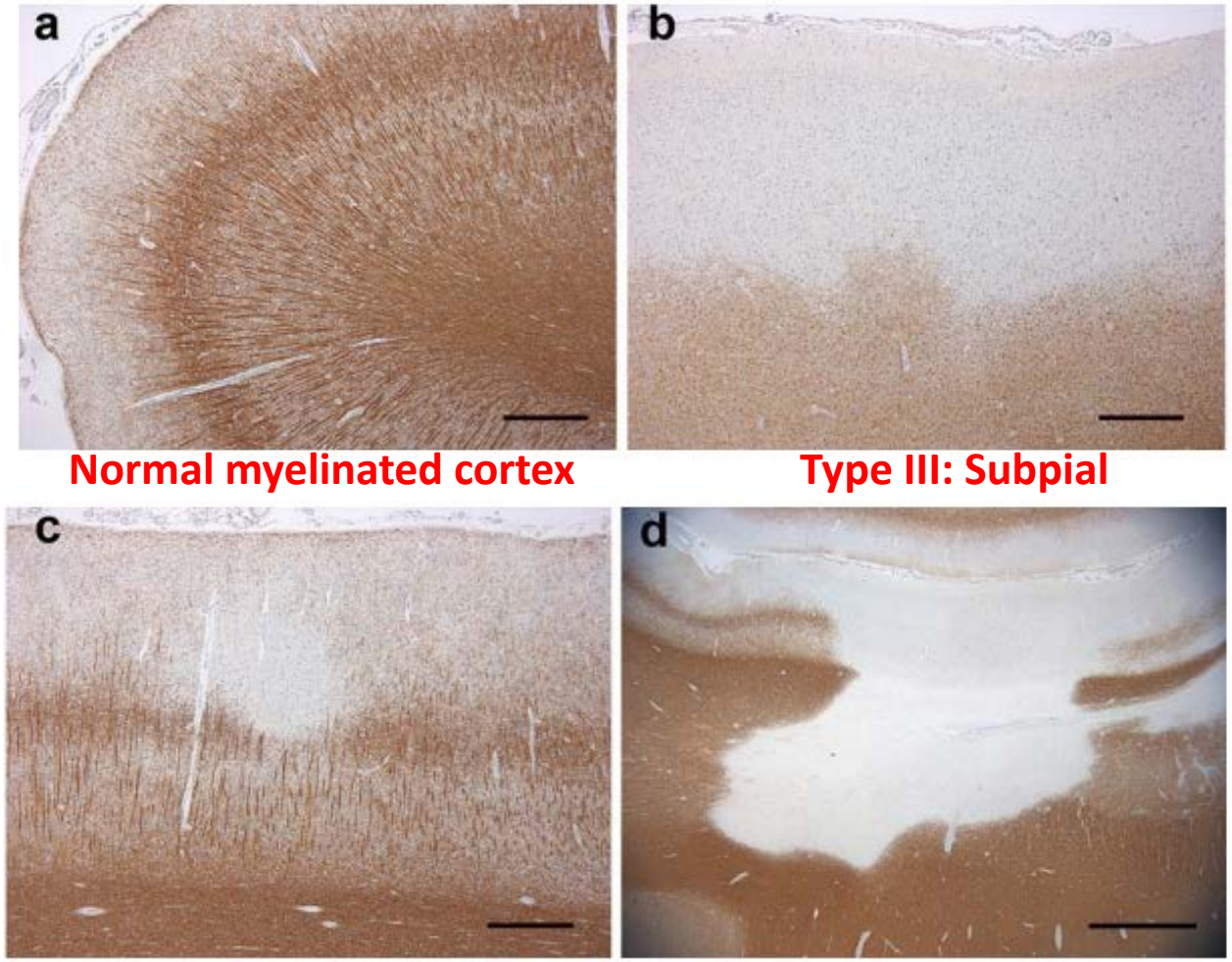
Pathology of grey matter plaques

- Gray matter demyelination expands from the pial surface into the deeper cortical layers
- Cortical lesions frequently have leptomeningeal immune cell infiltrates that are either diffuse or organized into lymphoid-like tissue aggregates.
- In contrast to the active white matter lesions, grey matter lesions contain relatively few inflammatory cells
- Demyelination and neuronal and axonal loss also are prominent in subcortical grey matter, such as the basal ganglia and cerebellum



Cold Spring Harb Perspect Med 2018;8:a028936
Matthews PM, et al. Pract Neurol 2016;16:279–287

Different types of cortical lesions



- Cortical lesions (CLs) contribute to physical and cognitive disability in multiple sclerosis
- Profound microglia activation
- Type I: Leukocortical (type I)
  - encompassed both white matter and cortex
- Type II: Intracortical
  - lesions resided entirely within the cortex, were usually small, and often contained a vessel at their center
- Type III: Subpial
  - lesions extend from the superficial pial surface into the deeper layers of cortex.
  - Most cortical lesions are subpial type

Cold Spring Harb Perspect Med 2018;8:a028936
Kuhlmann T, Ludwin S, Prat A, Antel J, Brück W, Lassmann H. An updated histological classification system for multiple sclerosis lesions. Acta Neuropathol. 2017;133(1):13-24.

Diffuse White Matter Injury

- Normal Appearing White Matter (NAWM) is highly abnormal, particularly in the progressive stage of disease
  - perivascular inflammatory infiltrates, moderate brain edema, diffuse microglia activation, diffuse axonal injury, and astrocytic gliosis
  - secondary to axonal destruction and neuronal damage within focal lesions, which gives rise to anterograde (Wallerian) and retrograde degeneration
  - Cellular and molecular changes suggesting functional deficits in axonal transport
  - Diffuse axonal injury in the NAWM occurs independently from focal demyelination
- Widespread microglia activation is prominent in normal-appearing white matter and there can be clusters of activated microglia
- The extent of which relates to the degree of inflammation in the overlying meninges

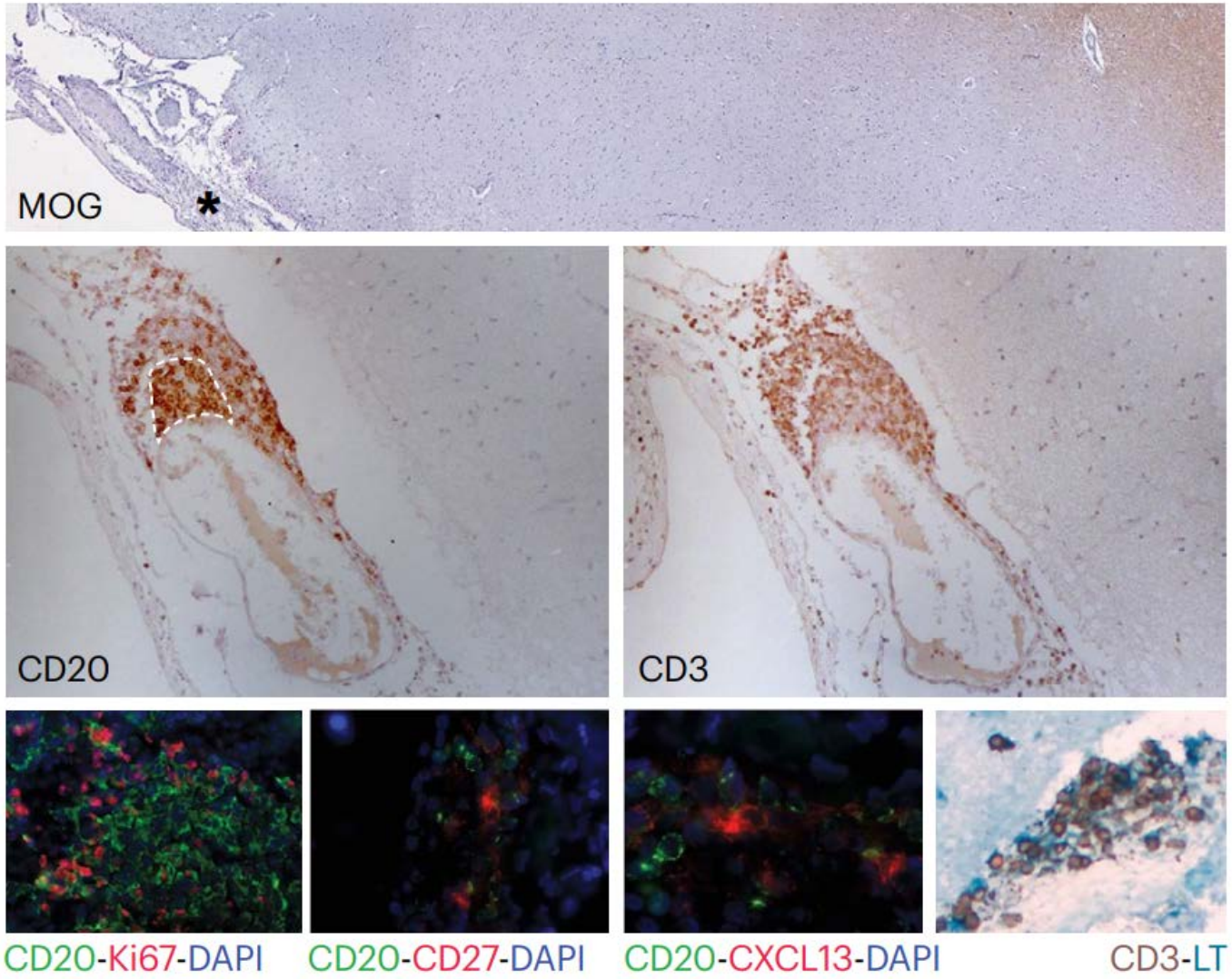
Cold Spring Harb Perspect Med 2018;8:a028936
Matthews PM, et al. Pract Neurol 2016;16:279–287

Meningeal inflammation: Pathology

- Meningeal immune cell infiltration is nearly universal in MS, but also heterogeneous
- Infiltrates can range from a few cells, to organized, lymphoid follicle-like structures
- Follicle-like structures are associated with
  - increased levels of pro-inflammatory cytokines in the CSF
  - decreased cortical thickness and increased cortical lesions
  - more severe disease course
- Present postmortem – suggests CNS compartmentalized inflammation is important even in later stages of disease

Cold Spring Harb Perspect Med 2018;8:a028936
Magliozzi R, Howell OW, Calabrese M, Reynolds R. Meningeal inflammation as a driver of cortical grey matter pathology and clinical progression in multiple sclerosis. Nature Reviews Neurology. 2023;19(8):461-76.

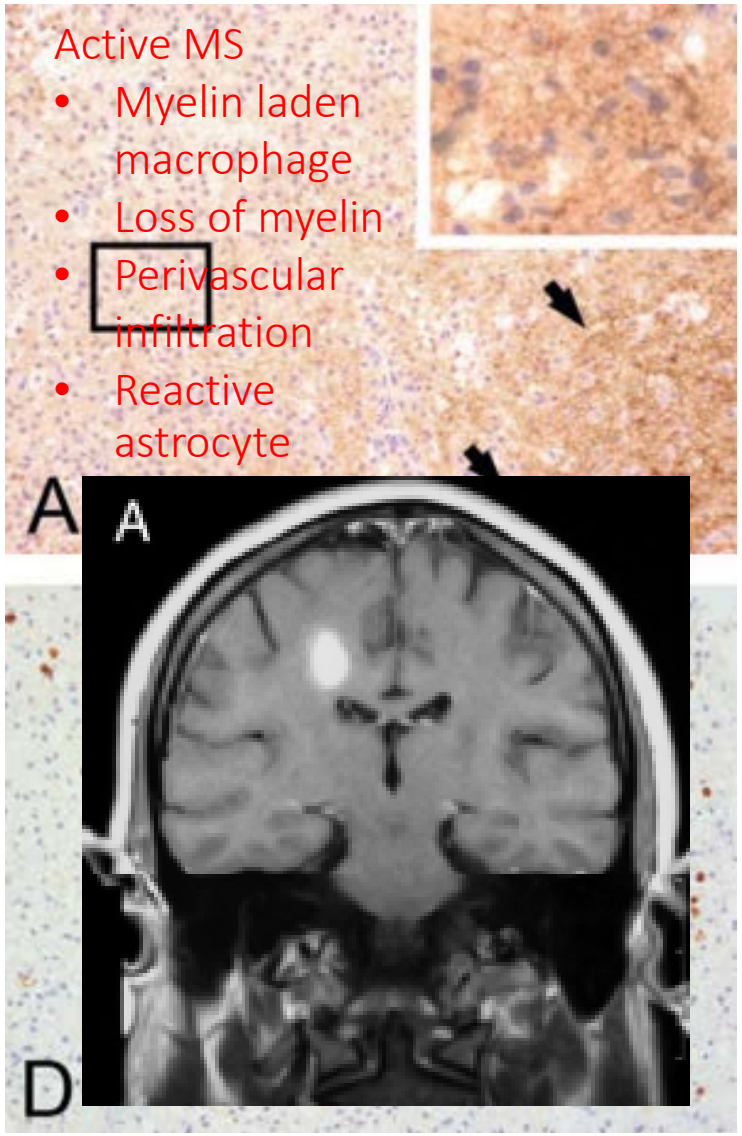
Meningeal inflammation: Pathology

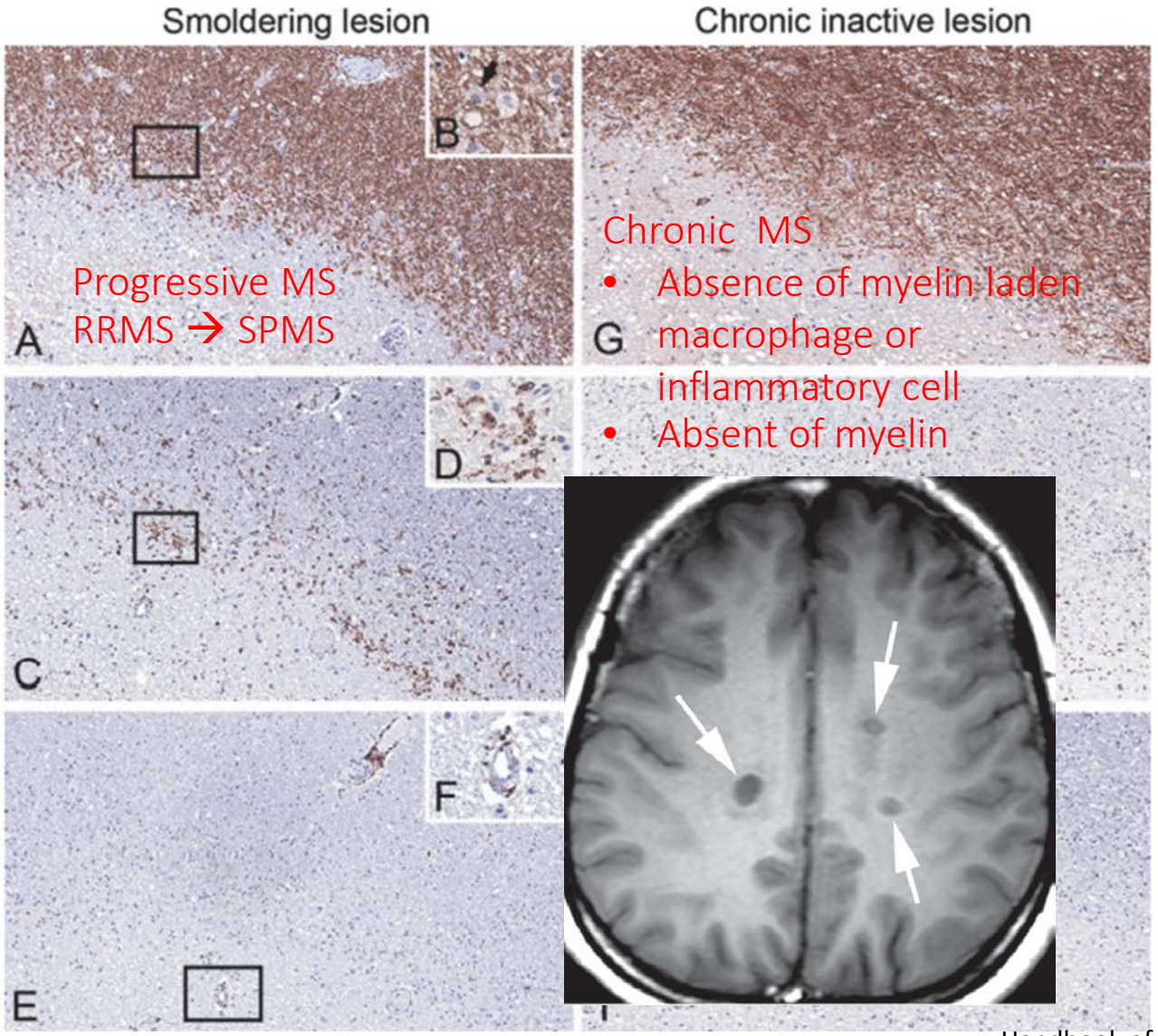


- CD3 – T cells
- CD20 – B cells
- Ki67 – proliferation
- CD27 – memory B cells
- CXCL13 – marker of follicular dendritic cells
- Subpial type III cortical lesions adjacent to inflamed meninges, containing a tertiary lymphoid-like structure
-

Magliozzi R, Howell OW, Calabrese M, Reynolds R. Meningeal inflammation as a driver of cortical grey matter pathology and clinical progression in multiple sclerosis. Nature Reviews Neurology. 2023;19(8):461-76.

Pathology of MS





Handbook of clinical neurology

Pathology in MS at different stage

Active Lesion

- Dominate in the RRMS
- Inflammatory cell mainly T cell and macrophage
- Active plaque
  - Initial response: CD8+ T-cell and microglia reactivation
  - Myelin debris -secondary recruitment of T cells, B cells and macrophage
- Myelin sheaths are the primary target of tissue destruction
- Extent of axonal injury and tissue destruction correlates better with the number of macrophages and CD8 cells
- Profound damage of BBB → Gadolinium enhancing

Lassmann H,Cold Spring Harb Perspect Med 2018;8:a028936

Pathology in MS at different stage

Progressive Lesions

- Inflammation compartmentalized behind intact BBB
- Mild BBB impairment can occur in conjunction with chronic lesions, irrespective of the presence or absence of inflammatory infiltrates
- CNT spaces of the brain, meninges and the large Virchow- Robin spaces large aggregates of inflammatory cells lymphatic follicles, tertiary lymphoid follicle

Lassmann H, Cold Spring Harb Perspect Med 2018;8:a028936

Pathology in MS at different stage

- All typical pathological features of MS are seen in all stages of the disease
- No qualitative difference in the pathology between relapsing and progressive MS
- The contribution of the pathological processes and alterations differs quantitatively

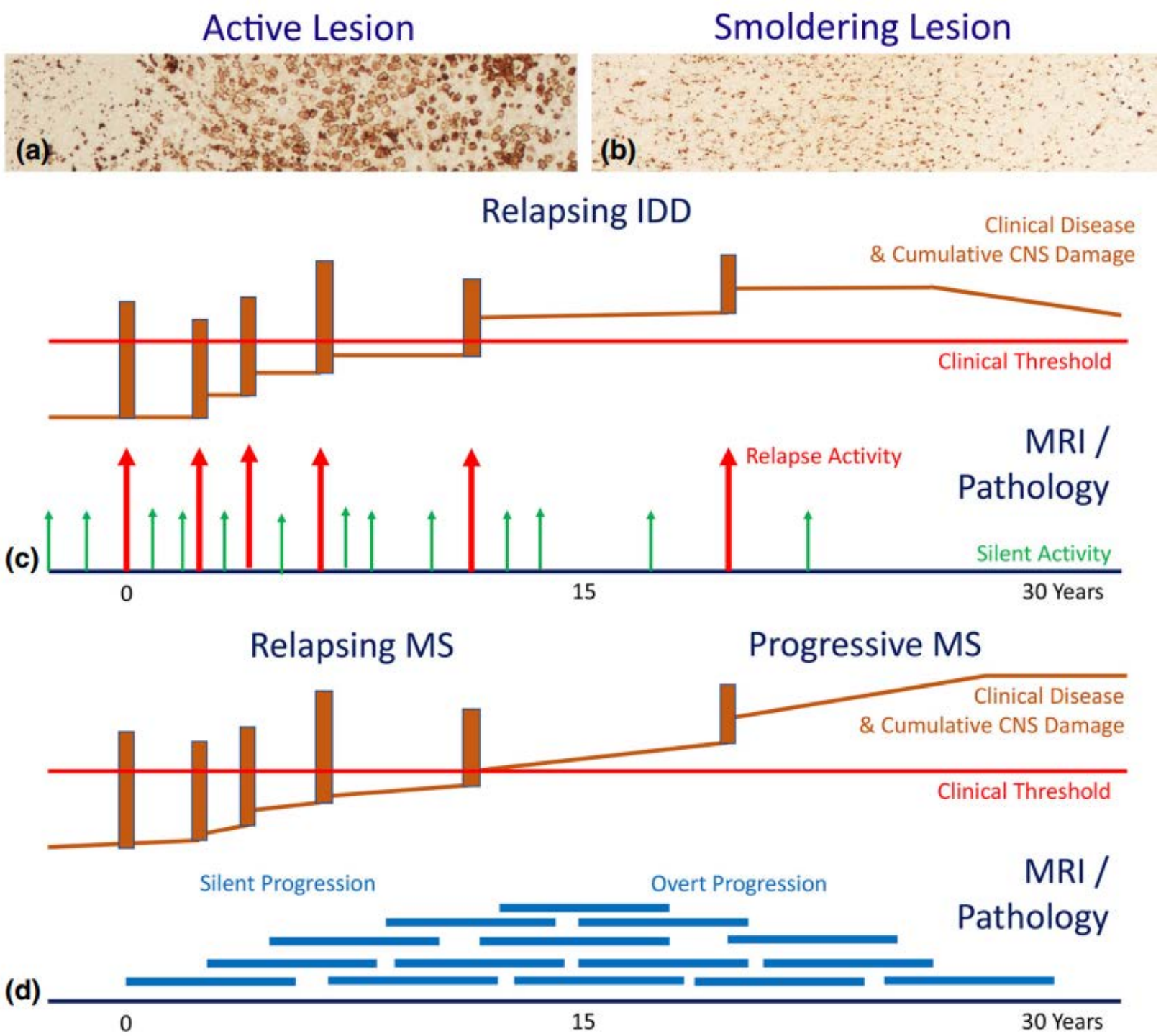
Active Lesion

- Focal new and active white matter lesions are most numerous in early (acute and relapsing)
- Cortical demyelination is already present in the earliest stages of MS

Progressive Lesion

- Slowly expanding lesions
- Cortical demyelination extent massively increases in progressive stage
- Diffuse changes in the normal-appearing white matter are very pronounced in patients with progressive MS
- permanent and destructive lesions in progressive MS also accumulate in low perfusion area

Lassmann H, Cold Spring Harb Perspect Med 2018;8:a028936



Eur J Neurol. 2022;29:2869–2877

Take Home Message

- Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), which gives rise to focal lesions in the gray and white matter and to diffuse neurodegeneration
- The pathological data support the concept that inflammation drives demyelination and tissue injury in all stages of the disease.
- Acute, active and chronic, inactive white matter plaques are distinguished by the nature and extent of the associated inflammatory responses, particularly from lymphocytes, macrophages and microglia.
- MS is not simply a disease of white matter: there can also be prominent grey matter demyelination and axonal and neuronal loss.
- Focal inflammatory infiltrates in the meninges and the perivascular induce demyelination or neurodegeneration through microglia activation

THANK YOU