

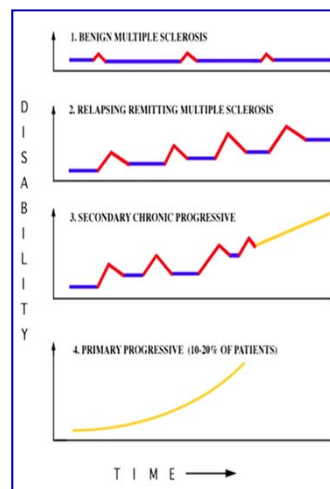
Multiple Sclerosis Pathology

- Introduction to MS
- Gross pathology of MS
- Cellular pathology
- Pathogenetic mechanisms

Prof R Reynolds 2012

MS SYMPTOMS & PATHOLOGY

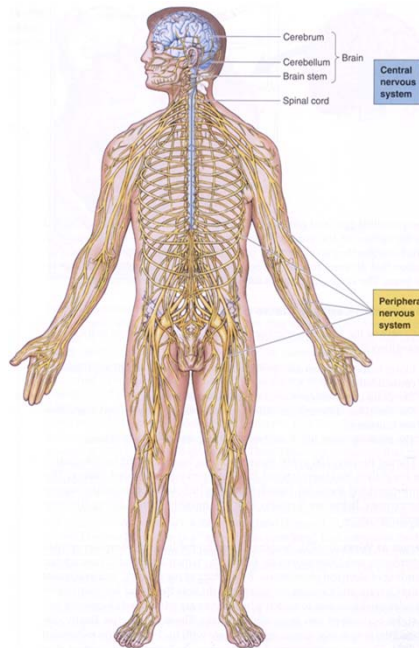
- MS is characterised by multiple episodes of the same or different neurological symptoms separated by periods of remission
- MS follows a very unpredictable and variable disease course from relatively benign forms to rapidly progressive forms.
- Although neurological recovery does occur during the early stages, the majority of MS cases develop chronic progressive symptoms eventually.



The central and peripheral nervous systems

CNS

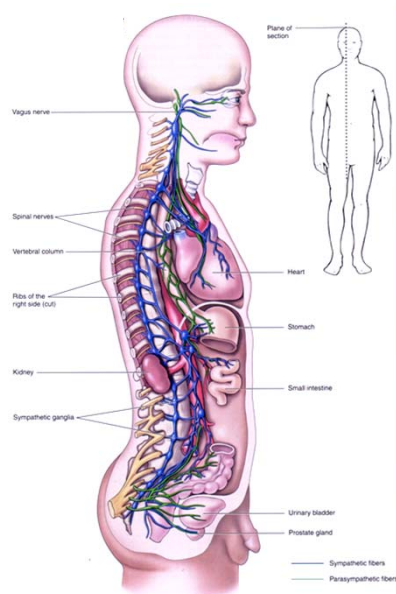
PNS



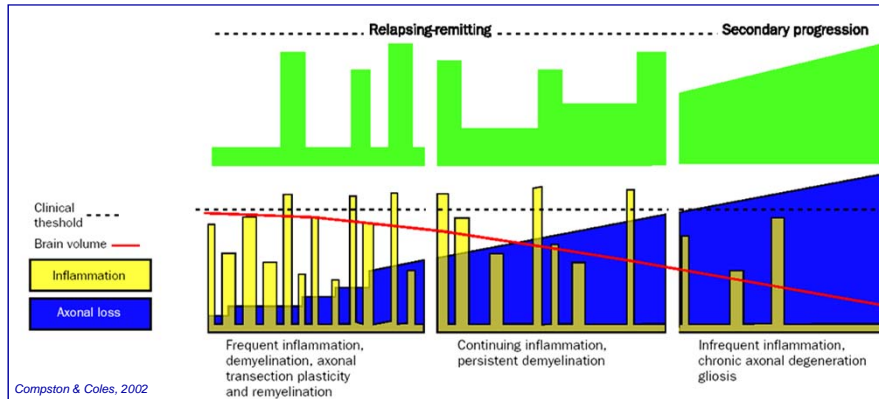
MS damages only the central nervous system

But other parts of the nervous system are affected

The autonomic nervous system



- Gut function
- Blood pressure
- Heart rate
- Kidney function
- Sweating
- Sexual function
- Bladder function



Sub-types or stages of MS

Acute MS – Marburg’s disease

- disease duration < 2 years

Relapsing-remitting

- duration of phase about 10 years

Progressive relapsing

- overlap during middle phase

Secondary progressive

- variable duration, no relapses

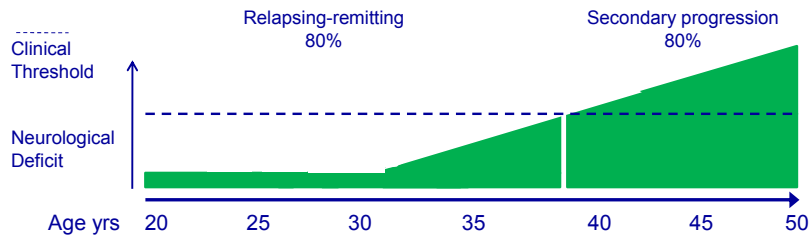
Primary progressive

- later onset, no relapses

Benign

- mild with no conversion

Multiple Sclerosis

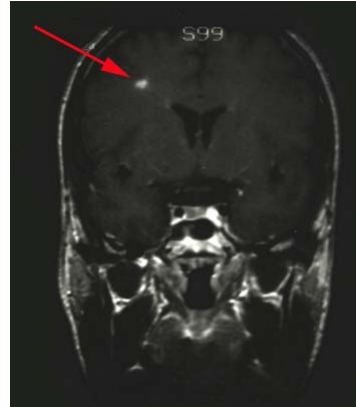
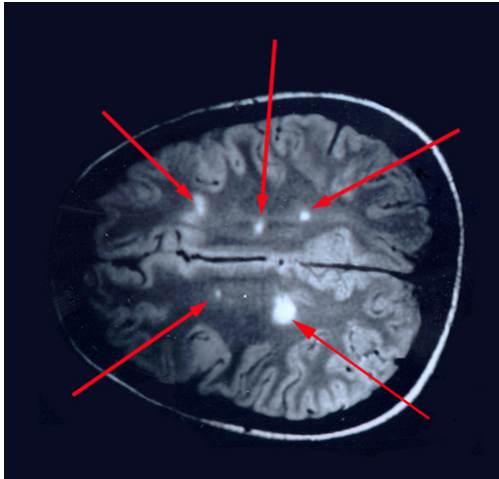


- Autoimmune demyelinating disease of the CNS
- Relapses linked to inflammatory activity
- Progression linked to neurodegeneration

Clinico-pathological correlations in MS

- | | |
|---|---|
| - inflammatory foci without demyelination | - acute relapses |
| - primary demyelination | - acute & chronic |
| - grey matter demyelination | - progressive |
| - axonal loss in lesions | - progressive symptoms |
| - grey matter neuronal and axonal loss | - progressive motor, sensory and cognitive |
| - diffuse white matter changes | - fatigue? |
| - diffuse grey matter changes | - motor, sensory and cognitive symptoms. Fatigue? |

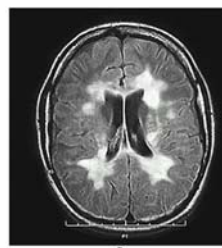
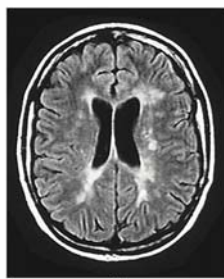
MRI in MS – multiple areas of hyperintense signal



Courtesy of Dr J Rose, Univ. of Utah

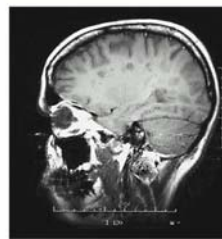
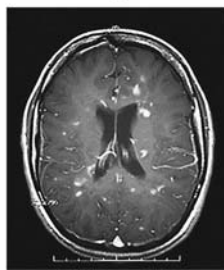
MRI Scans of the Brain of a 25-Year-Old Woman with Relapsing–Remitting Multiple Sclerosis

Initial scan

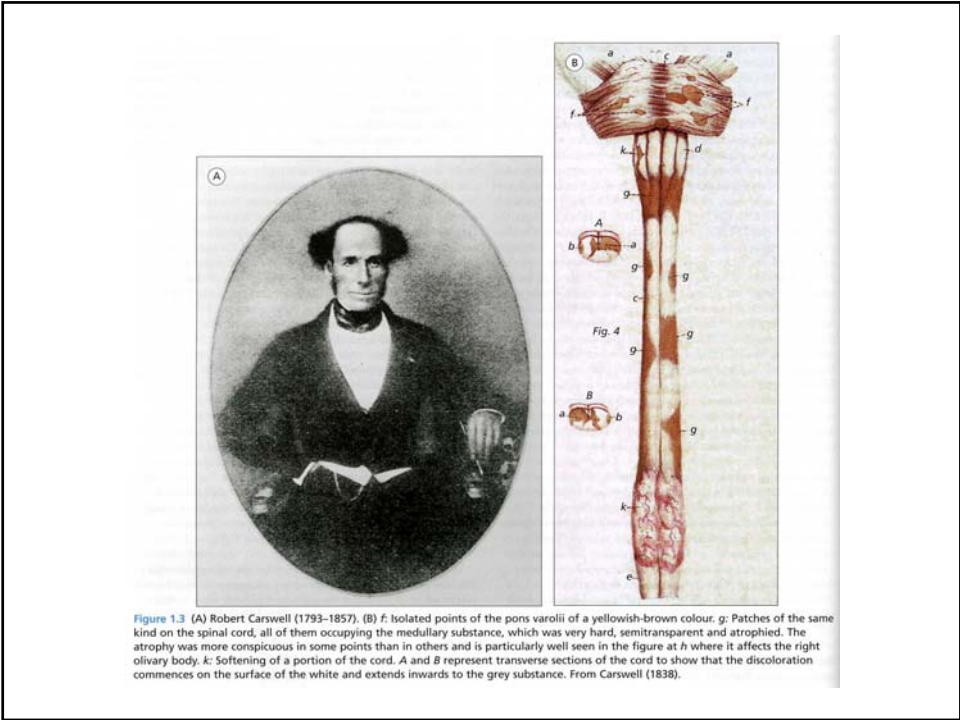


Scan 9 months later

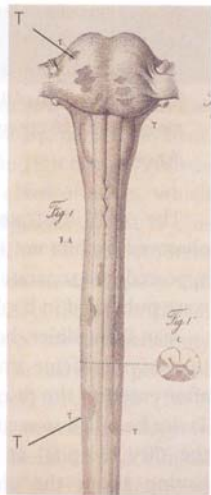
Gadolinium-Enhancing areas



Focal Tissue loss



MS Pathology



Cruveilhier (c1841)

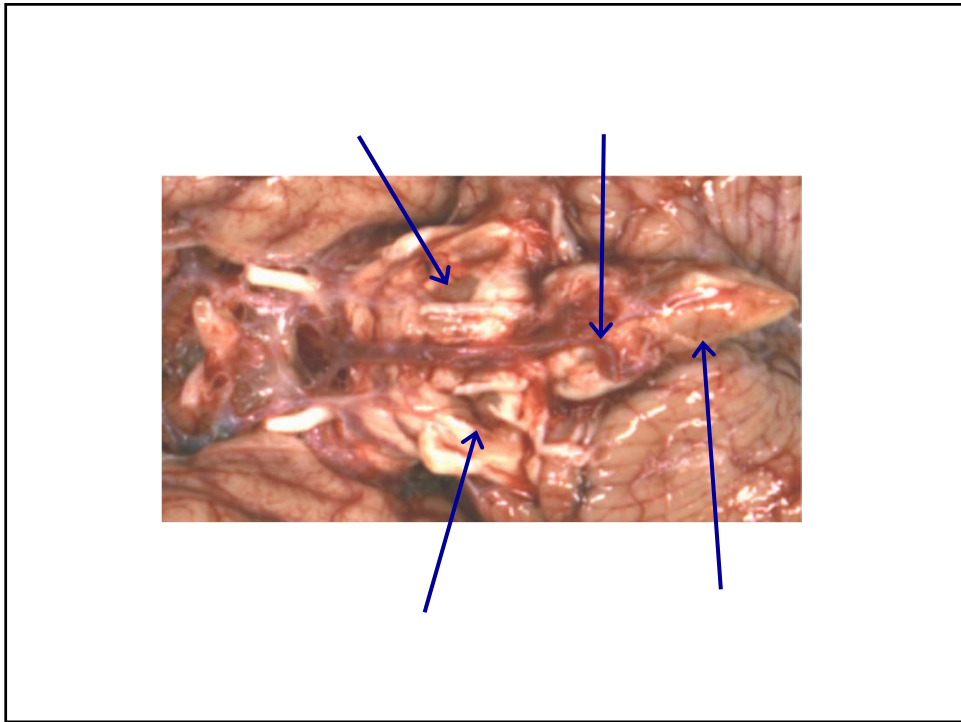
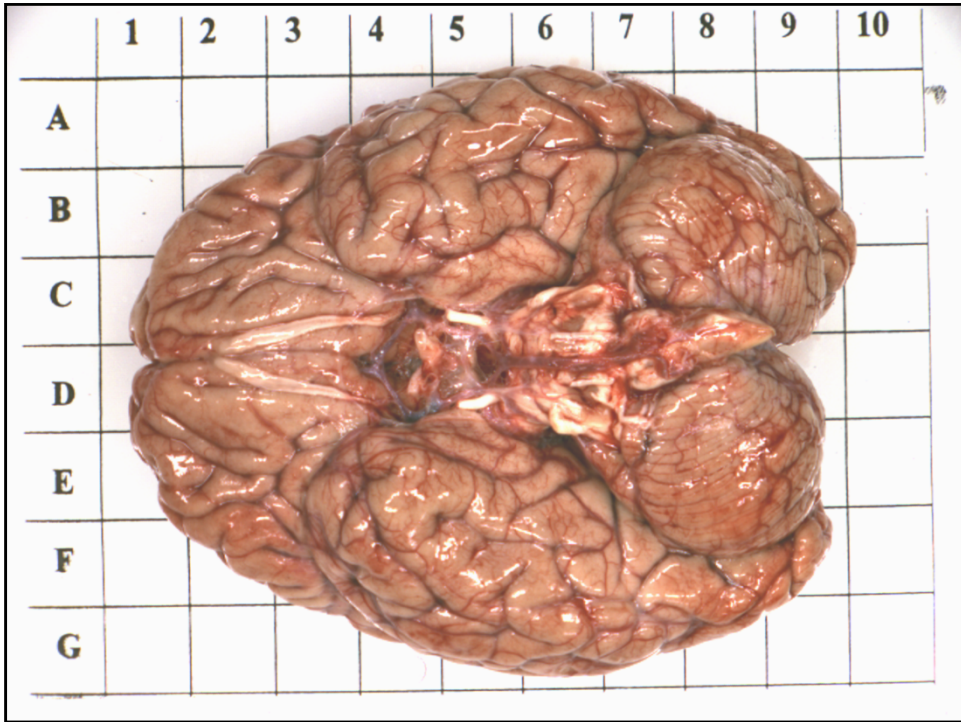


The essential CNS lesion in MS which can be identified at post-mortem and can occur at any site where myelin sheaths are present.

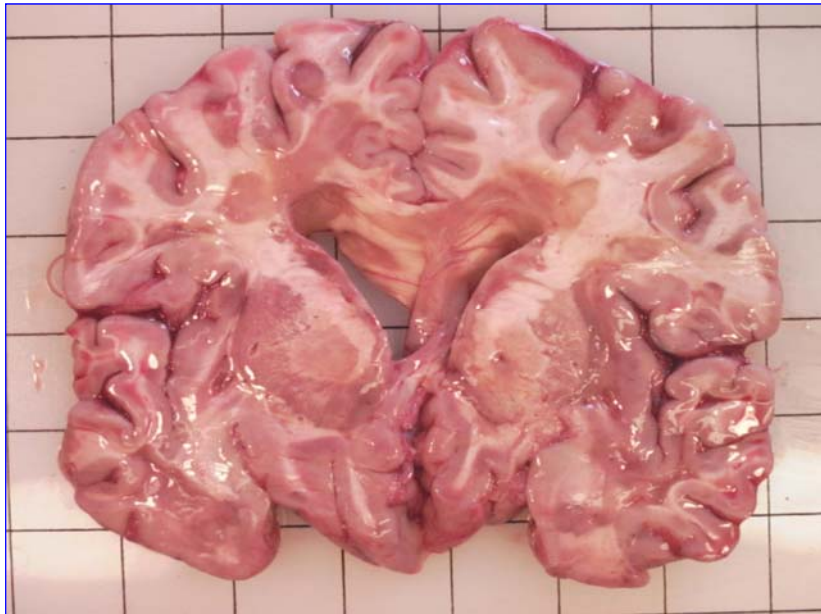
Gross Pathology of MS

- Inflammation
- Demyelination
- Axonal loss
- Neurodegeneration

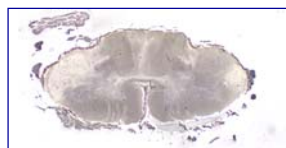




What can we learn from post-mortem studies?



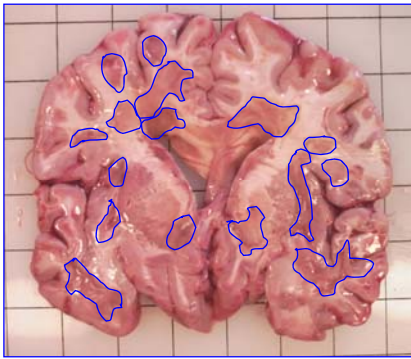
Damage can occur anywhere in the brain and spinal cord



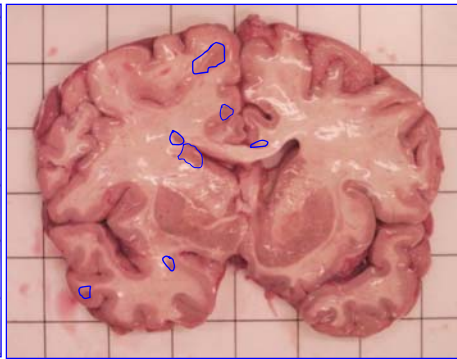
But it is difficult to ascribe every symptom to a particular lesion and not all lesions cause symptoms

Why are symptoms so varied

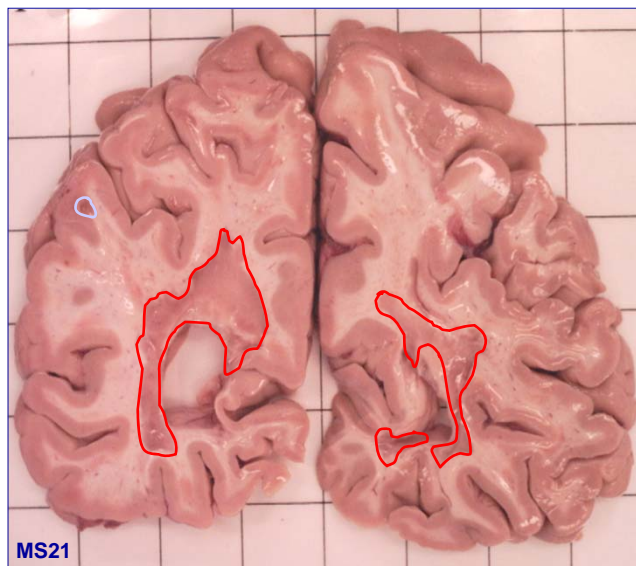
Because the amount and location of damage to the nervous system is different in each person with MS



Disease duration <20 years, age 44



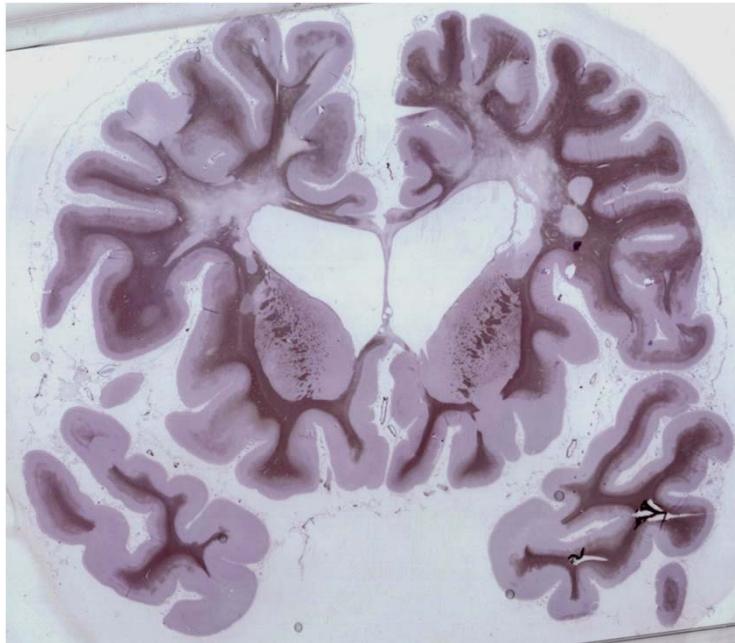
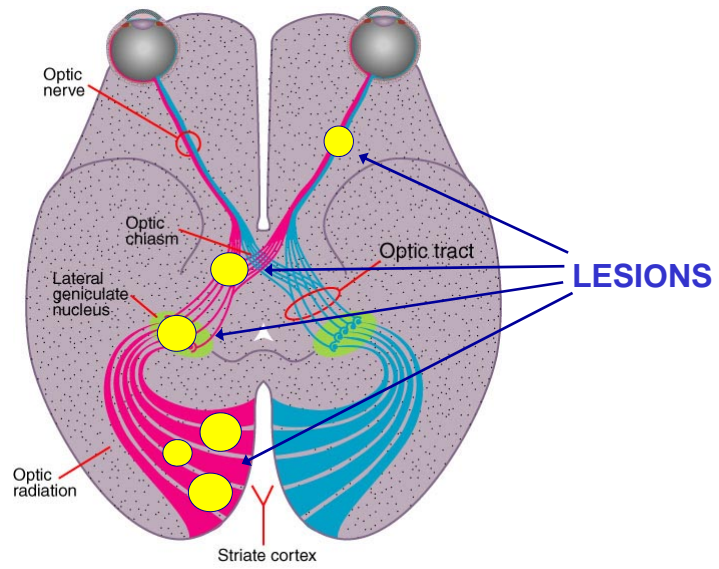
Disease duration 35 years, age 71



MS21

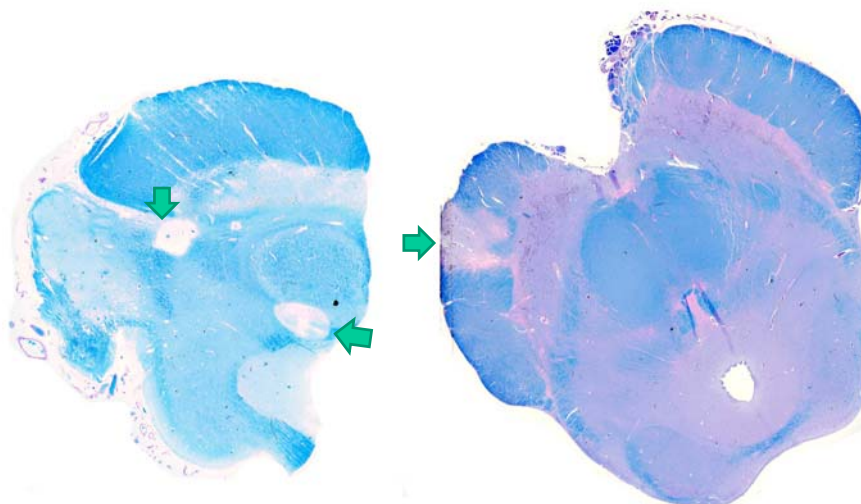
Extensive lesions often follow the lateral ventricles

A particular set of symptoms could be caused by damage in different parts of a system

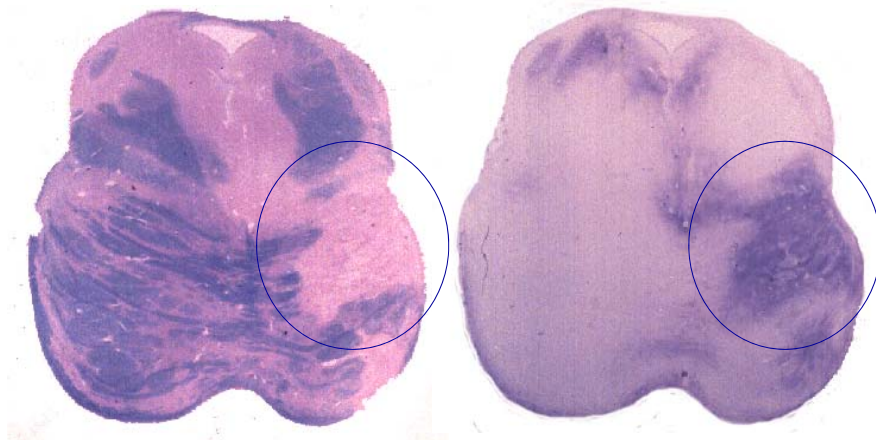




Optic nerve in MS. Transverse section through optic nerve in which only a peripheral crescent of myelin can still be stained



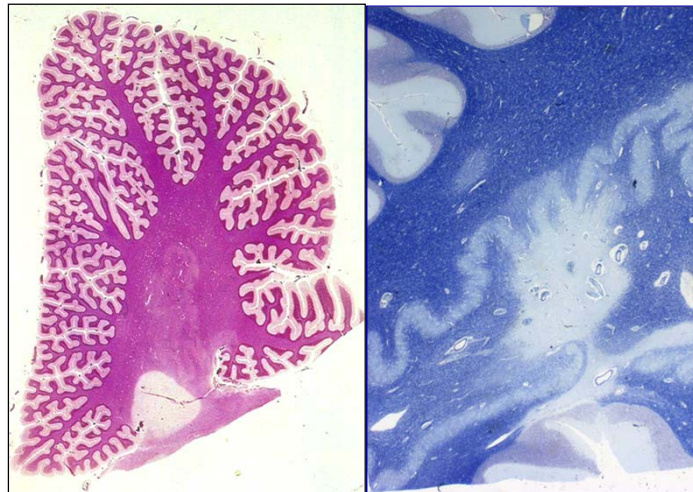
Midbrain. Lesions are common in the substantia nigra and at many levels of the pyramidal tracts



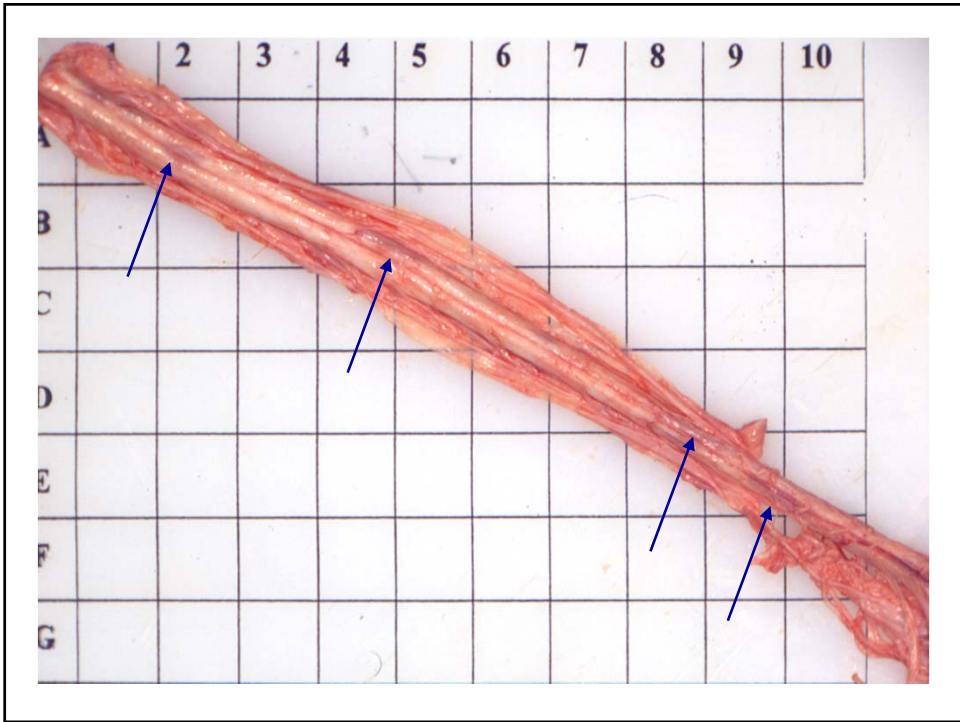
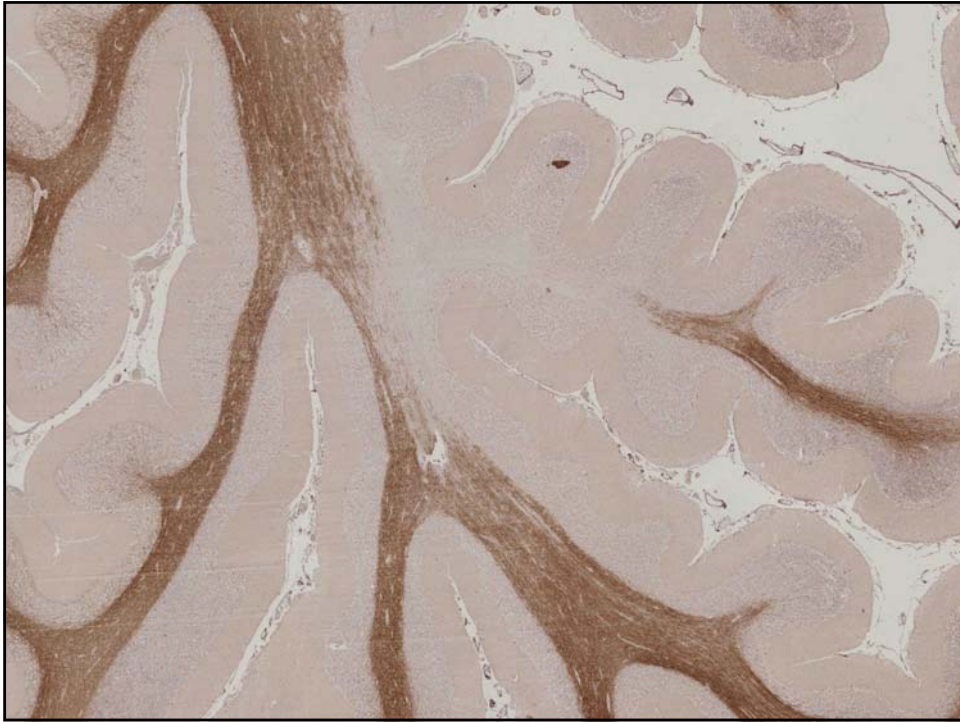
Luxol-fast blue/PAS

Holzer

Brainstem. Lesions are common in the pons and are likely to have major clinical significance

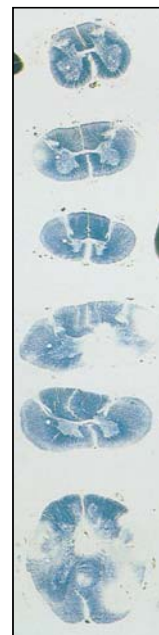
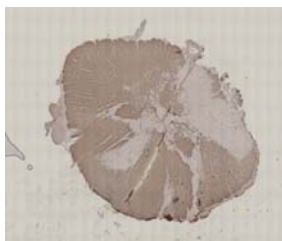
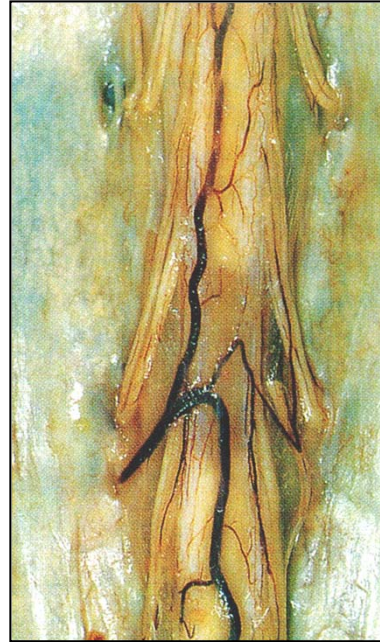


Lesions in the deep cerebellar white matter, nuclei and peduncles



Spinal Cord Pathology

- chronic MS plaque on posterior surface of thoracic spinal cord
- spinal cord lesions often appear shrunken due to loss of axons as well as myelin sheaths



S1

L3

T6

C7

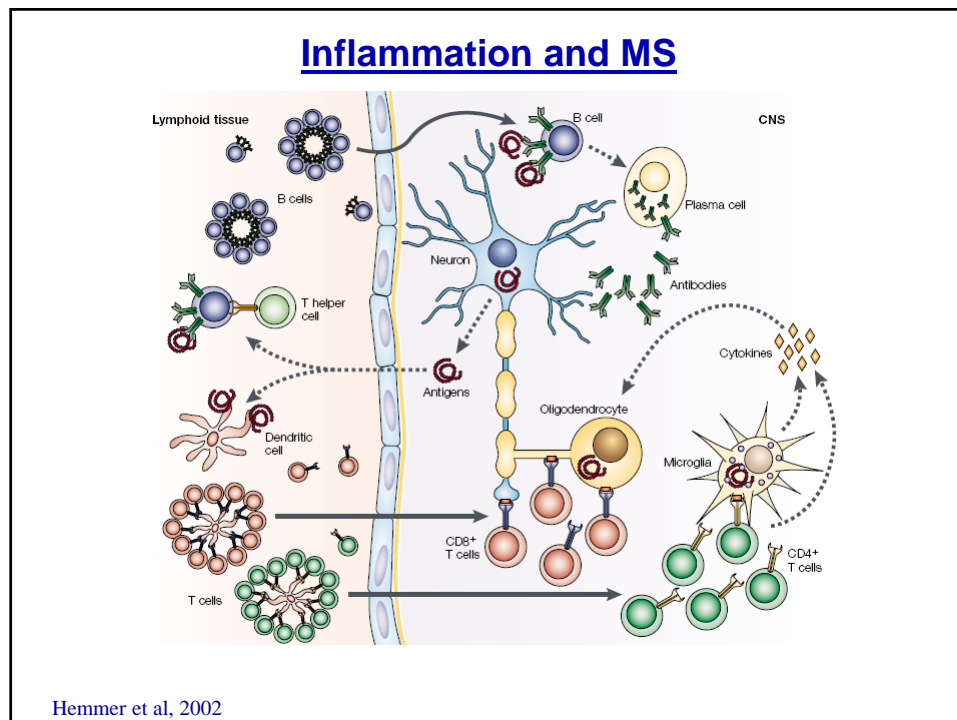
C4

MED

Lesions are often found at multiple levels of the cord but do not follow any particular pattern

Cellular Pathology of MS

- Inflammation
- Demyelination
- Axonal loss
- Neurodegeneration



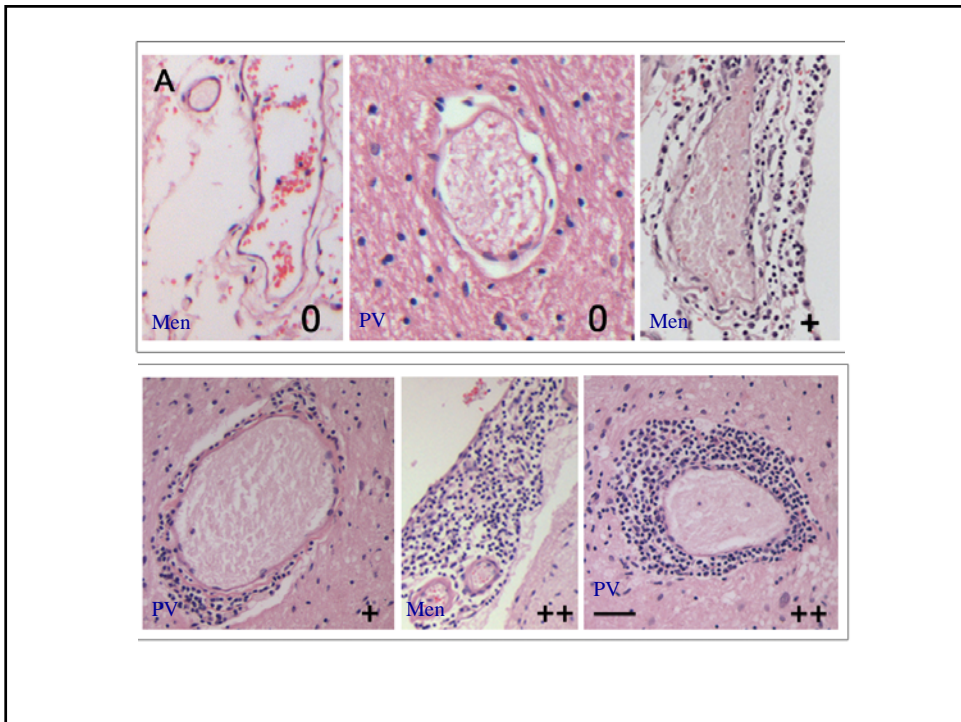
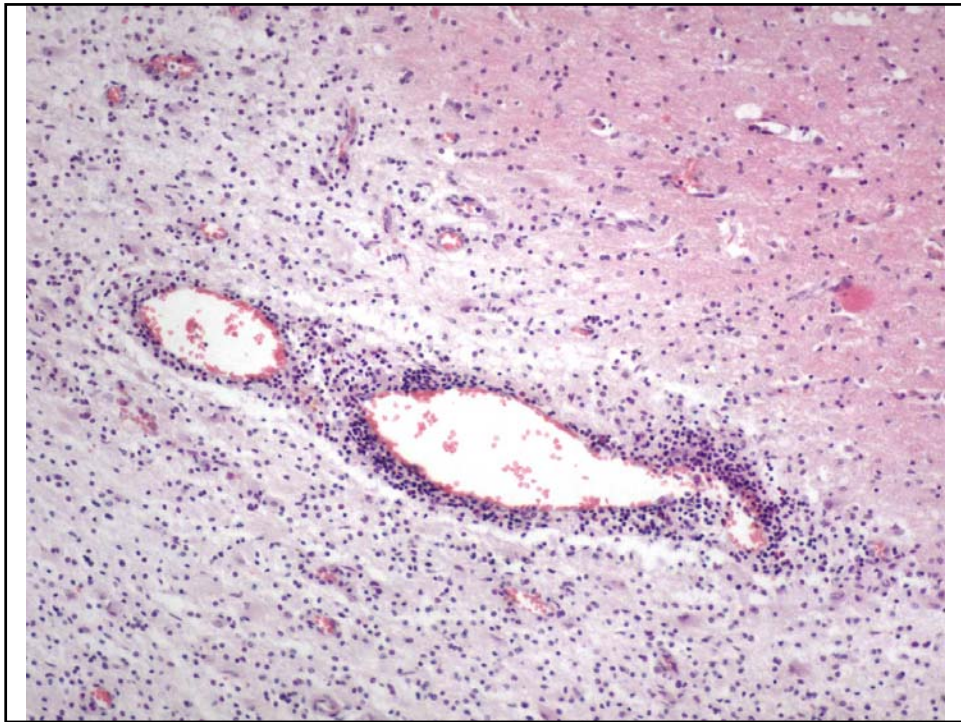
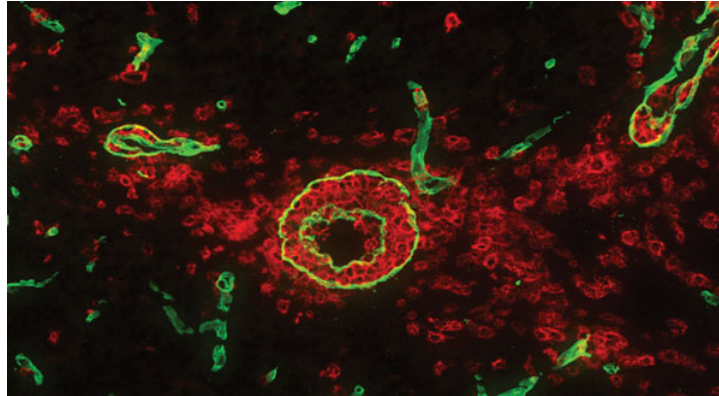


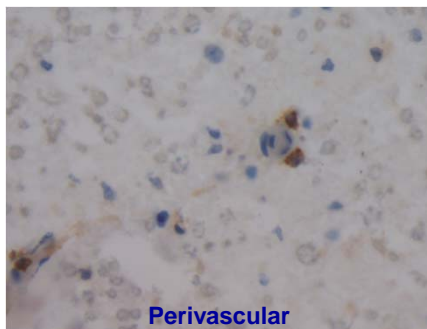
Figure 1 Brain section showing laminin in the basement membranes (green)



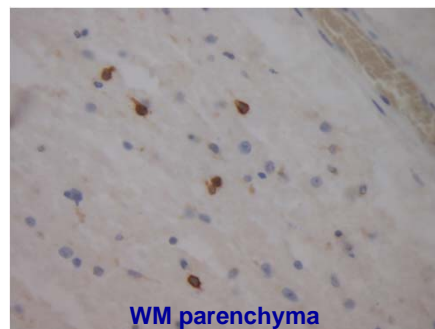
Kathryn Senior (2009) Laminins control T-cell entry into the CNS
Nat. Rev. Neurol. doi:10.1038/nrneuro.2009.76

nature
REVIEWS NEUROLOGY

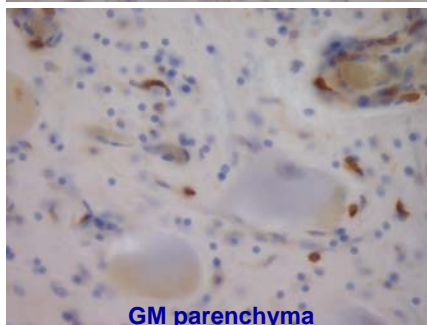
CD4+ T-cells



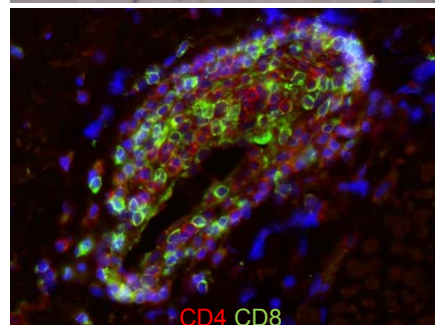
Perivascular



WM parenchyma

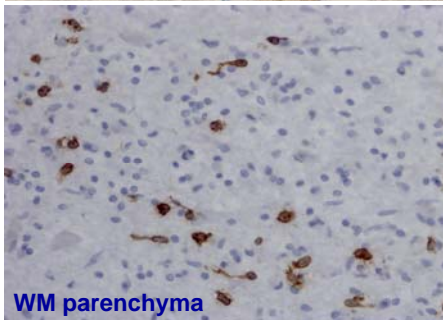
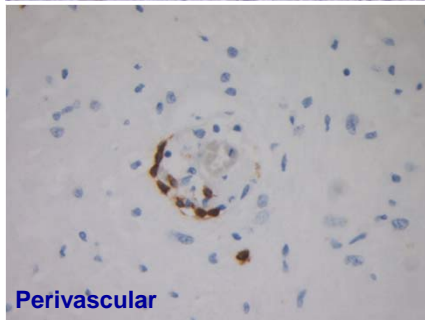
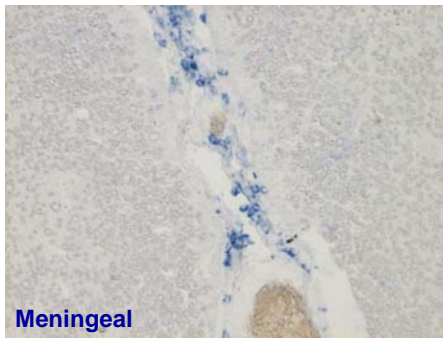
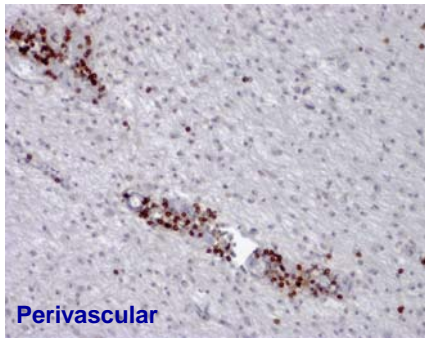


GM parenchyma

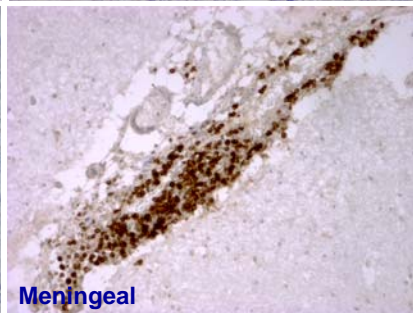
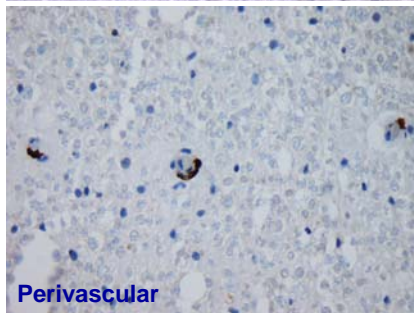
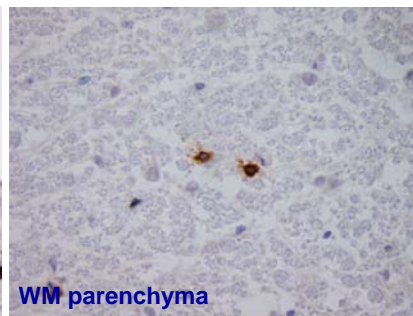
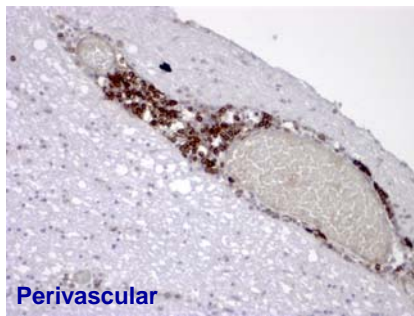


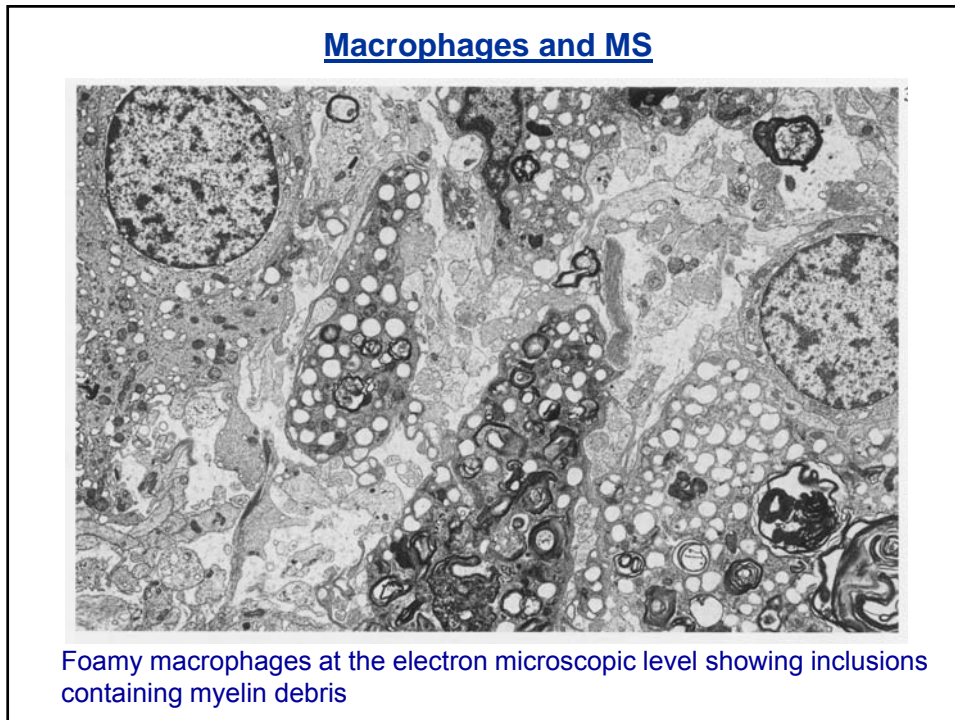
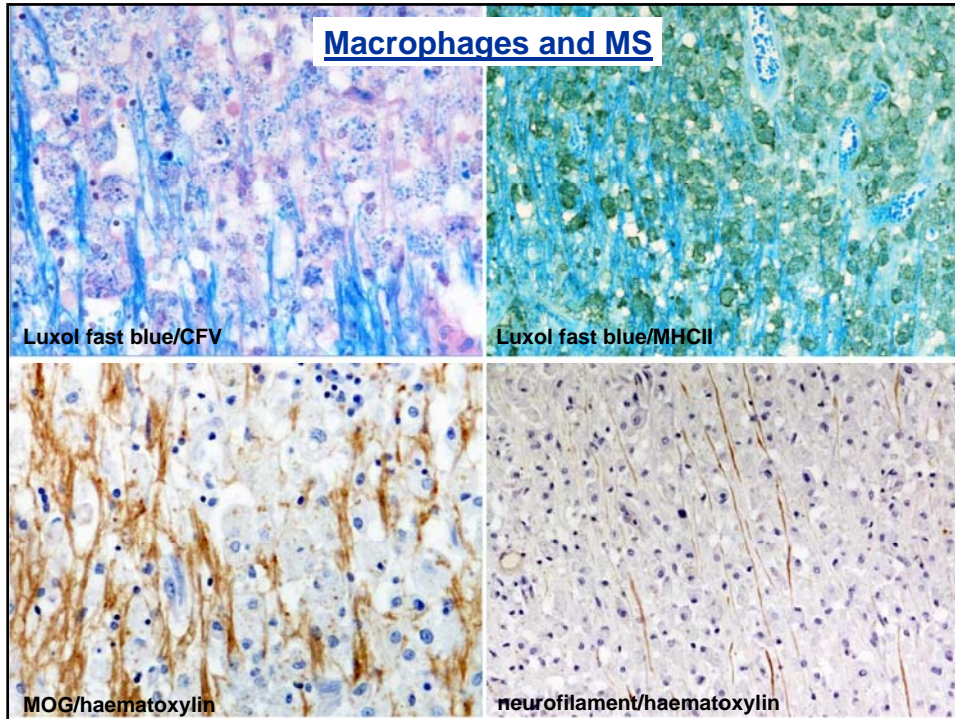
CD4 CD8

CD8+ T-cells

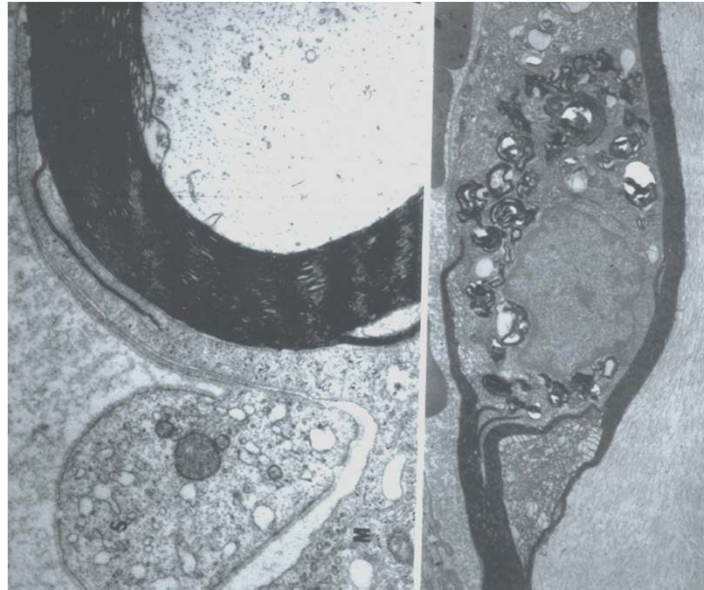


CD20+ B-cells and plasma cells





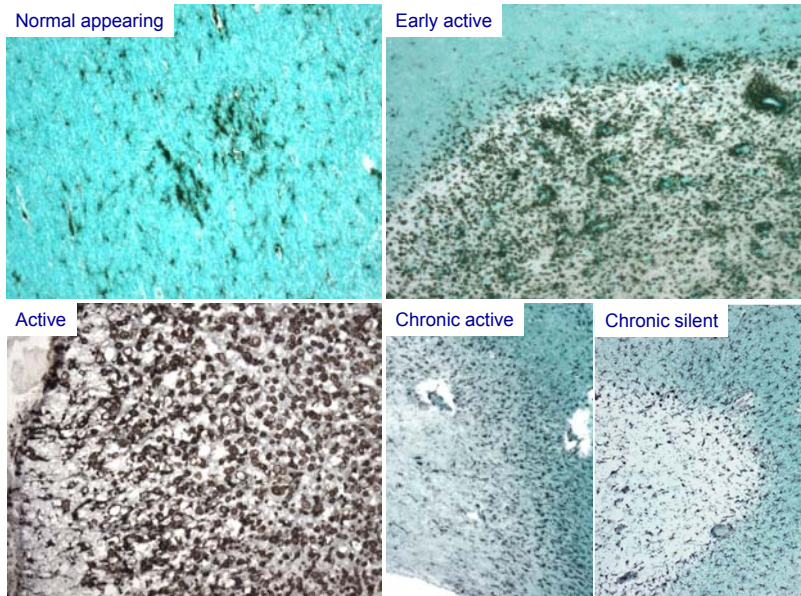
Macrophages and MS



Lesion stages

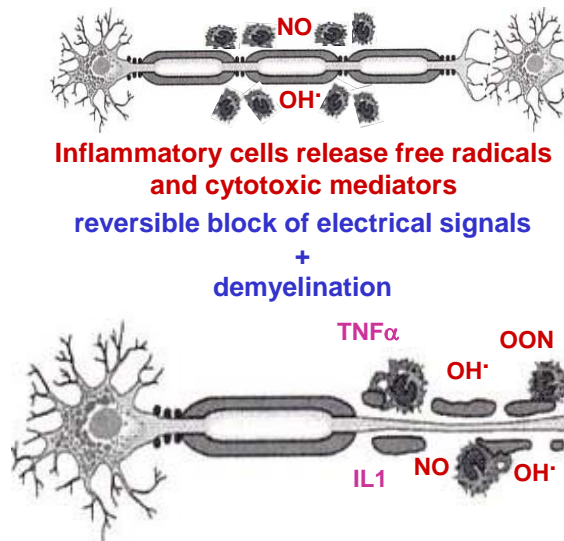
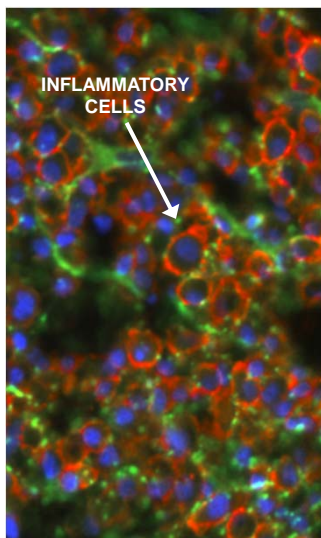
- **Acute active:** macrophages throughout the lesion with synchronous myelin destruction.
- **Chronic active:** numerous macrophages at expanding plaque edge; centre contains few cells.
- **Chronic inactive:** hypocellular plaques with no macrophages and no ongoing demyelination.
- **Shadow Plaque:** represent remyelinated lesions with thin myelin sheaths.
- **Destructive plaques:** destruction of axons, oligos, astros and myelin loss - Marburg type MS and Devic's disease.

STAGES OF MS LESION FORMATION



All stages can be seen at any one time point in the MS brain and spinal cord

Inflammation produces transient symptoms

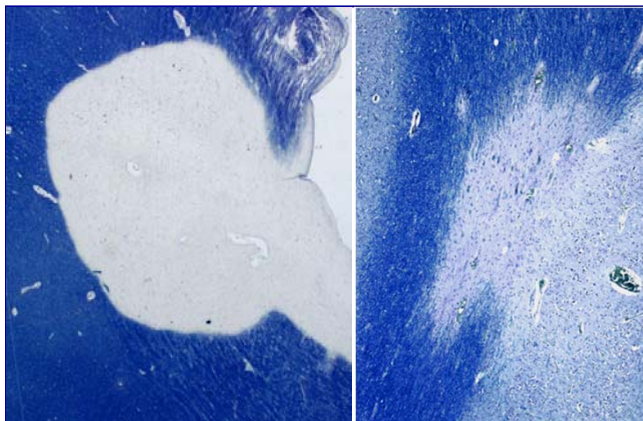
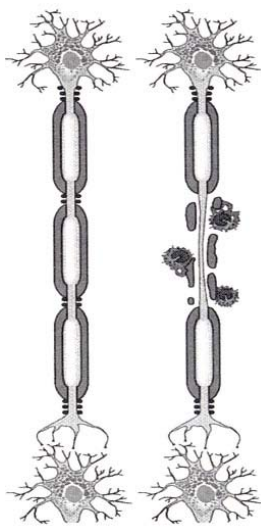


Immunomodulatory treatments aim to stop these effects

Inflammatory mechanisms of neuronal dysfunction

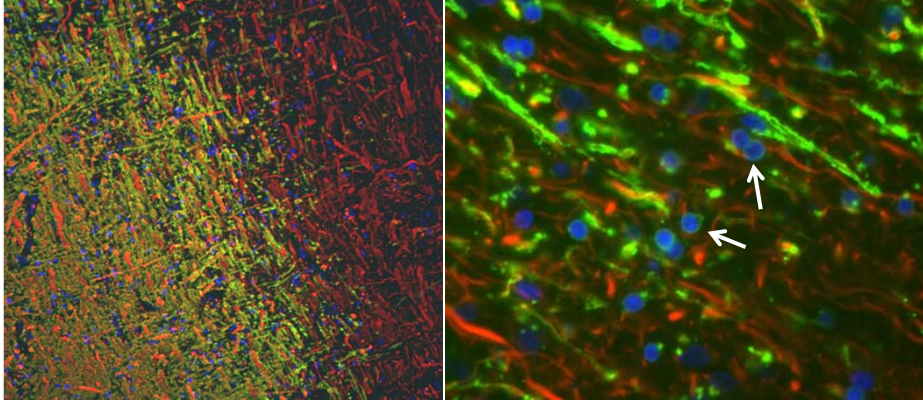
- release of free radicals by peripheral immune cells and activated microglia
 - Nitric oxide (NO), peroxynitrite (OON⁻), hydroxyl radicals (OH⁻)
- glutamate release by microglia resulting in excitotoxicity
- hypoxia
- cytotoxic cytokine release by immune cells and microglia
 - TNF, lymphotoxin, IL1 β , interferon- γ

Demyelination in MS

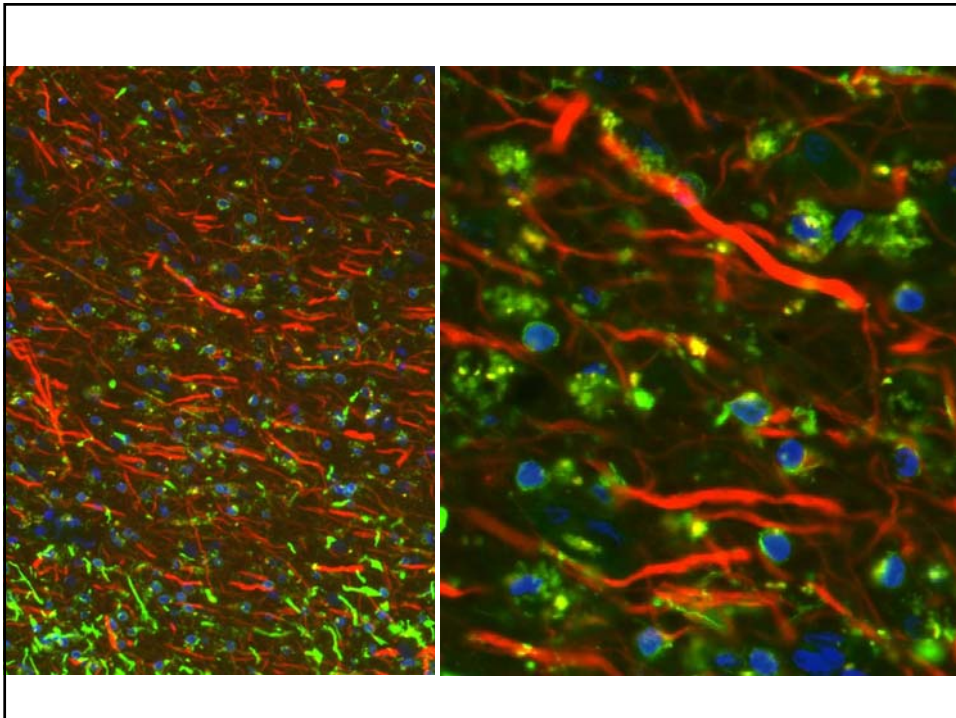


The borders of chronic silent lesions are usually well defined whereas the borders of active lesions are more ragged

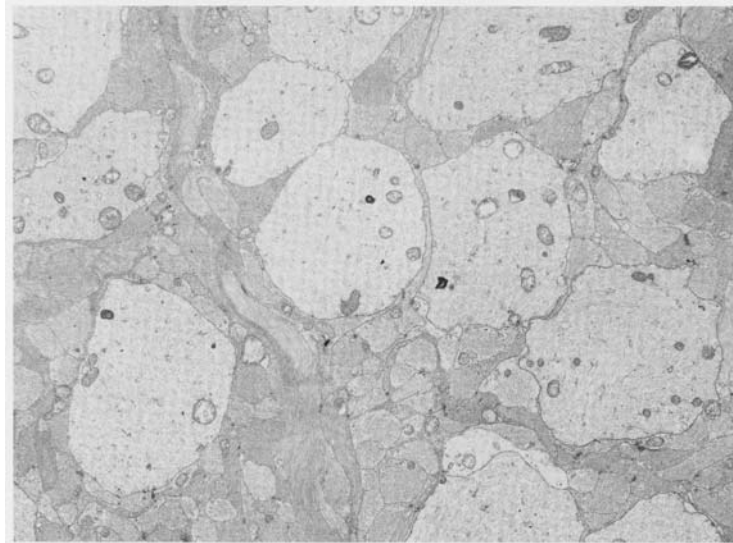
Demyelination in MS Oligodendrocytes in MS lesions



Oligodendrocytes are generally absent from the centre of chronic lesions although increased numbers are often seen at the lesion edge. MBP-expressing cells were found in large numbers at the edge of some MS lesions.

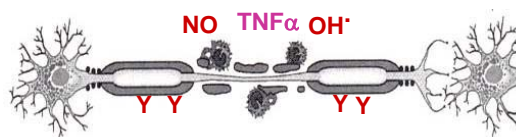
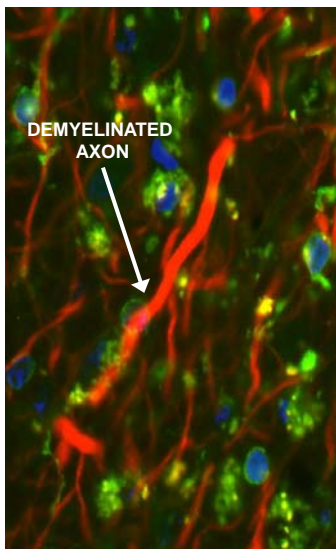


Demyelination in MS

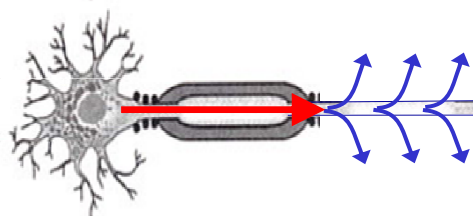


Bare axons surrounded by the fibrous processes of astrocytes in a chronic MS plaque

Demyelination can produce chronic symptoms



Inflammatory cells release antibodies and cytotoxic mediators that damage myelin



Without myelin electrical signals leak out and fade away and axons become more vulnerable to damage

Mechanisms of demyelination

- release of free radicals by peripheral immune cells and activated microglia leading to oligodendrocyte death
 - Nitric oxide (NO), peroxynitrite (OON⁻), hydroxyl radicals (OH⁻)
- glutamate release by microglia resulting in excitotoxicity to oligodendrocytes
- cytotoxic cytokine release by immune cells and microglia
 - TNF & lymphotoxin- α are both toxic to oligodendrocytes
- Anti-myelin antibodies and complement
 - multiple possible antigens

A white matter lesion centric view of MS pathology



Clinico-pathological correlations in MS have focussed primarily on white matter inflammation and demyelination (based on MRI)

Lack of correlation between disease progression and inflammation/demyelination

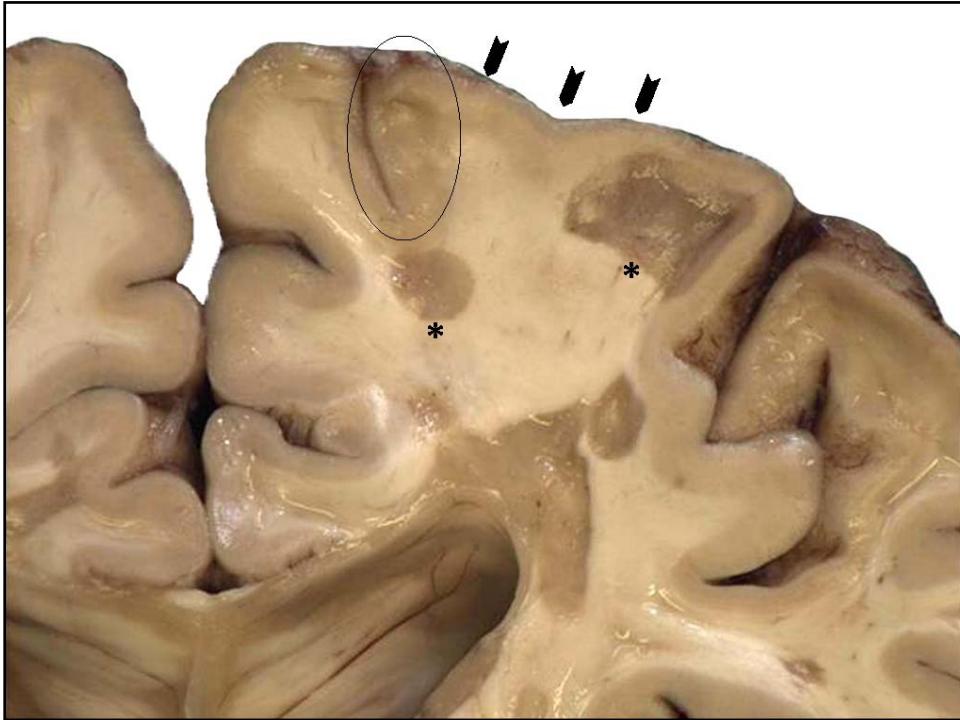
- inflammation and demyelination are key features of MS visible on MRI
- MRI lesion load and rate of appearance of new lesions correlates poorly with clinical progression
- immunomodulatory therapies reduce relapse rate but fail to prevent long term progression of disability

Good correlation between disease progression and grey matter atrophy

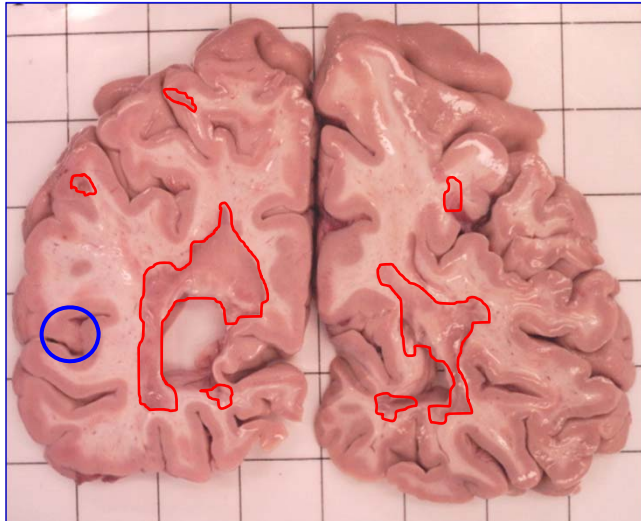
(Fisniku et al, 08)

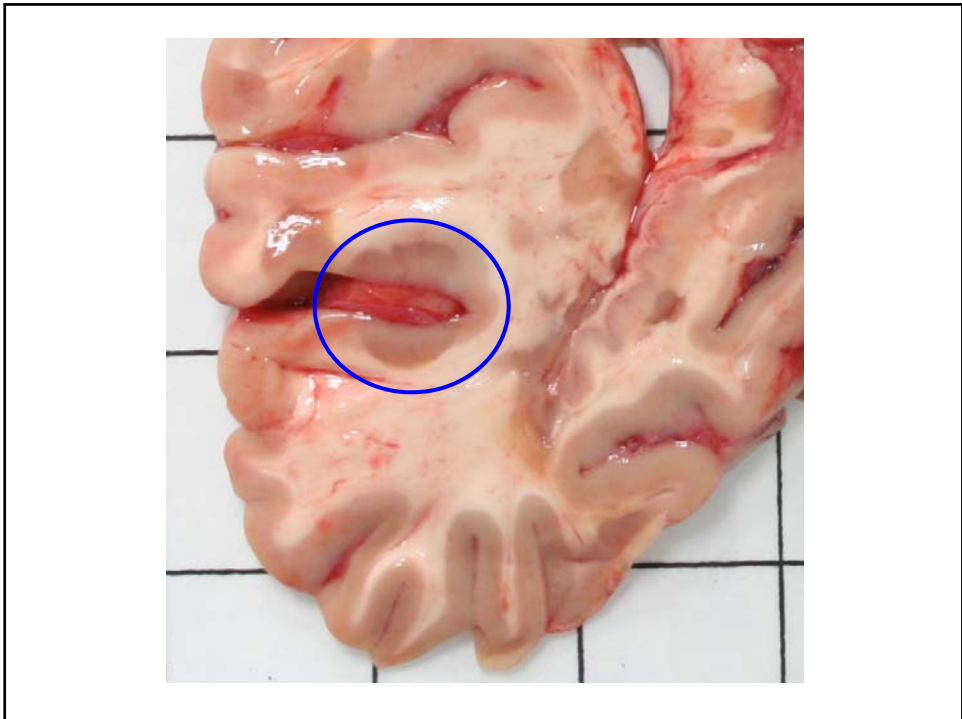
Cortical Pathology

- Earlier either overlooked or underestimated but recently attracted increased attention
- Chronic MS: average 15-25% cortical demyelination, even up to 70%
- Extensive cortical demyel - in 90% pts in Ch MS.
- Not only cortex but deep grey matter and spinal GM.

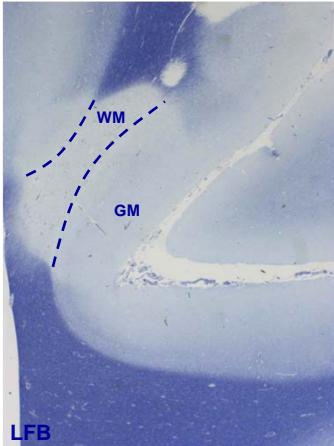


Multiple areas of damage to the grey matter

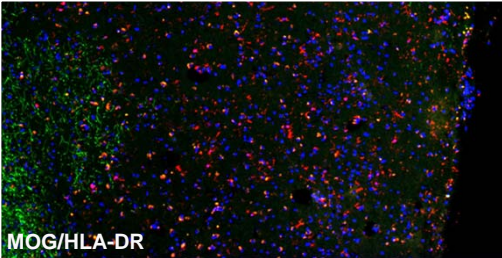
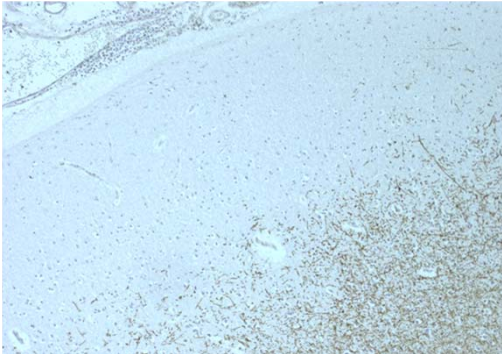




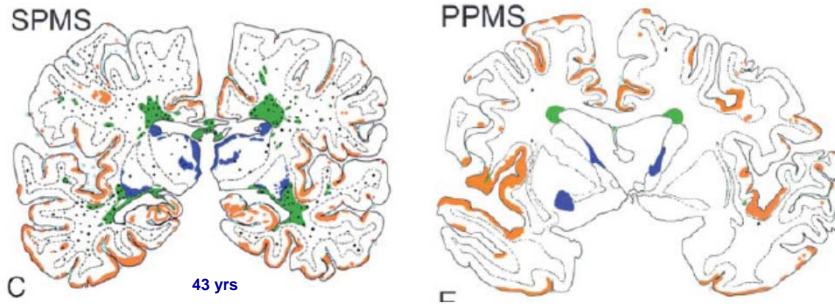
Pathogenesis of grey matter lesions



Grey matter lesions are best identified using myelin protein immunostaining



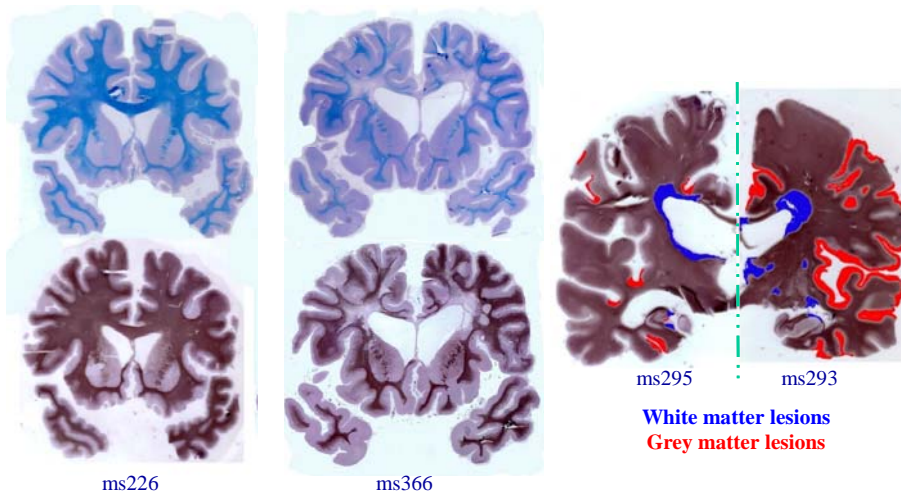
In many MS cases cortical grey matter demyelination covers as extensive an area as WM demyelination



Kutzelnigg et al, 2005

- type I leucocortical lesions
- type II intracortical lesions
- type III subpial lesions – cover greatest area of neocortex

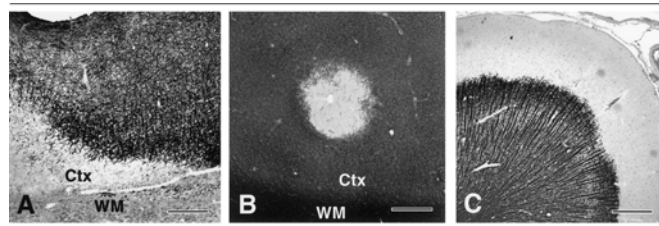
Grey matter demyelination is extensive in some cases



ms295 ms293

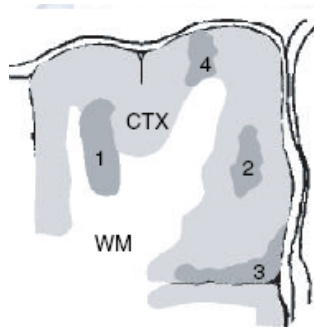
White matter lesions
Grey matter lesions

Grey matter lesion location rather than inflammatory activity defines type



Peterson, AnnNeurol 2001

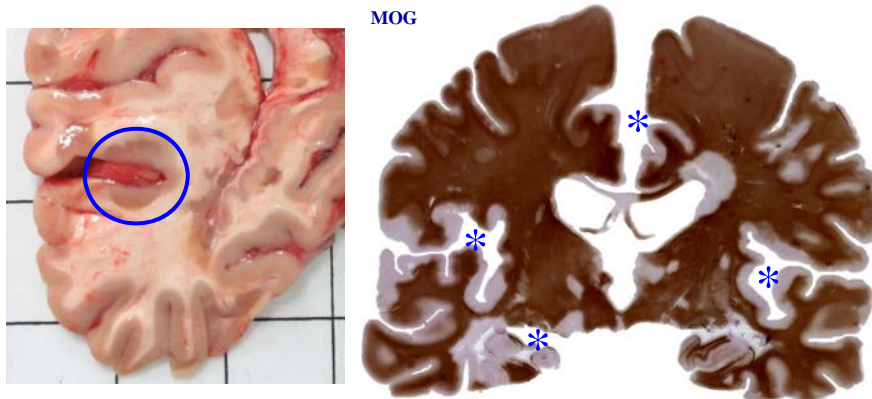
type 1 leucocortical lesions; type 2 intracortical lesions; type 3 subpial lesions



Type 4= extend the entire width of the GM to the WM

• Type 3 lesions account for the largest area of cortical demyelination. Seen as a 'ribbon' of demyelination that can often extend over multiple gyri

Grey matter demyelination is extensive and often covers a greater area than WM demyelination



- Sub-pial lesions are commonest and extend over multiple gyri
- GM demyelination also extensive in other CNS areas that are exposed to the CSF

Is the degree of cortical pathology is controlled by the level of the inflammatory milieu in the CSF of the subarachnoid space?

Meningeal inflammation and lymphoid-like structures in MS

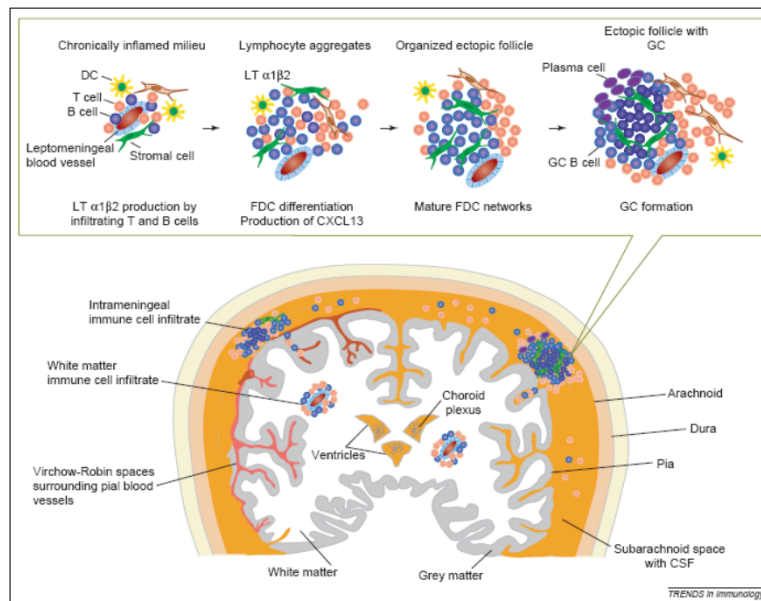


The presence of the tertiary lymphoid structures in the depths of the cerebral sulci:

- reduced CSF flow
- protected microenvironment
- favours the homing and retention of inflammatory cells

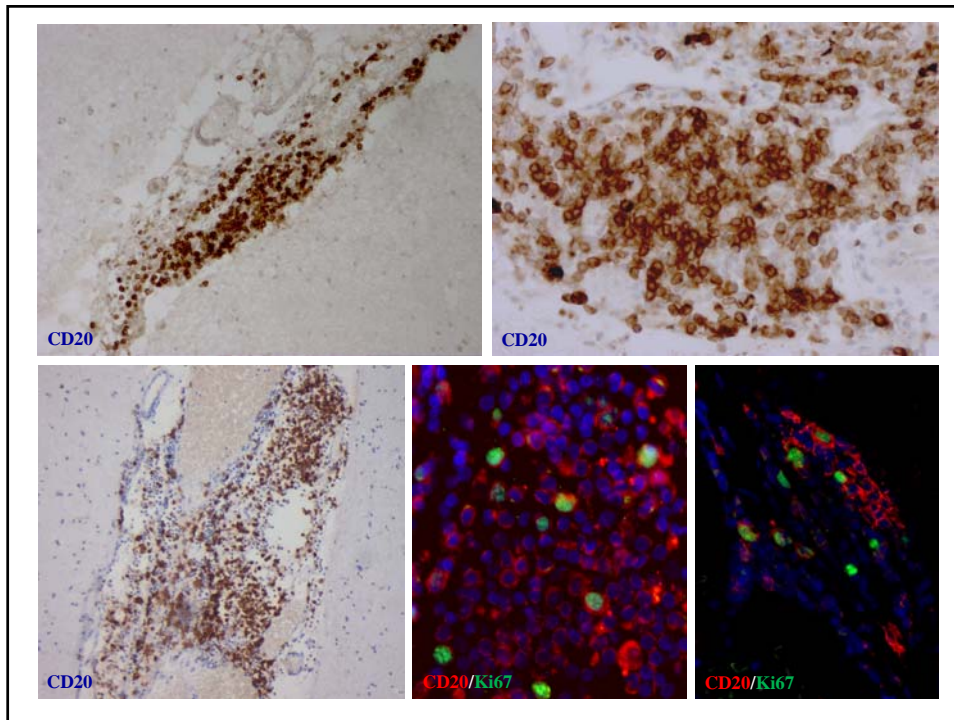
Serafini et al 2004 Brain Pathol

A role for B-cells in cortical pathology

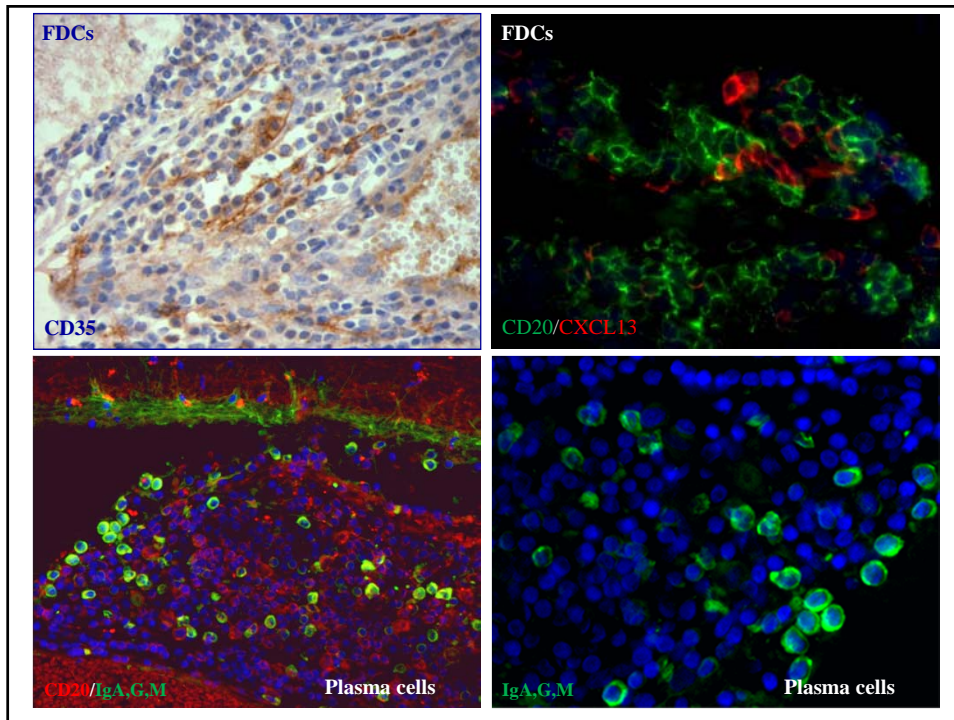
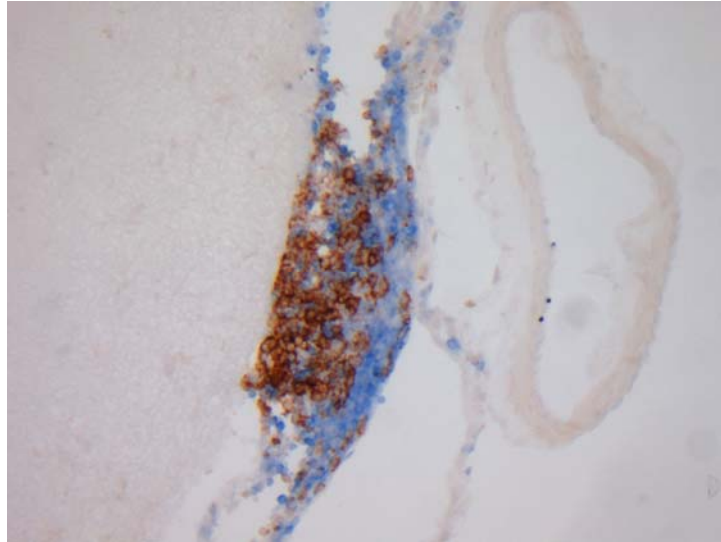


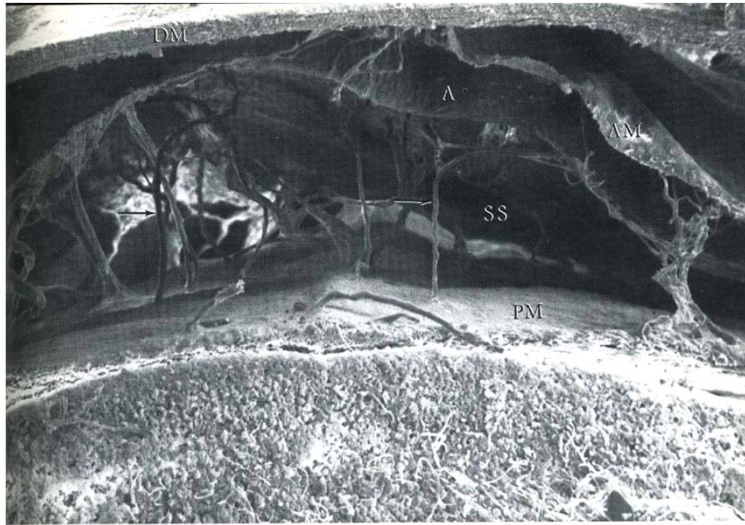
Tertiary lymphoid structures are a feature of MS grey matter pathology:

- ectopic meningeal lymphoid structures characterised as B-cell follicles due to: CD20+ B-cells; Ki67+ B-cells; Ig+ plasma cells; CD35+ FDCs; CXCL13+ FDCs; CD3+ & CD8+ T-cells
- cellular composition reminiscent of tertiary lymphoid structures: sites of B cell activation, clonal expansion and maturation
- hallmark of a range of autoimmune conditions such as Hashimoto's thyroiditis, Graves disease, rheumatoid arthritis where they associate with a more damaging disease.



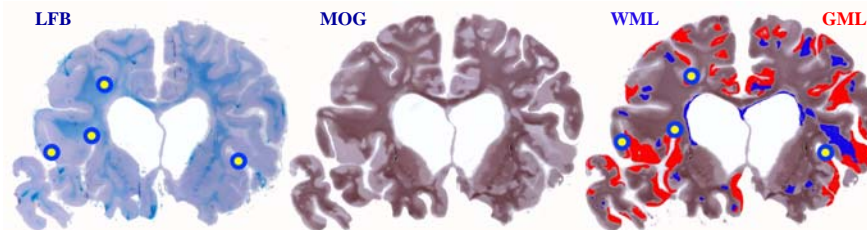
T-cell and B-cell zones?



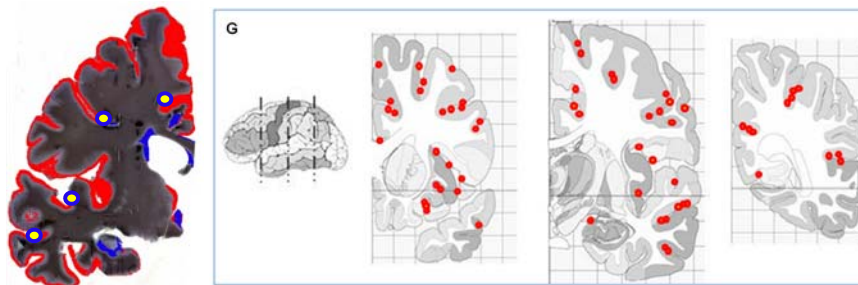


- the formation of true tertiary lymphoid structures with a germinal centre is constrained by the architecture of the subarachnoid space, a fluid filled space with variable rate of flow.
- architecture of the subarachnoid space may determine the structure, size and organisation of the tertiary lymphoid follicles

B cell follicles and cortical pathology



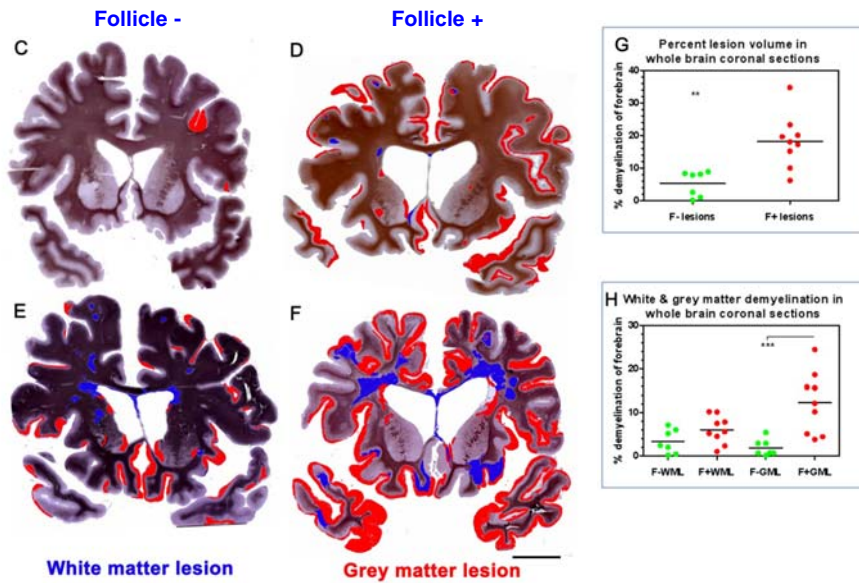
● Location of meningeal follicle



Analysed whole hemispheric sections to study frequency and distribution in forebrain

- Variable in size and location
- Found in 18.1% of blocks analysed (6-67%)

F+ cases have proportionally greater GM demyelination

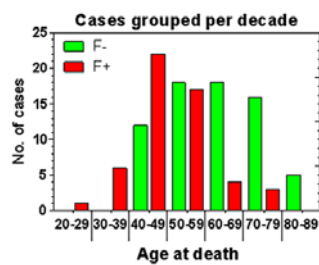
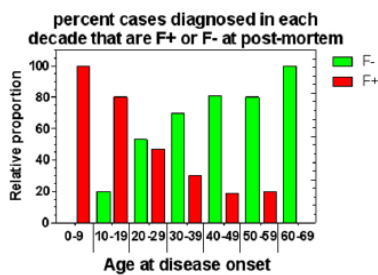
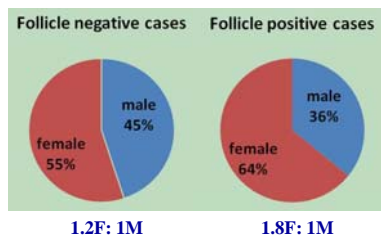


Incidence and clinical outcome measures of F+ and F- cohorts

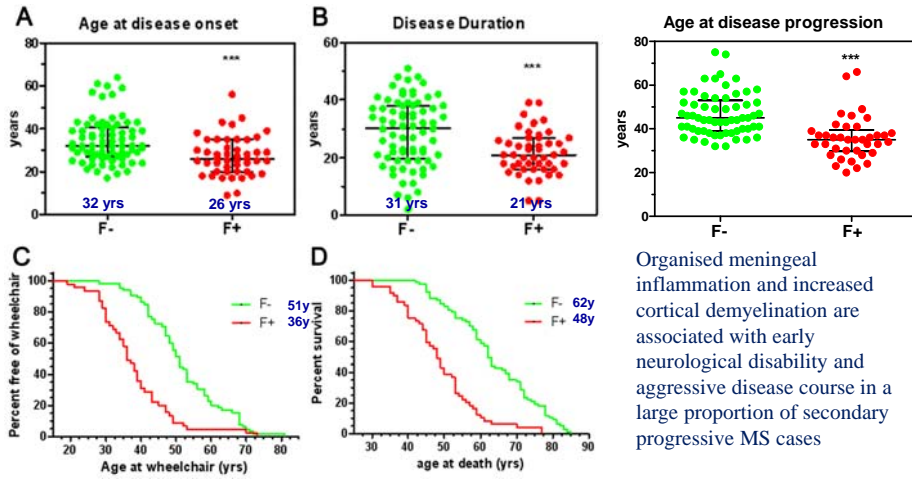
- Substantial proportion of MS are F+

126 cases screened → 49 cases meningeal follicles = 40%

- Greater female bias

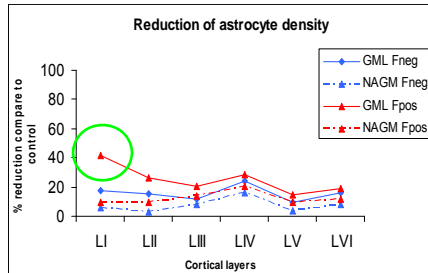
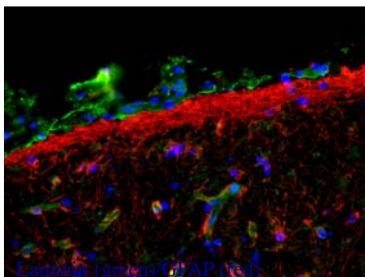
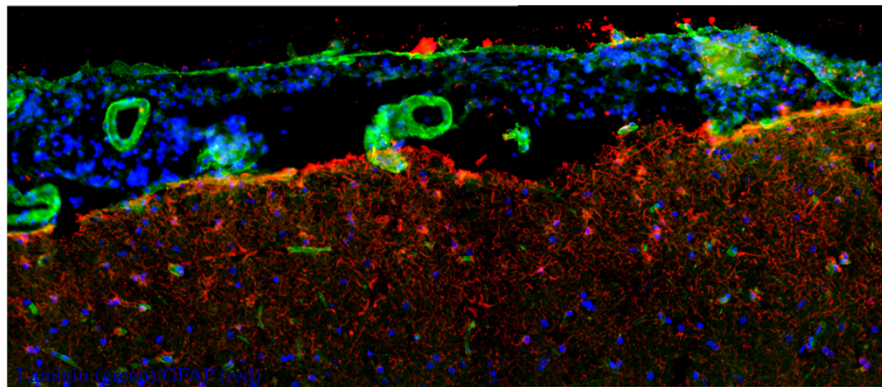


Incidence and clinical outcome measures of F+ and F- cohorts

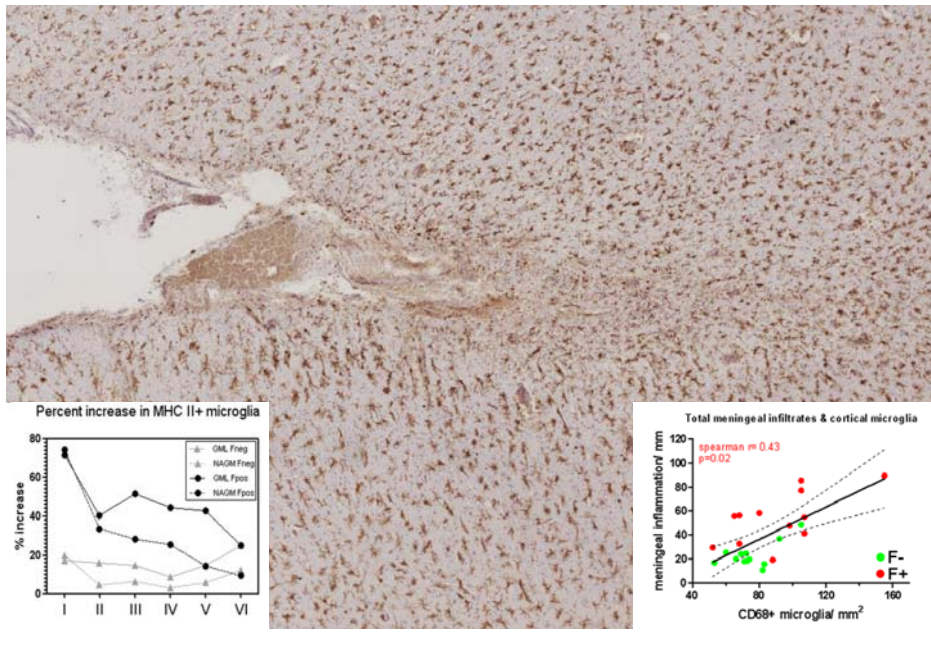


Organised meningeal inflammation and increased cortical demyelination are associated with early neurological disability and aggressive disease course in a large proportion of secondary progressive MS cases

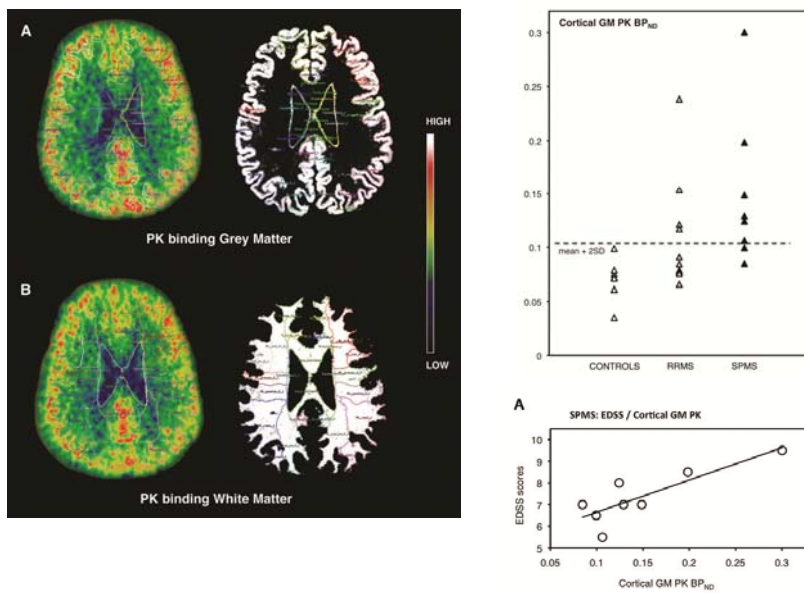
Howell et al, 2011



A gradient of microglial numbers and activation state



In vivo PET imaging of cortical pathology



Clinico-pathological correlations in MS

- | | |
|---|--|
| - inflammatory foci without demyelination | - acute relapses |
| - primary demyelination | - acute & chronic |
| - axonal loss in lesions | - progressive symptoms |
| - grey matter demyelination | - progressive |
| - grey matter neuronal and axonal loss | - progressive motor, sensory and cognitive |
| - diffuse white matter changes | - fatigue? |
| - diffuse grey matter changes | - motor, sensory and cognitive symptoms |

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