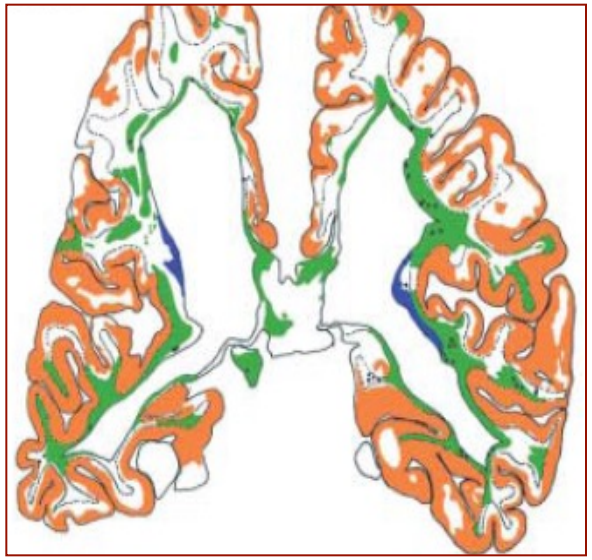
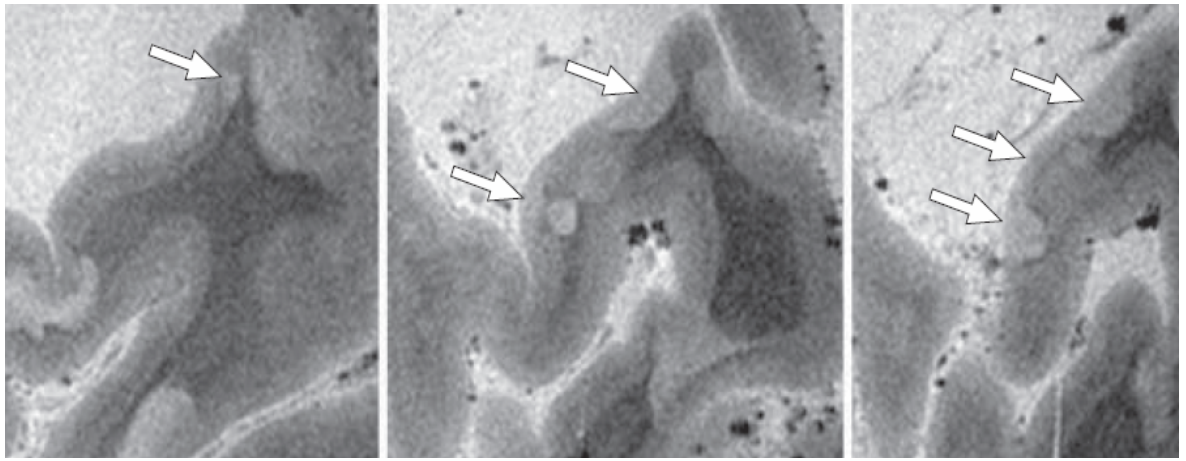
There is no cortical injury in multiple sclerosis

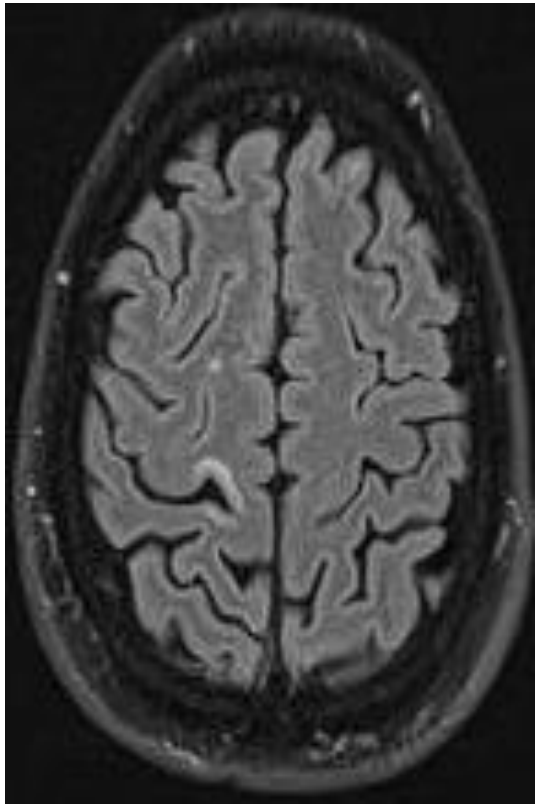
MRI features in MS
Cortical / juxtacortical lesions



Kutzelnigg et al. Brain 2005



Pitt et al. Arch Neurol 2010



- Cortical lesions present in 68-85% of MS patients
- Intracortical lesions missed in 95% of cases (cMRI)
- DIR provides a 5-fold increase in detection
- MRI visible lesions highly correlate with overall number of cortical lesions (r=0.96)

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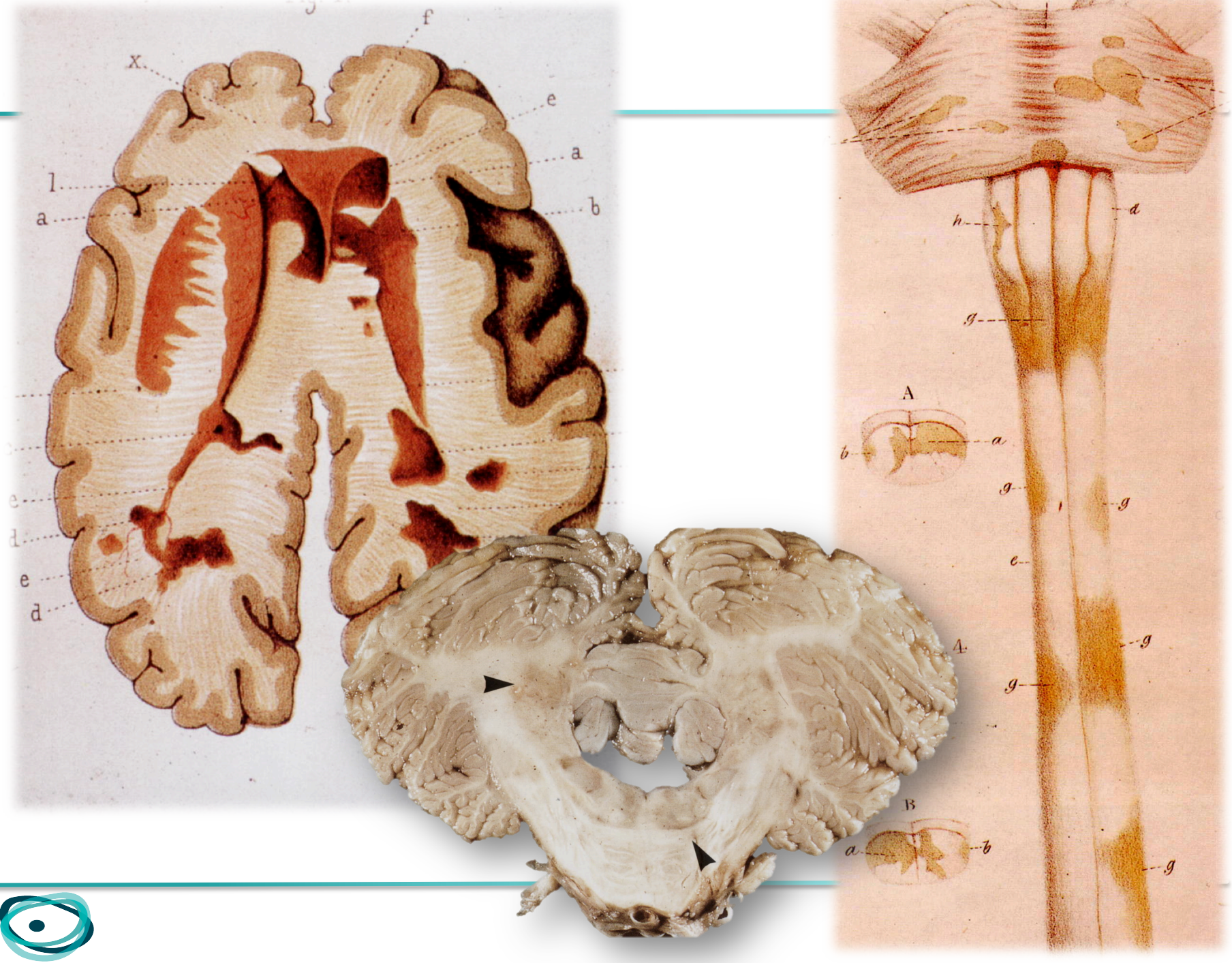
Geurts J, Vrenken H. Neurology 2010
Seewan et al. Mult Scler 2011

Lesions in multiple sclerosis are patchy distributed



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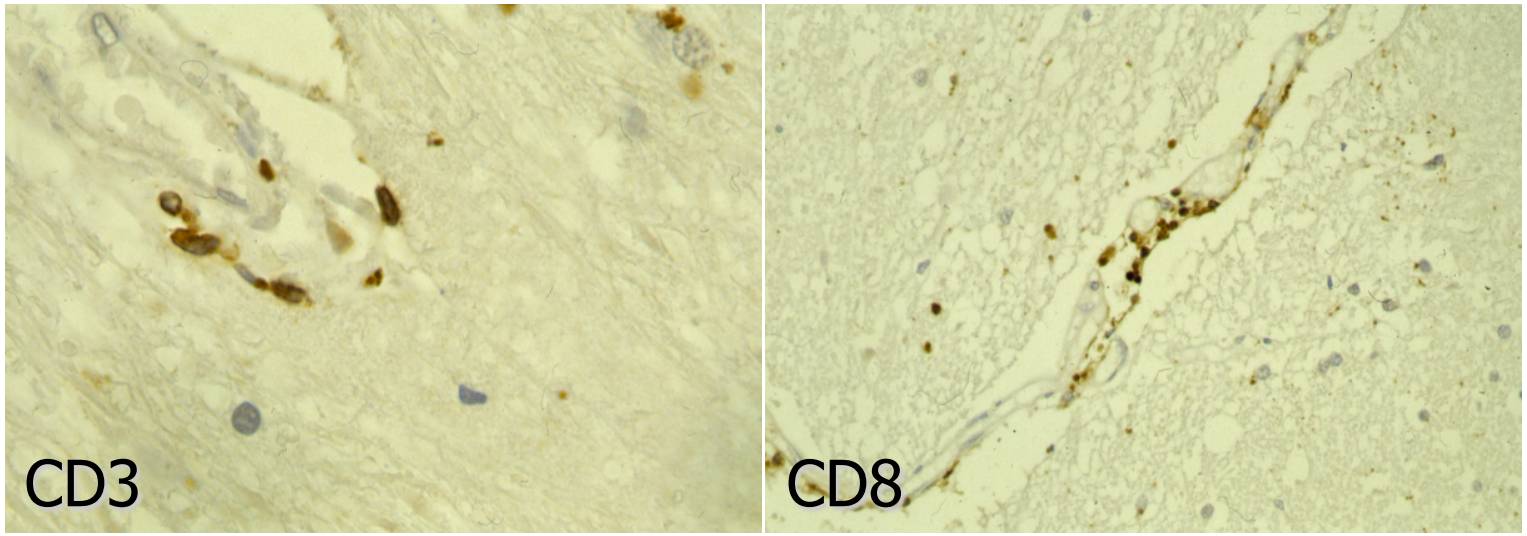
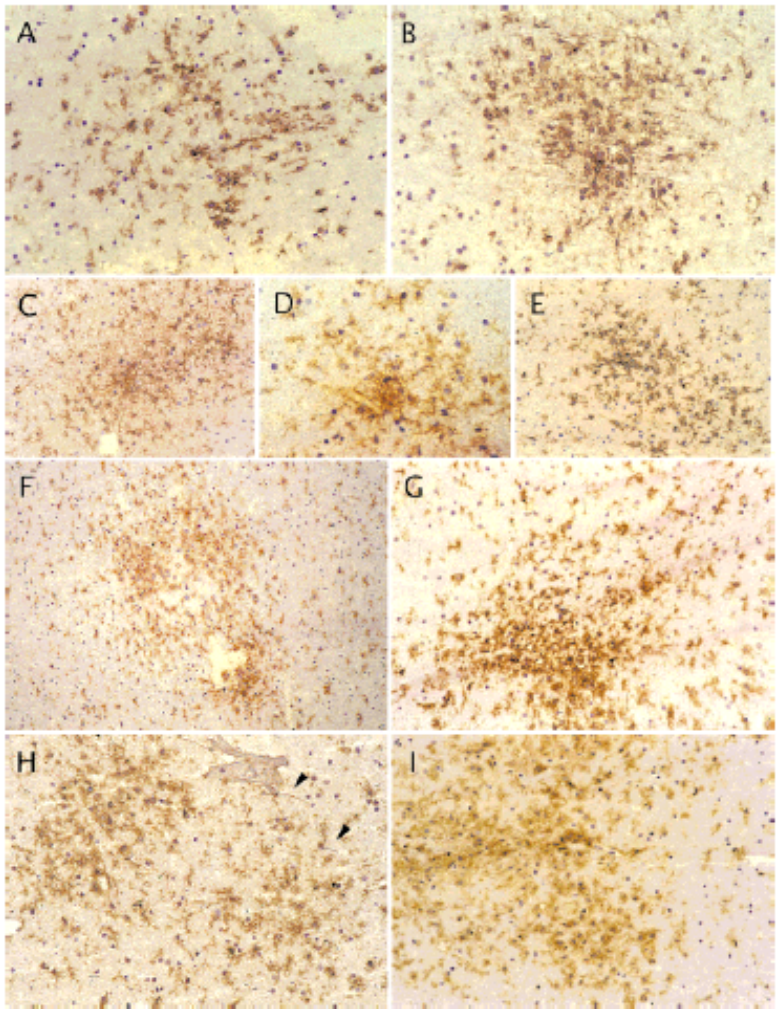
Perivenous lymphocytic infiltrates in MS NAWM



Allen et al., 1979; Traugott et al., 1983; Kutzelnigg et al., 2005; Moll et al., 2008

Foci of microglia activation in the (pathologically) NAWM

- Clusters of activated microglia with increased expression of MHC class I and II molecules
- Increased expression of transcription factors for MHC genes



Gobin et al., 2001

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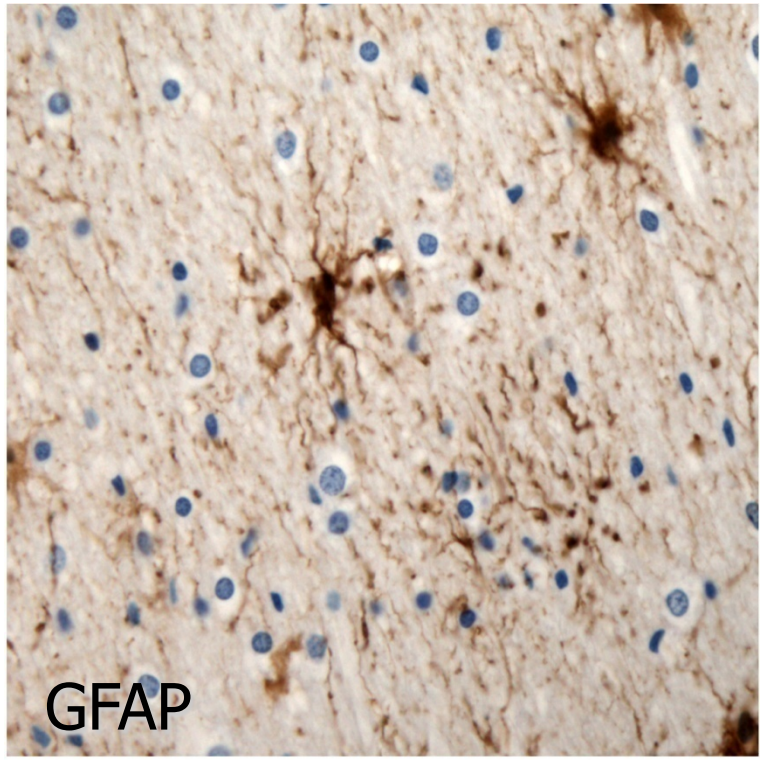
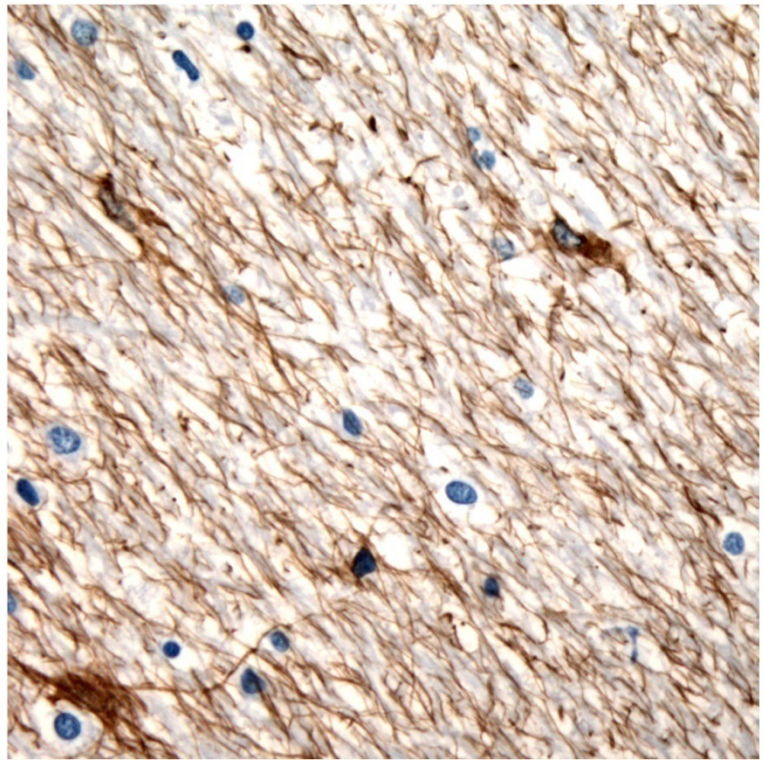
Astrogliosis in MS NAWM

Control WM



MS NAWM



Allen et al., 1979; Seewann et al., 2009

There is no cognitive involvement in multiple sclerosis

Cognitive impairment in MS

Prevalence of cognitive dysfunction in MS

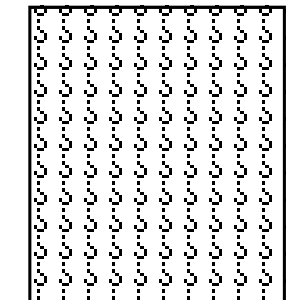
	No. of patients	Prevalence (%)
Clinic-based studies		
Parsons et al. [38]	17	65
Surridge [39]	18	61
Staples and Lincoln [40]	64	60
Peyser et al. [41]	52	54
Bertrando et al. [42]	22	55
Medaer et al. [43]	46	65
Rao et al. [44]	44	64
Heaton et al. [21]	100	56
Lyon-Caen et al. [45]	30	60
Community-based studies		
Rao et al. [9]	100	43
McIntosh-Michaelis et al. [10]	147	46

Amato, Zipoli & Portaccio.

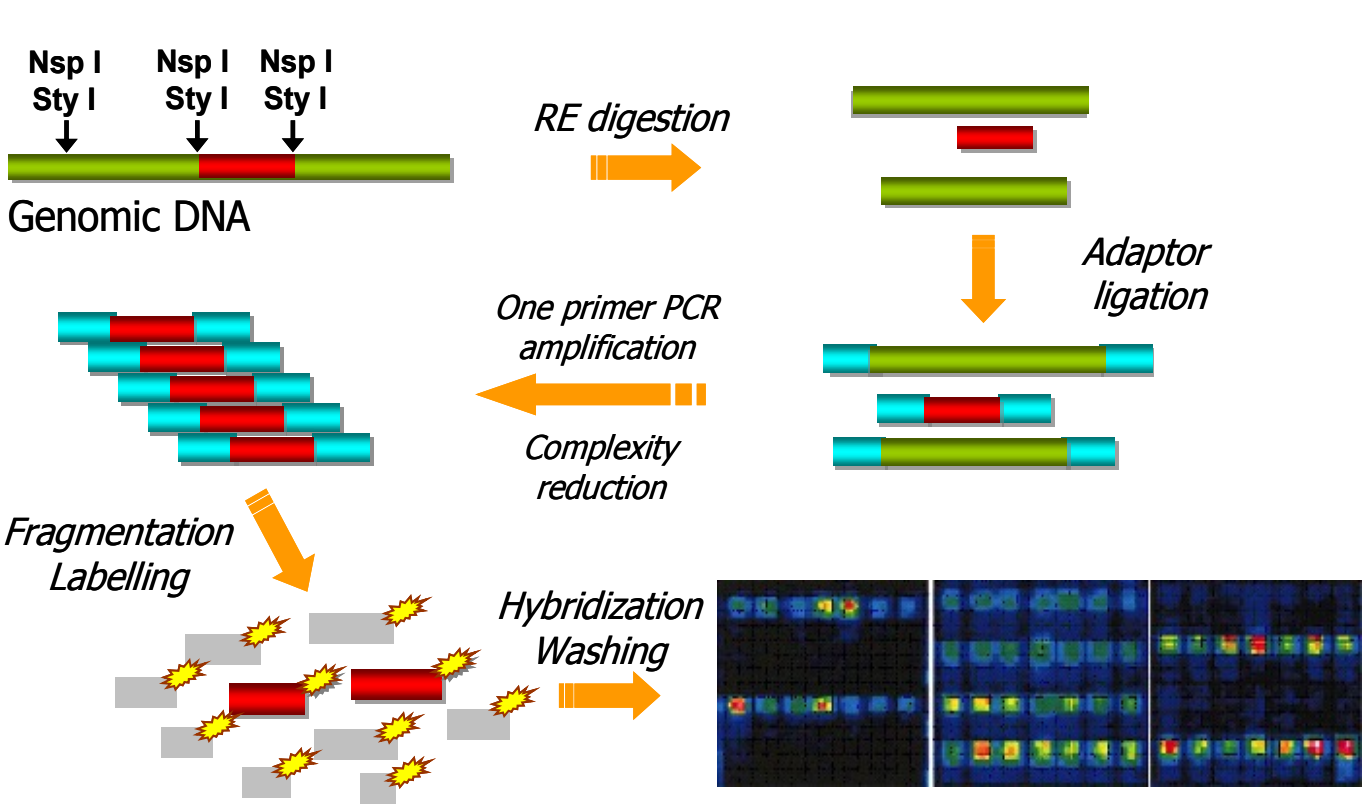
J Neurol Sci 2006

HLA DR2 is the only gene involved in the risk of having multiple sclerosis

New technologies for genotyping...



SNP arrays



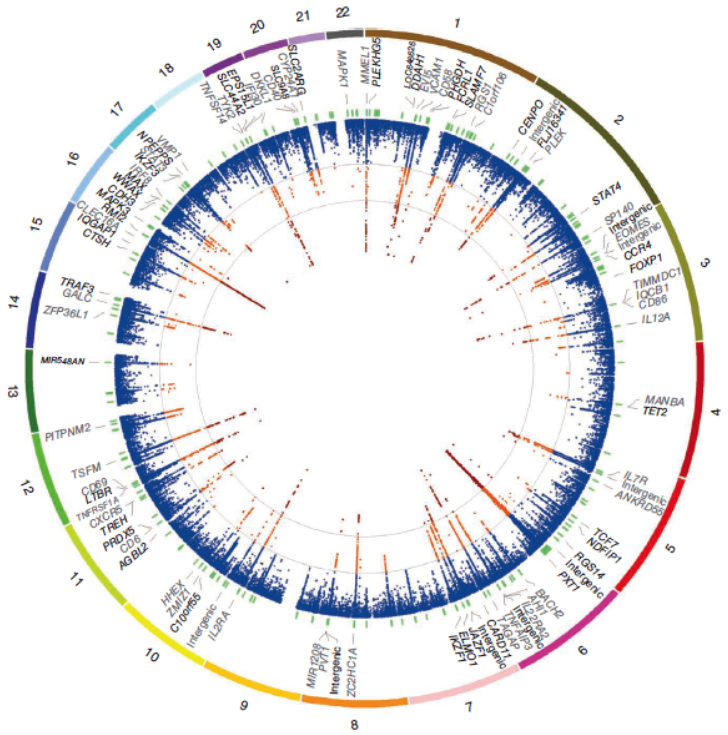
> 1 million of SNPs!!

International Multiple Sclerosis Genetics Consortium (IMSGC, https://www.imsgc.org/)

IMSGC & WTCCC2 Nature (2011) 476; 214-9

Genetics of MS

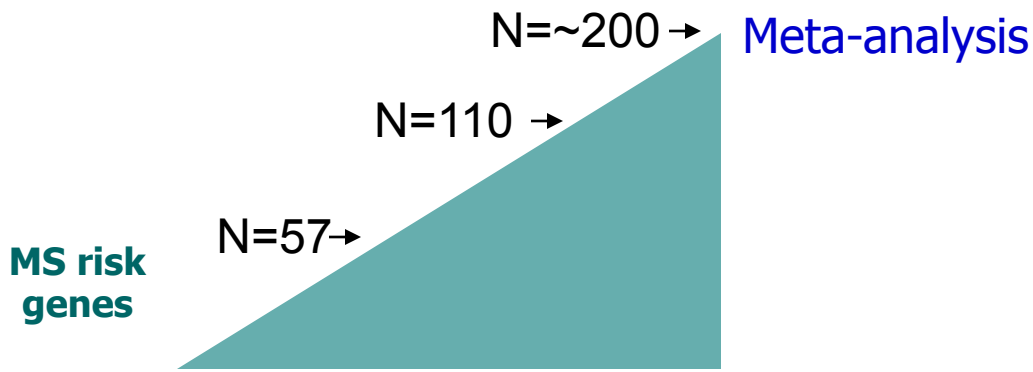
Immunochip



IMSGC, Nat Genet 2013; 45:1353

14,498 cases

24,091 controls



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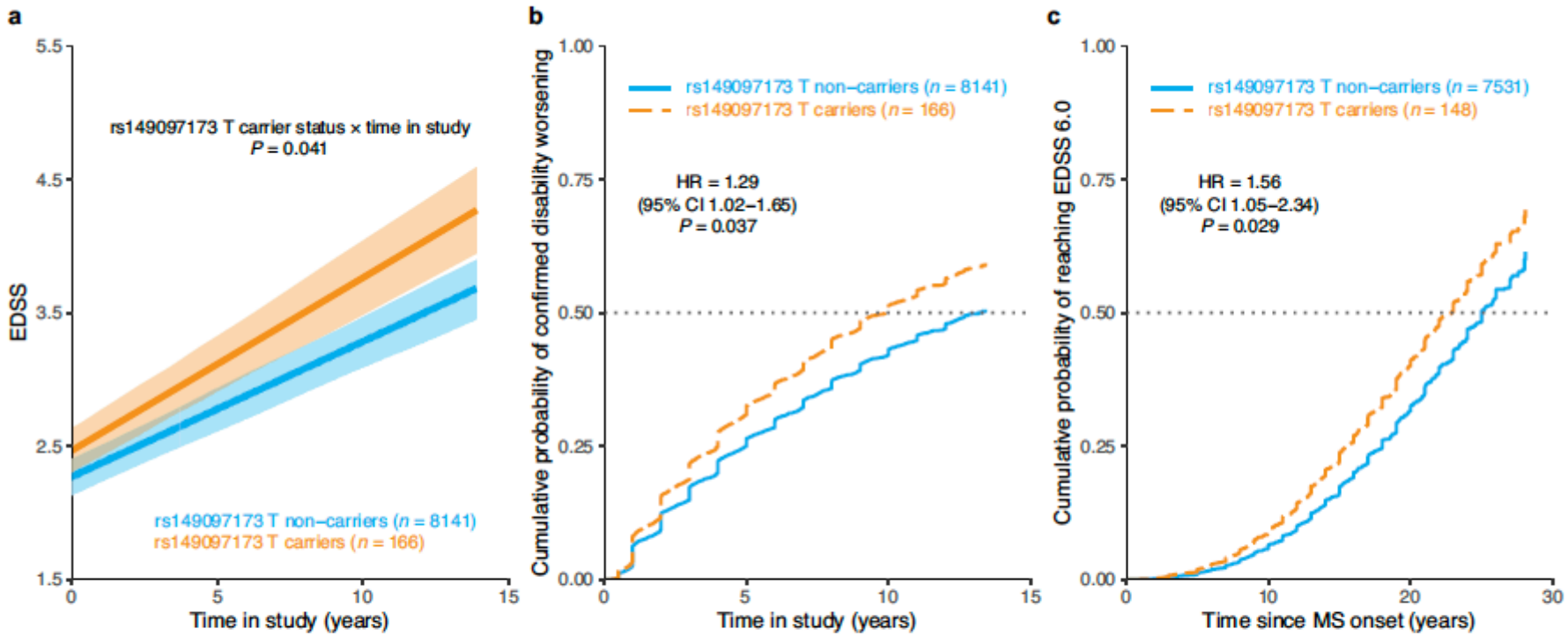
Locus for severity implicates CNS resilience in progression of multiple sclerosis

Article



Extended Data Fig. 4 | Association of rs149097173 with longitudinal disability outcomes. a, Adjusted mean EDSS scores over time by carrier status for rs149097173 predicted from LMM analysis. Shaded ribbons indicate the standard error of the mean over time; *P* value from LMM. **b**, Covariate-adjusted cumulative incidence of 24-week confirmed disability worsening for the same groups of individuals. **c**, Covariate-adjusted cumulative incidence of requiring a walking aid; carriers had a 2.2-year shorter median time to require a walking aid. HR and two-sided *P* values were obtained from Cox proportional hazards models using imputed allele dosage (**b**–**c**; Methods). Results were not significant after adjusting for multiple testing across two variants (see Fig. 3 for rs10191329 associations) and three outcomes ($P < 0.05/6$), although the latter are not expected to be independent. CI, confidence interval; HR, hazard ratio.

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Nature 2023

The diagnosis of multiple sclerosis is challenging and can take years to be established

Diagnostic criteria

- Allison and Millar (1954)
- McAlpine (1965)
- Schumacher (1965)
- Rose (1976)
- Poser (1983)

- Symptoms suggestive of MS
- Dissemination in time and space
- Exclusion of other diseases
- Diagnosis can be made by clinical assessment alone