



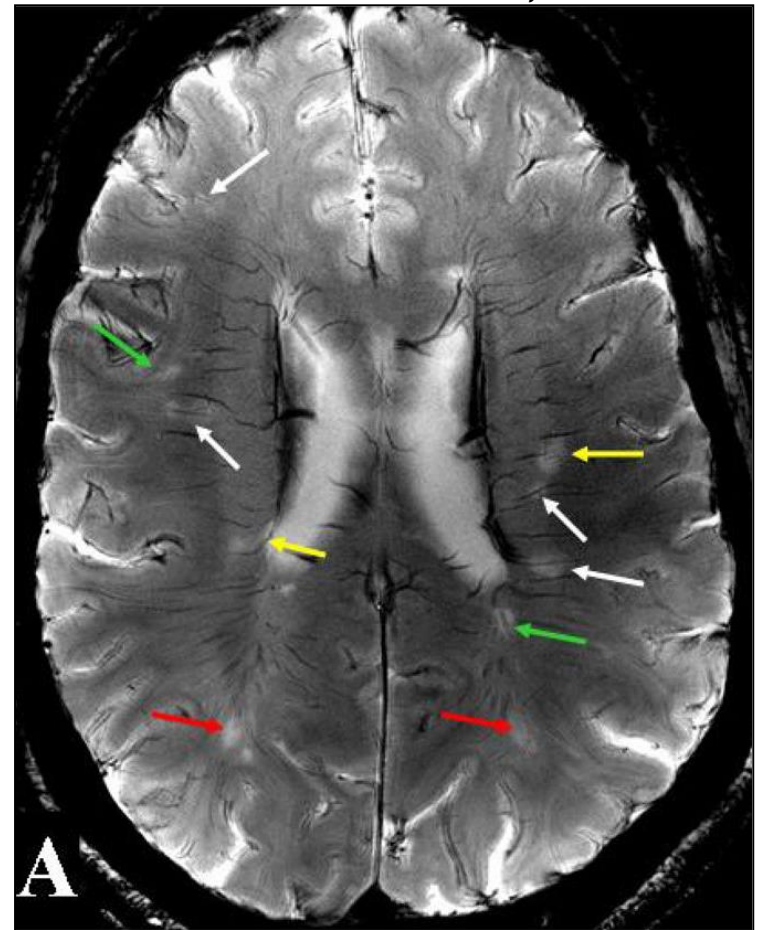
Interleuchina 17 e deficit cognitivi nella sclerosi multipla

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Perugia*

Cognitive impairment in MS

- High prevalence ranges (from 40% to 70%)
- Deep impact on patient's lives, disease management, and society
- Lack of treatments

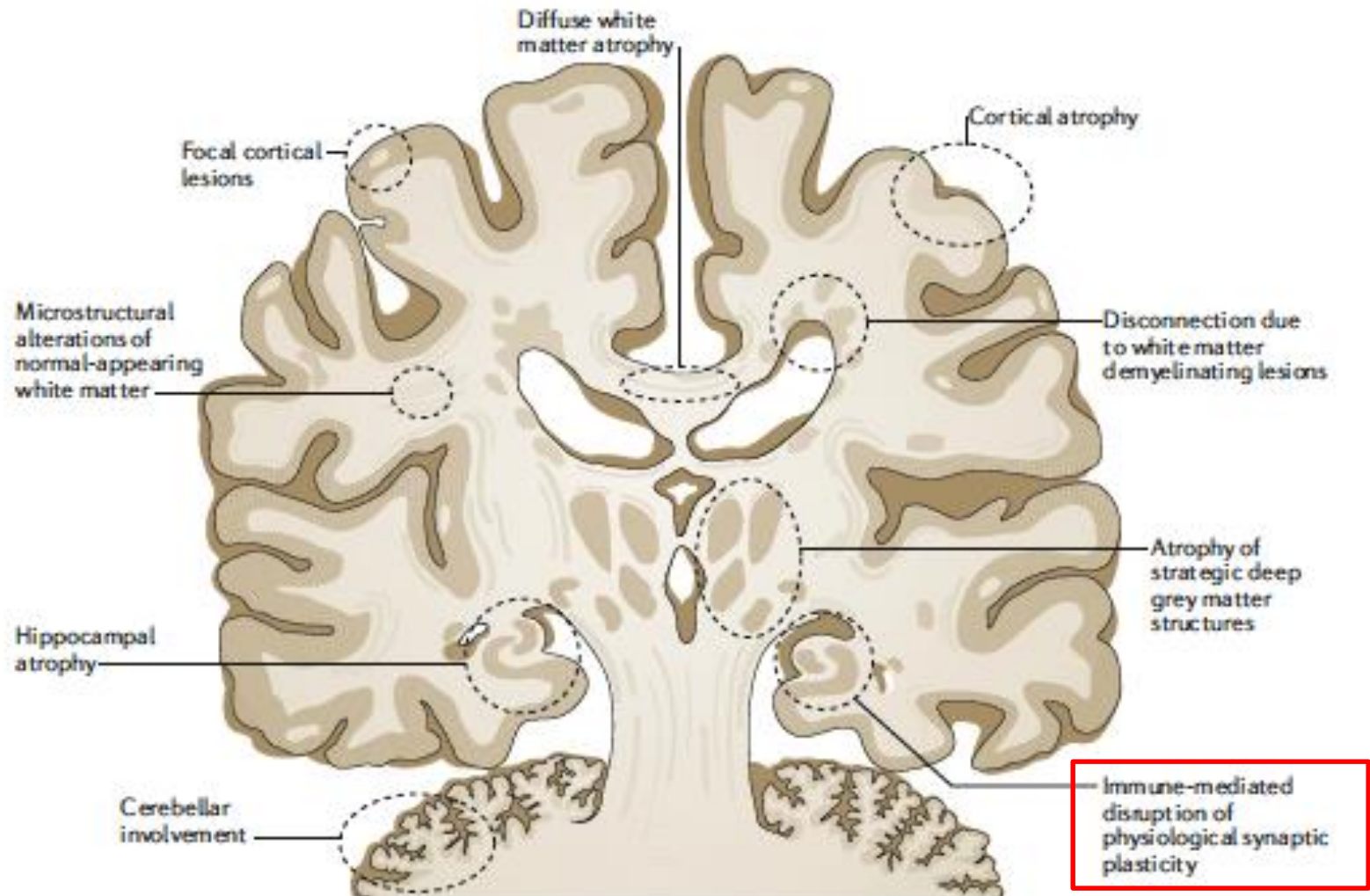


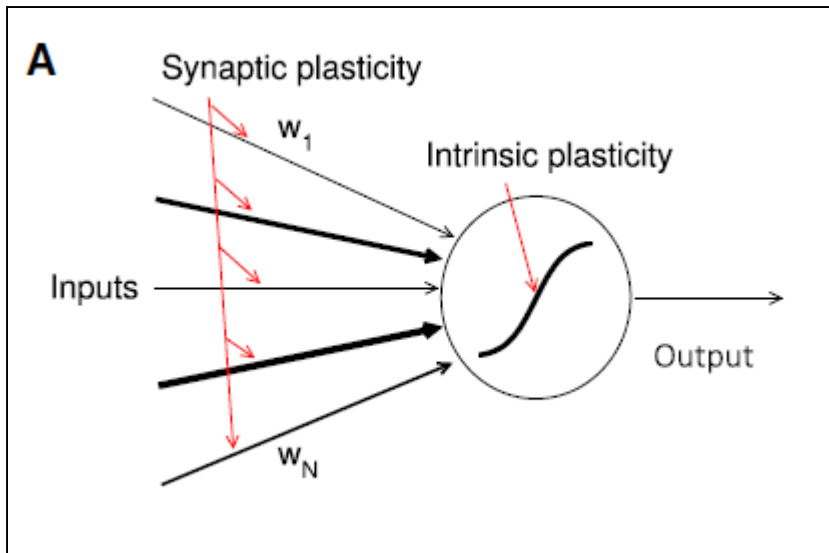
Lesions location in strategic
white matter tracts



“Disconnection” syndrome

Mechanisms underlying MS-related CI

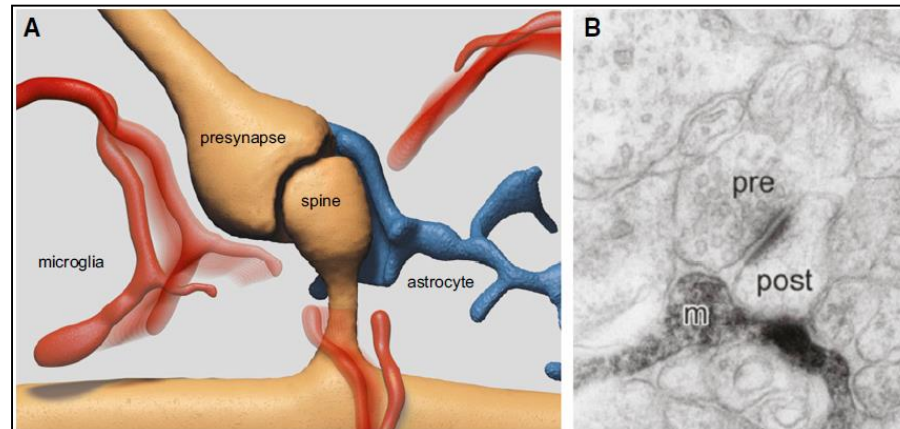




Synaptic plasticity shapes connectivity maps by establishing connection patterns and by assigning synaptic weights

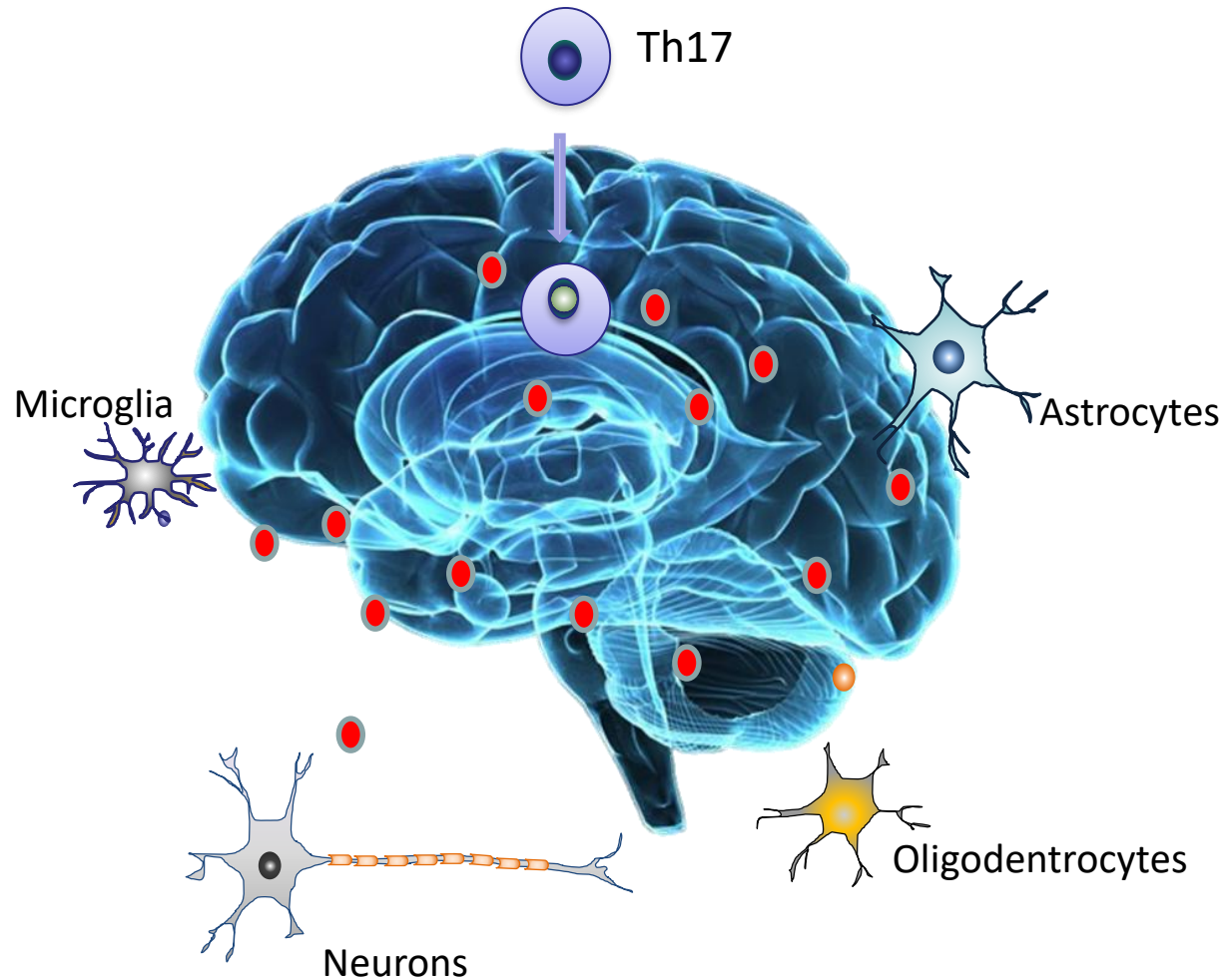
Synaptic activity triggers intrinsic plasticity and drives the (re)activation of memory engrams

Titley et al., *Neuron*, 2017



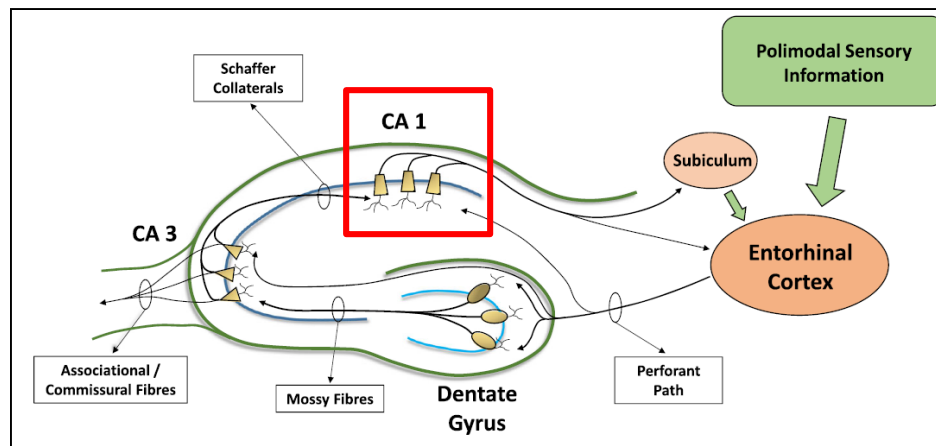
Kettenmann et al., *Neuron*, 2013

Interleukin 17, MS pathogenesis and the neuro-immune interaction

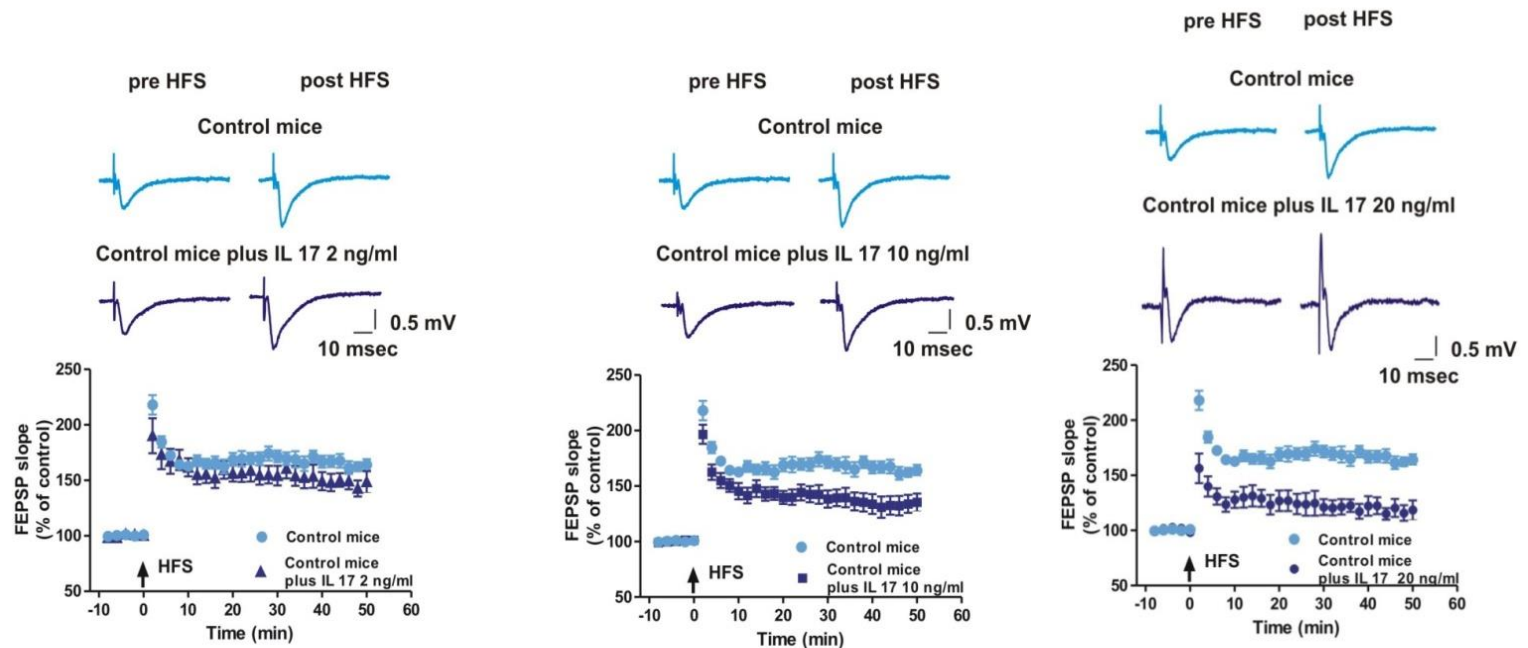


IL-17-mediated alterations of synaptic plasticity ?

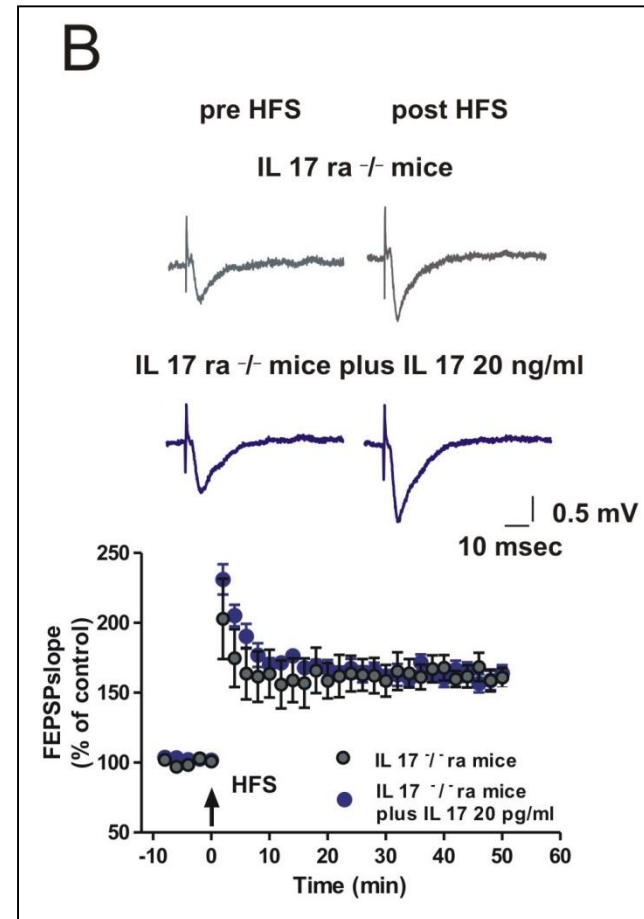
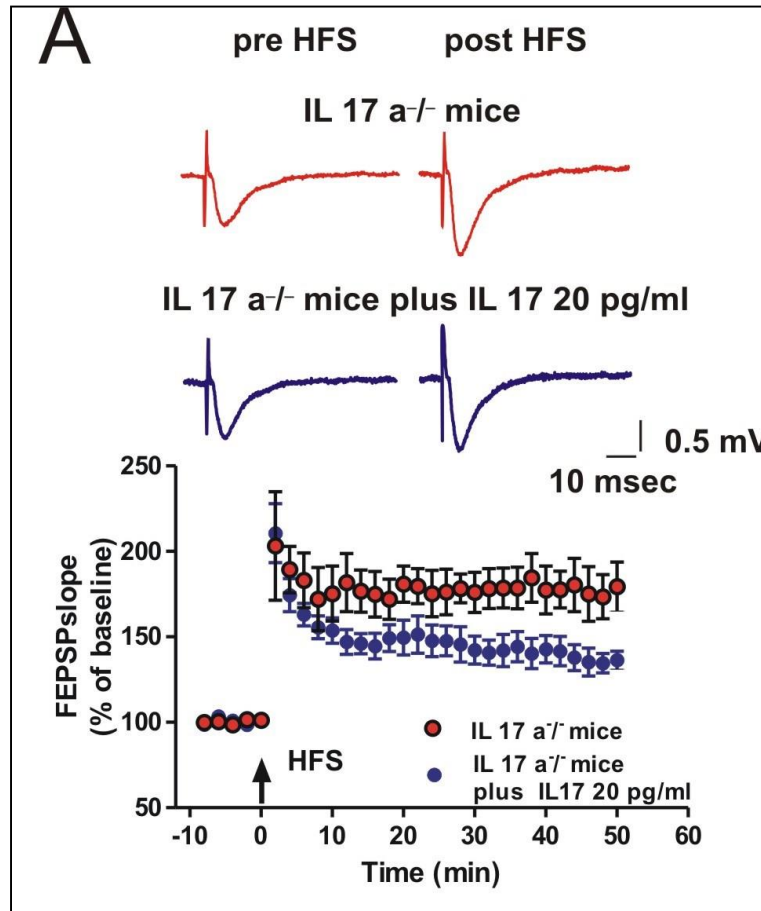
IL-17-mediated cognitive deficits ?



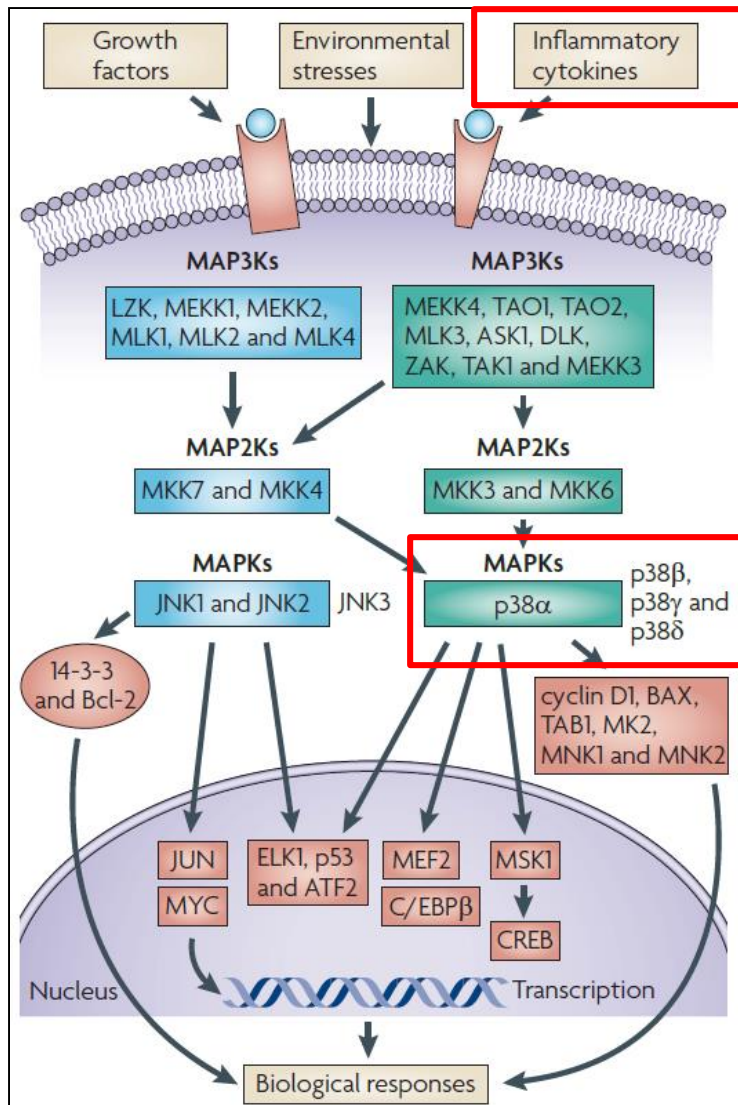
IL-17 dose-dependently blocks hippocampal synaptic plasticity



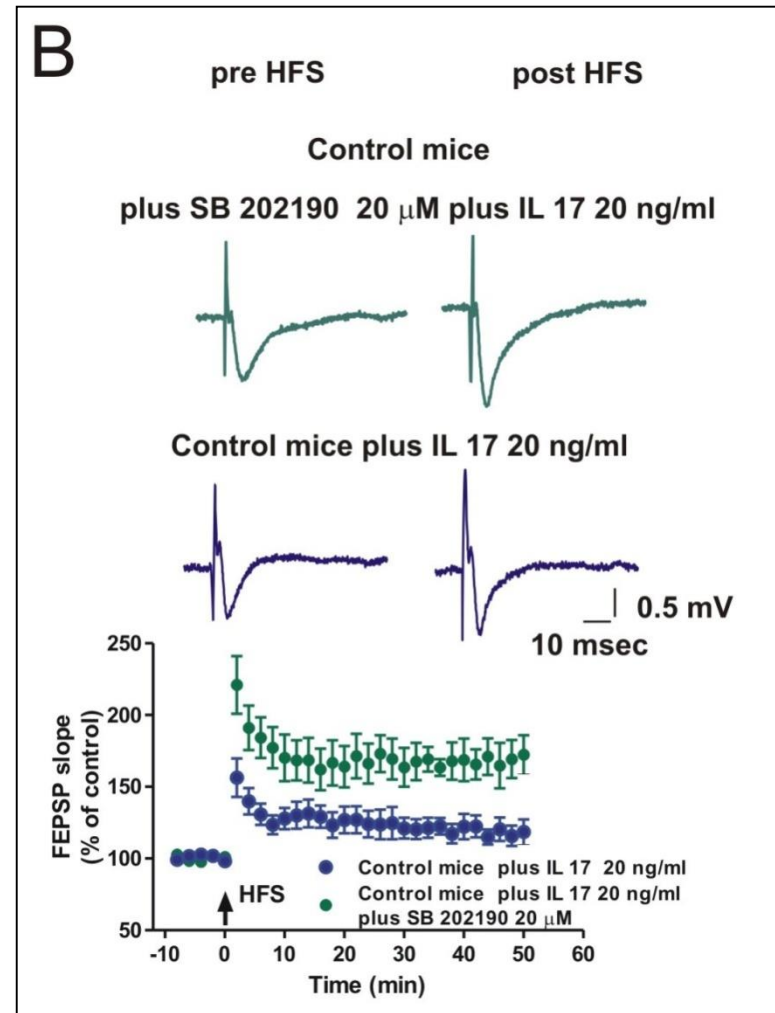
KO models confirm the role of IL17 in hippocampal LTP



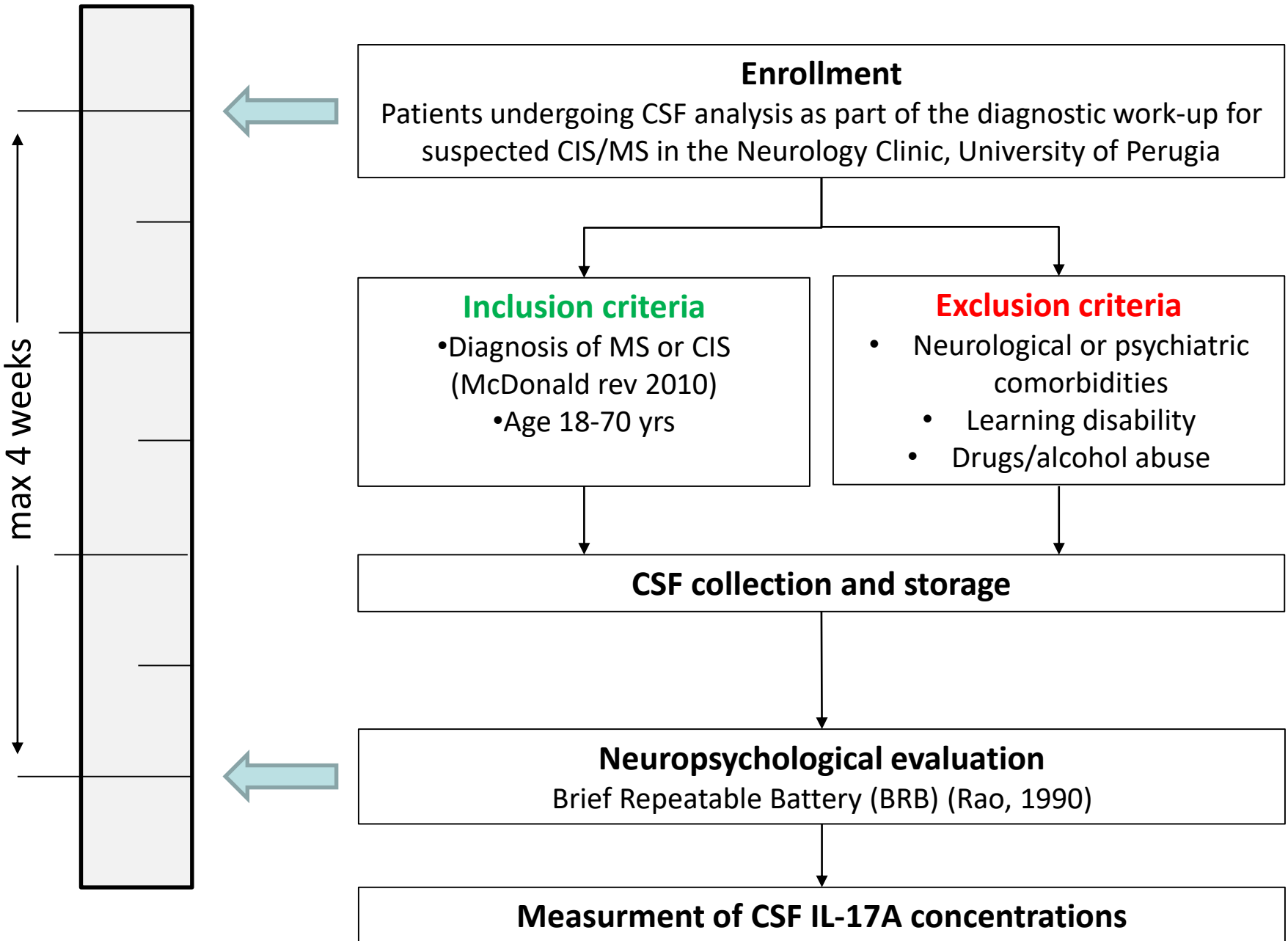
Role of p38 MAPK in IL-17-mediated loss of hippocampal LTP



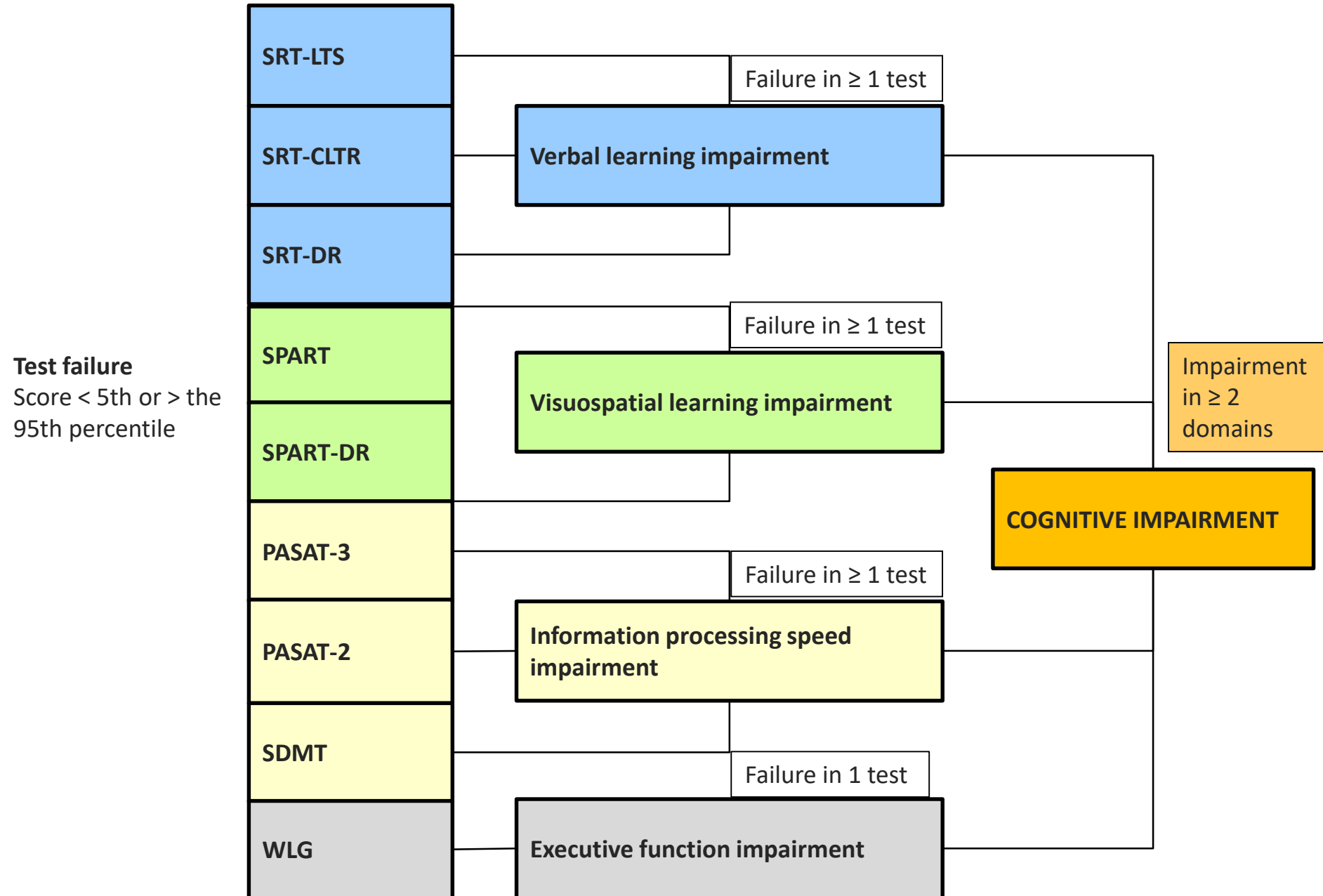
Wagner and Nebreda, *Nat Rev Cancer*, 2009



Study design



BRB Scoring (according to Ruano et al, MSJ 2016)

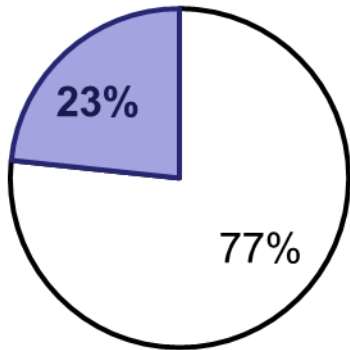


Patients characteristics

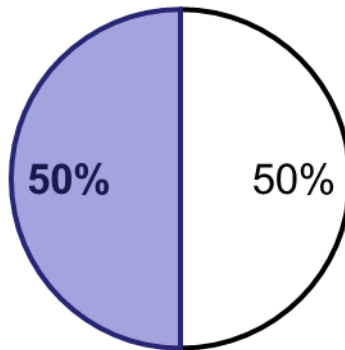
Main demographics, clinical and MRI features at baseline	
N	30
Sex female (n of patients;%) - (F:M)	21 (70%) - (2.3:1)
Age – yrs (mean \pm SD)	40.1 \pm 2.1
Clinical phenotype (n of patients;%)	
• CIS	13 (43.4%)
• RRMS	10 (33.3%)
• PMS	7 (23.3%)
EDSS at baseline (mean \pm SD)	2 \pm 1.2
• Disease duration – yrs (mean \pm SD)	1.7 \pm 3.4
Recent relapse* (n of patients;%)	19 (63.3%)
• OCB positive (n of patients;%)	24 (80%)
CNS segments MRI available (n of patients;%)	
Brain	30 (100%)
Cervical cord	24 (80%)
Thoracic cord	5 (16.7%)
MRI characteristics	
T2 lesions per patient (mean \pm SD)	9.9 \pm 7.6
0 Gd+ lesion	15 (50%)
1 Gd+ lesion	10 (33.3 %)
> 1 Gd+ lesions	5 (16.7%)

Prevalence of single domains and overall cognitive impairment

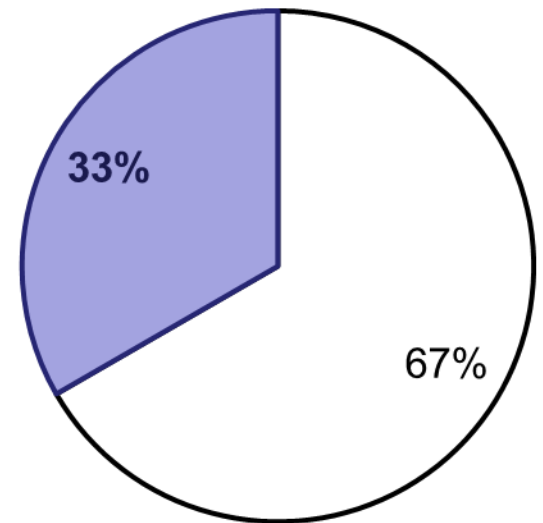
Verbal learning



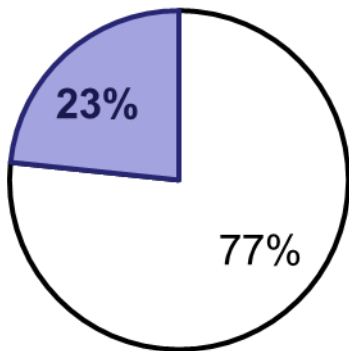
Information processing speed



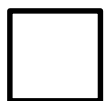
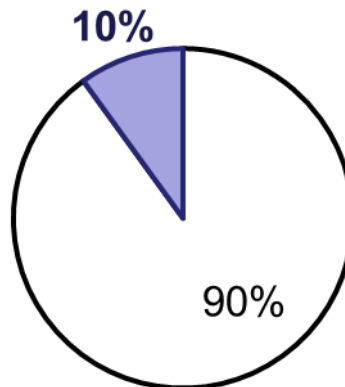
Cognitive impairment



Visuospatial learning



Executive function



Not impaired



Impaired

CSF IL-17A and patients characteristics

CSF IL-17A: 8.8 ± 2.3 pg/mL (median 8.1, range 4.1-14.4)

Demographics

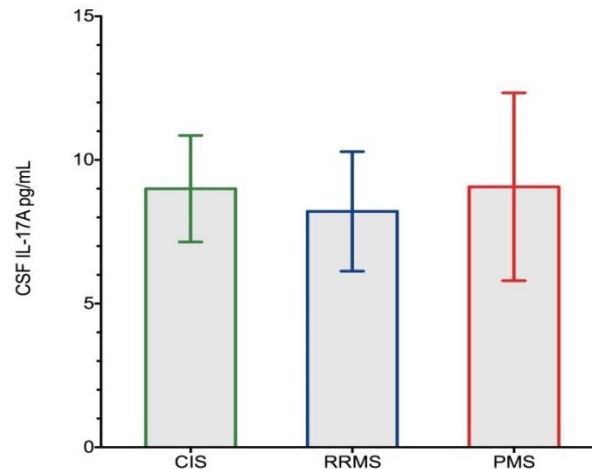
- No correlation with age
- No gender effect

Clinical

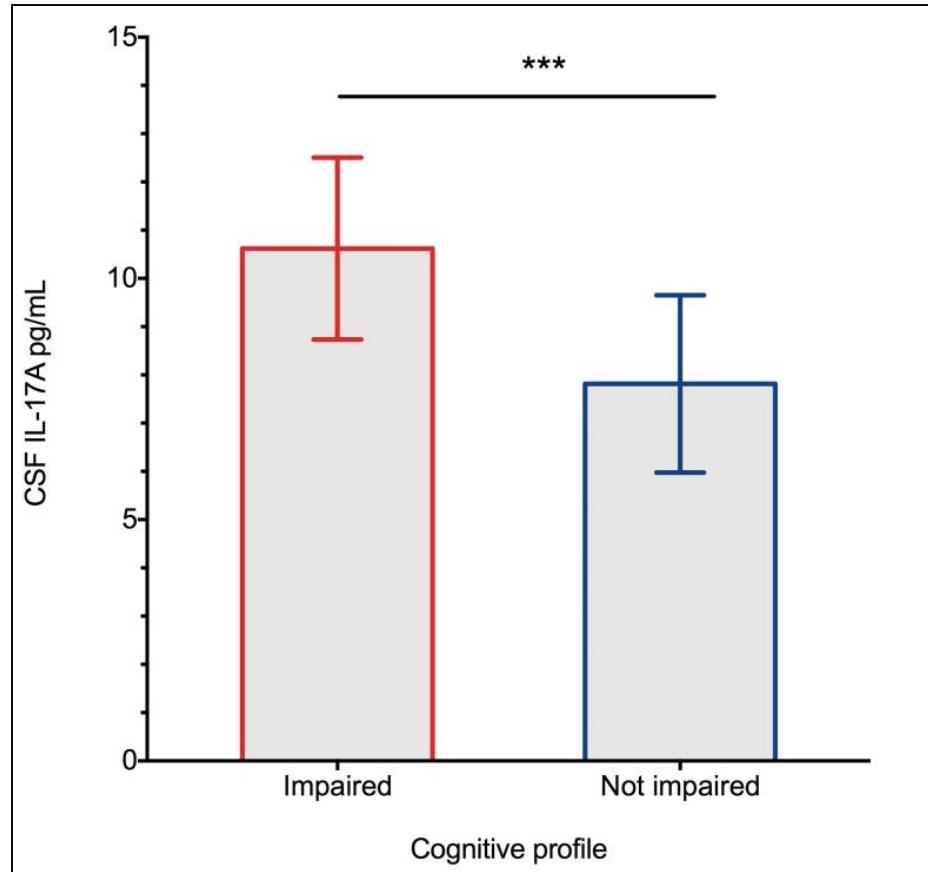
- No correlation with EDSS
- No correlation with recent relapse
- No difference between OCB+ and OCB-
- No differences between CIS, RRMS and PMS

MRI

- No correlation with n T2 lesions
- No correlation with n Gd+ lesions

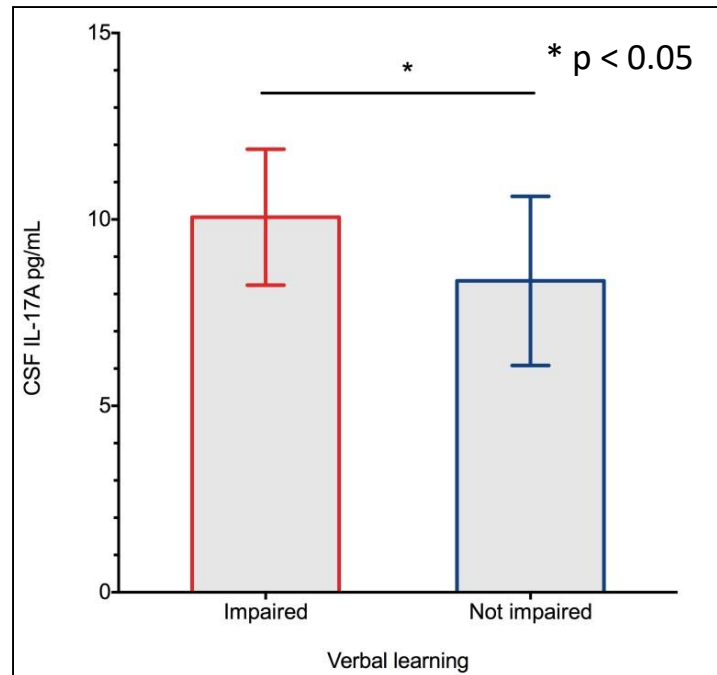
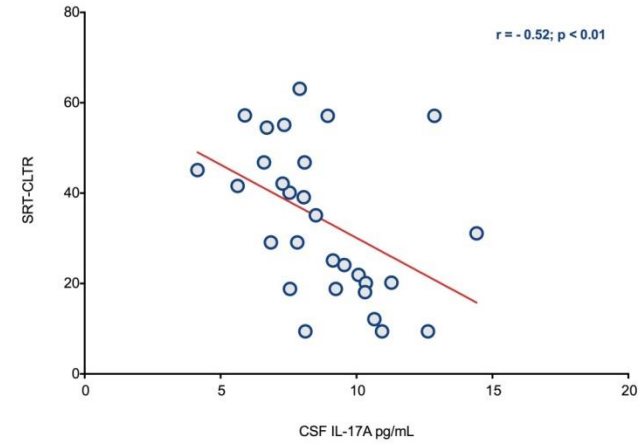
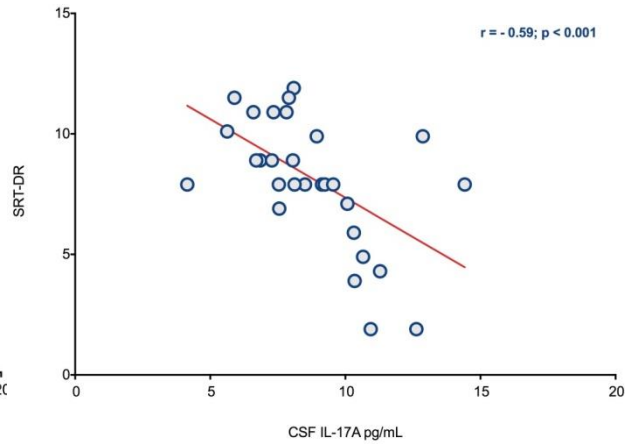
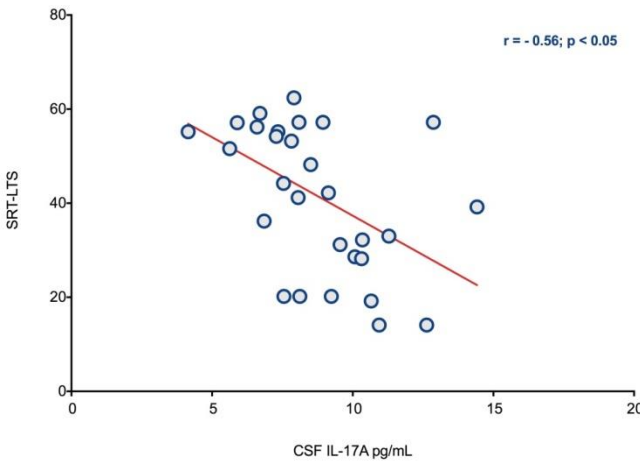


CSF IL-17A and cognitive impairment

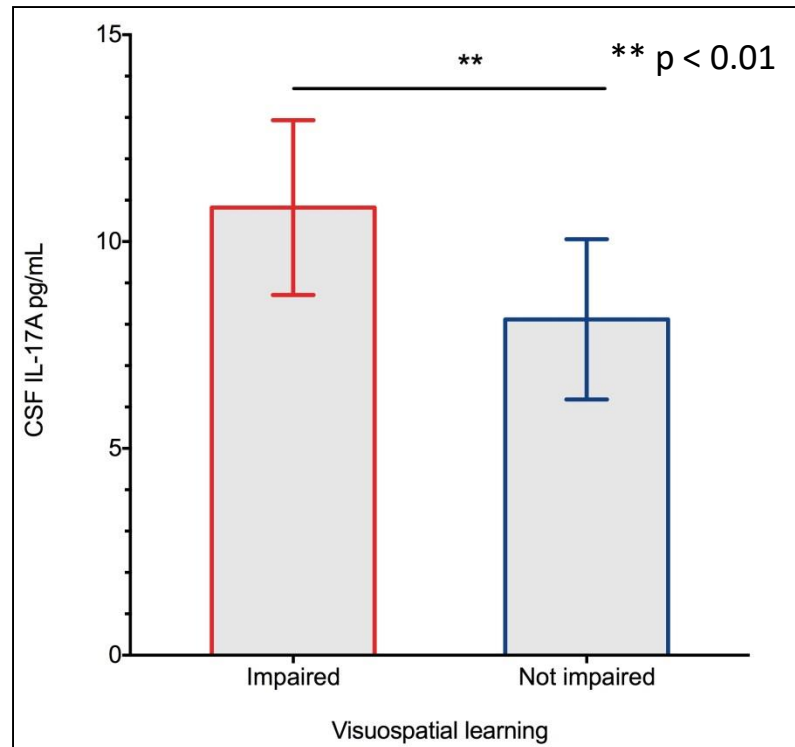
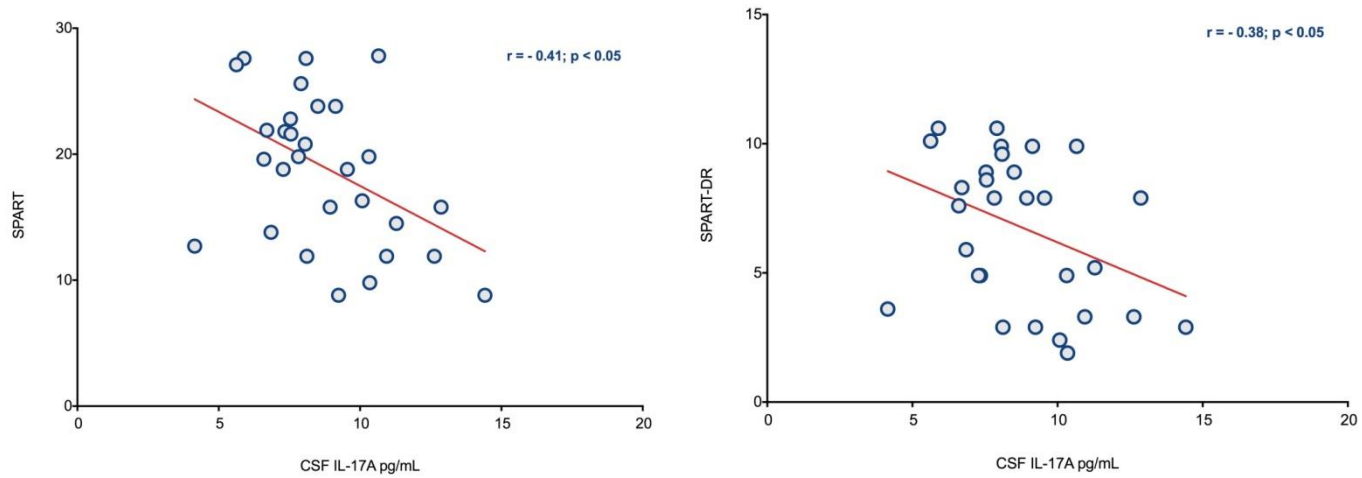


*** $p < 0.001$

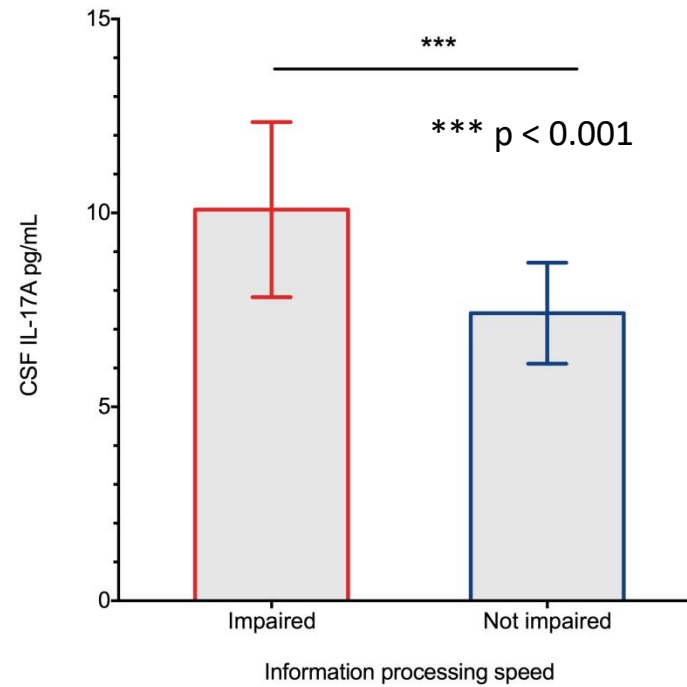
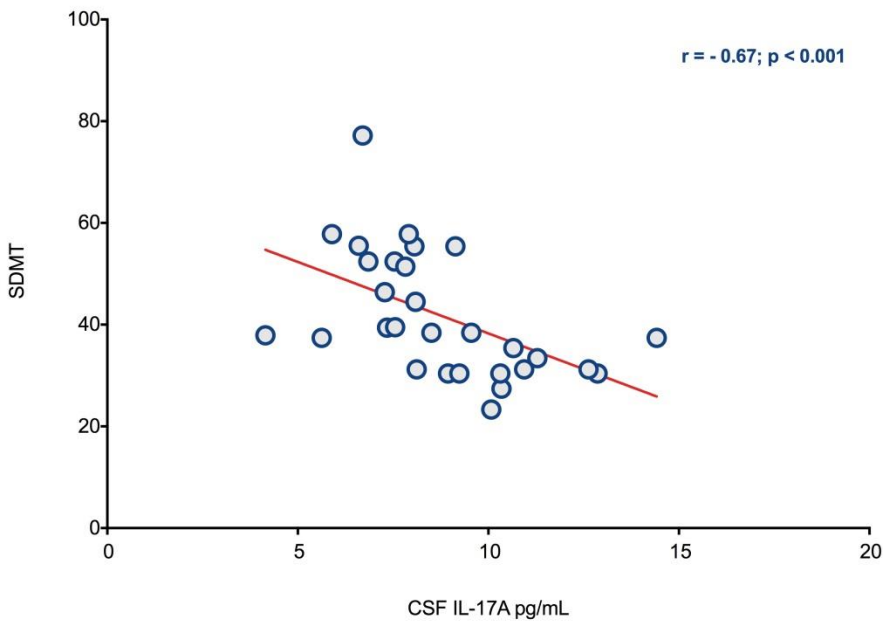
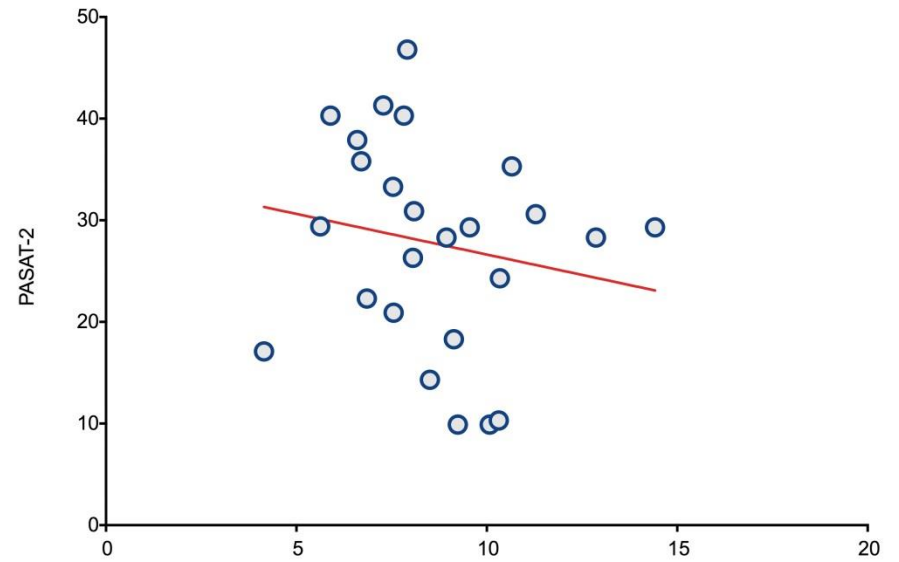
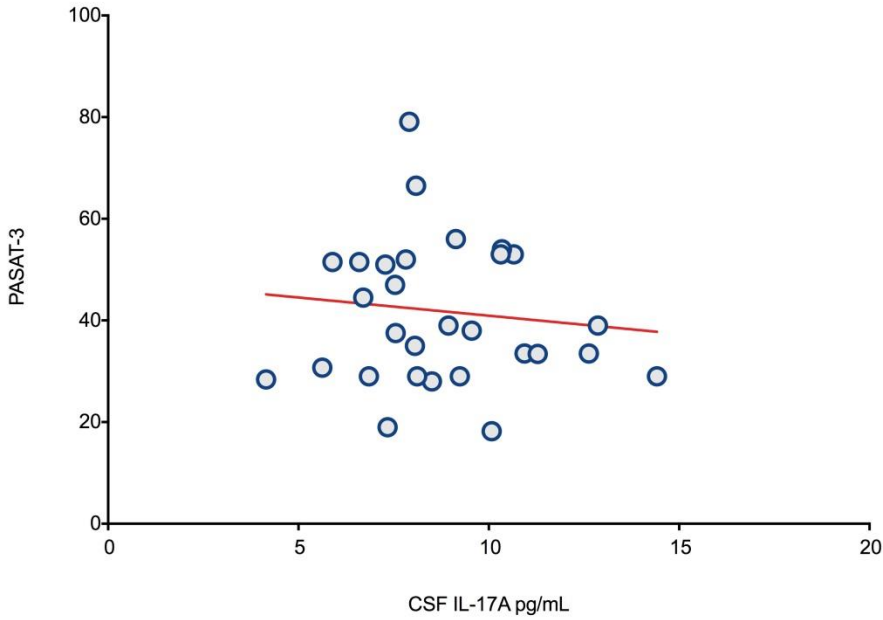
CSF IL-17A and verbal learning



CSF IL-17A and visuospatial learning



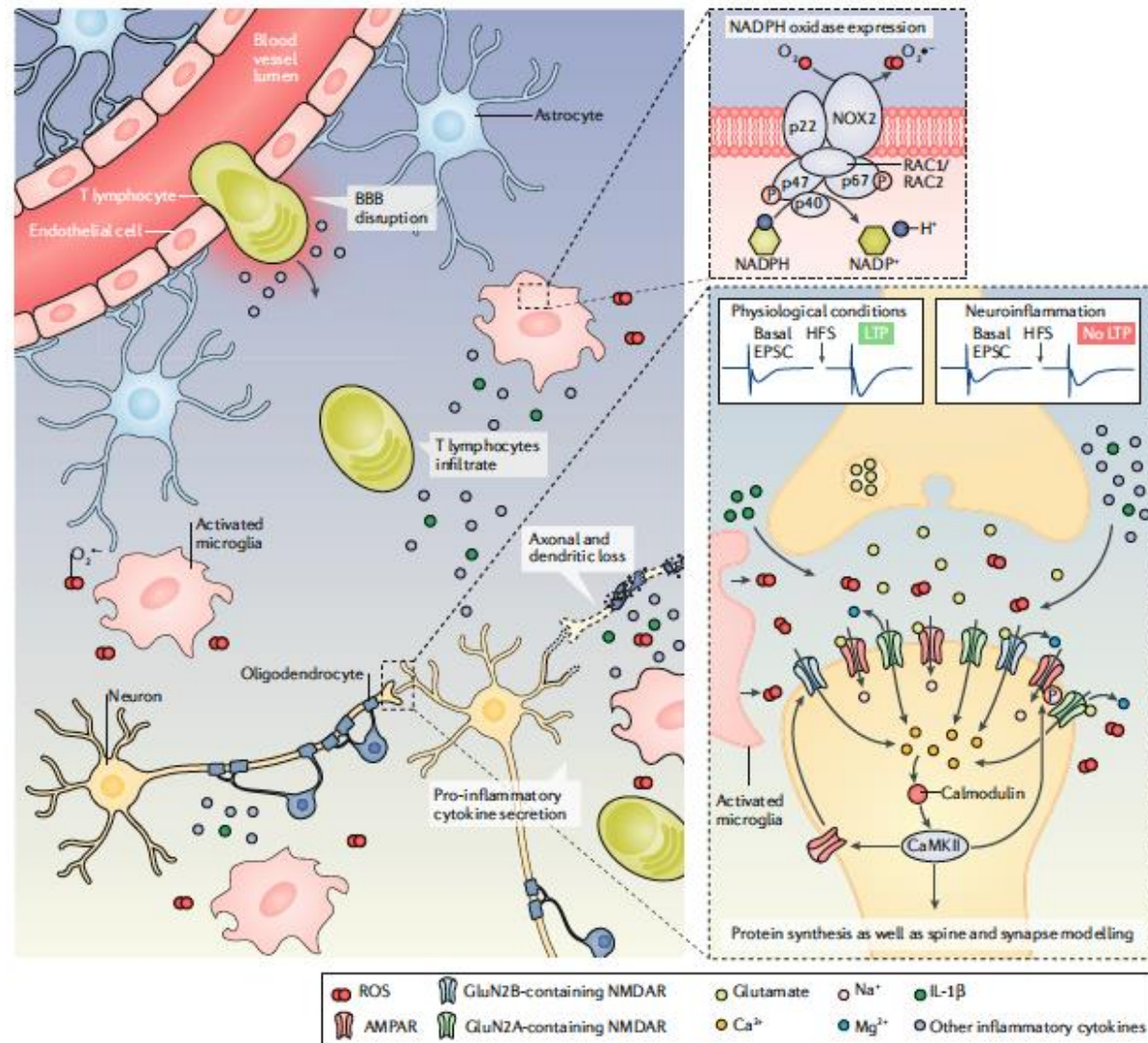
CSF IL-17A and information processing speed



Conclusions

- IL-17 dose-dependently impairs hippocampal neuroplasticity via a mechanism depending on its receptor and p38 MAPK
- The CSF levels of IL-17 are correlated with patients' performances in neuropsychological tests (IPS, verbal and visuo-spatial memory)

Immune system-mediated **alterations of synaptic plasticity** could influence **neuronal circuits dynamics** and represent a key pathogenic step in the **pathogenesis of MS-related CI**



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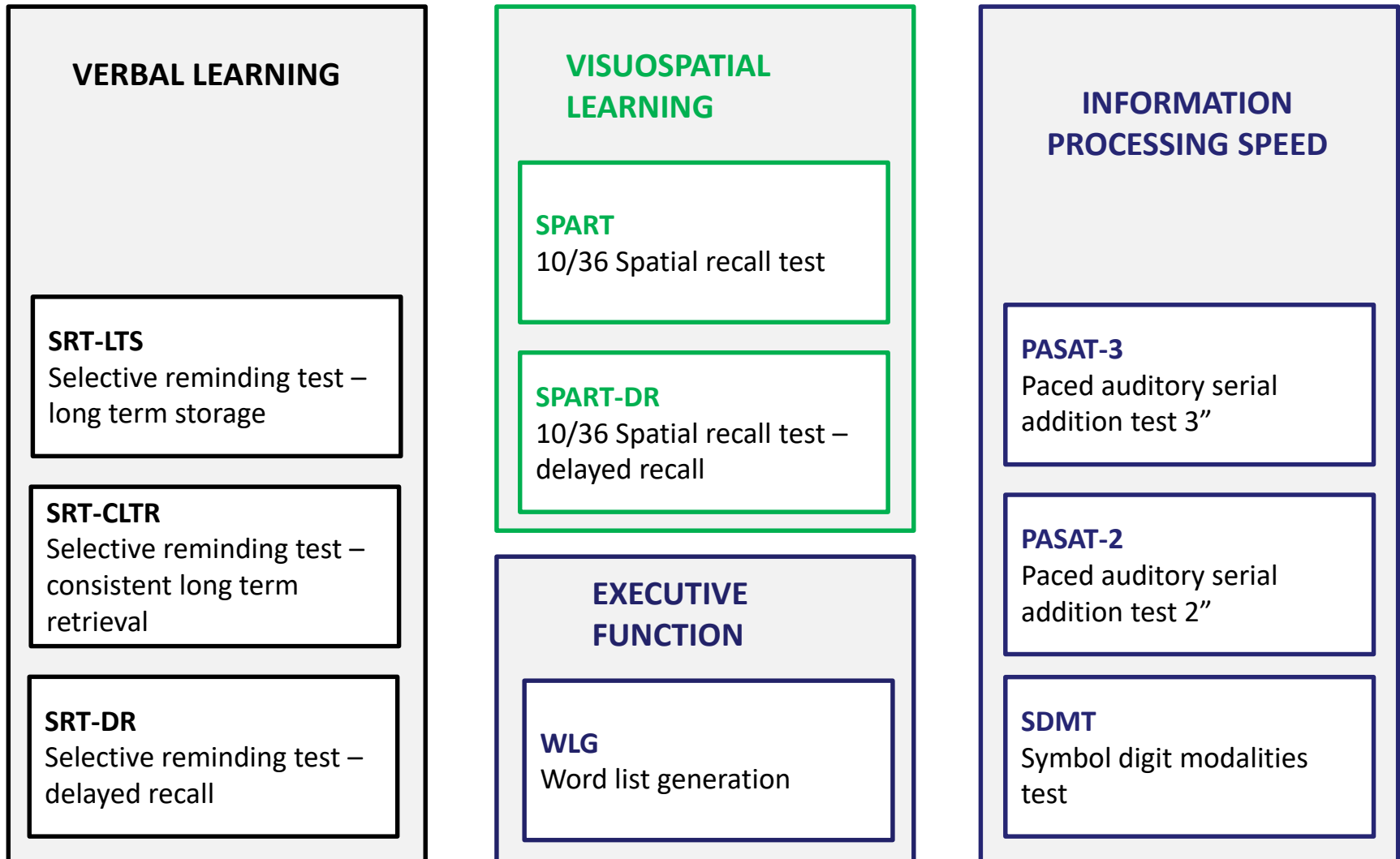
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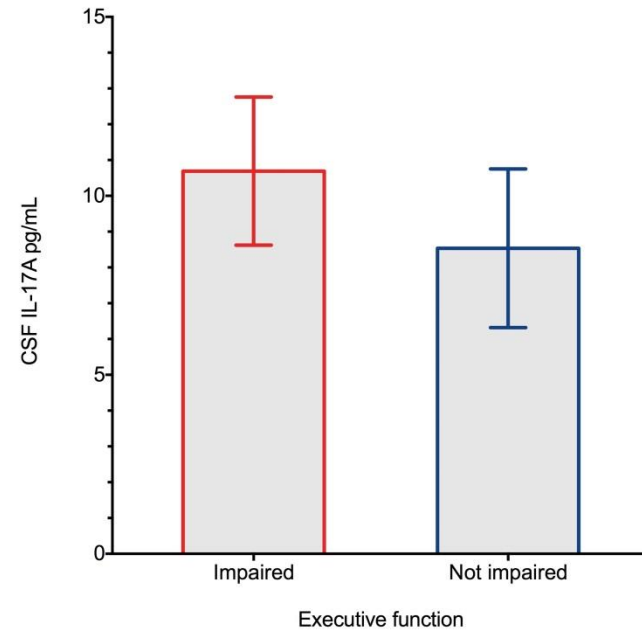
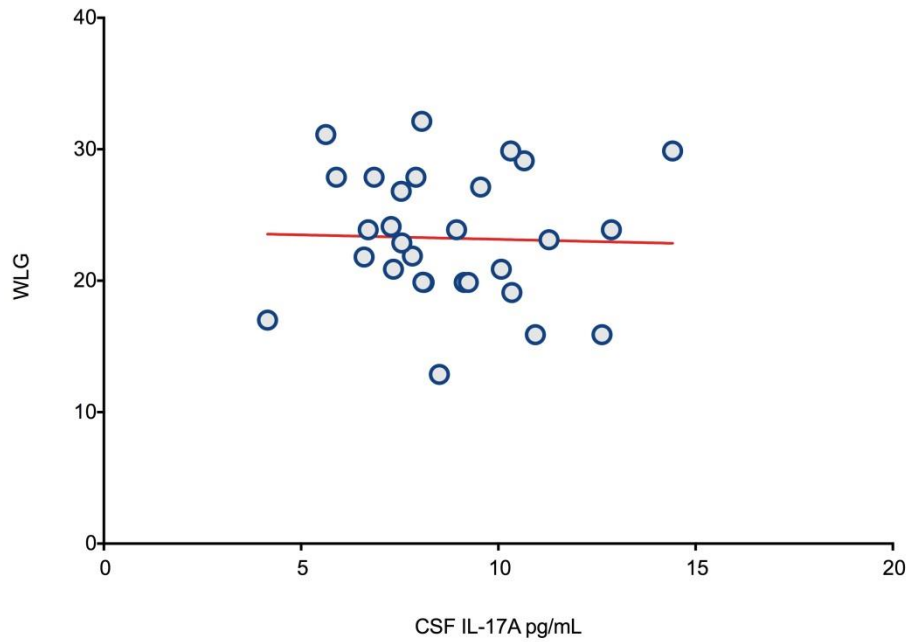
Supported by:



Brief Repeatable Battery – BRB (Rao, 1990)

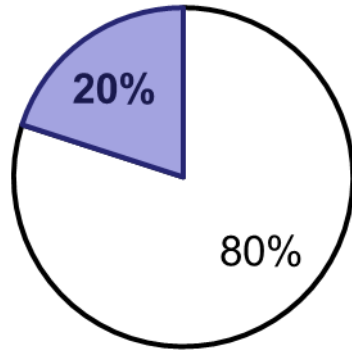


CSF IL-17A and executive function

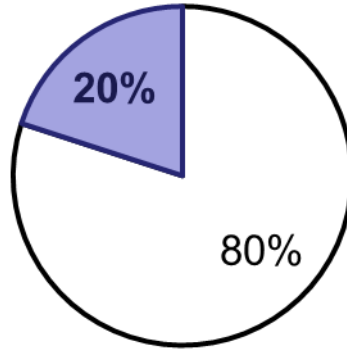


Prevalence of BRB tests failure

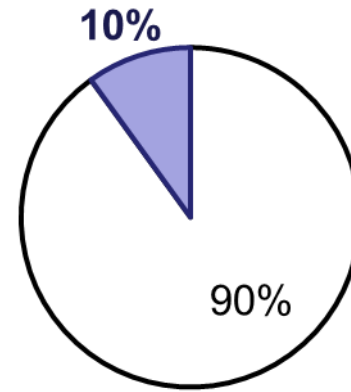
SRT-LTS



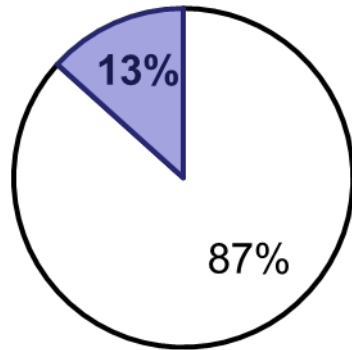
SPART



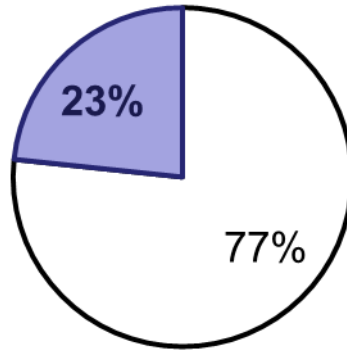
PASAT-3



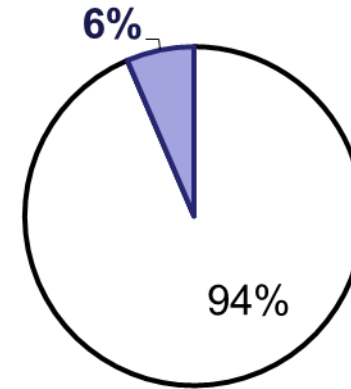
SRT-CLTR



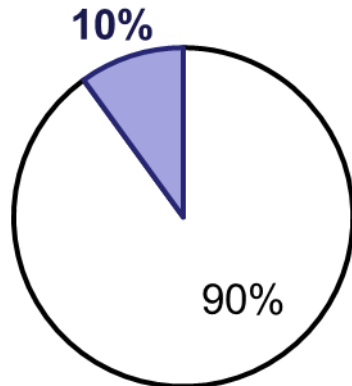
SPART-DR



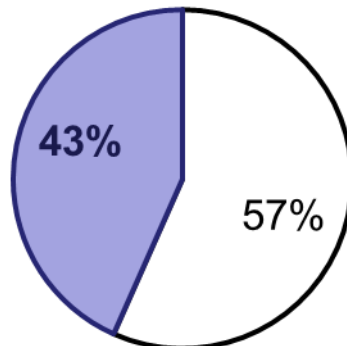
PASAT-2



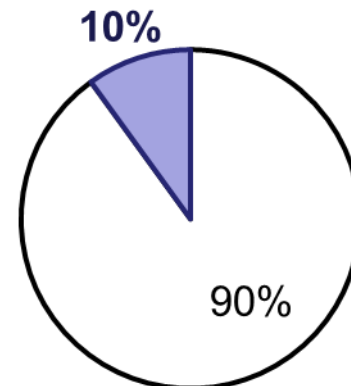
SRT-DR



SDMT



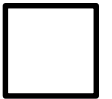
WLG



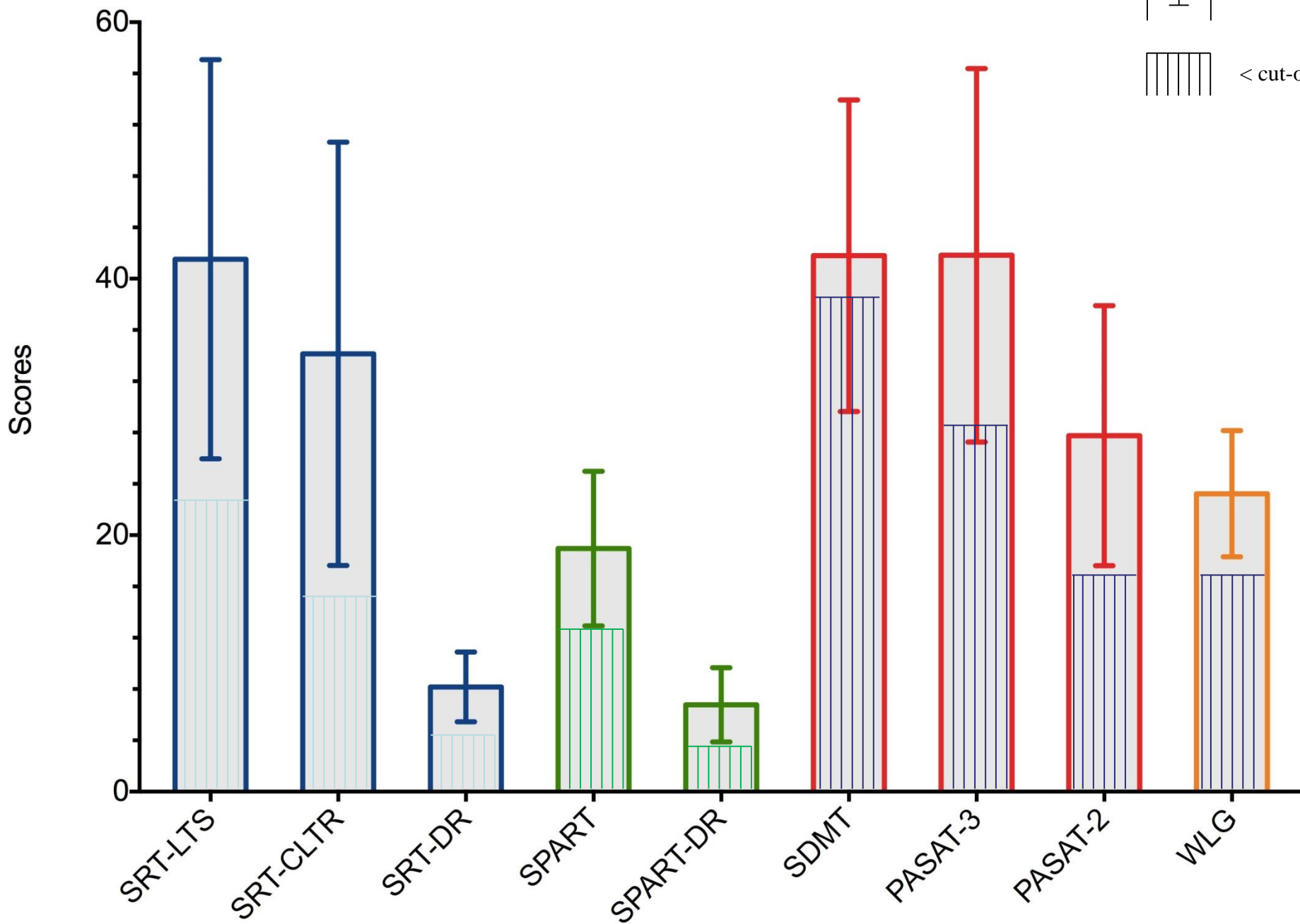
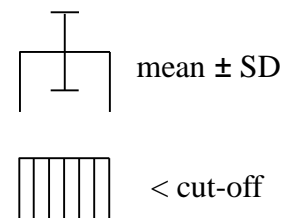
score < cut-off



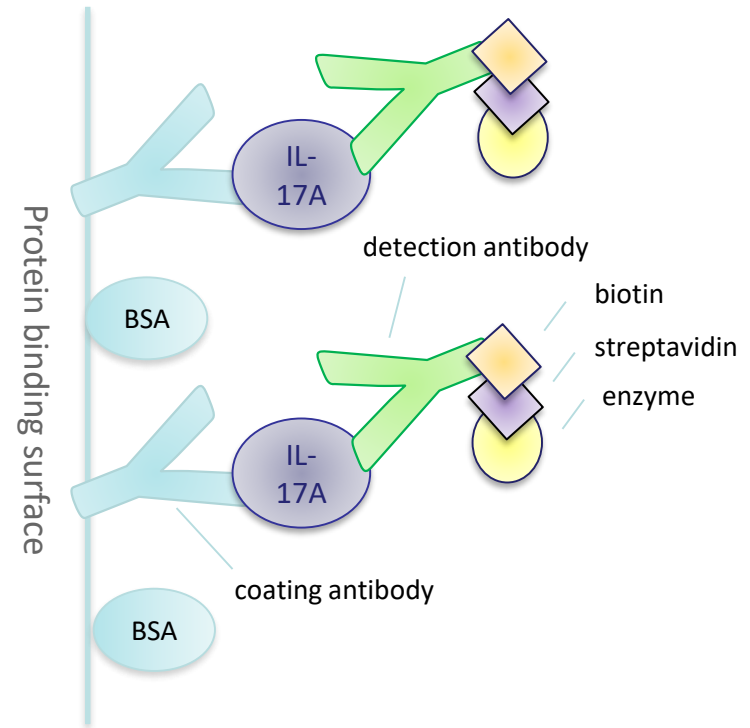
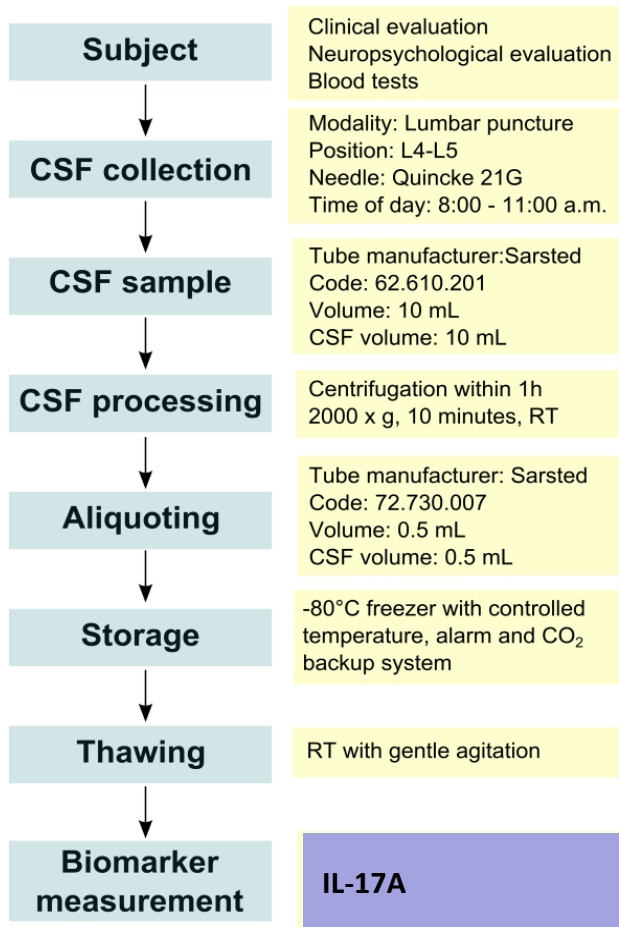
normal score



BRB Scores



CSF collection, storing and analysis



Commercially available sandwich ELISA kit
(BioLegend, San Diego, CA, USA)



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Department of Medicine
University of Perugia



Section of Pathology
Department of Experimental Medicine
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