



Microglial activation causes selective dentate gyrus disruption and memory impairment in experimental multiple sclerosis

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Memory impairment in multiple sclerosis

- Frequent: up to 50% of patients with MS

(Planche et al, *Eur J Neurol*, 2015)

- Early: up to 25% of patients with CIS

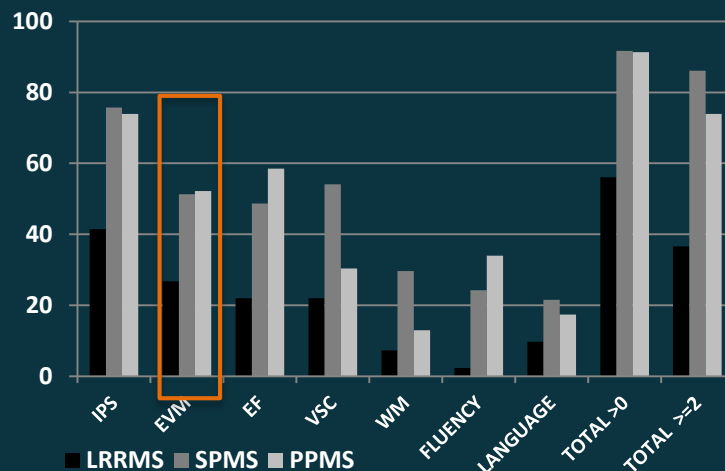
(Feuillet et al., *Mult Scler*, 2004)

- Correlated with hippocampal volume in MS

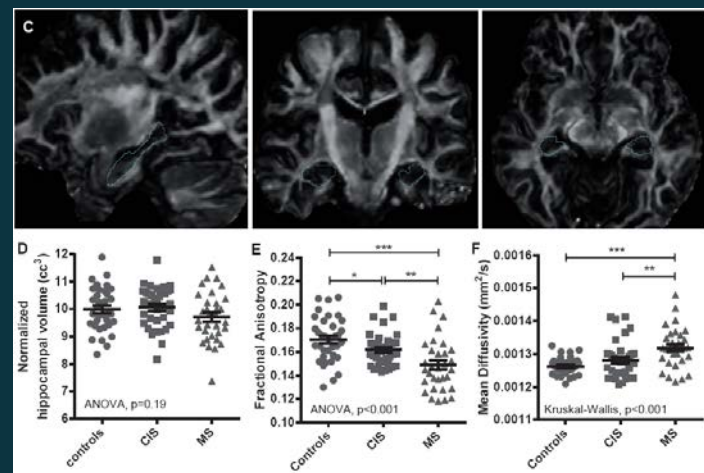
(Sicotte et al., *Brain*, 2008) and with hippocampal microstructural damage in CIS (Planche et al., under review)

- Early cellular modifications?

- Hippocampal subfields more vulnerable than others?



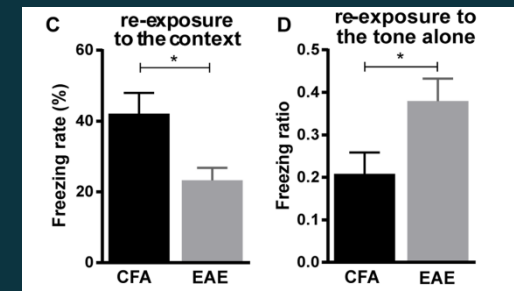
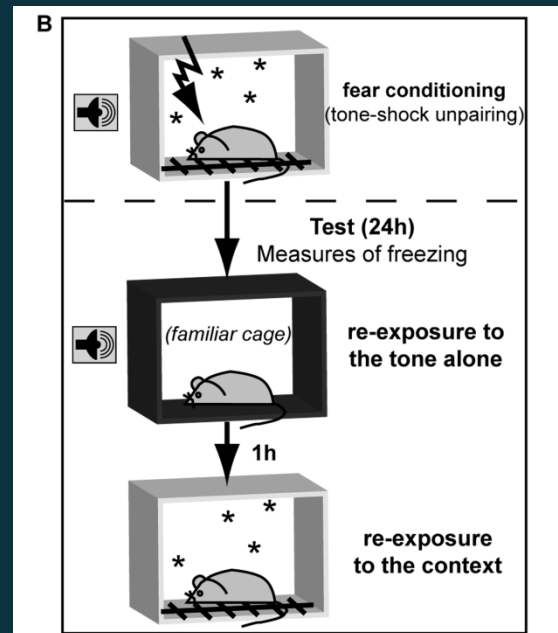
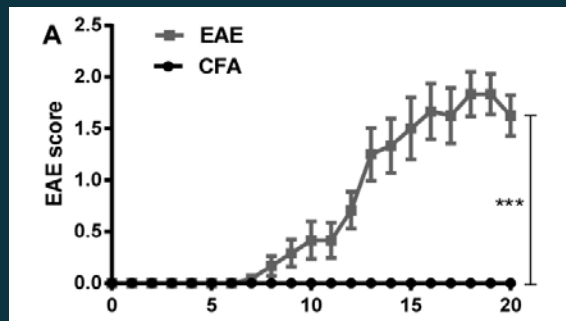
(Planche et al, *Eur J Neurol*, 2015)



(Planche et al., under review)

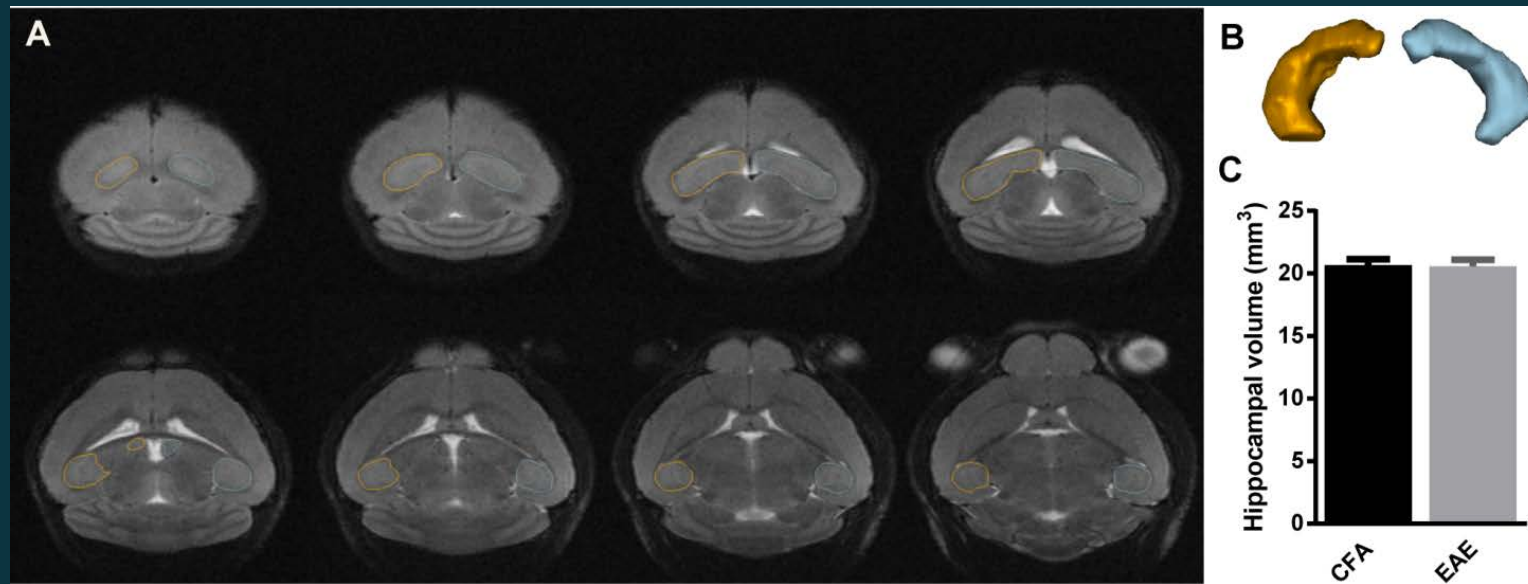
- **Behaviour:** hippocampal-dependant memory impairment?
- **Morphological MRI:** hippocampal atrophy?
- **Diffusion tensor imaging:** hippocampal microstructural damages (layer-by-layer analyses)?
- **Histology:** neuronal death? glial pathology? MRI-histological correlations?
- **Electrophysiology:** functional impairment of neuronal circuits?
- **Pharmacology:** cause and effect?

Animal behaviour: contextual fear conditioning



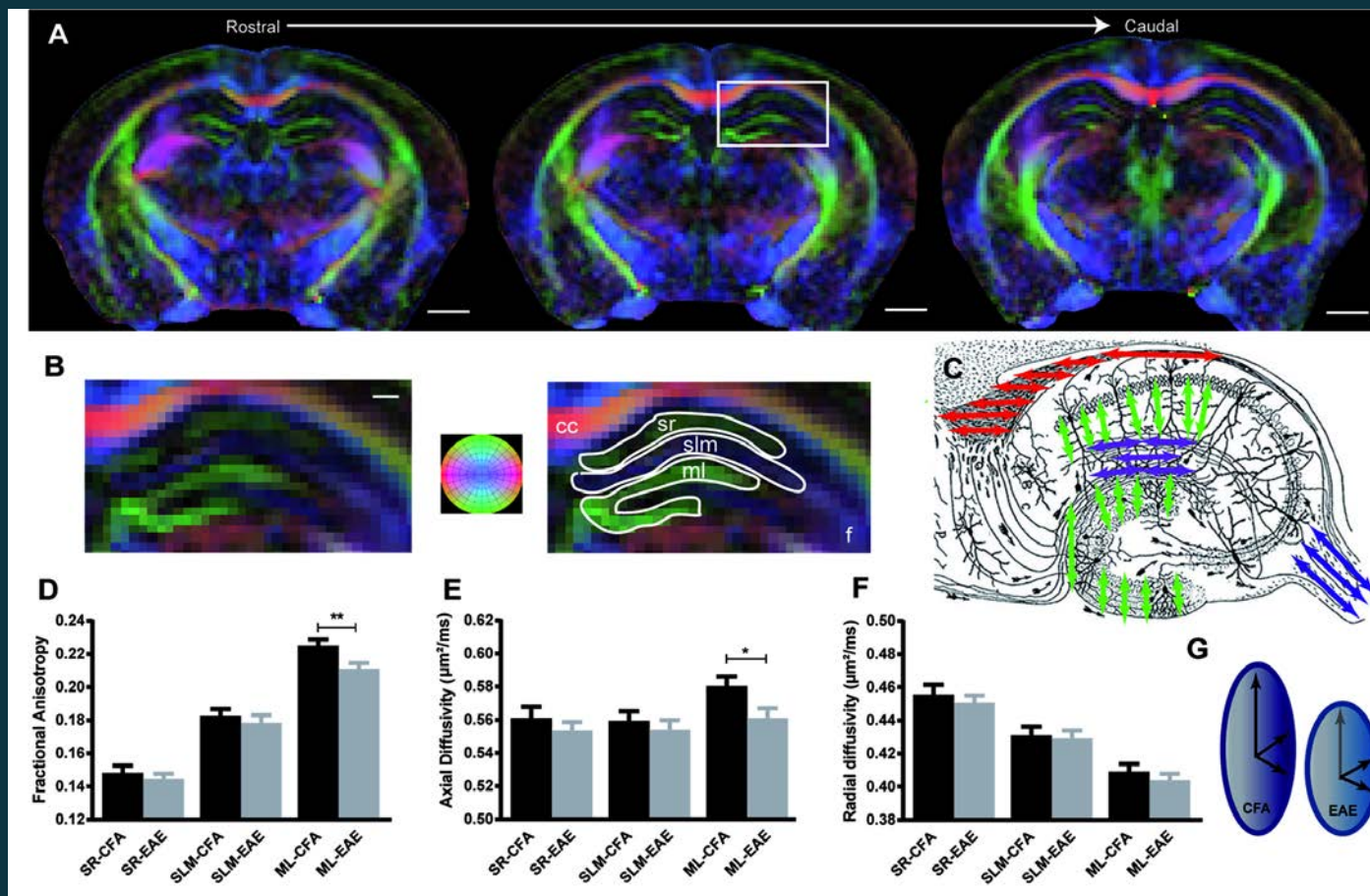
EAE-mice showed an early hippocampal-dependent memory deficit

Volumetry of hippocampus



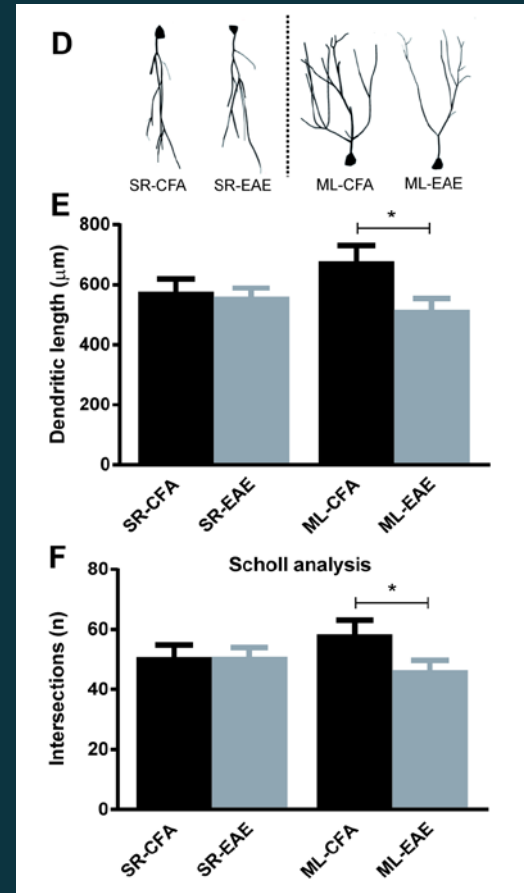
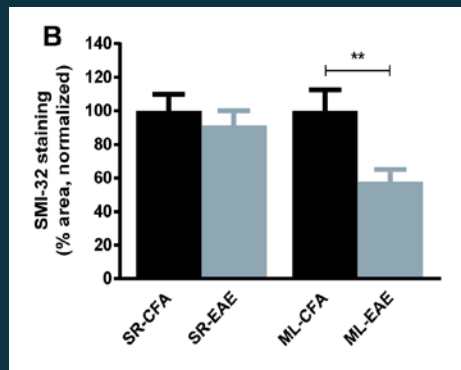
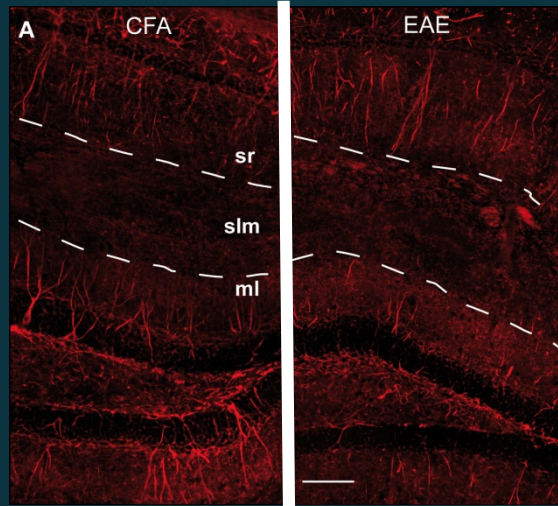
EAE-mice did not show hippocampal atrophy as measured with T2-volumetry MRI

Diffusion tensor imaging: the microstructure of the hippocampus in EAE-mice



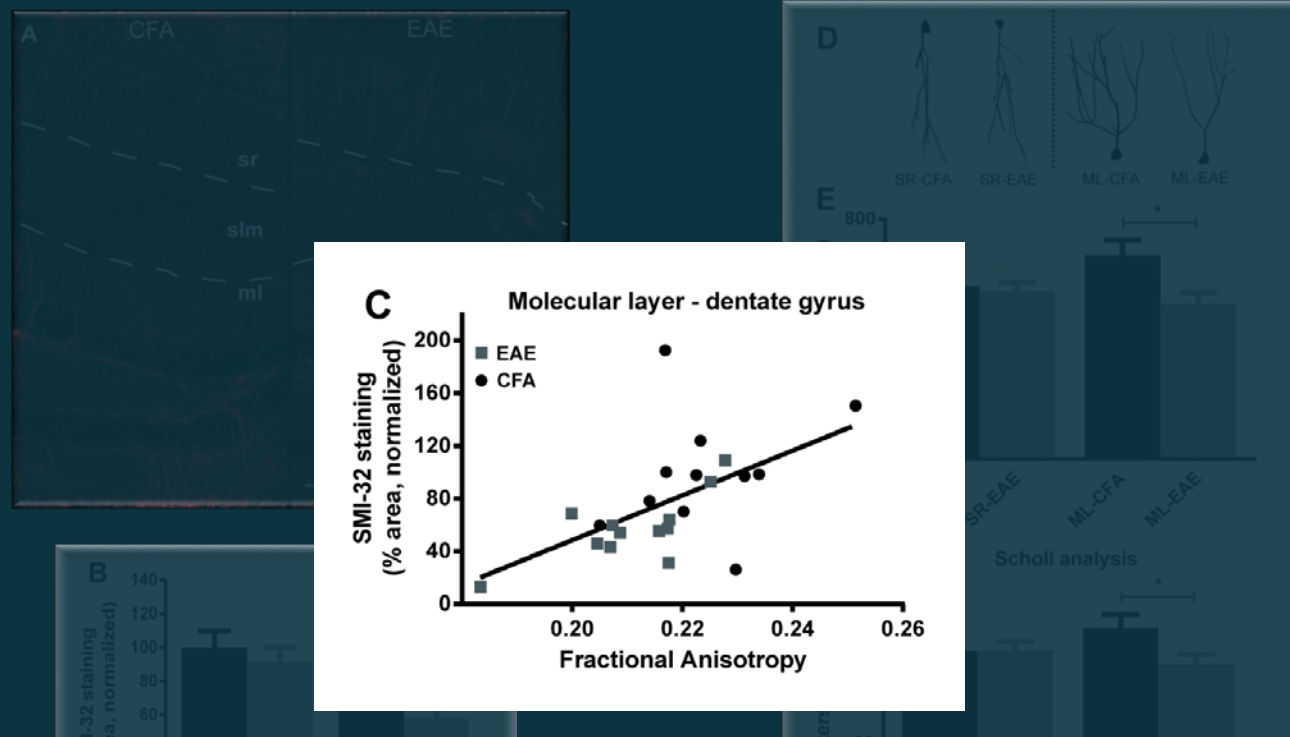
***In vivo* DTI revealed selective microstructural modifications in the molecular layer of the dentate gyrus of EAE-mice**

Histological correlates (1)



EAE-mice showed a selective and early neurodegenerative process in the dentate gyrus

Histological correlates (1)



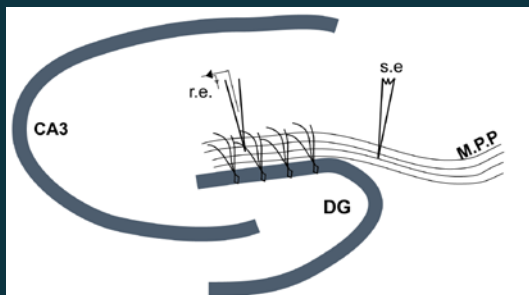
The loss of neurites was correlated with FA and AD in the molecular layer of the dentate gyrus

EAE-mice showed a selective and early neurodegenerative process in the dentate gyrus

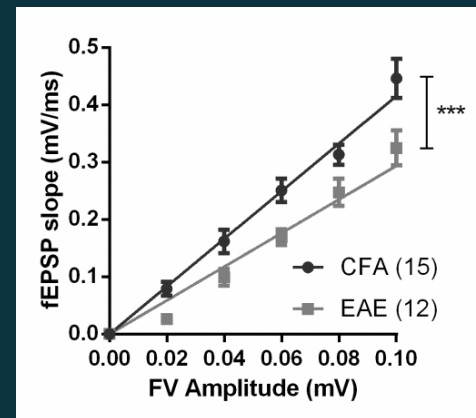
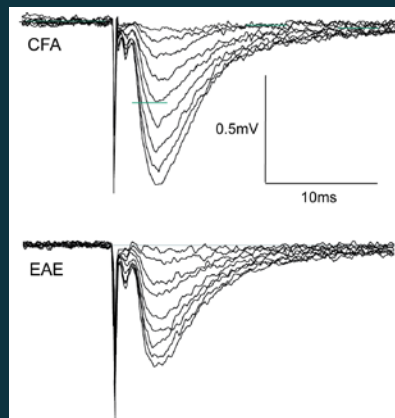
Electrophysiology

Input/Output

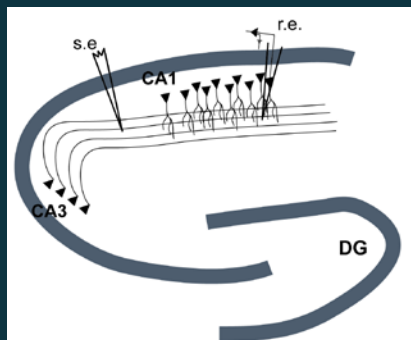
MPP – DG:



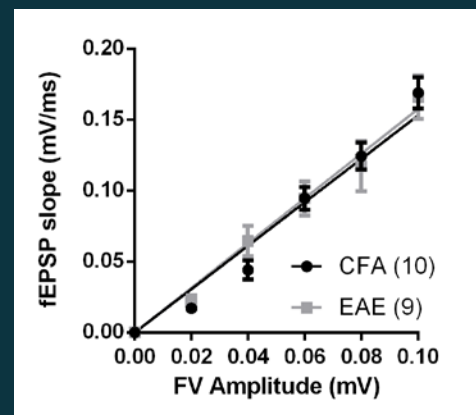
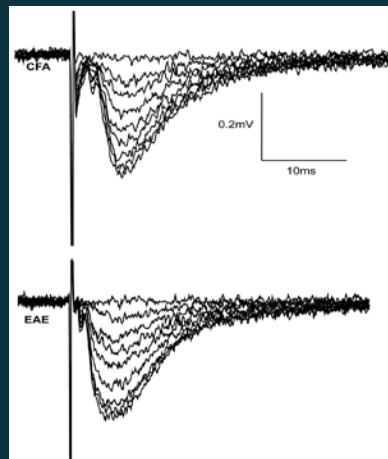
(extracellular recording)



CA3 – CA1



(extracellular recording)

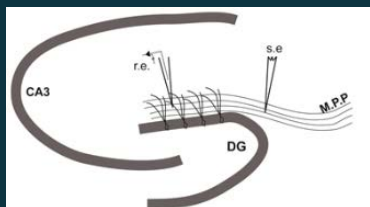


Electrophysiological recordings confirm differential neuritic/synaptic vulnerability in the dentate gyrus of EAE mice

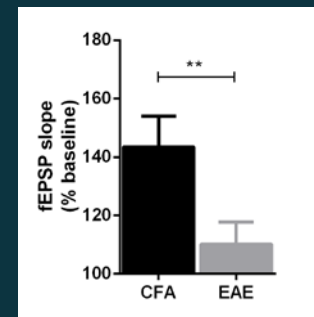
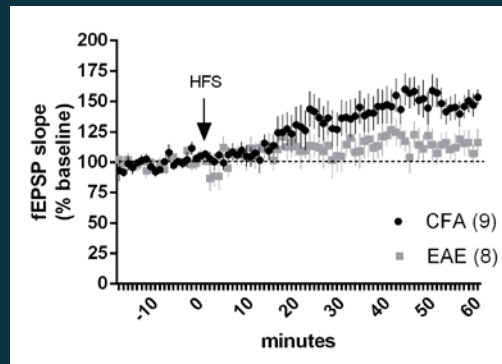
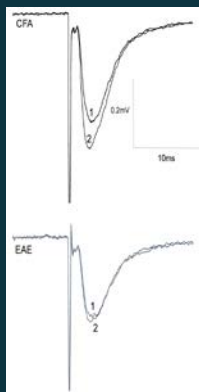
Electrophysiology

Synaptic plasticity

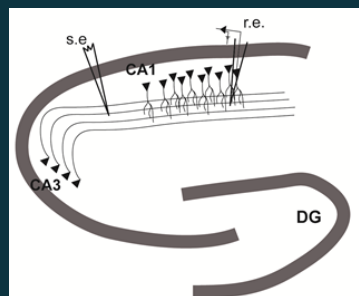
MPP-DG



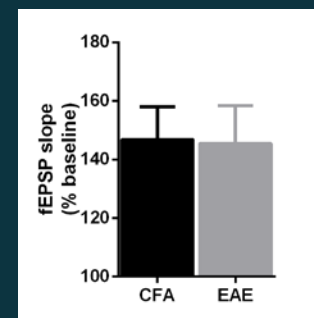
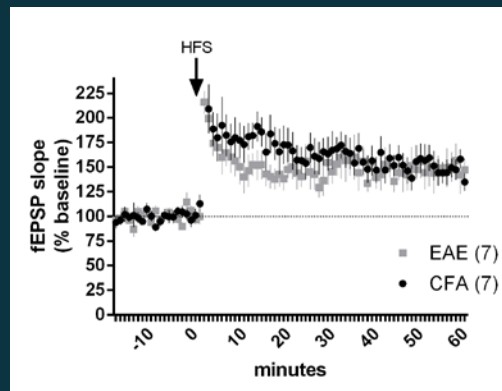
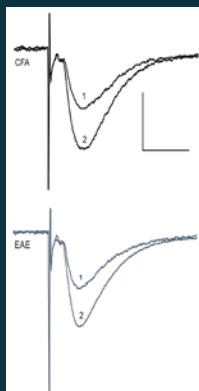
(extracellular recording)



CA3-CA1



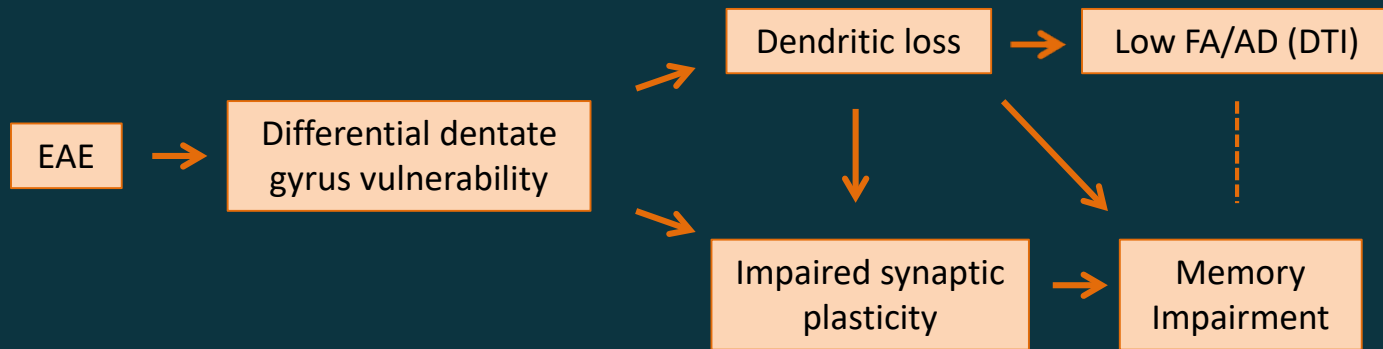
(extracellular recording)



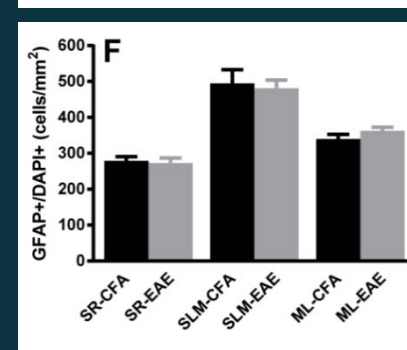
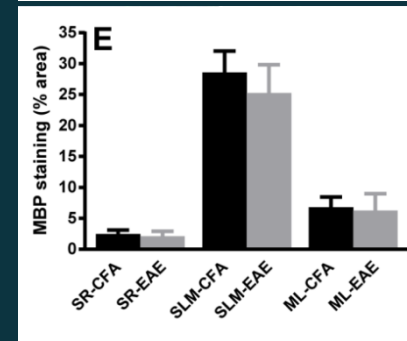
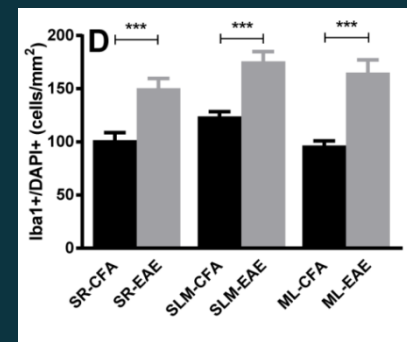
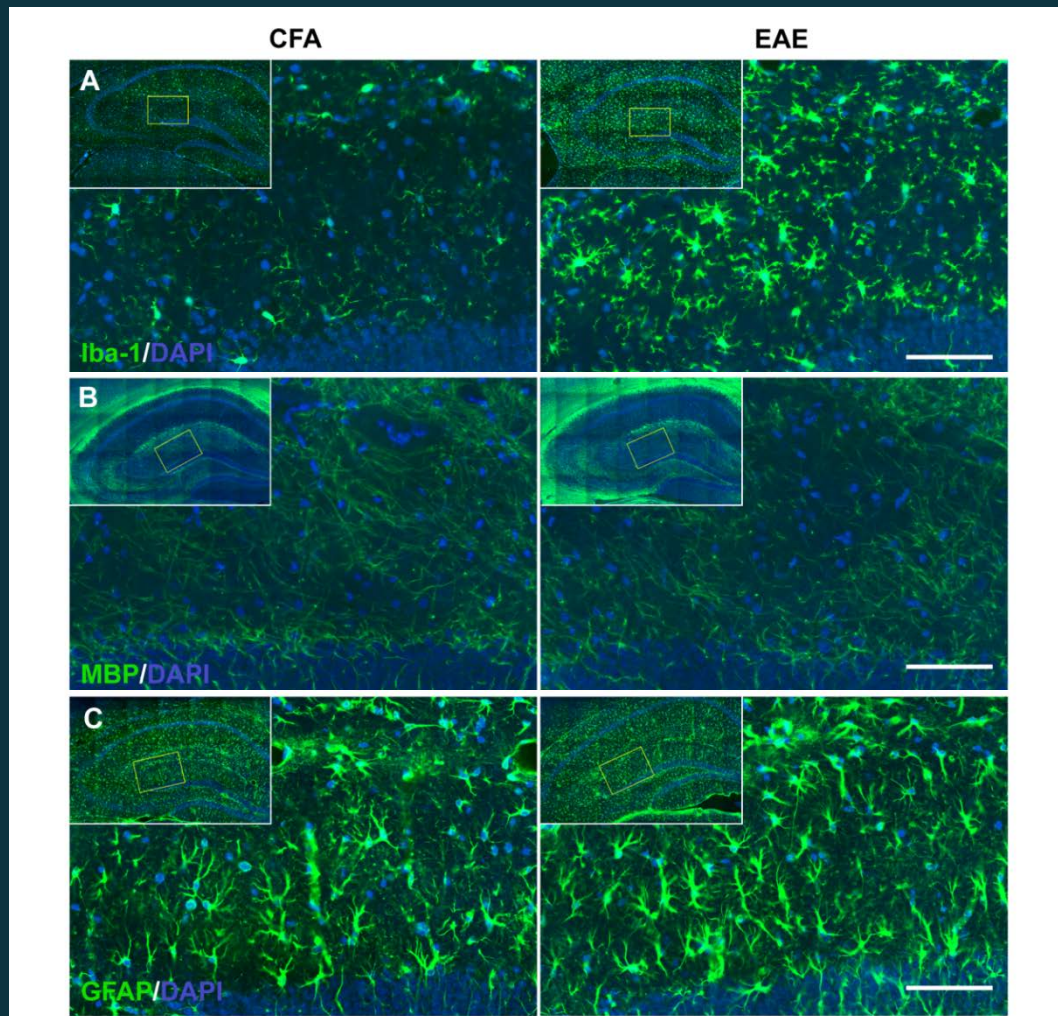
Long term potentiation is impaired in the dentate gyrus of EAE-mice but not in the CA1 subfield

Bullet point summary

1. Differential dentate gyrus vulnerability in EAE mice with early memory impairment
2. *In vivo* DTI correlates with these early microstructural changes and is more sensitive than MRI measure of atrophy

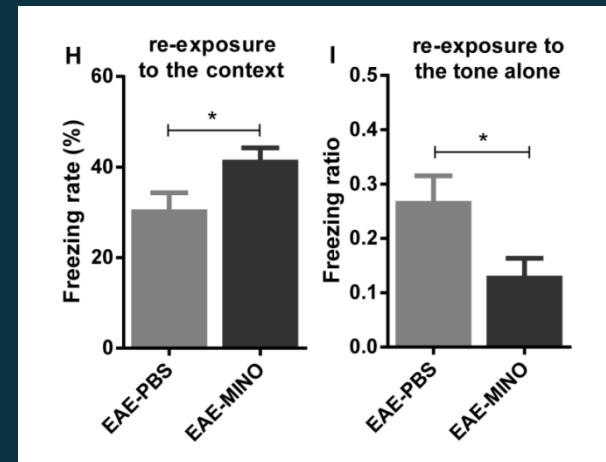
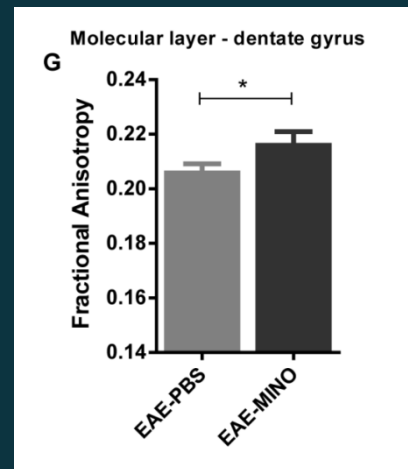
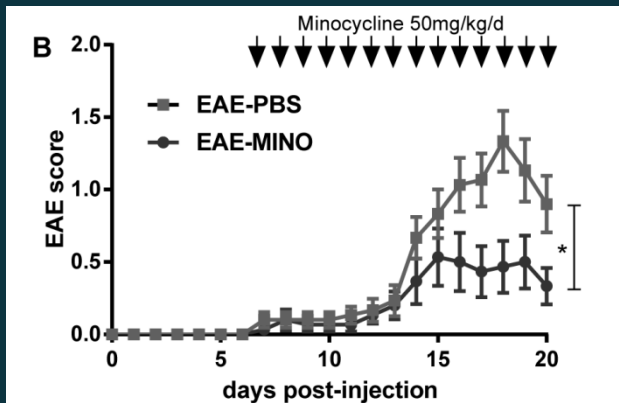
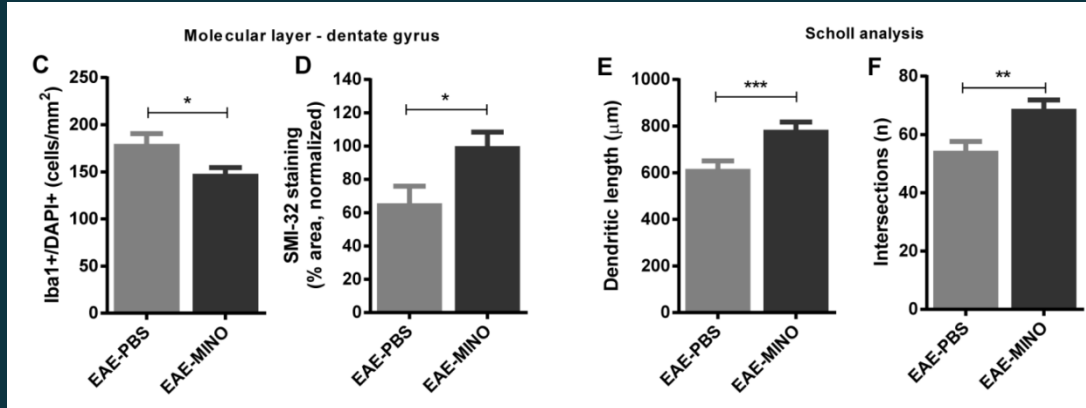
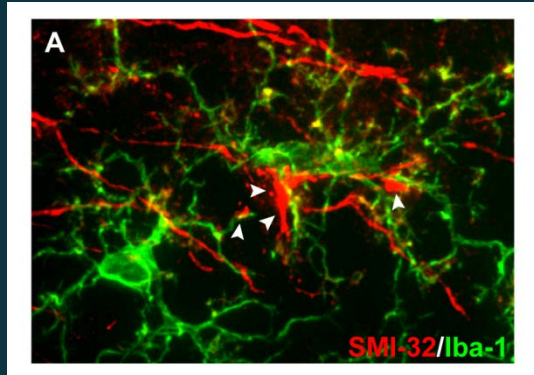


Histological correlates (2)



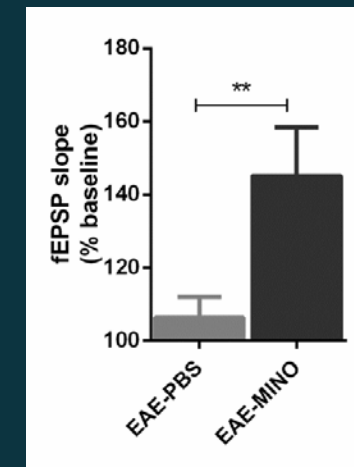
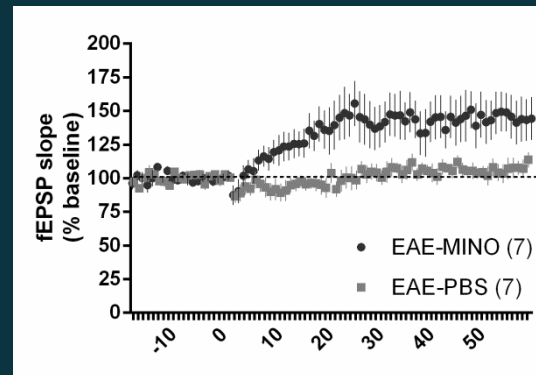
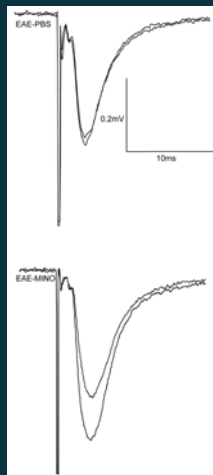
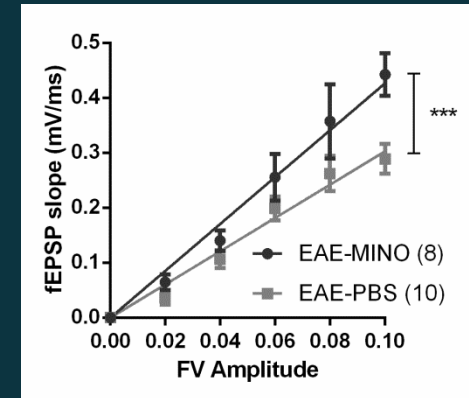
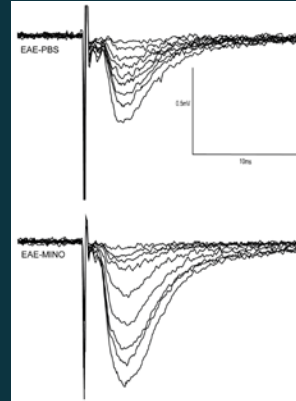
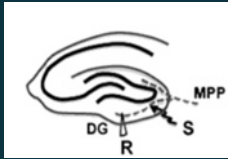
EAE-mice showed diffuse microglial reactivity in the hippocampus but no demyelination, no cellular infiltration and no astrocytic proliferation.

Systemic minocycline treatment (1)



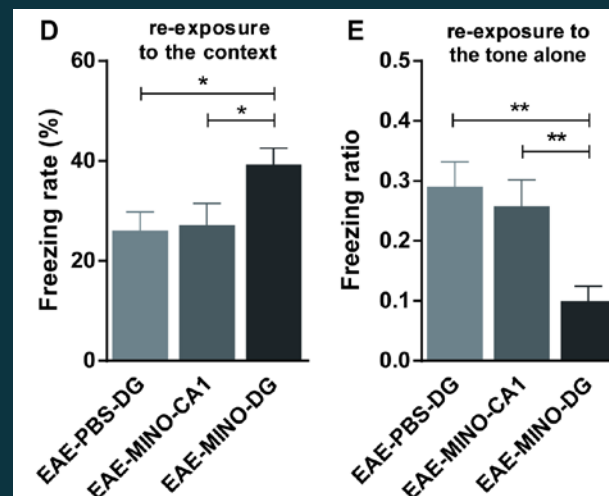
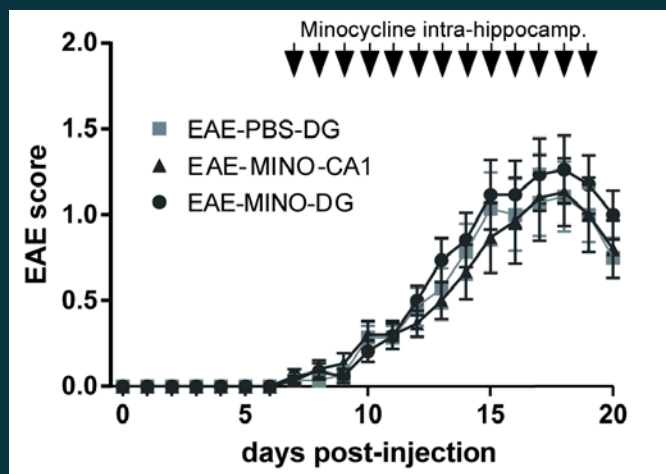
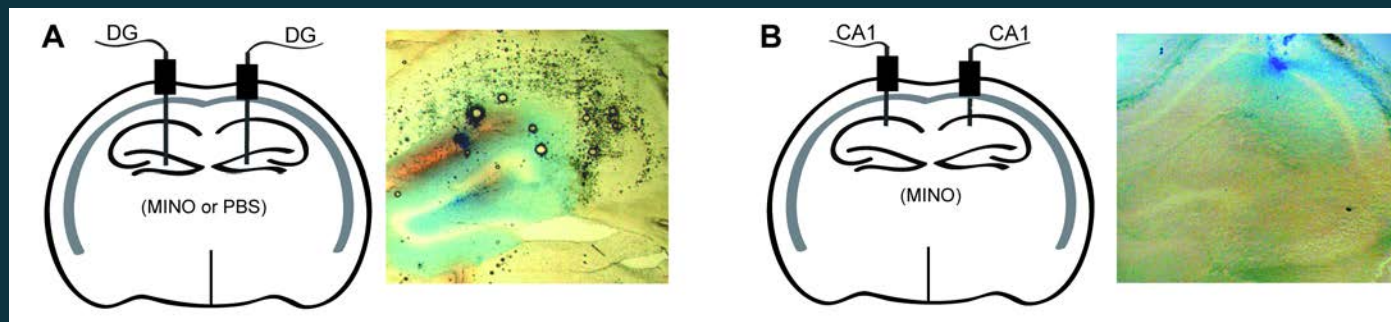
Systemic minocycline treatment (2)

MPP-DG



Minocycline treatment preserved EAE-mice from memory impairment and prevented DTI, histological and electrophysiological abnormalities.

Intra-hippocampal minocycline treatment

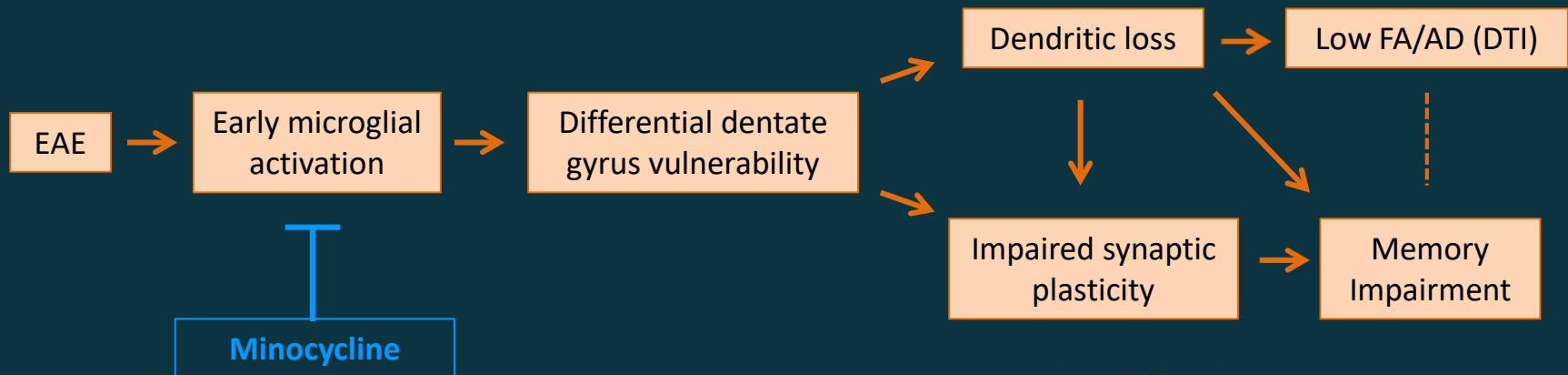


Selective inhibition of dentate gyrus microglial activation was sufficient to prevent memory impairment in EAE-mice

Conclusion

Microglial activation causes selective dentate gyrus disruption and memory impairment in EAE

1. Differential dentate gyrus vulnerability in EAE mice with early memory impairment
2. Activated microglia causes dendritic loss and impairs synaptic plasticity in the molecular layer of the DG
3. *In vivo* DTI correlates with these early microstructural changes and could be used as a biomarker of therapeutic response
4. Minocycline is a potential neuroprotective treatment which could prevent memory impairment in MS





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