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)
Methods

**Experimental Autoimmune Encephalomyelitis**

- **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
EAE-mice did not show hippocampal atrophy as measured with T2-volumetry MRI
*In vivo* DTI revealed selective microstructural modifications in the molecular layer of the dentate gyrus of EAE-mice.
EAE-mice showed a selective and early neurodegenerative process in the dentate gyrus
Histological correlates (1)

Results

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.
Electrophysiological recordings confirm differential neuritic/synaptic vulnerability in the dentate gyrus of EAE mice.
Long term potentiation is impaired in the dentate gyrus of EAE-mice but not in the CA1 subfield.
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
EAE-mice showed diffuse microglial reactivity in the hippocampus but no demyelination, no cellular infiltration and no astrocytic proliferation.
Systemic minocycline treatment (1)
Minocycline treatment preserved EAE-mice from memory impairment and prevented DTI, histological and electrophysiological abnormalities.
Intra-hippocampal minocycline treatment

Results

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