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Poster n°69

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# Neuroinflammatory processes induced during EAE also affect the hippocampus and its associated cognitive processes

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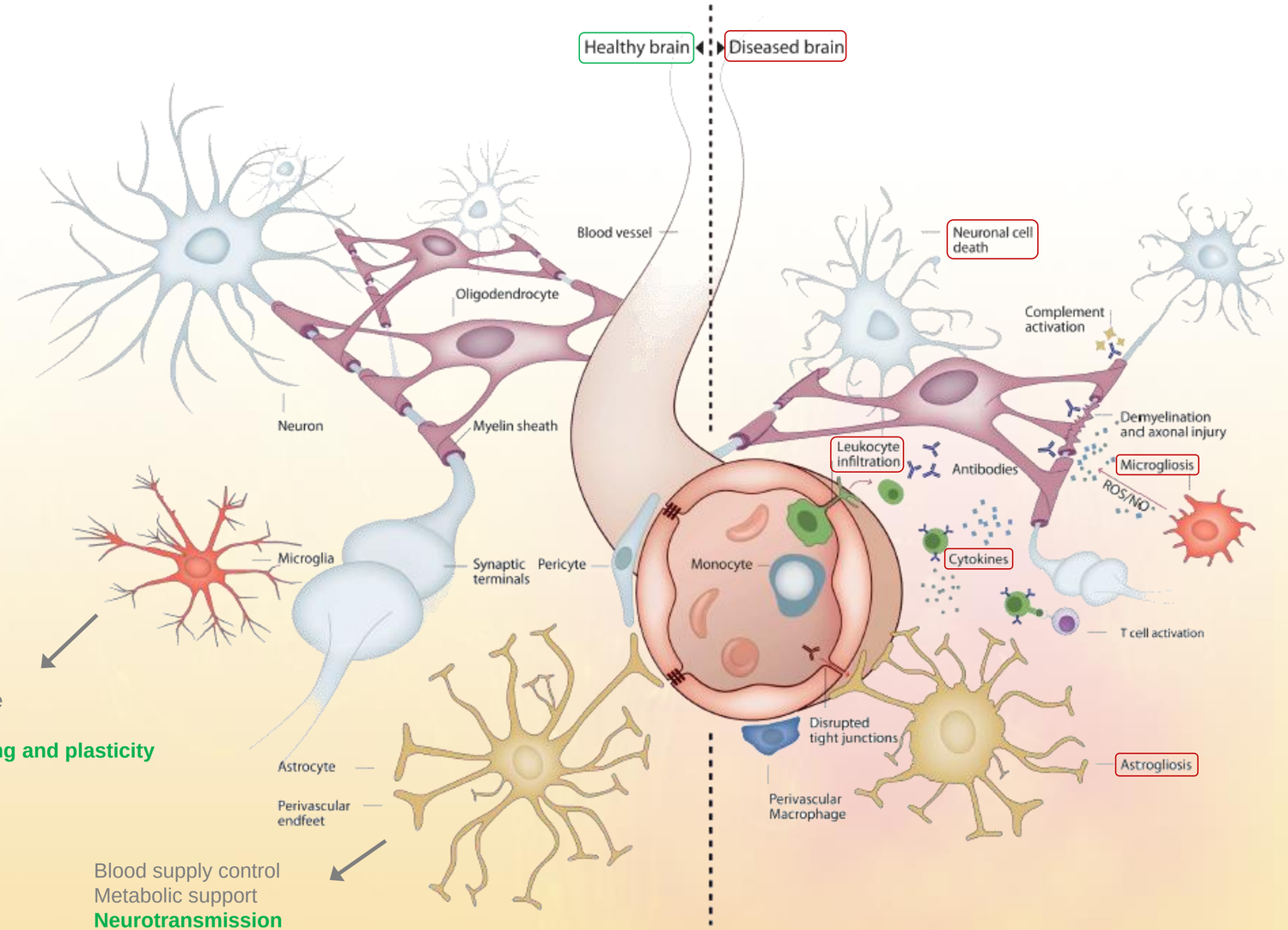
# Immune mechanisms influence synaptic plasticity and cognition in physiological and pathological conditions




Debris clearance
Immune surveillance
**Neurotransmission**
**Synaptic remodeling and plasticity**

Blood supply control
Metabolic support
**Neurotransmission**
**Synaptic remodeling and plasticity**

**Neuronal dysfunctions**
**Disrupted neurotransmission**
**Synaptic plasticity alterations**
**Memory impairments**

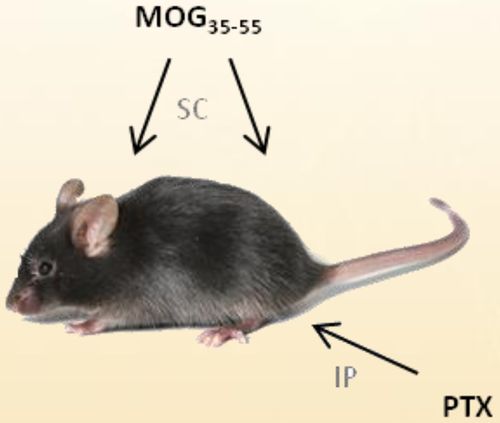
Sankowski et *al.*, 2015

## Aim

To investigate and deepen the effects of neuroinflammation on neuronal network activity and synaptic plasticity of the hippocampus and to highlight the inflammatory actors implicated in cognitive disorders

## Experimental model of multiple sclerosis (MS)

Experimental autoimmune encephalomyelitis (EAE)

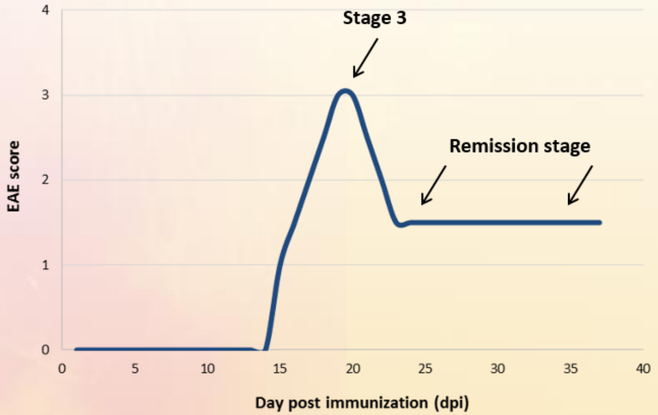



Induction of EAE

| EAE score | Motor Symptoms |
|---|---|
| 0 | No motor problems |
| 1 | Limp tail |
| 2 | Weakness of hind legs |
| 3 | Complete paralysis of hind legs |
| 4 | Complete hind leg and partial front leg paralysis |
| 5 | Severe paralysis, euthanasia |

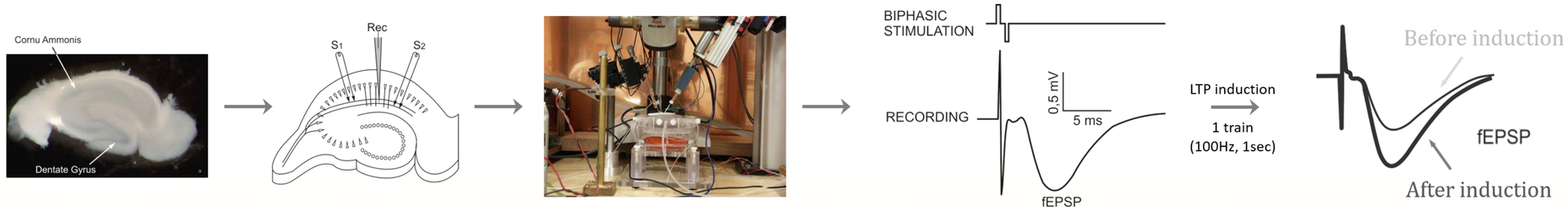
EAE scoring

**Two main stages**

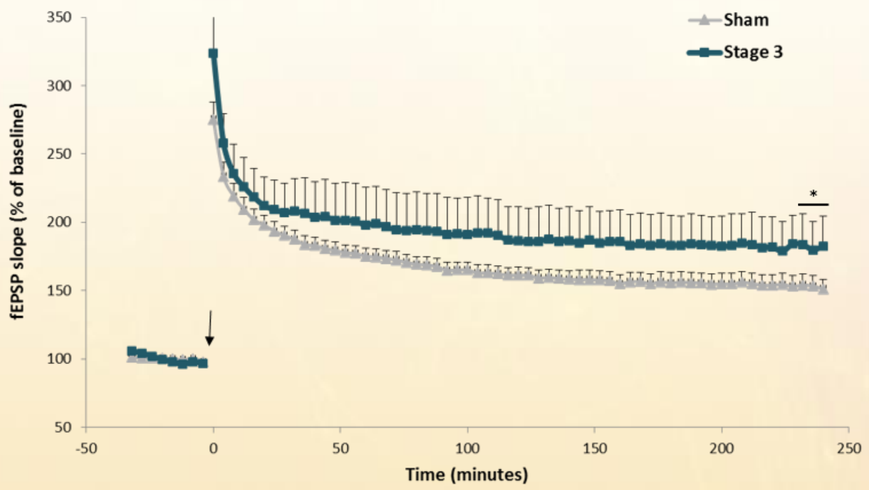


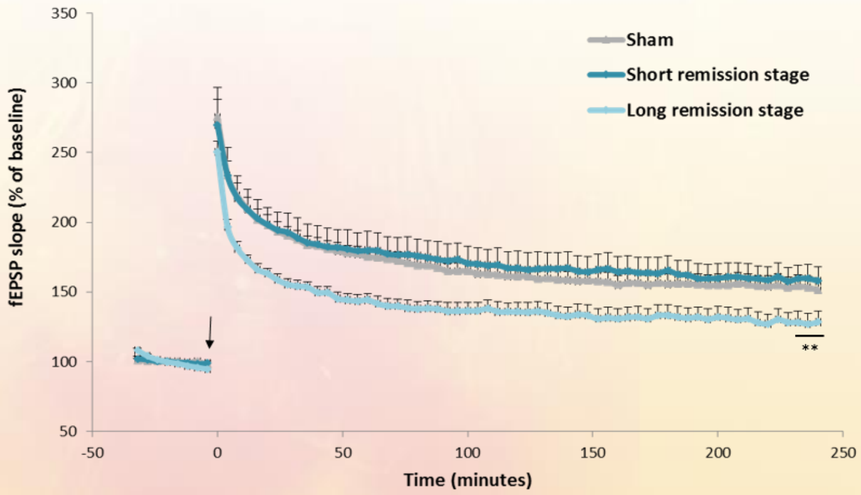

Evolution of EAE

# Hippocampal synaptic plasticity is modified during the course of EAE




Hippocampal slice | Electrodes positioning | Recording chamber | fEPSP recording | LTP induction



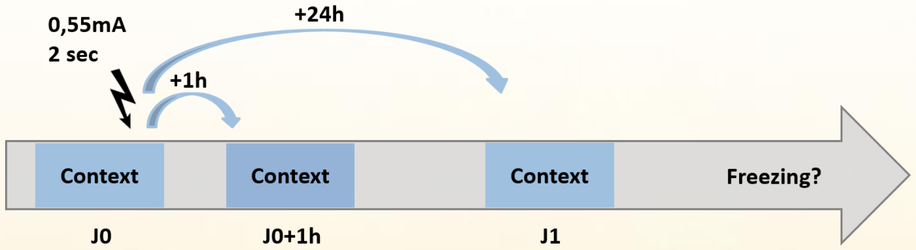




**Hippocampal synaptic plasticity of EAE mice was analysed at different stages of EAE.** *Ex vivo* electrophysiological recordings (LTP measurements) were made on acute hippocampal slices by measuring fEPSP slope before and after LTP induction (arrow). The level of potentiation is enhanced at the peak of EAE (stage 3, motor paralysis) but progressively decreases during the remission stage (motor improvement) to reach a level significatively lower than the control one. So we observed an inverse correlation between hippocampal synaptic plasticity and motor function in mice during EAE.

# Remitting mice present a cognitive impairment with CFC

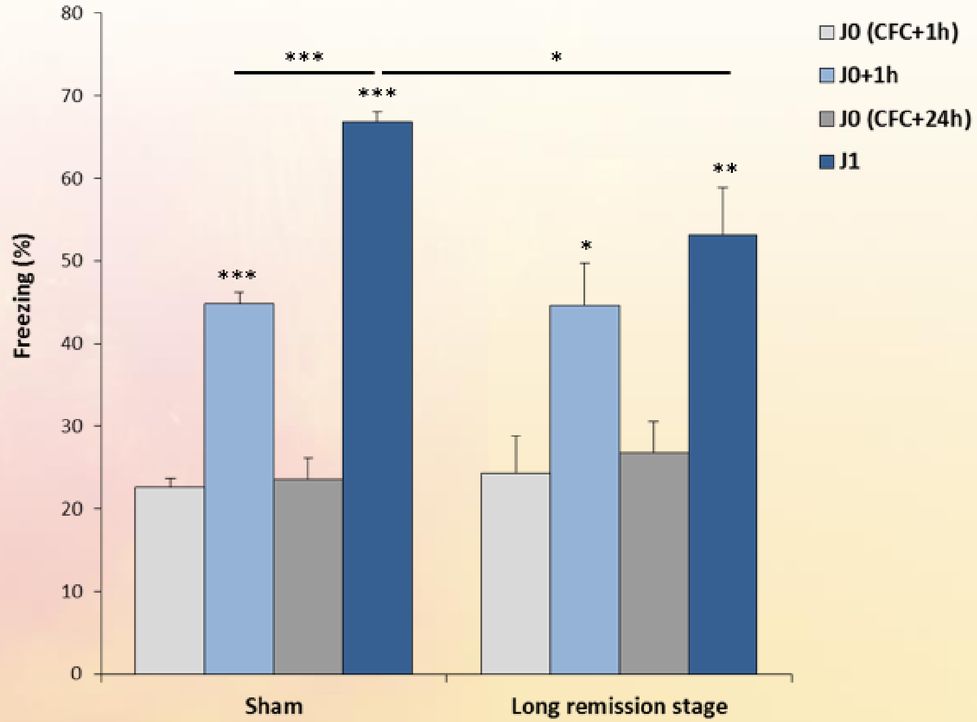
**Spatial learning of remitting mice during EAE was investigated by the contextual fear conditioning (CFC).**

The CFC is a hippocampus-dependent behavioral test allowing to evaluate the ability of mice to learn and remember an association between a neutral conditioned stimulus (environmental cues) and an aversive unconditioned stimulus (electric footshock). Mice are permitted to walk a few minutes into a conditioned chamber before receiving the aversive stimulus (J0). After a delay time (1h or 24h), mice are reexposed to the same context without any electrical shock and freezing behavior during the test is measured as an index of fear memory.




**Short term memory** → CFC+1h → J0 vs J0+1h

**Long term memory** → CFC+24h → J0 vs J1

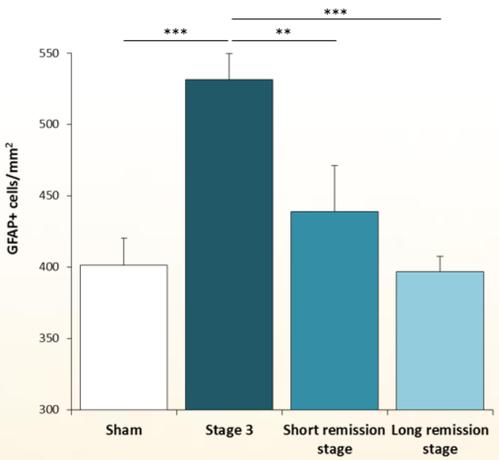



Similar freezing behavior was obtained with the CFC+1h between shamed and EAE mice. However remitting mice present a lower freezing 24h after the learning episode (J1) compared to sham. This suggests that a cognitive impairment develops during the remission stage of EAE and implies long term but not short term memory. These *in vivo* results correlate with the previous electrophysiological data showing a deficit of hippocampal synaptic plasticity in remitting mice.

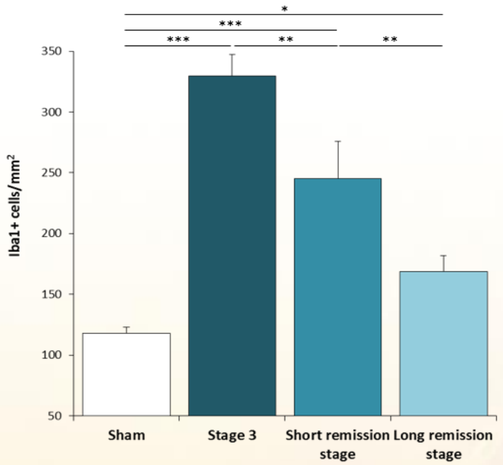
# Glial cells are activated and proinflammatory cytokines are produced in the hippocampus of EAE mice

**Glia**

### Astrocytes



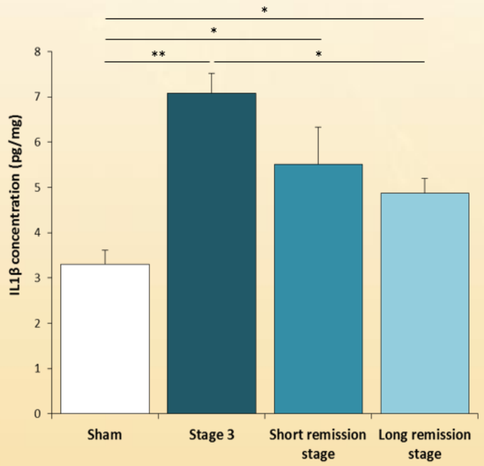

### Microglia



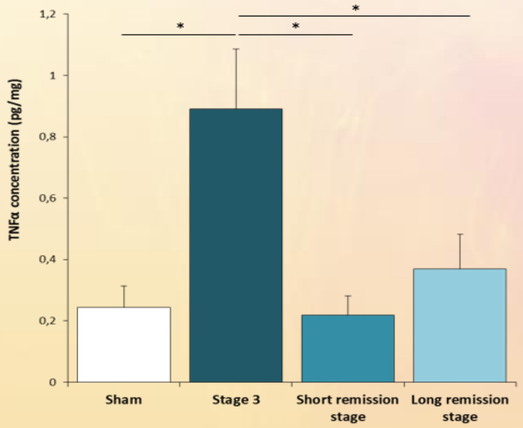

**Activation of glial cells (astrocytes and microglial cells) was evaluated by IHC in the hippocampus of EAE mice.**
Quantification of GFAP+ cells (astrocytes, left) and Iba1+ cells (microglial cells, right) in the hippocampus during EAE revealed that the number of both glial cells follows the disease progression as it enhances during the peak of EAE and then decreases during the remission stage. The activation profile between astrocytes and microglia is similar but microglial proliferation is more important than astrocytes at the stage 3 and remains high during the remission stage compared to shamed mice. So microglia could be involved in synaptic modifications observed during the remission stage.

**Cytokines**

### IL1β




### TNFα




**Production of proinflammatory cytokines (IL1β and TNFα) was assessed by sandwich ELISA experiments.**
Quantification of IL1β and TNFα concentration in the hippocampus of shamed and EAE mice revealed a production of both cytokines during EAE which follows the disease progression. The level of IL1β and TNFα is higher at the peak of EAE and then decreases during the remission stage. This profile is similar to the activation profile of glial cells suggesting the development of an inflammatory state in the hippocampus during EAE possibly linked to synaptic plasticity modifications.

# Conclusion

Neuroinflammation developed during EAE also affect cognitive structures like hippocampus and lead to cognitive impairments.

Different results were obtained depending on the stage of EAE:

| The hippocampus during the course of EAE | Stage 3 | Remission stage |
|---|---|---|
| 1. Synaptic plasticity modifications | ↗ | ↘ |
| 2. Cognitive impairment | | Yes |
| 3. Demyelination | No | No |
| 4. Alterations of structural integrity | No | No |
| 5. Glial cells proliferation (astrocytes and microglia) | +++ | + |
| 6. Proinflammatory cytokines production (IL1β and TNFα) | +++ | + |

Inflammatory processes (glial cells, cytokines) → ? → Hippocampal synaptic plasticity