A11/00

Binge alcohol intake triggers microglial activation and TNF-dependent aberrant synaptic pruning, causing synapse loss and increased anxiety

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The authors declare no conflict of interest.

SCIENCE SIGNALING | RESEARCH ARTICLE

ALCOHOL ADDICTION

Daily alcohol intake triggers aberrant synaptic pruning leading to synapse loss and anxiety-like behavior

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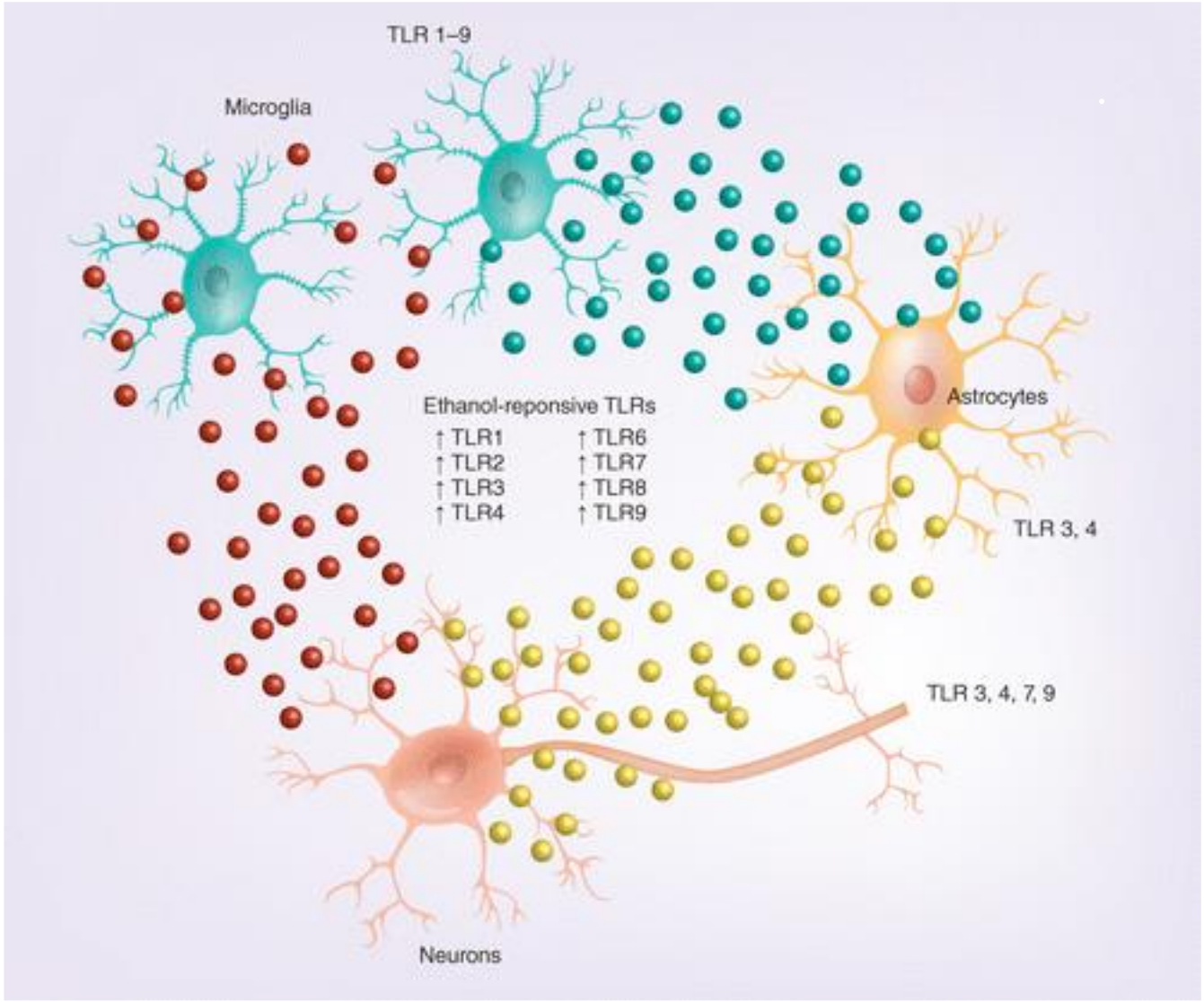
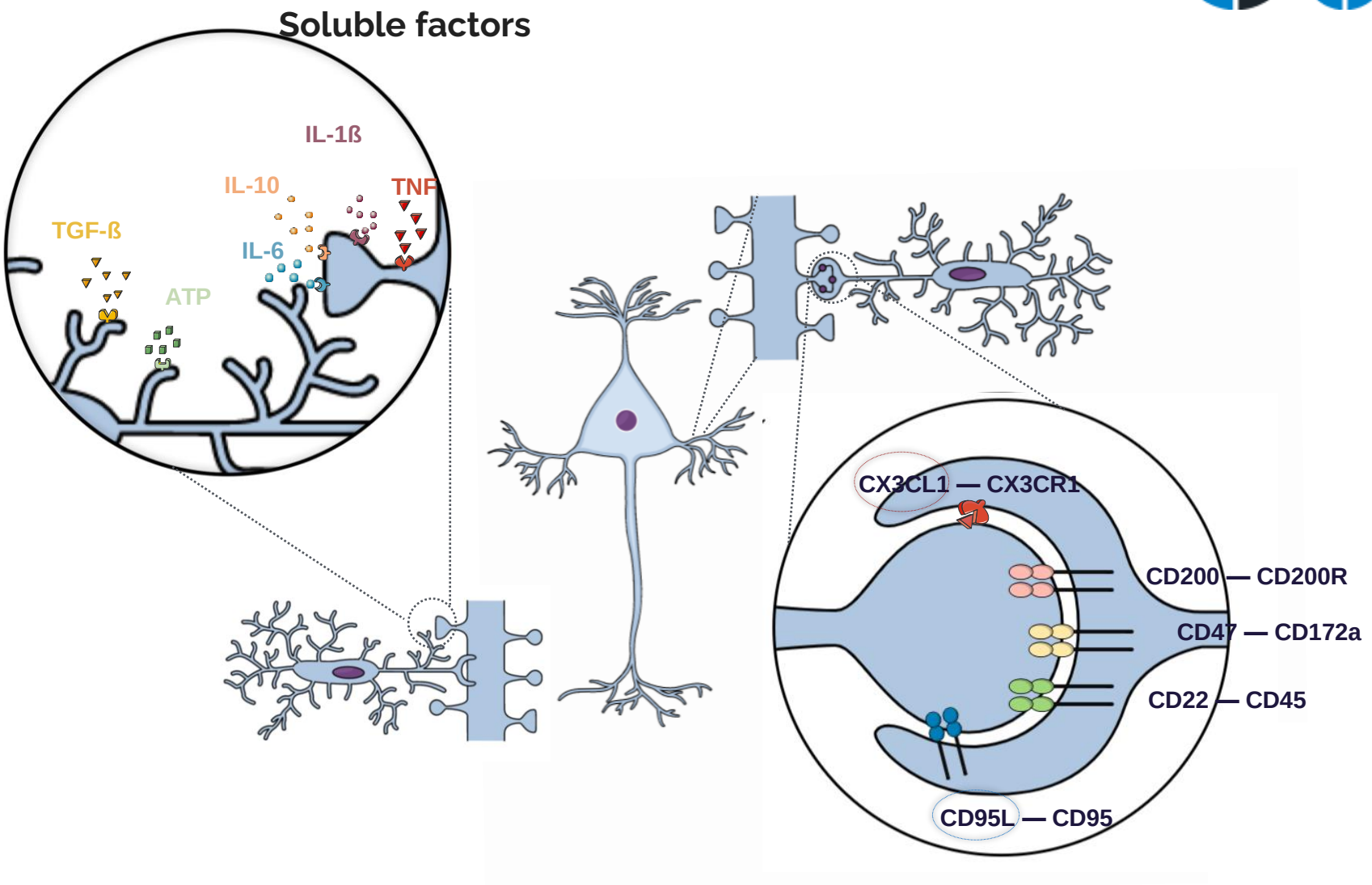
Neuroimmune responses, or a glia-neuron crosstalk



Warden et al. 2016

Neuron-microglia crosstalk



Why is this relevant?

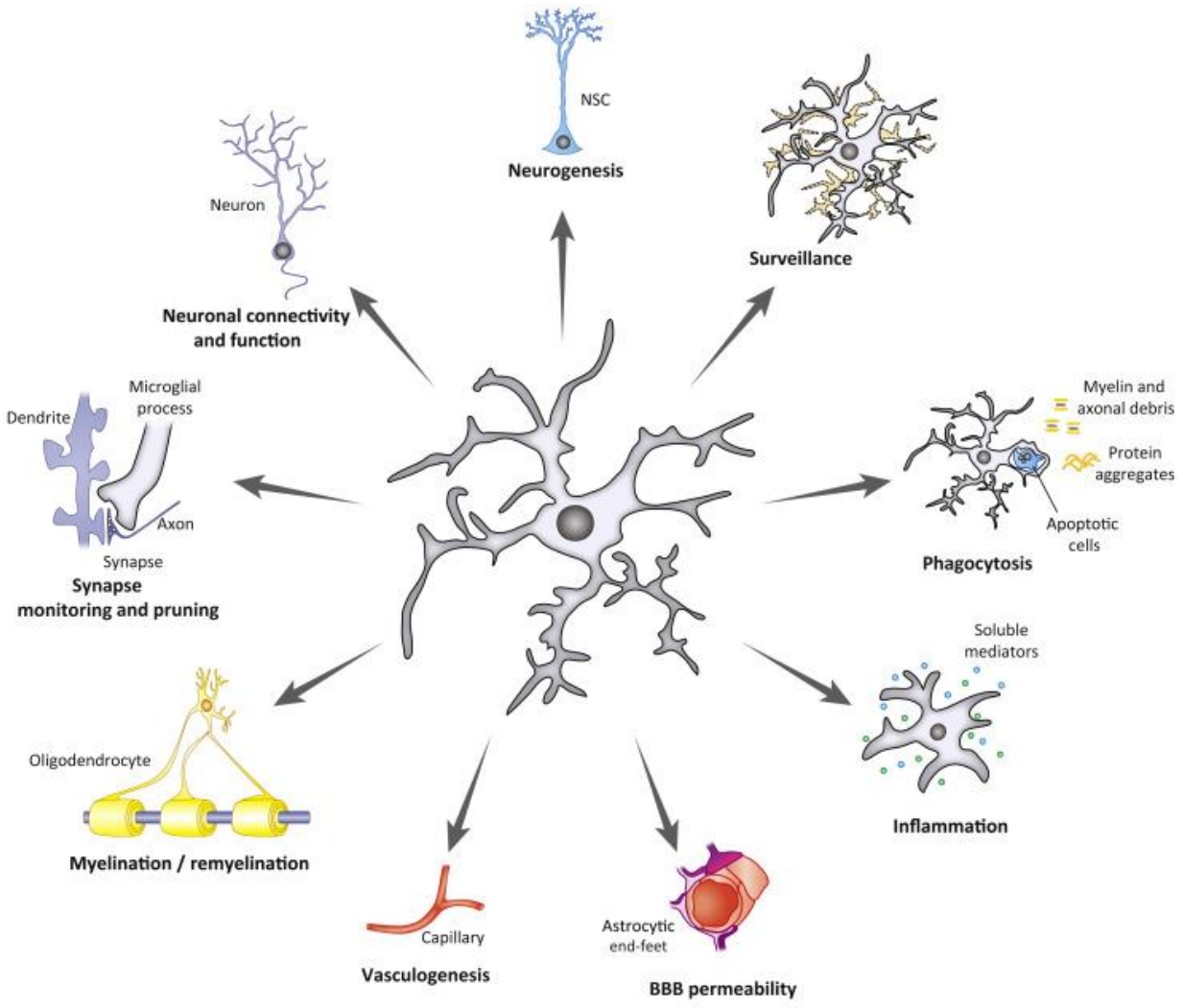
Intoxication stage - glial reactivity is likely involved in the reshaping of neuronal circuites underlying addiction.

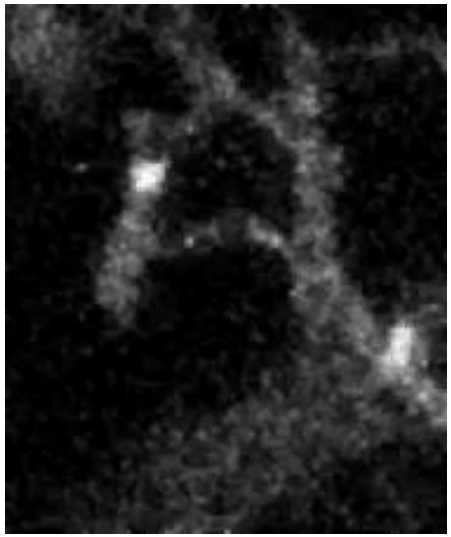
Withdrawal stage - glia-neuron interaction seems to promote a "sickness behaviour syndrome" that increases the probability of relapse.

Relapse rates

Limiting glial reactivity may be relevant to control the addictive behaviour and reduce relapse rates.

Microglia cells, not “resting” at all!





Nimmerjahn, Kirchhoff and Helmchen, Science

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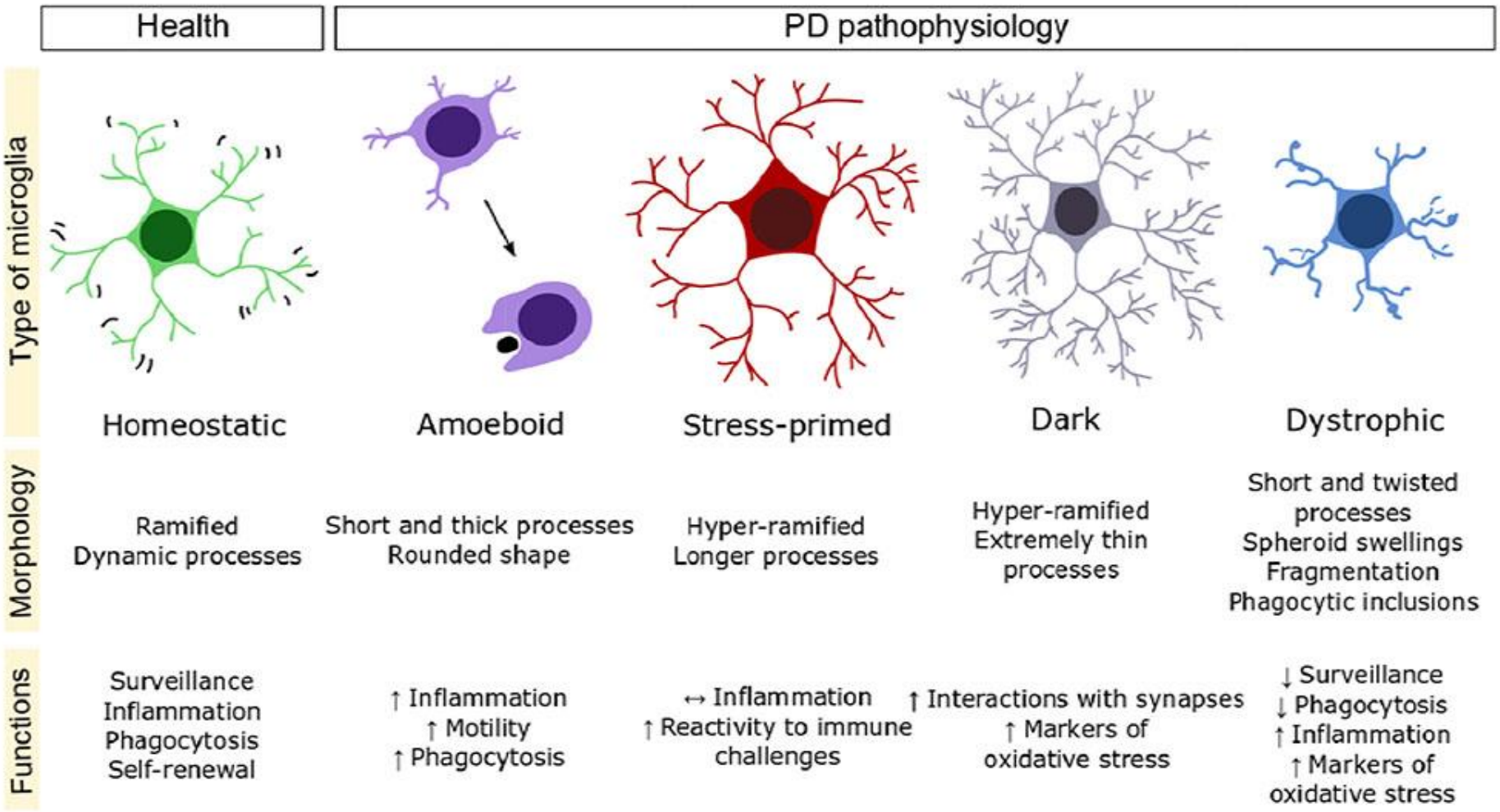
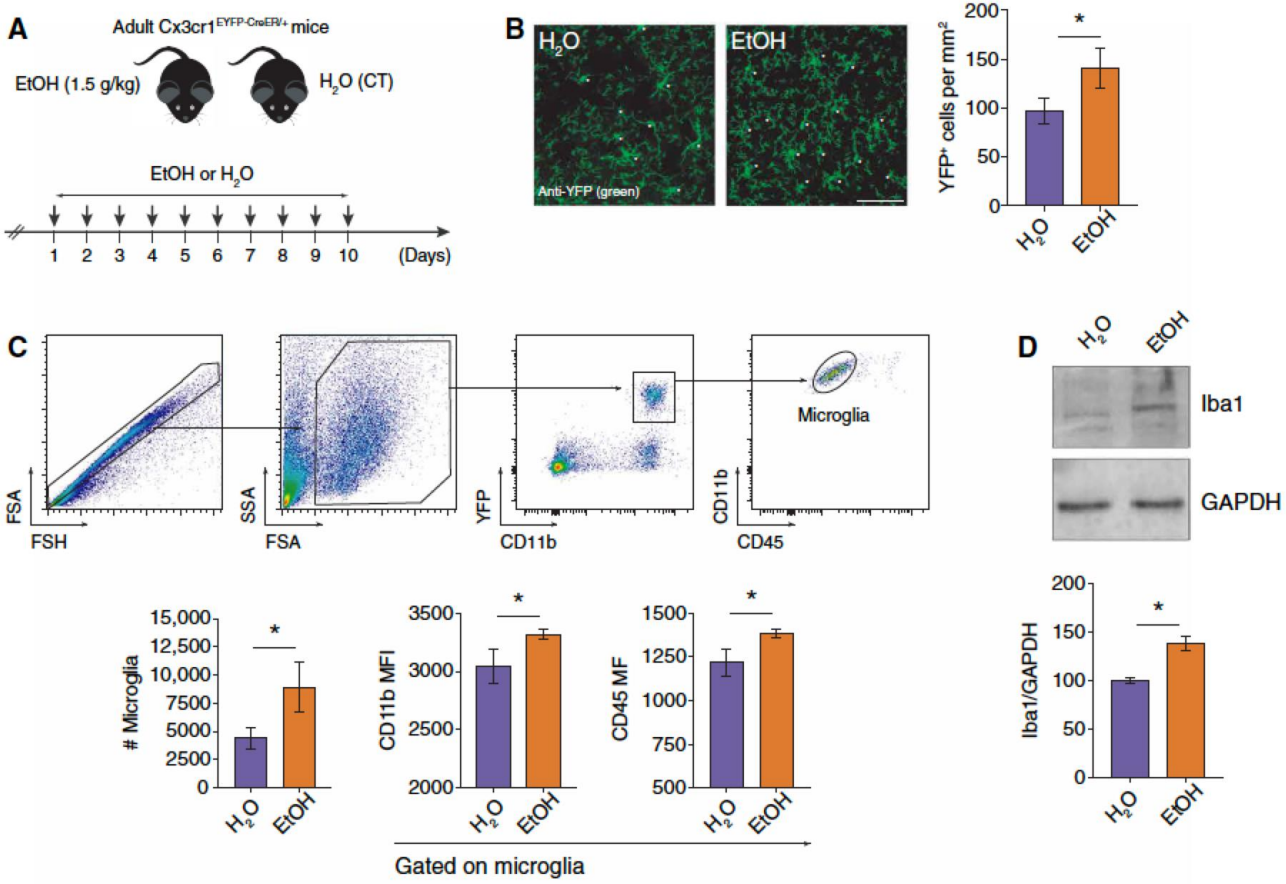
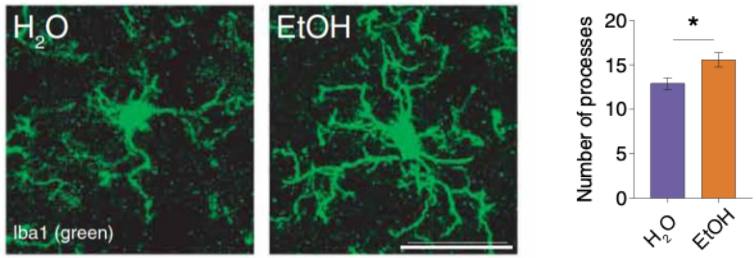
Disease-associated microglia (DAM)



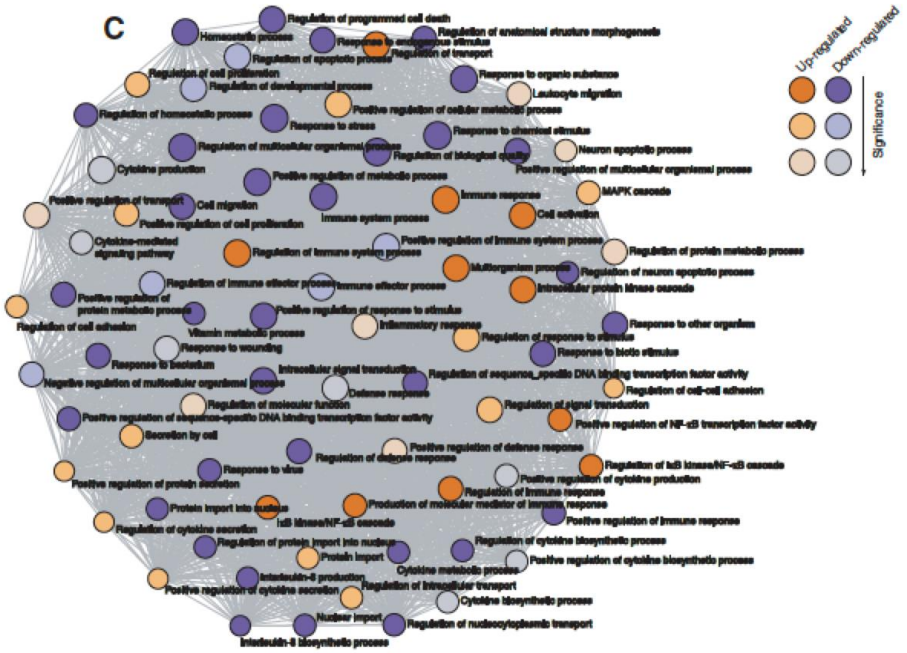
Daily alcohol intake induces microgliosis

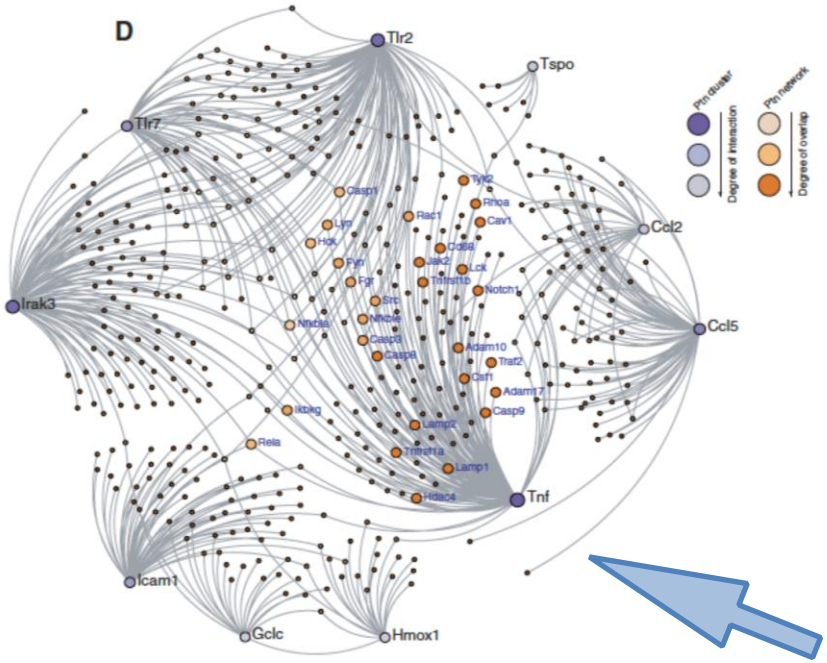




Binge alcohol led to expansion and increased activation of the microglial population.

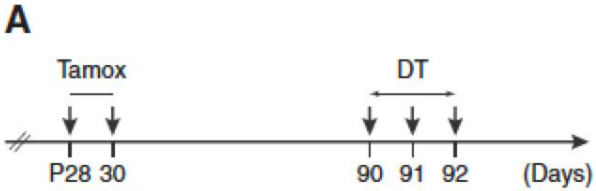
Alcohol intake triggers a TNF-associated neuroimmune response

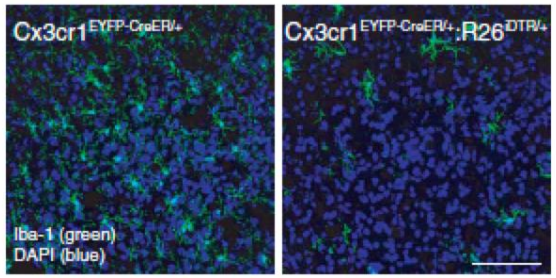


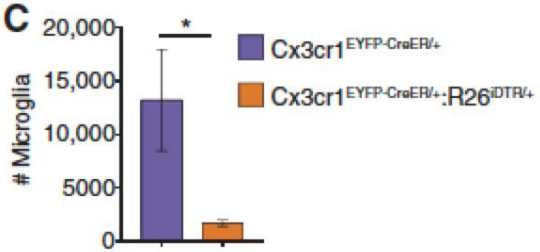


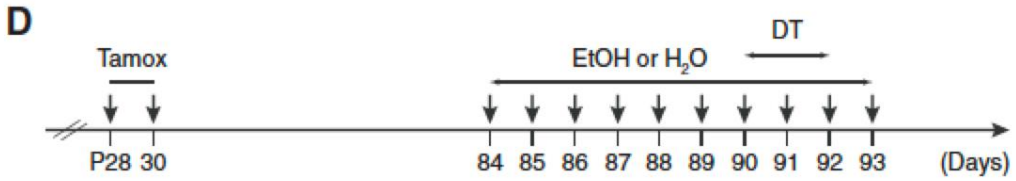
We analysed how microglia related genes were affected by alcohol exposure, and found a strong association with TNF.

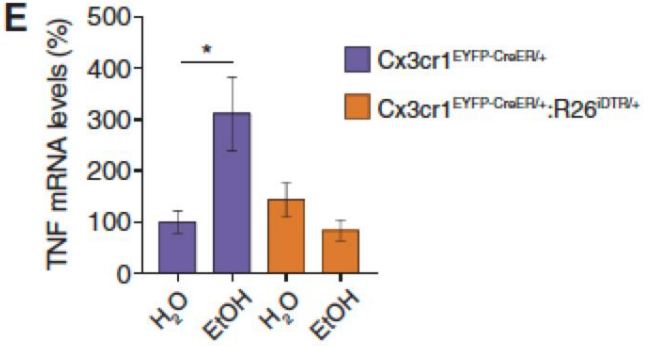
Alcohol-elicited production of TNF is driven by microglia in the prefrontal cortex

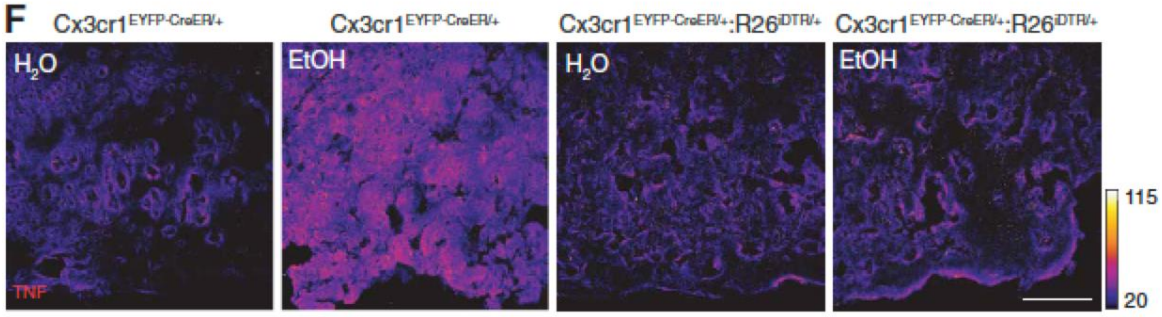


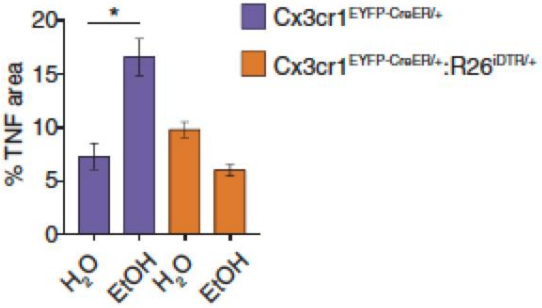




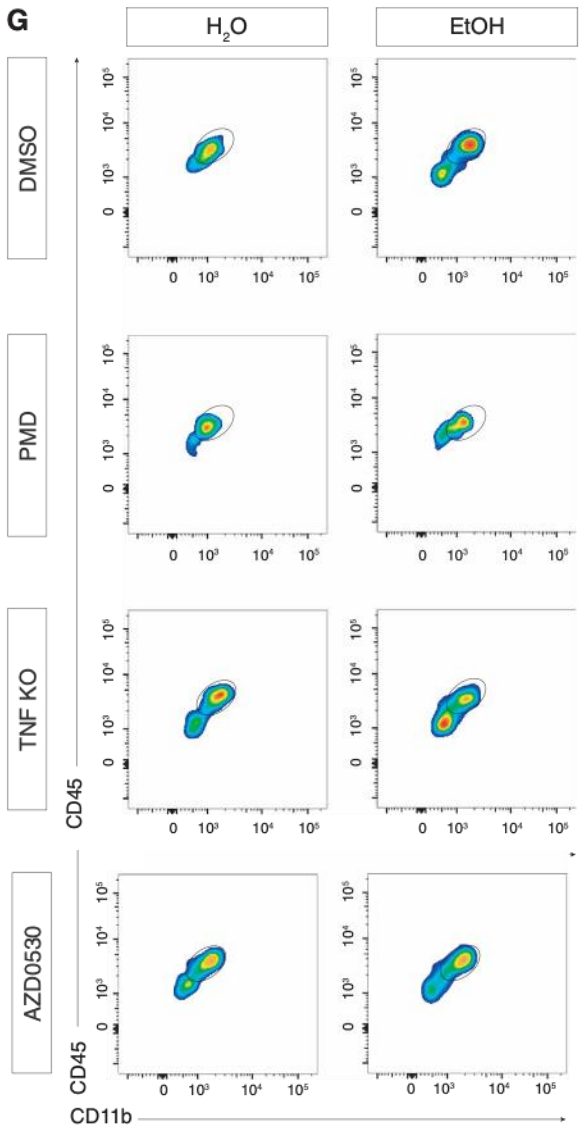




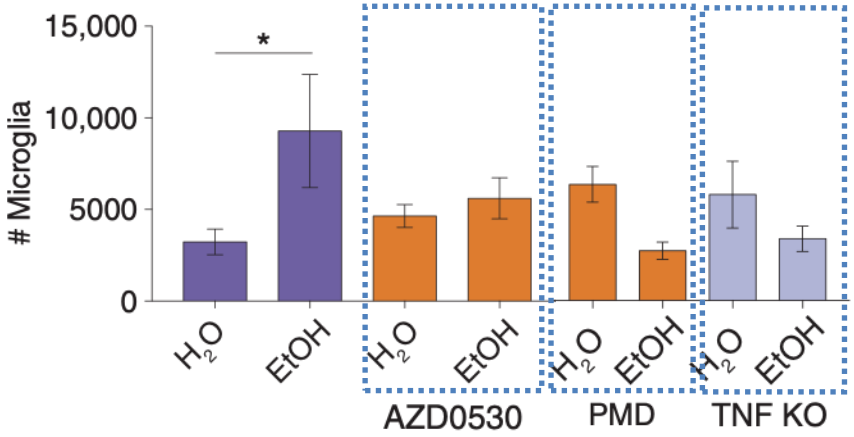




Silencing TNF prevents alcohol-driven microgliosis

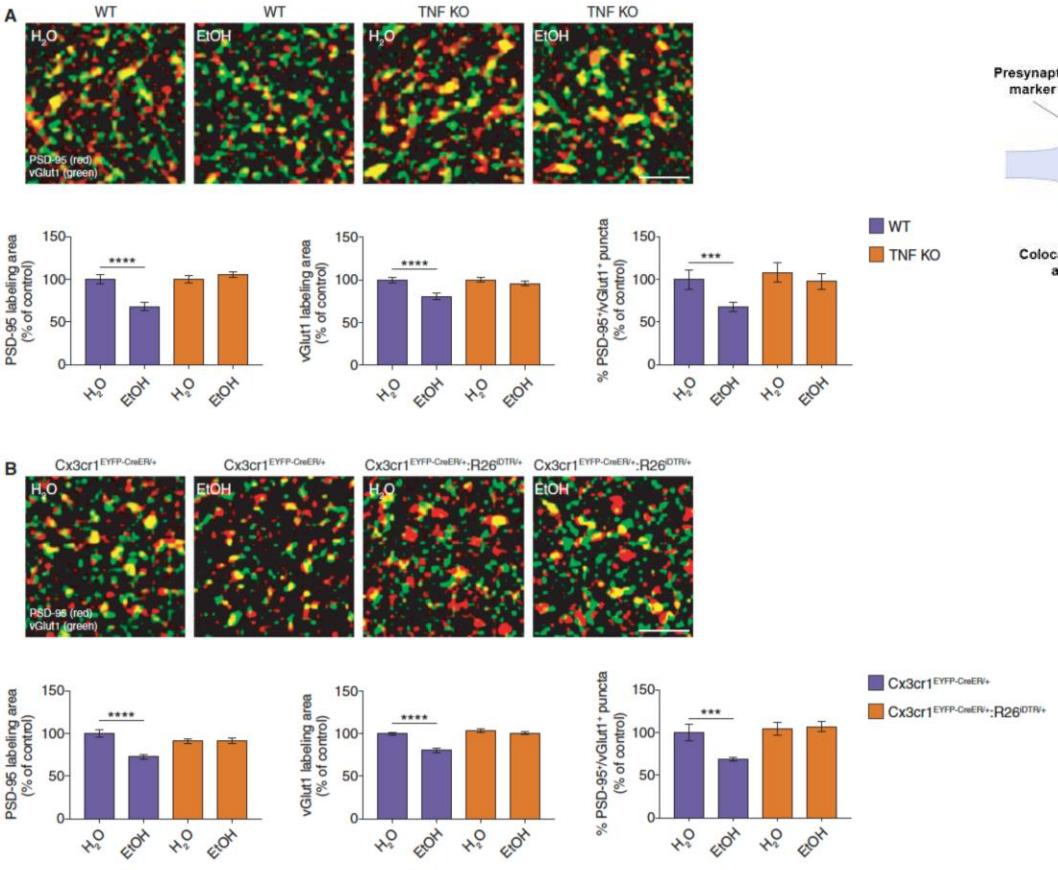


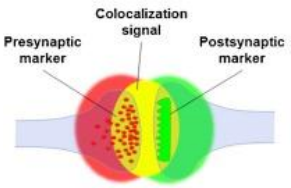
Using AZD0530 or Pomalidomide (blocks TNF production)



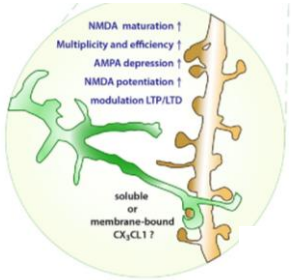
Alcohol intake in mice treated with AZD530, pomalidomide (PMD), or in TNF KO mice, does not cause microglia expansion.

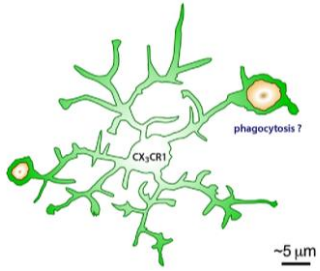
Alcohol-elicited synapse loss is microglia dependent





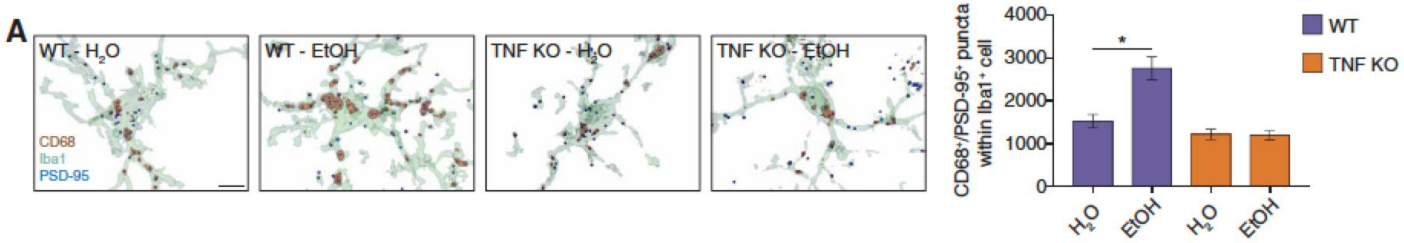
Colocalization reveals structurally accomplished synapses



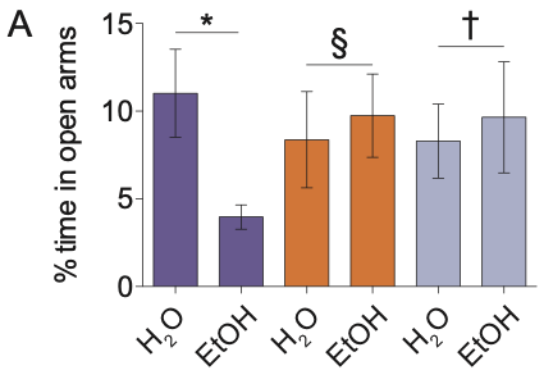


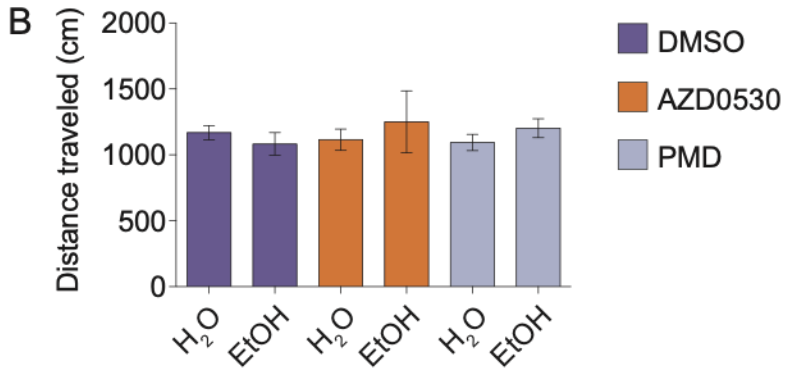
Adapted from Paolicelli at 2016

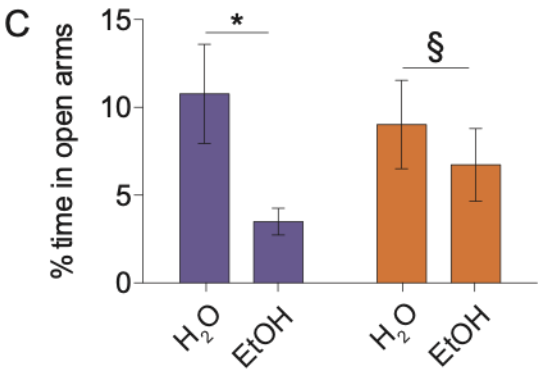
Co-localisation of PSD-95 inside microglia

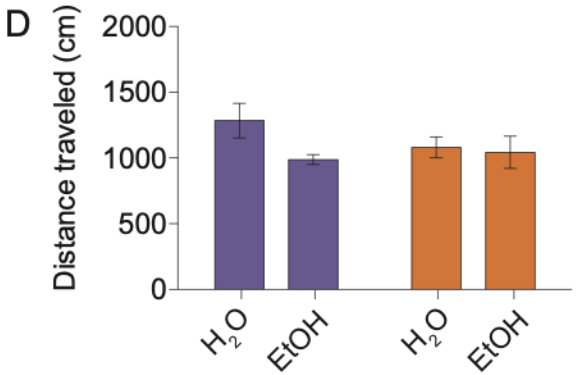


Blocking TNF production prevented alcohol-induced anxiety-like behaviour



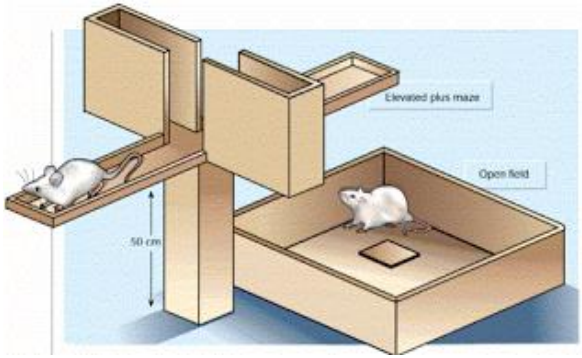






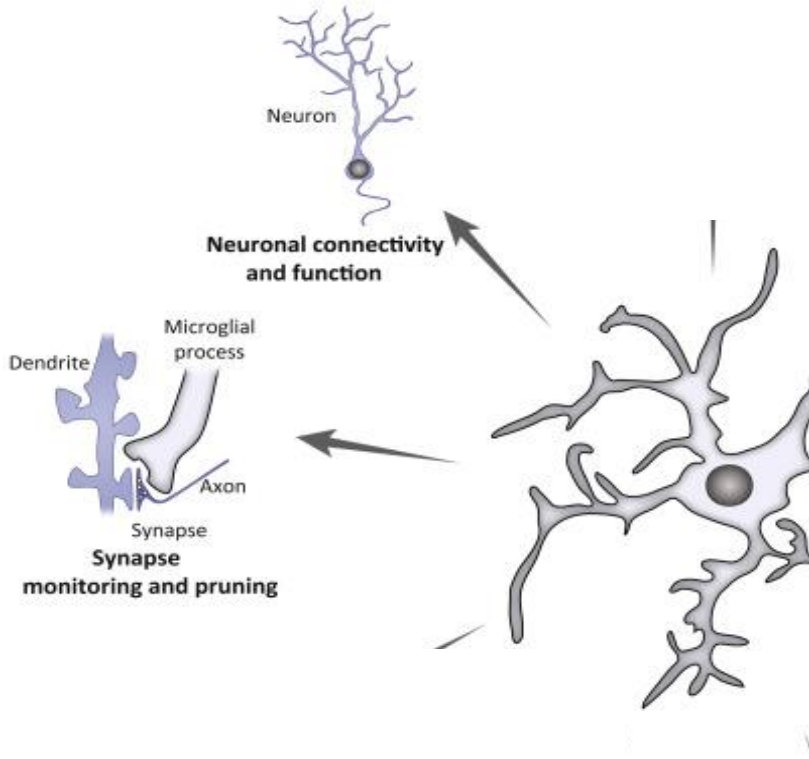
Cx3cr1$^{EYFP\text{-}CreER/+}$

Cx3cr1$^{EYFP\text{-}CreER/+}$:R26$^{iDTR/+}$



In summary, our data show that:

1. Repeated alcohol intake results in microgliosis;
2. Under repeated alcohol, reactive microglia increase TNF production;
3. These activated microglia engage in incresed pruning;
4. Leading to increased anxiety;
5. Blocking TNF production prevented all this events;



We are now exploring how these mechanisms are regulated in long-term exposure to alcohol.

A11/00

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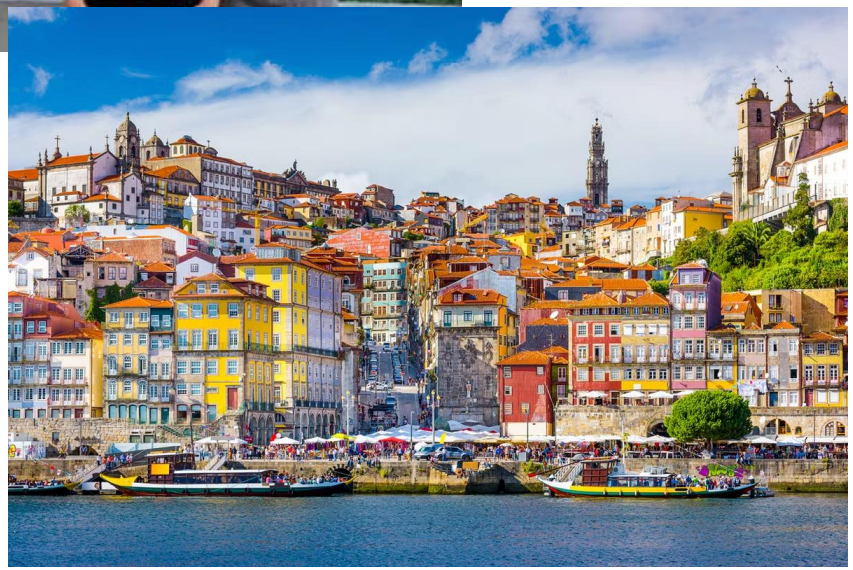

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NORTE2020 PORTUGAL 2020
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CCDRn Comissão de Coordenação e Desenvolvimento Regional do Norte
FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR
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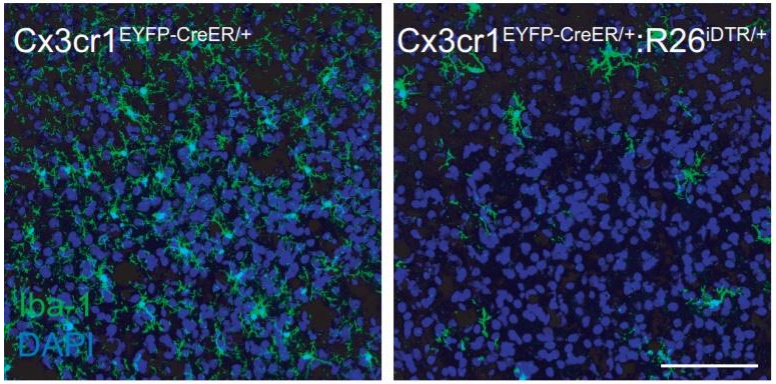
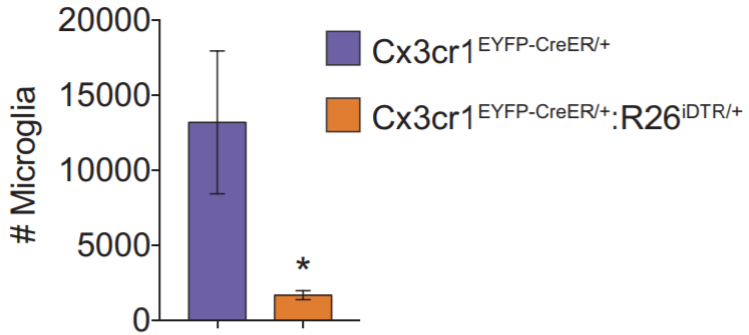
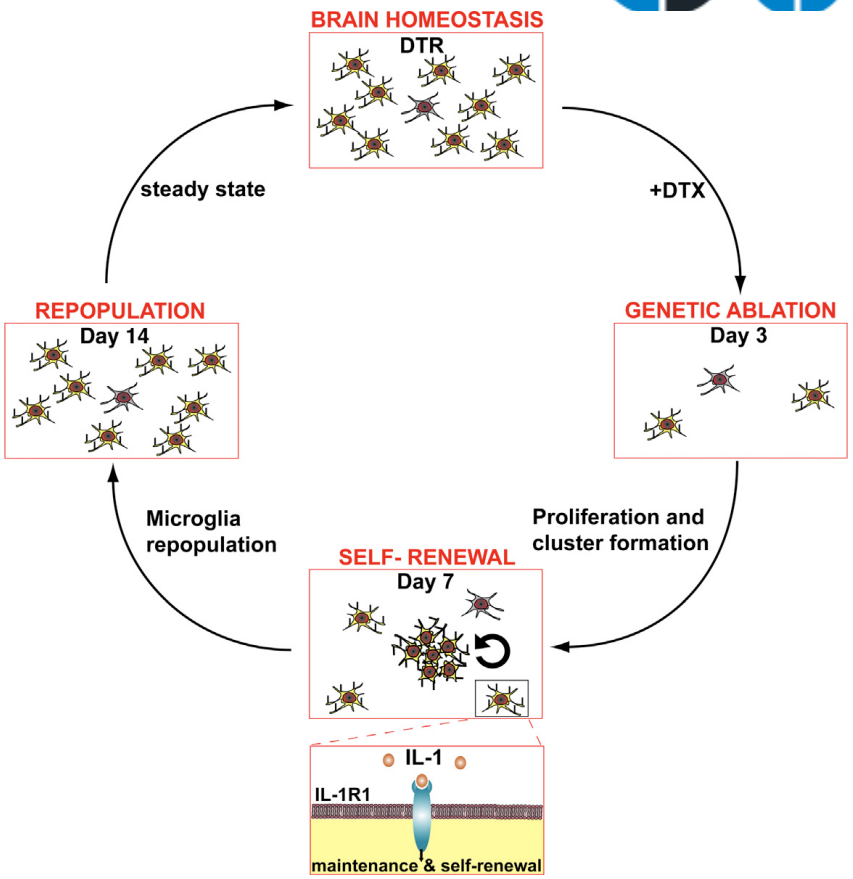
2. What if we remove microglia?







Bruttger et al., 2015, Immunity

Microglial cells were depleted with an efficiency around to 90%

Microglia repopulate within 5 days of depletion after DT administration.