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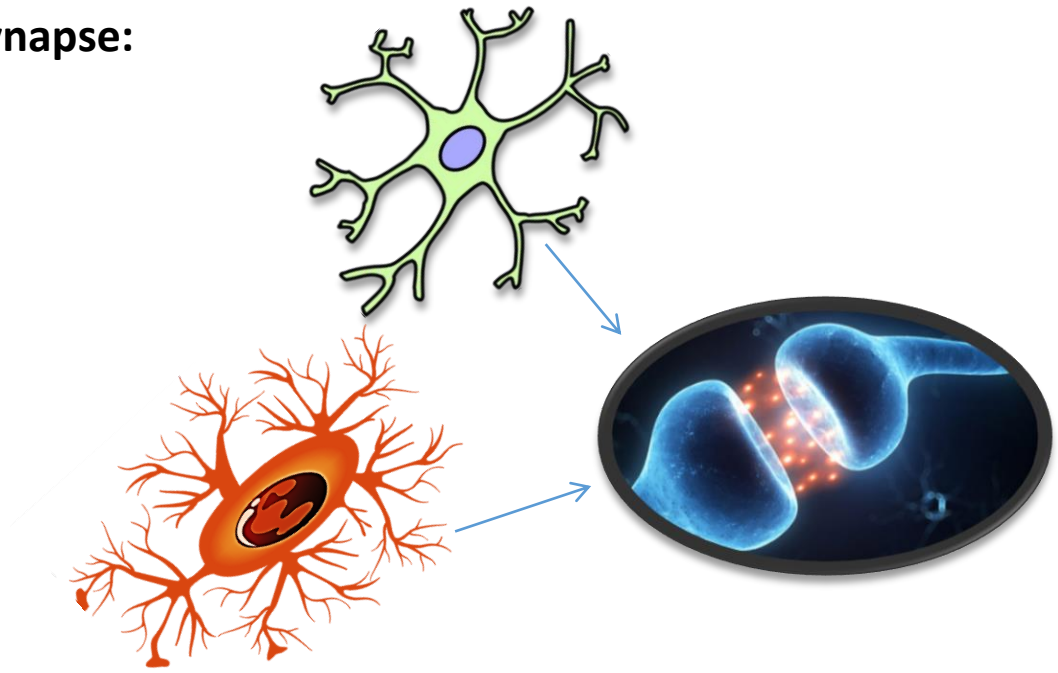
Current Opinion in Neurobiology

The interplay between neurons and glia in synapse development and plasticity

Jeff A Stogsdill and Cagla Eroglu

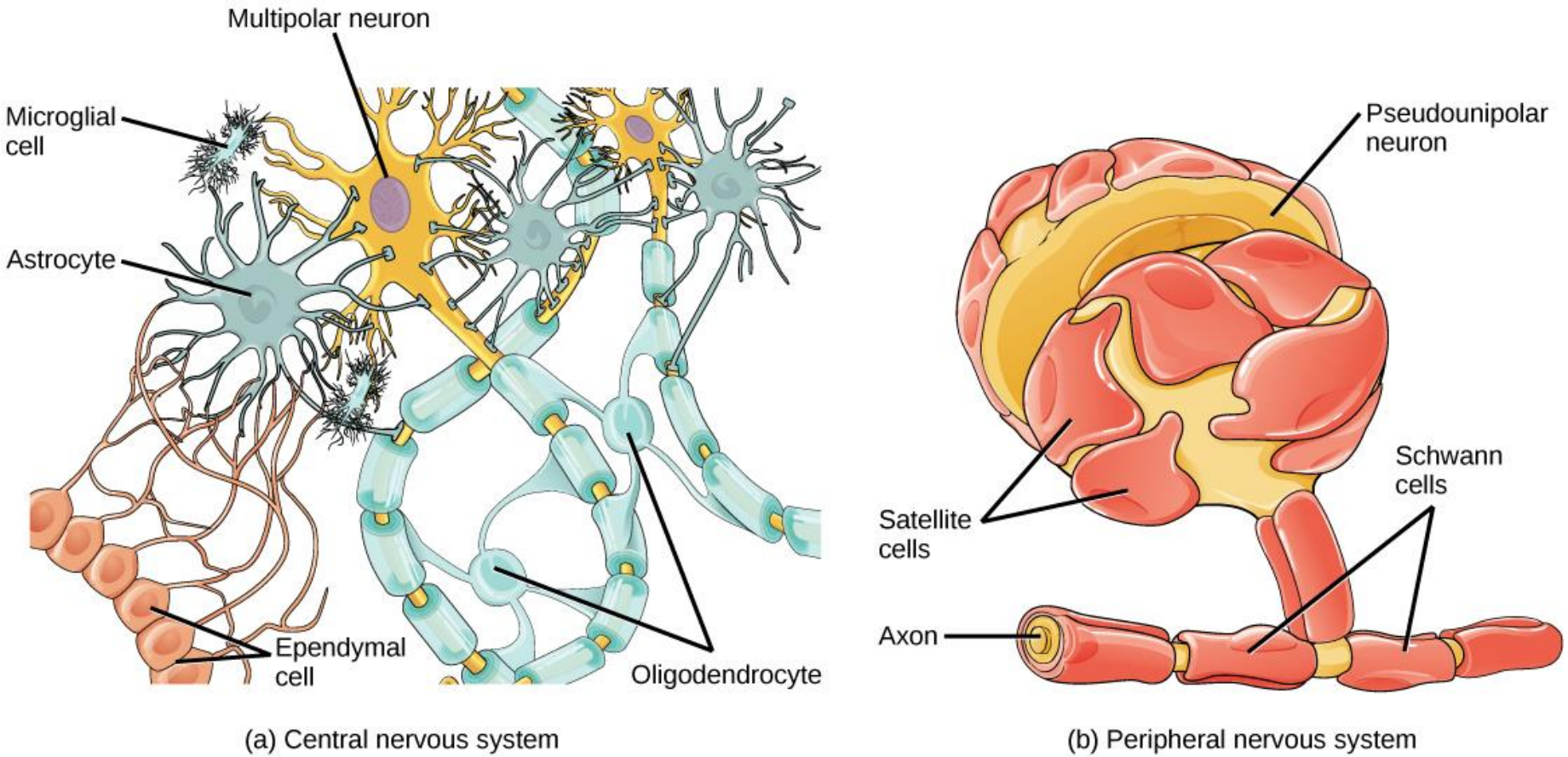
Role of mammalian perisynaptic glia in synapse:

1. **Development**
2. **Maturation**
3. **Plasticity**



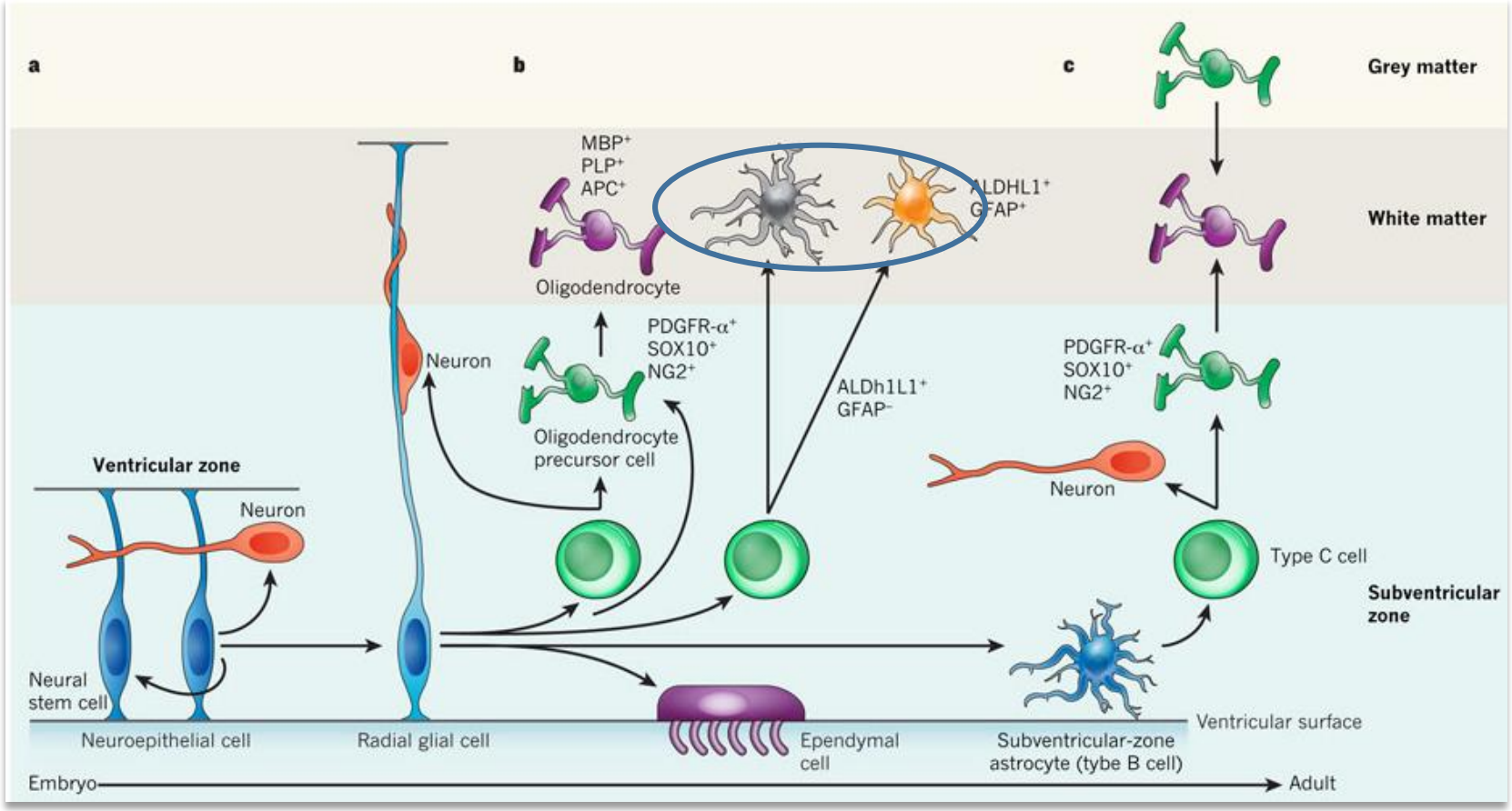
Ghibaudi Marco
Stajano Daniele

NEURONS AND GLIA

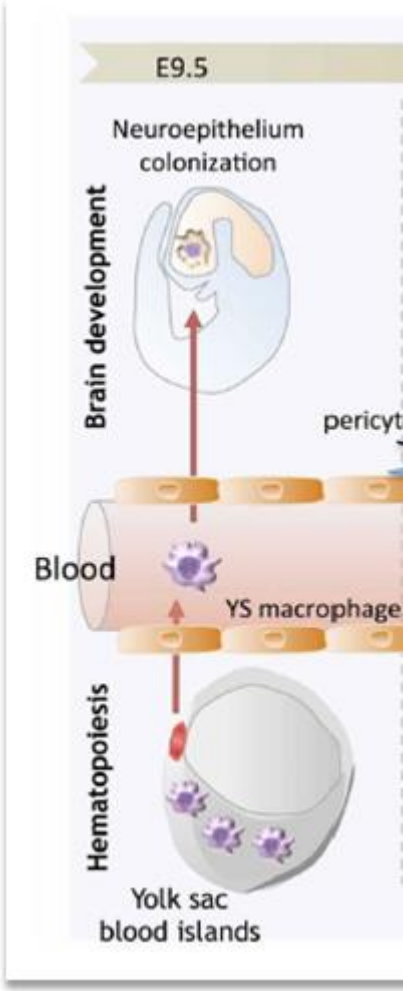


Glial cells are non-neuronal cells that maintain homeostasis, form myelin, and provide support and protection for neurons in the central and peripheral nervous systems

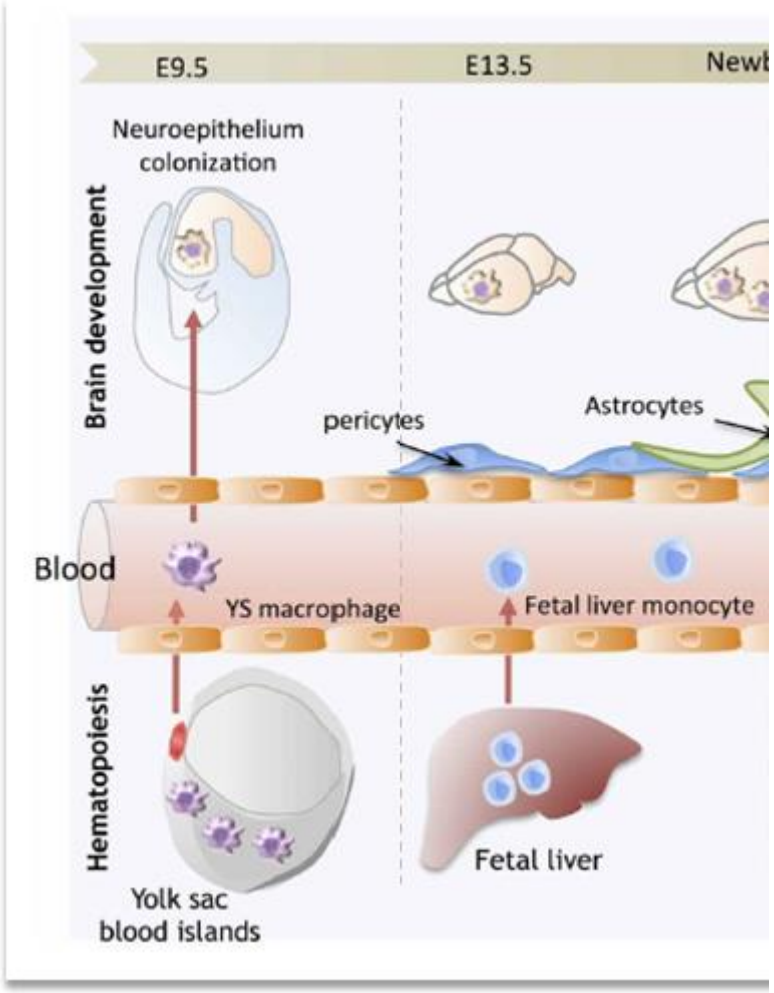
ASTROCYTES AND MICROGLIA DEVELOPMENT



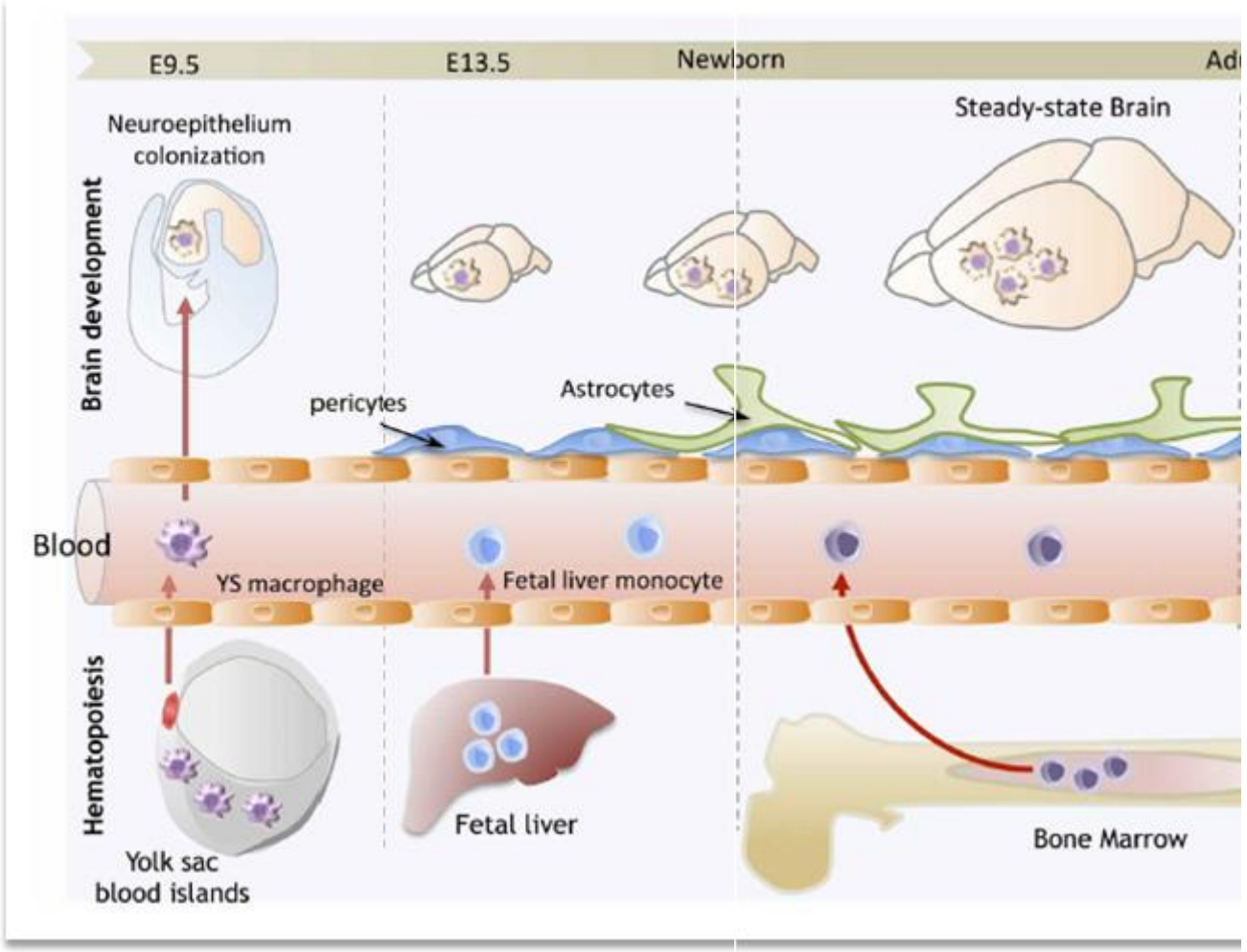
Radial glia can become astrocytes, as well as producing intermediate progenitors that expand in number before producing astrocytes. Protoplasmic astrocytes and fibrous astrocytes might arise from common or independent progenitors.



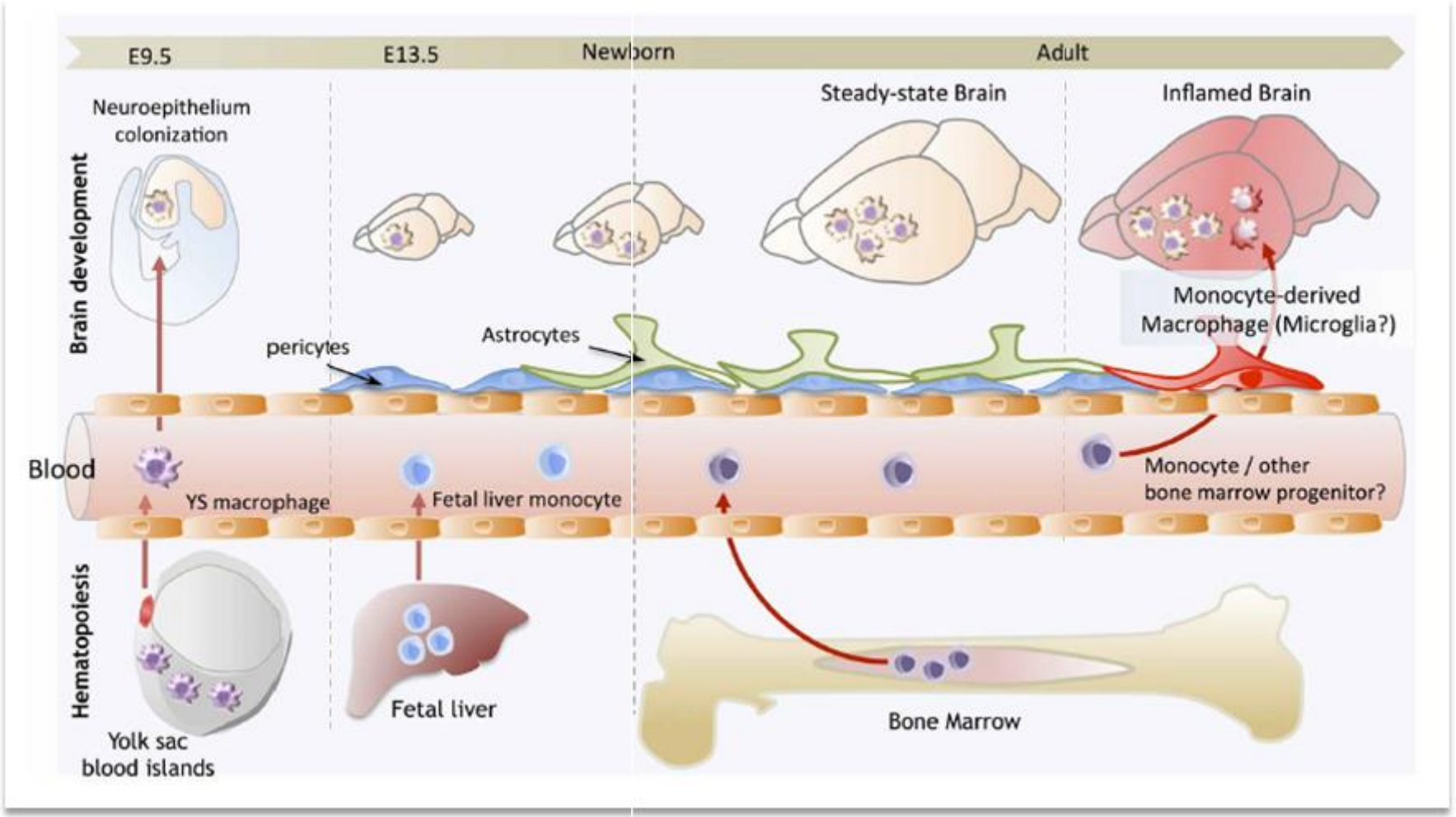
1) **Primitive macrophages exit the yolk sac blood islands, colonize the neuroepithelium and give raise to microglia**



1) **Primitive macrophages exit the yolk sac blood islands, colonize the neuroepithelium and give raise to microglia**
2) **Embryonic microglia expand and colonize the whole CNS until adulthood**

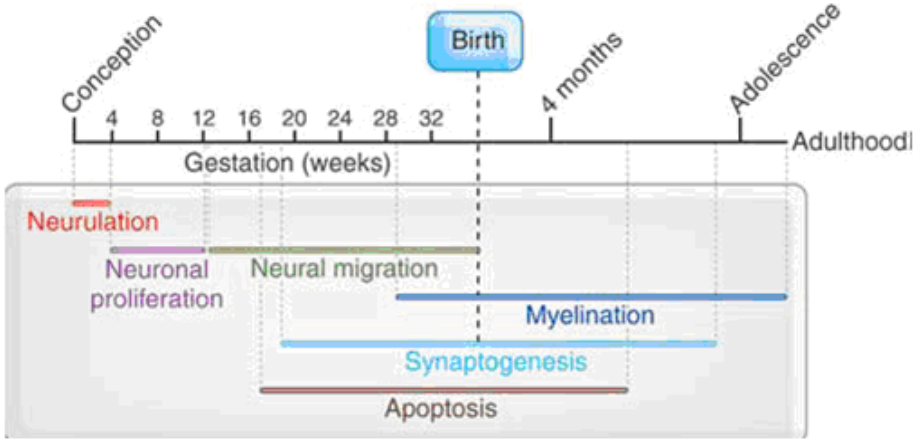


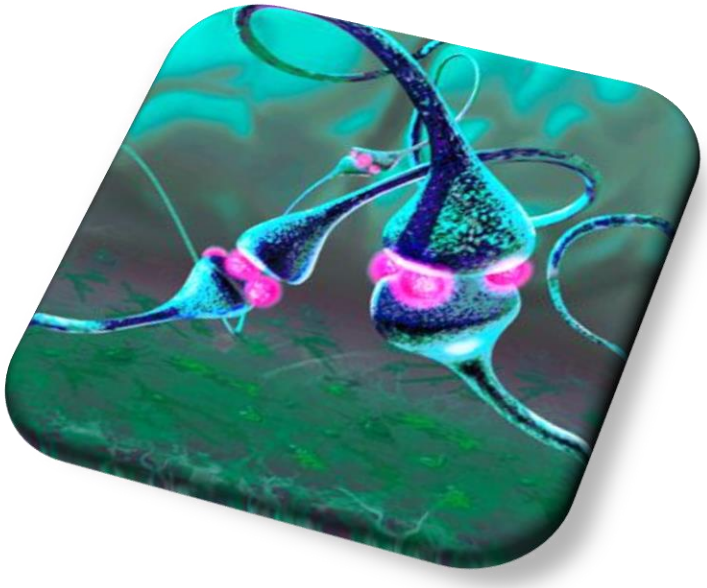
1) Primitive macrophages exit the yolk sac blood islands, colonize the neuroepithelium and give raise to microglia
2) Embryonic microglia expand and colonize the whole CNS until adulthood
3) In steady state conditions, embryonically-derived microglia will maintain themselves until adulthood

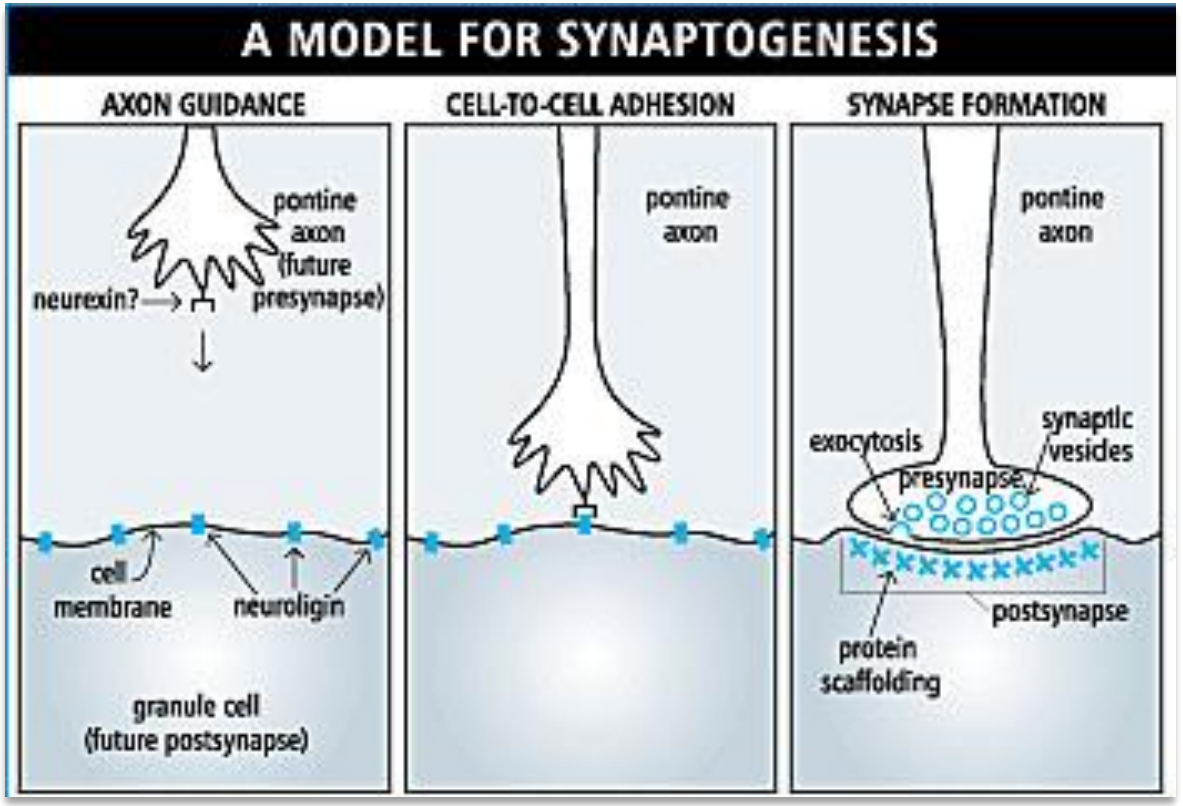


1) **Primitive macrophages exit the yolk sac blood islands, colonize the neuroepithelium and give raise to microglia**
2) **Embryonic microglia expand and colonize the whole CNS until adulthood**
3) **In steady state conditions, embryonically-derived microglia will maintain themselves until adulthood**
4) **During certain inflammatory conditions, the recruitment of monocytes or other bone marrow-derived progenitors can supplement the microglial population to some extent**

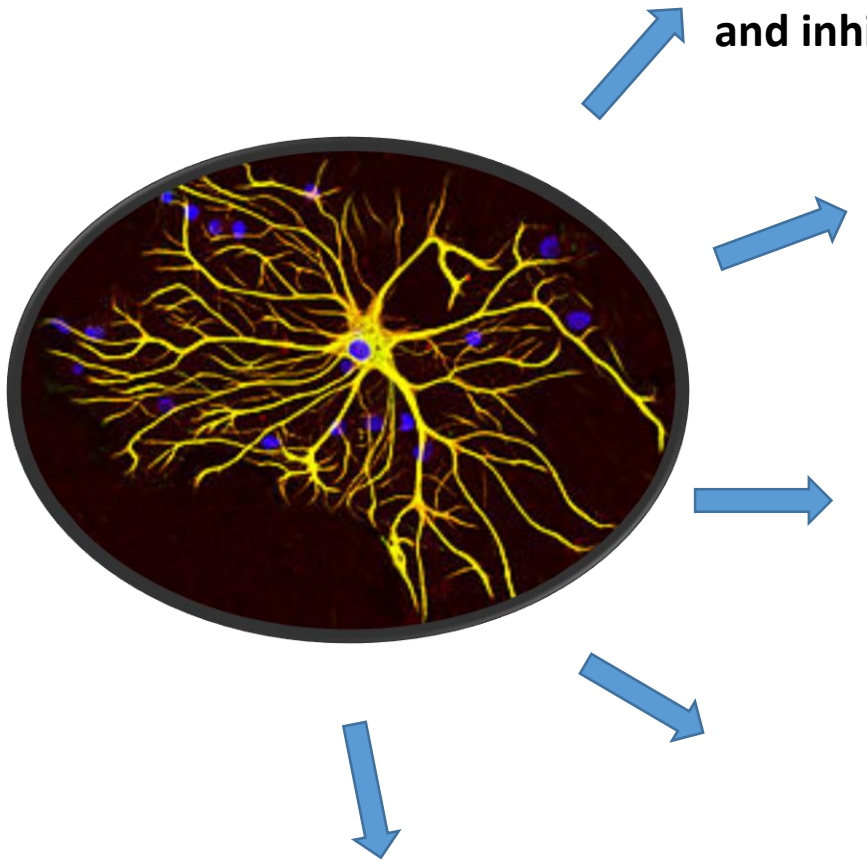
SYNAPTOGENESIS





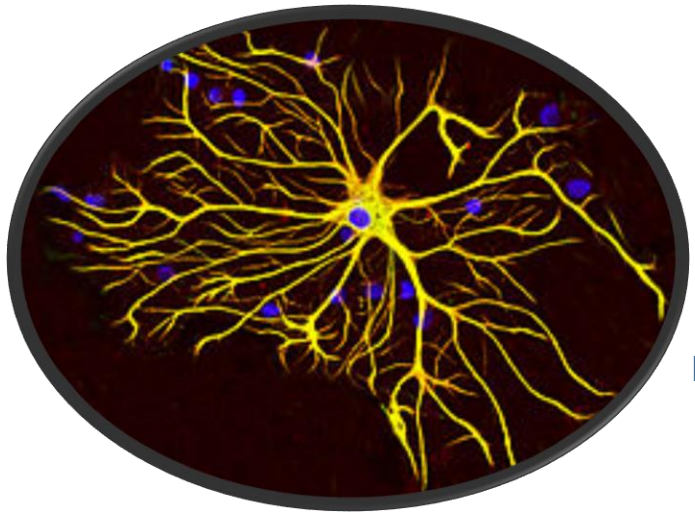


SYNAPSE FORMATION



Gamma-protocadherins -> Regulation of both excitatory and inhibitory synapses formation

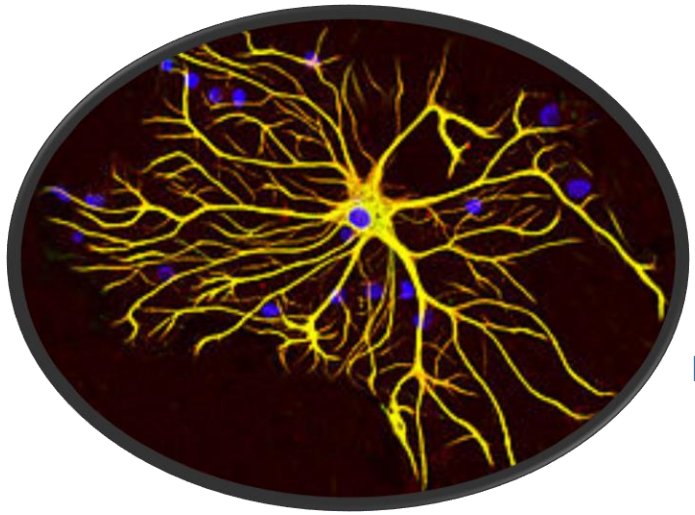
SYNAPSE FORMATION



Gamma-protocadherins -> Regulation of both excitatory and inhibitory synapses formation

TGF-beta -> Control over excitatory synapses formation in CNS

SYNAPSE FORMATION



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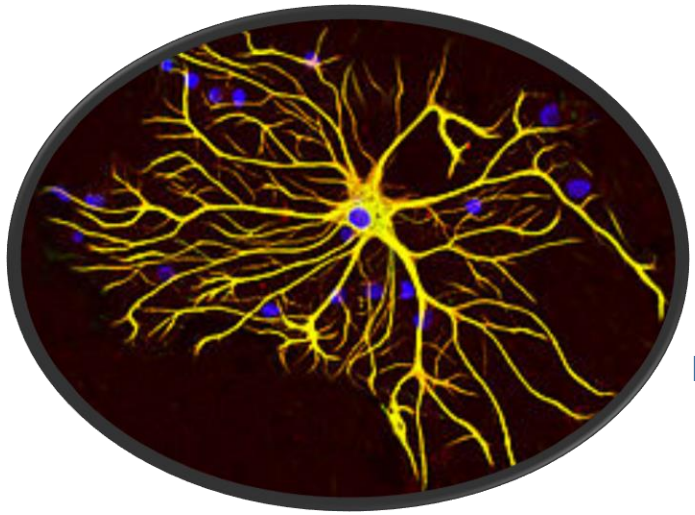

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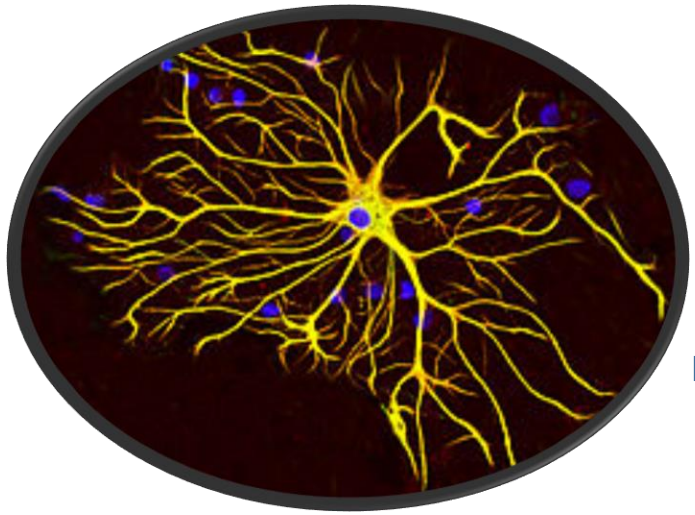

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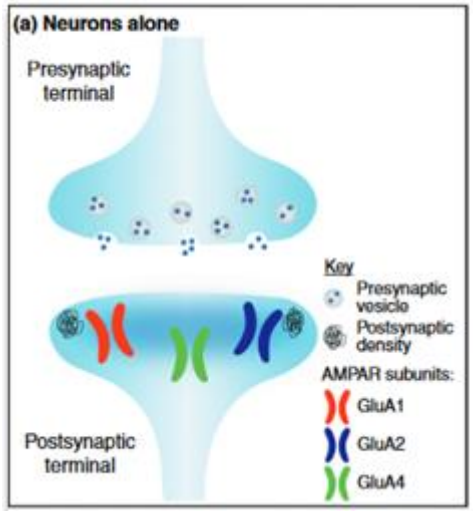
Thrombospondin -> Formation of post-synaptically silent excitatory synapses

Astrocyte signals regulate synaptic glutamate receptors



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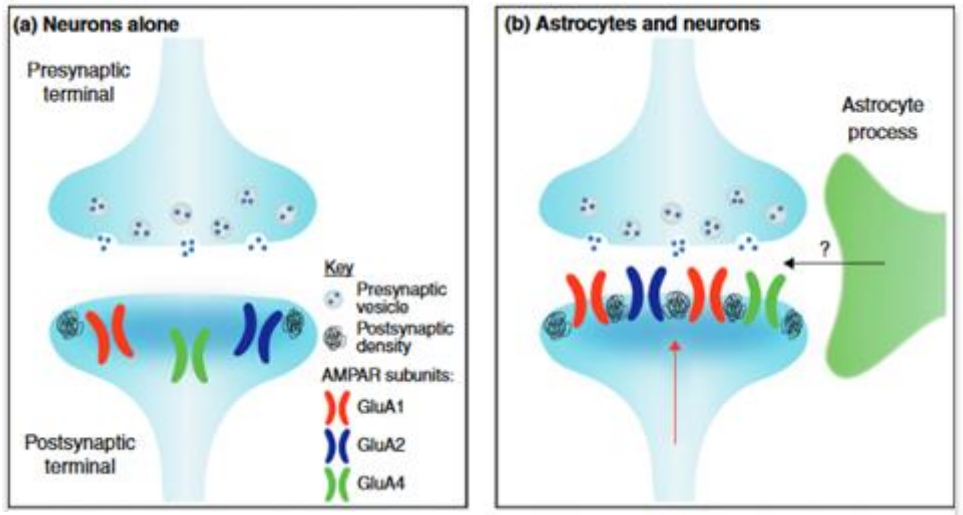
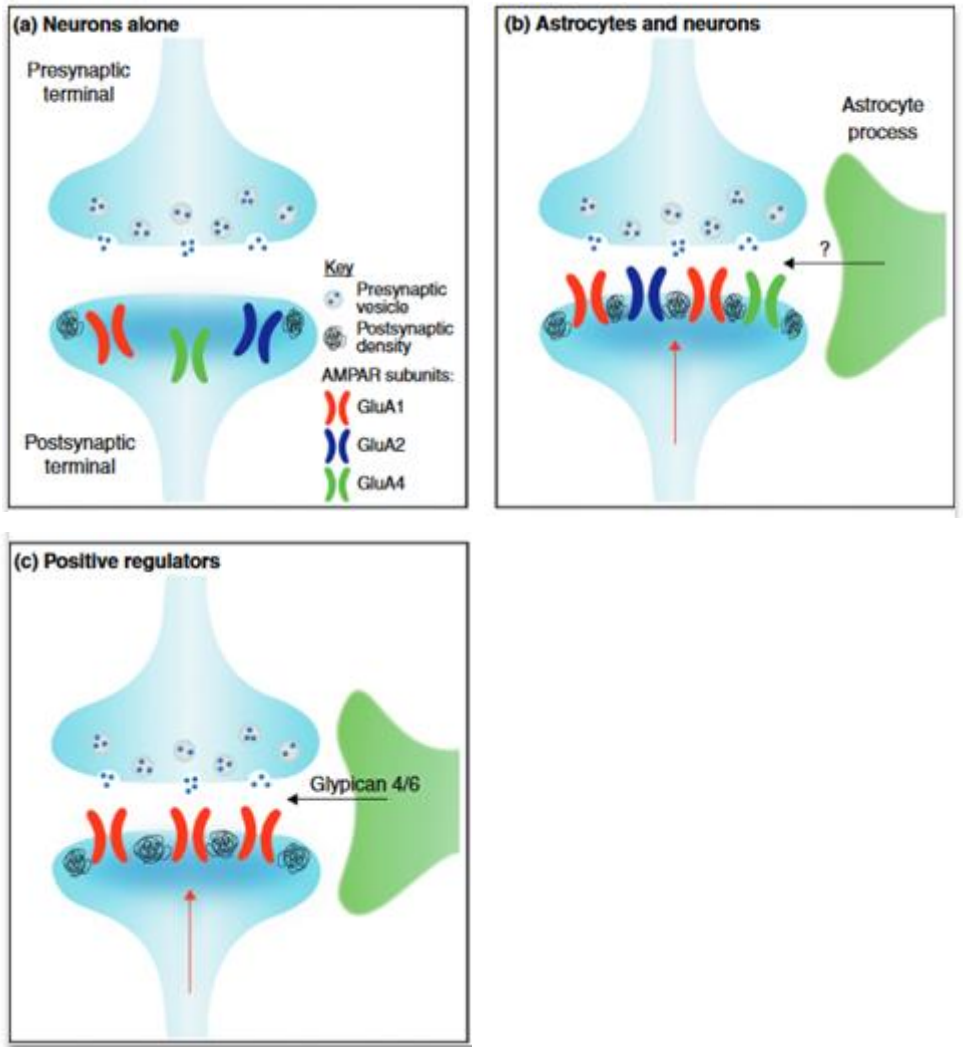


The presence of astrocytes enhances synapse formation between neurons and increases the number of AMPA receptors incorporated into synapses

Astrocyte signals regulate synaptic glutamate receptors



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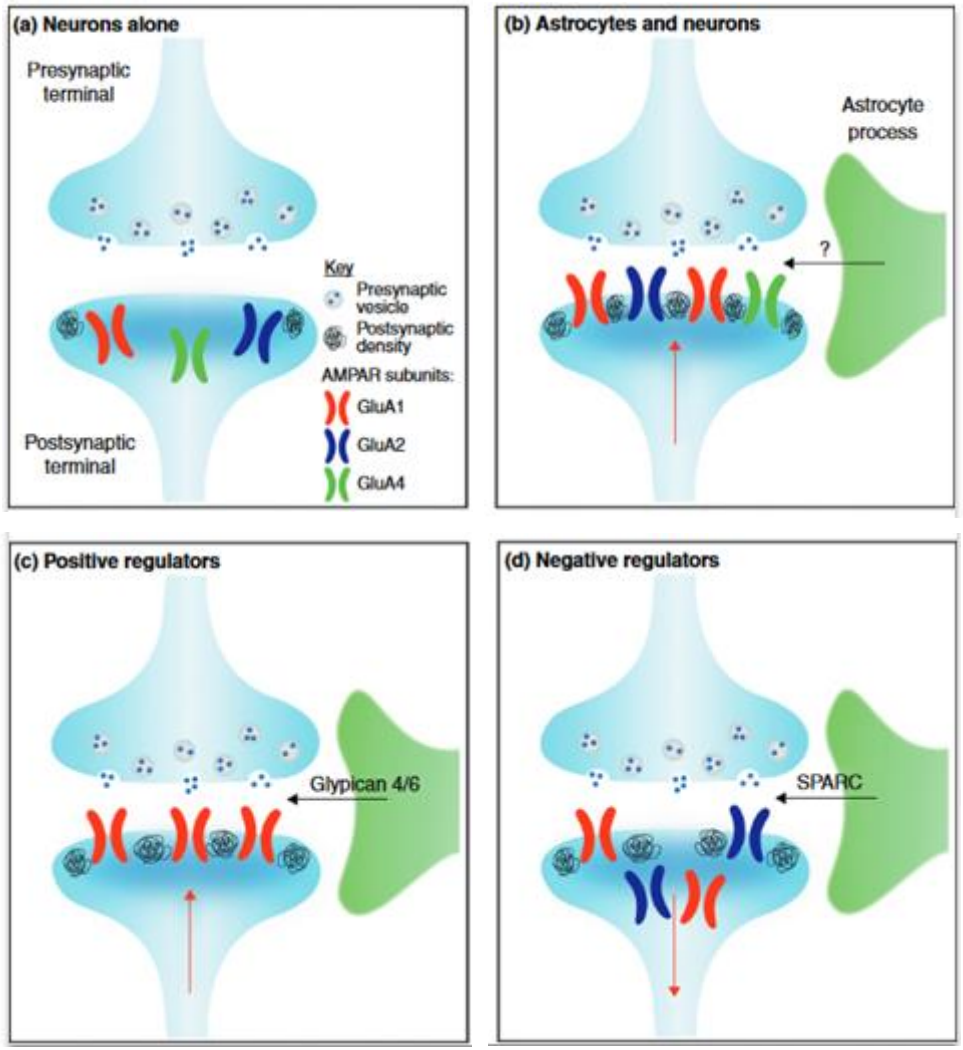
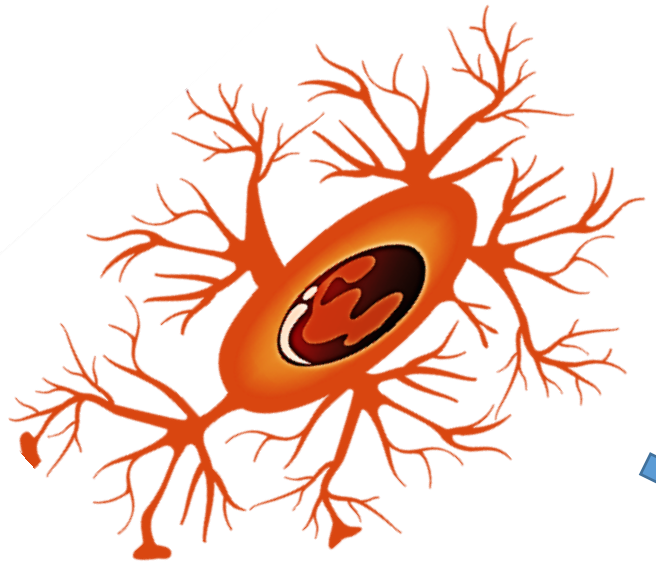


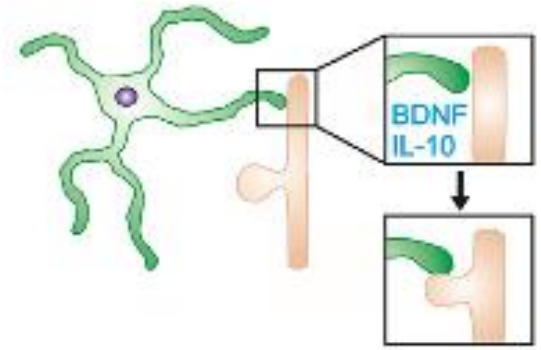
The presence of astrocytes enhances synapse formation between neurons and increases the number of AMPA receptors incorporated into synapses

Astrocytes also secrete negative regulators of AMPA receptors that decrease synaptic levels of AMPA receptors and synaptic strength, including SPARC.

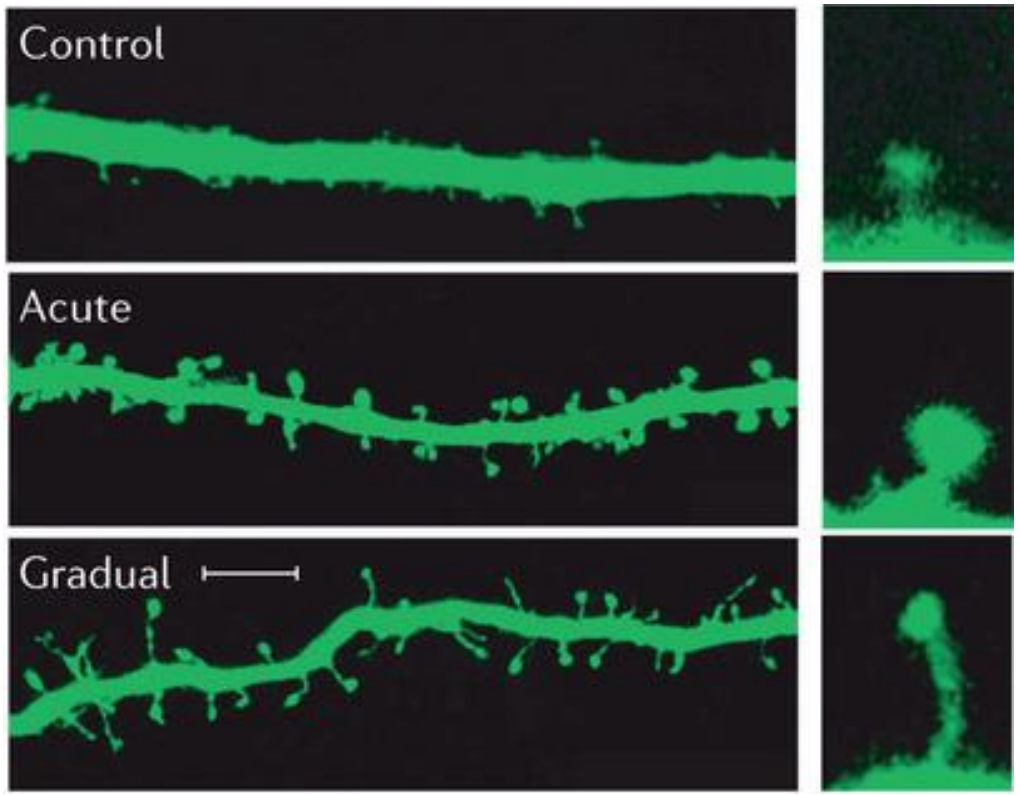


SPARC -> Inhibits the synaptogenic function of Hevin

BDNF -> Controls excitatory synapse formation

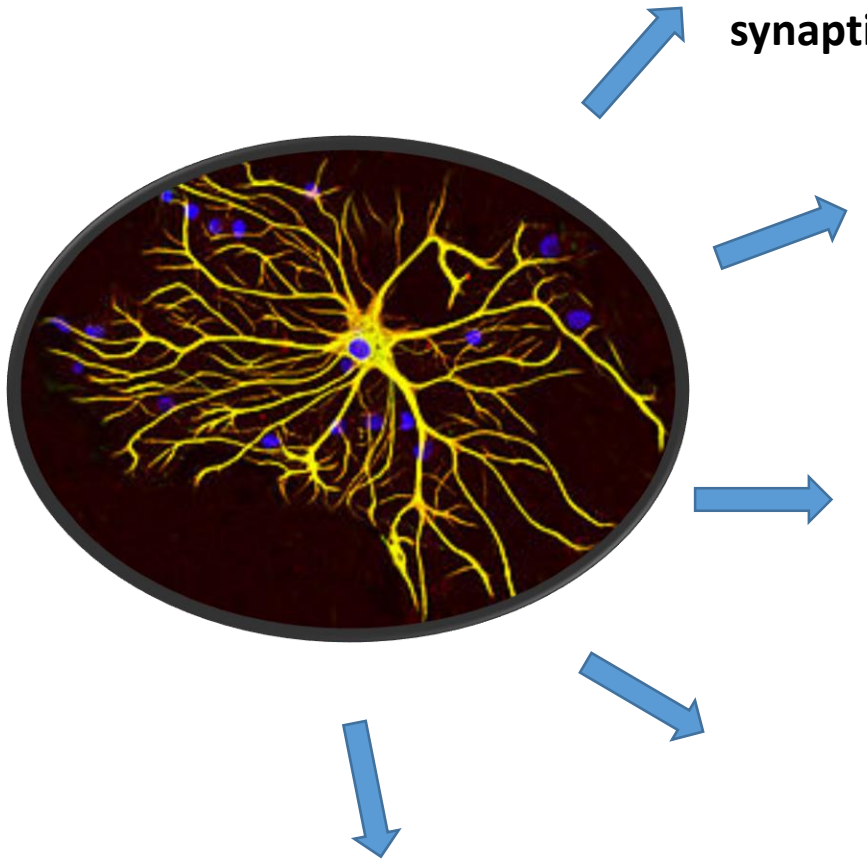


Formation of new synapses mediated by BDNF or IL-10 signaling



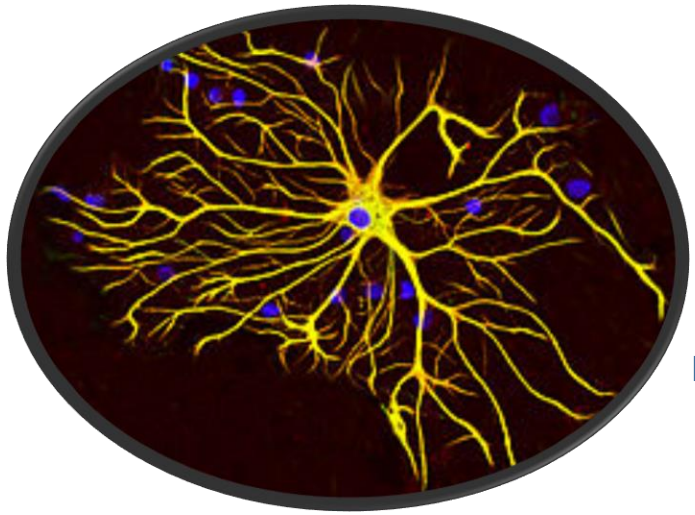
Acute application of BDNF preferentially increases the number of large spines (middle panel), whereas a gradual increase of BDNF stimulates spine motility and preferentially increases the number of filopodia (right panel). (Bai Lu et al.; 2013)

SYNAPSE MODULATION



CSPGs -> Determines surface AMPAR mobility and synaptic strength

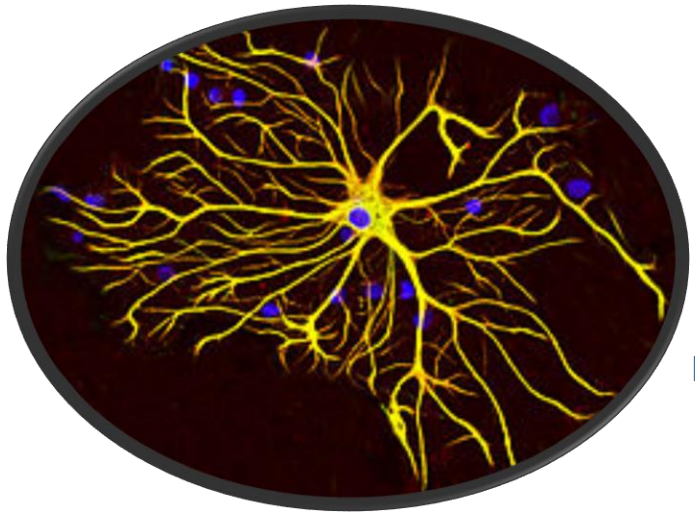
SYNAPSE MODULATION



CSPGs -> Determines surface AMPAR mobility and synaptic strength

Hevin -> Required for ODP in the visual cortex

SYNAPSE MODULATION



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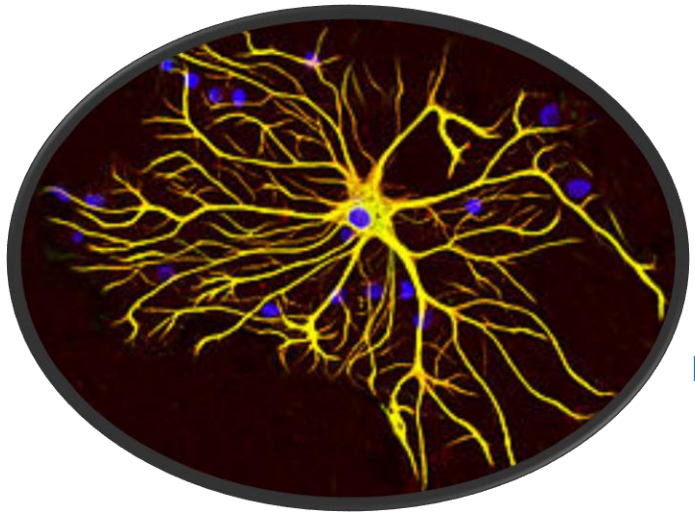

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D-serine -> Controls NMDAR-dependent synaptic integration of adult-born neurons

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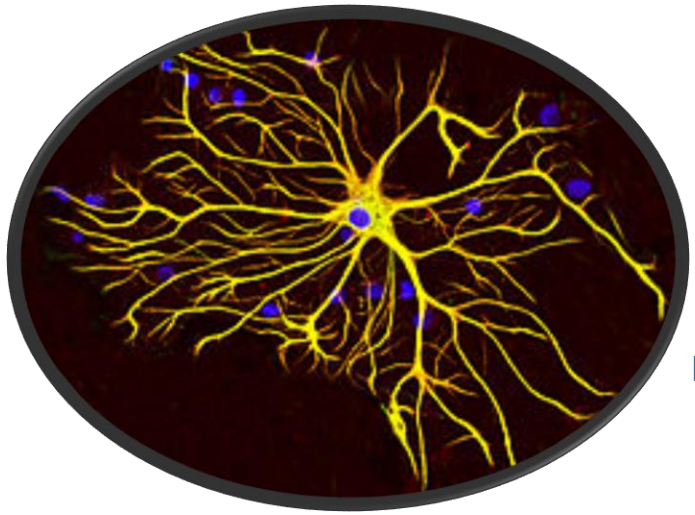


CSPGs -> Determines surface AMPAR mobility and synaptic strength

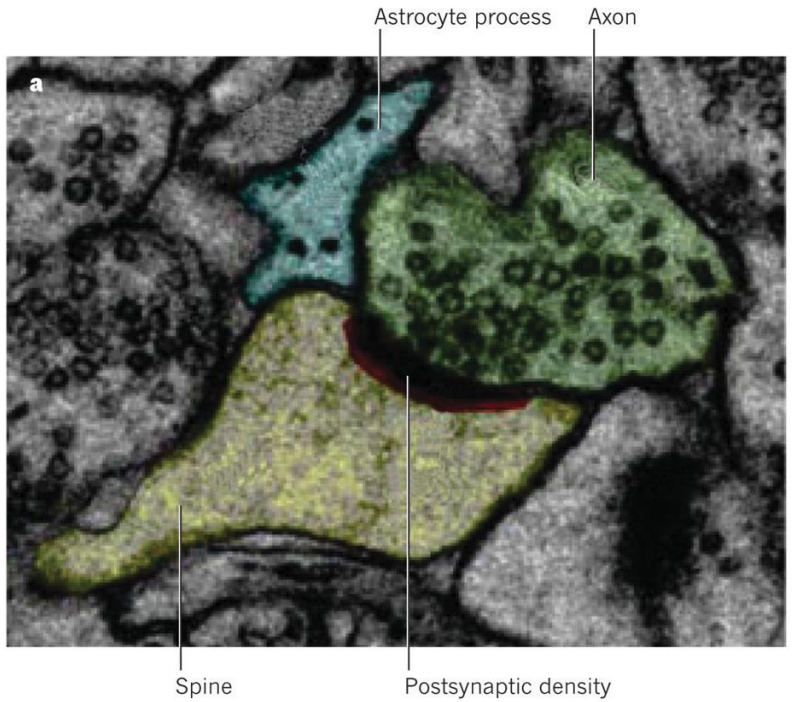
Hevin -> Required for ODP in the visual cortex

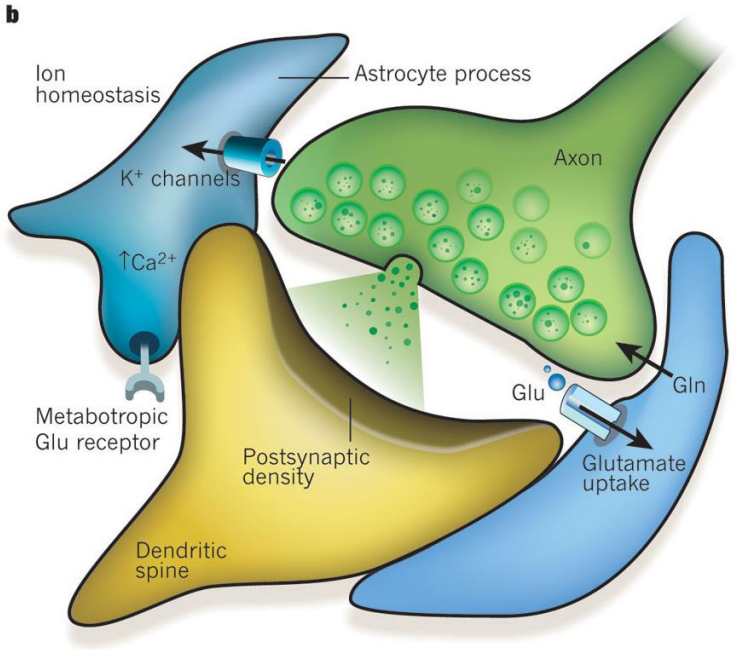
CX30 -> Regulates synaptic contact of astrocytes processes

D-serine -> Controls NMDAR-dependent synaptic integration of adult-born neurons

MEGF10/MERTK -> Regulates engulfment of unwanted synapses by astrocytes

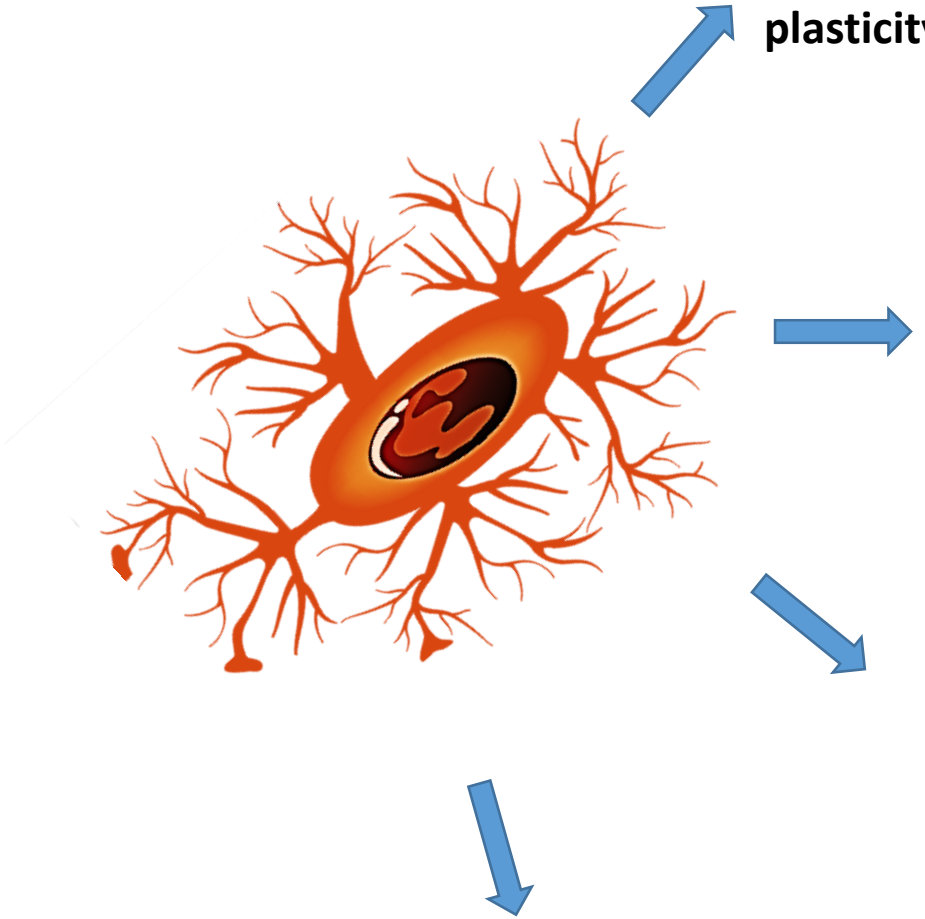
Perisynaptic astrocyte processes contain transporters that take up glutamate (Glu) that has been released into the synapse and return it to neurons in the form of glutamine (Gln)

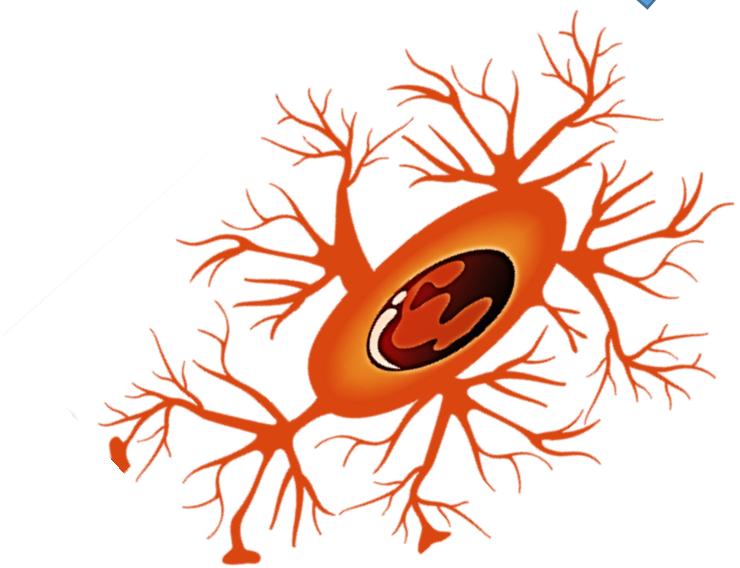




Glutamate receptors on astrocytes sense synaptic glutamate release, which in turn induces a rise in Ca^{2+} concentration in the astrocytes

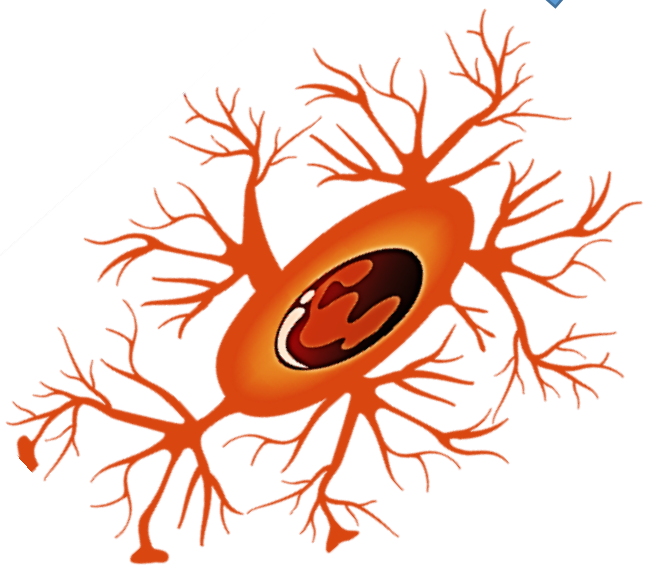
TNF-alpha -> Regulates AMPARs-dependent synaptic plasticity





TNF-alpha -> Regulates AMPARs-dependent synaptic plasticity

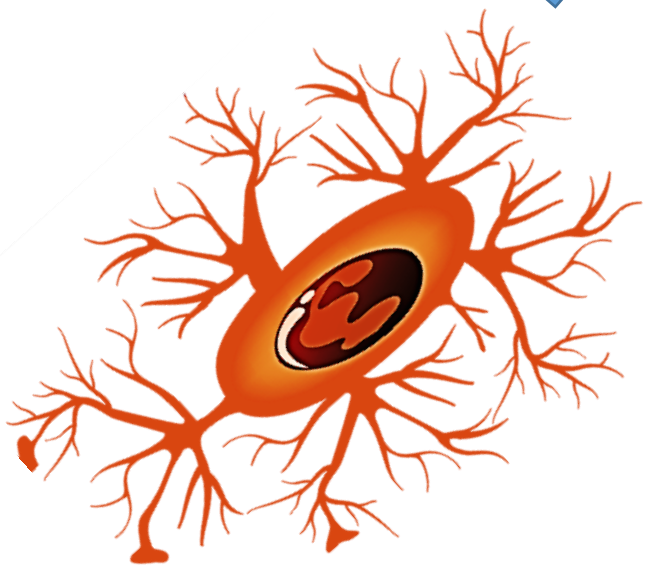
P2Y12 -> Required for ODP in visual cortex



TNF-alpha -> Regulates AMPARs-dependent synaptic plasticity

P2Y12 -> Required for ODP in visual cortex

CX3CR1 -> Controls synaptic pruning



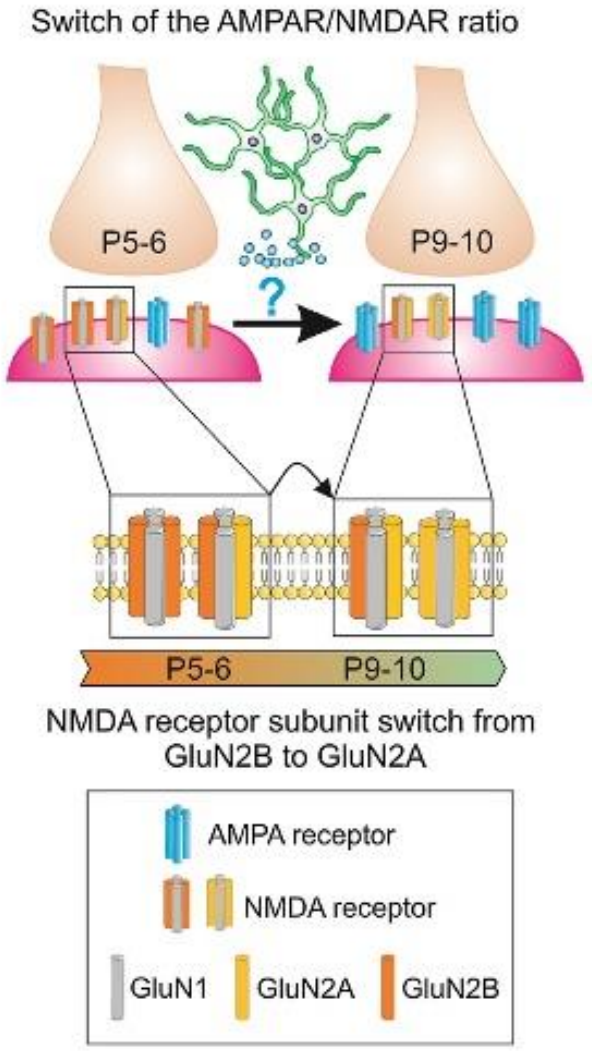
TNF-alpha -> Regulates AMPARs-dependent synaptic plasticity

P2Y12 -> Required for ODP in visual cortex

CX3CR1 -> Controls synaptic pruning

CR3 and CR4 -> Controls synaptic pruning

Regulation of the functional expression of synaptic AMPA and NMDA receptors at thalamocortical synapses of the barrel cortex



"It is worth noting, however, that impaired functional expression of synaptic AMPA and NMDA receptors have been also observed in another mutant mouse with a loss of function of the microglial adaptor protein ***DAP12****"* (Mosser et al.; 2017)

GluN1/GluN2A receptors have a higher probability of opening in response to glutamate and also a higher peak open probability than GluN1/GluN2B

SYNAPTIC PRUNING

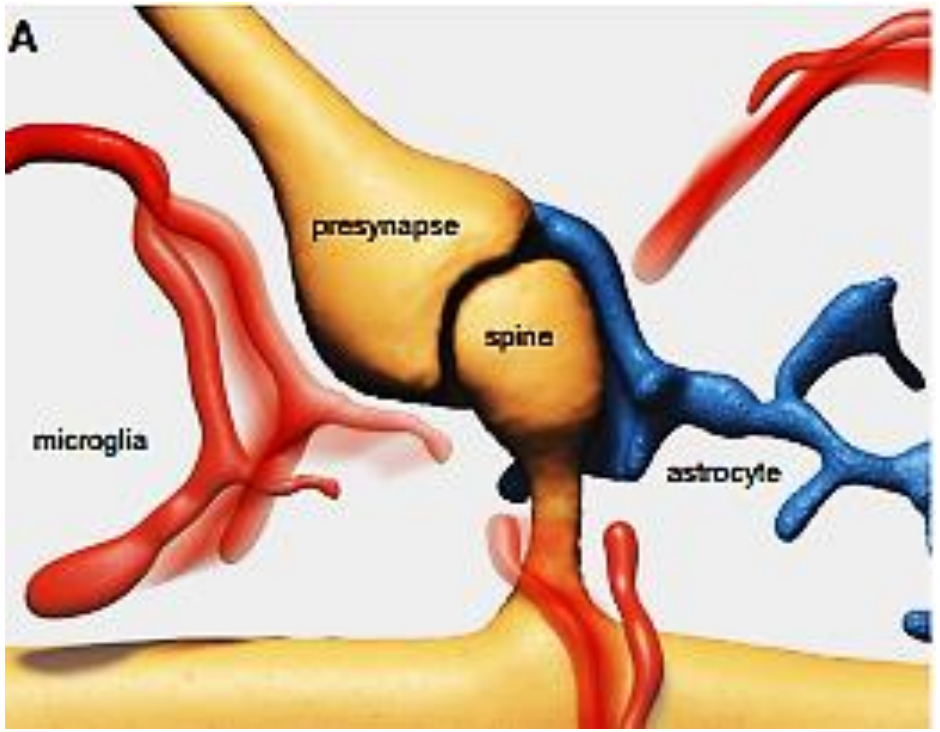
It occurs mainly during synaptogenesis, but also in adulthood

Control of synapsis number

Perfomed by both astrocytes and microglia

Highly regulated and activity-dependent

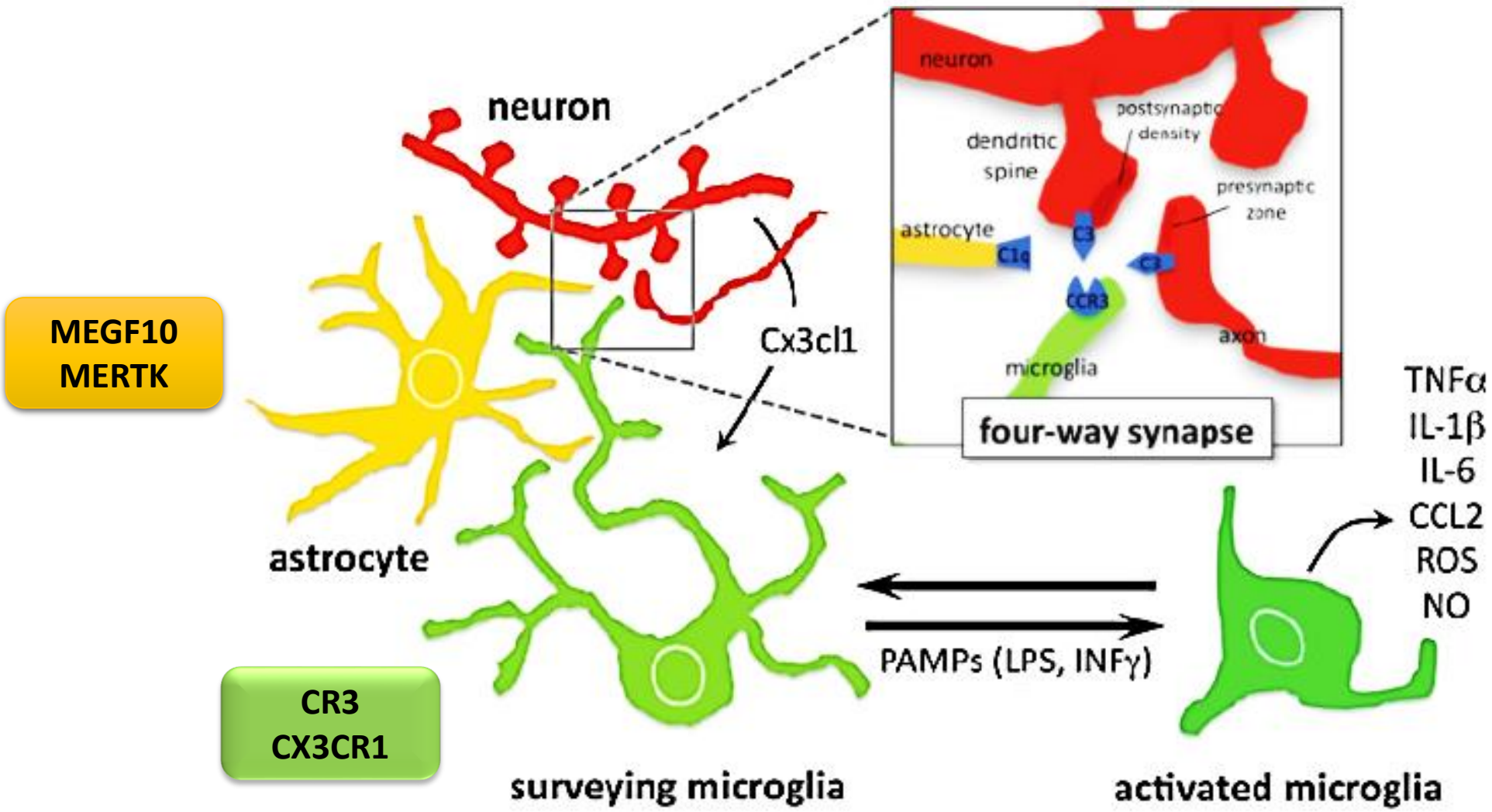
Both Excitatory and Inhibitory synapsis elimination



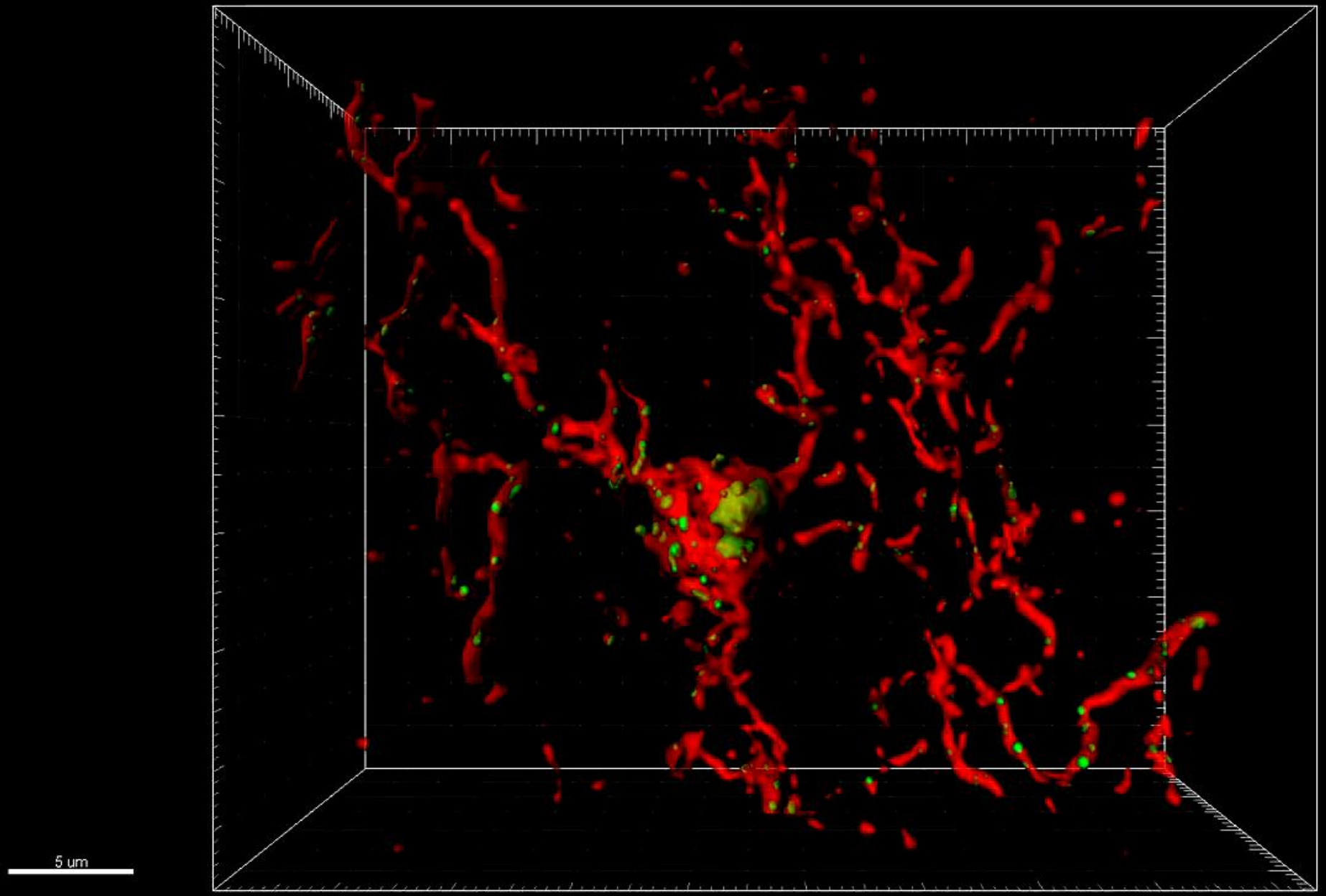
Impaired pruning

- synaptic transmission
- decreased functional brain connectivity
- deficits in social interaction
- repetitive-behavior phenotypes
- Cognitive impairment

PRUNING MOLECULAR RECOGNITION



In vivo mouse model: Microglia engulf synaptic material after Aβ 1-42 injection



GLIA: Housekeeper or Executive partener?

Neurons-glia
Positive feedback

Correct maintance and function of neuronal circuits

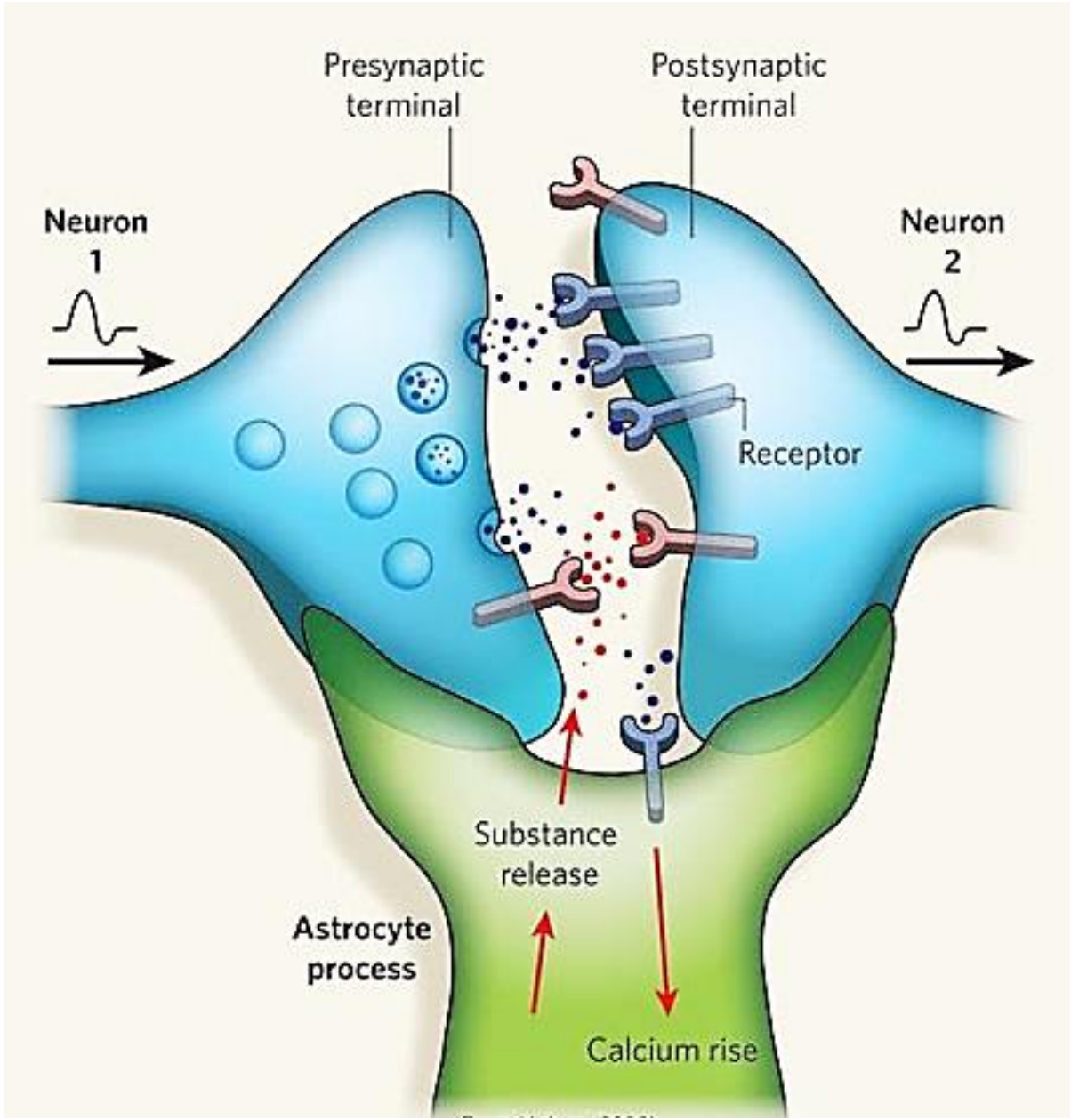
Neuronal activity sensing

Glial excitation

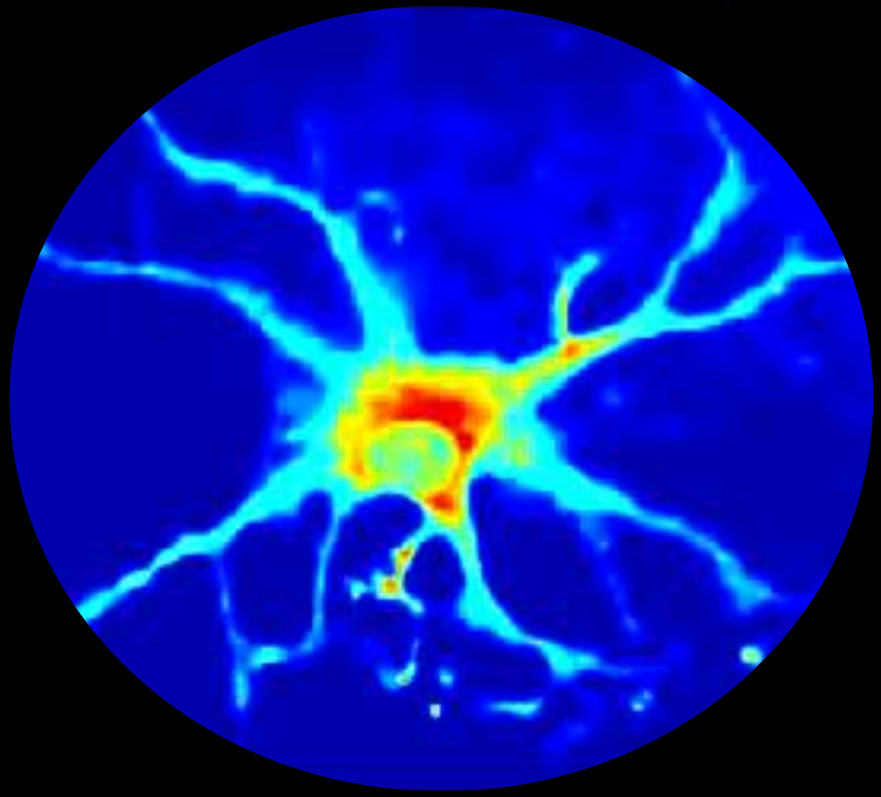
VS

Gliotransmitters release
Ion buffering

Synaptic plasticity regulation *on demand*



In vitro Astrocyte Calcium Imaging



[Ca2+] (nM)

0 100 200 300 400 500 600

CLINICAL ASPECTS

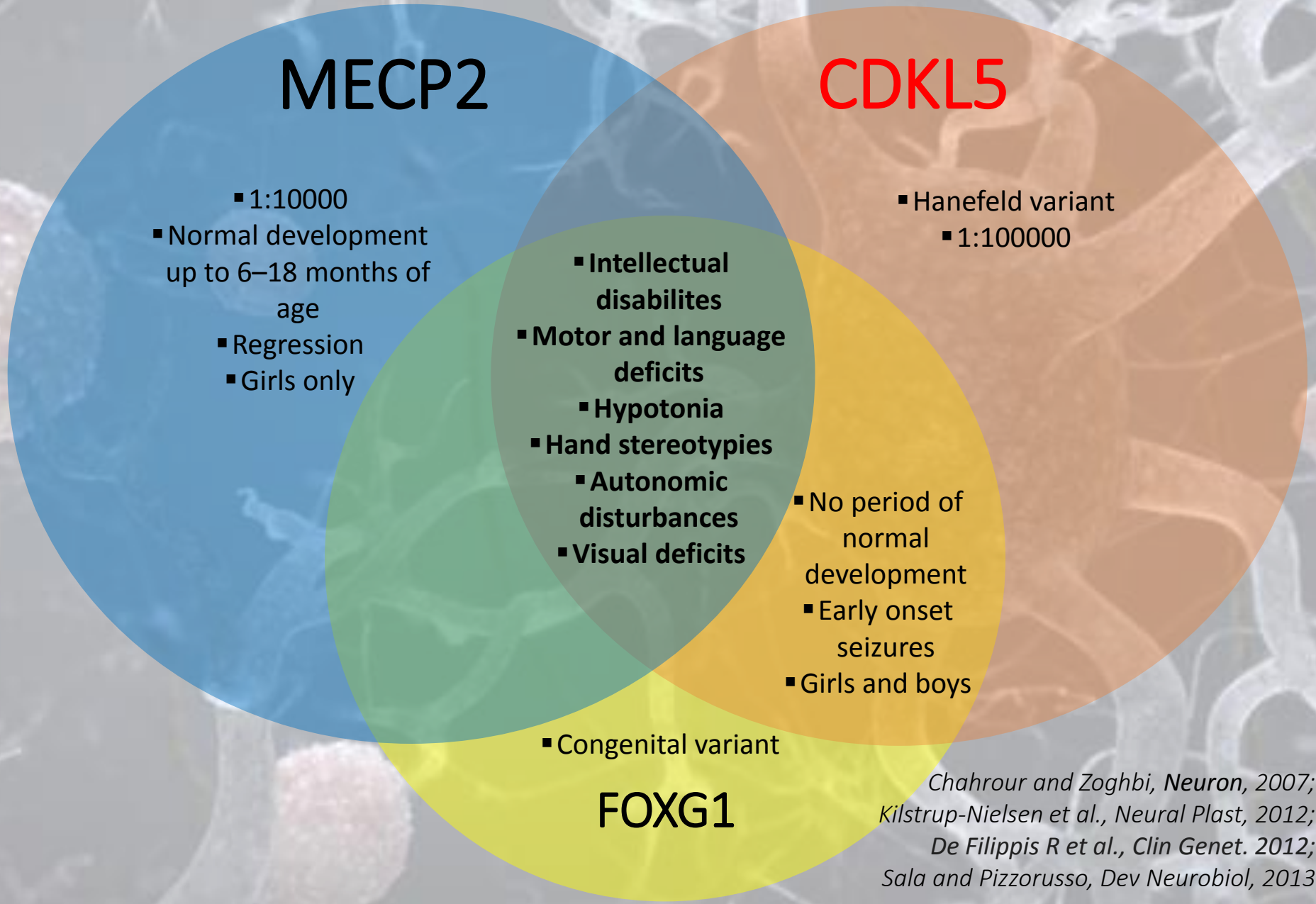
Neurodevelopmental disease

- Rett Syndrome
- Down Syndrome
- Fragile X syndrome
- Autistic Spectrum Disorder
- Schizophrenia

Neurodegenerative disease

- Alzheimer's disease
- Parkinson's disease
- Huntington's disease
- Amytrophic lateral sclerosis
- Inflammaging

RETT SYNDROME

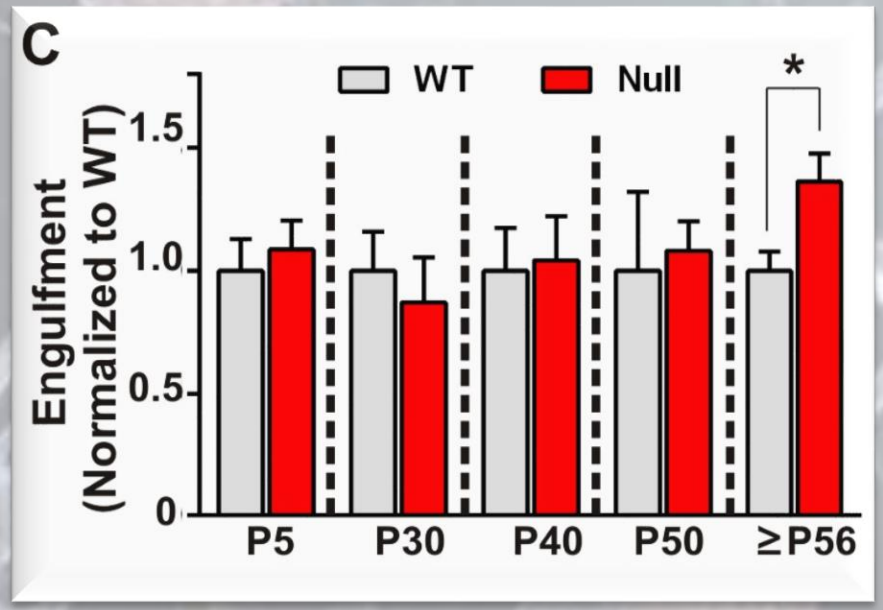


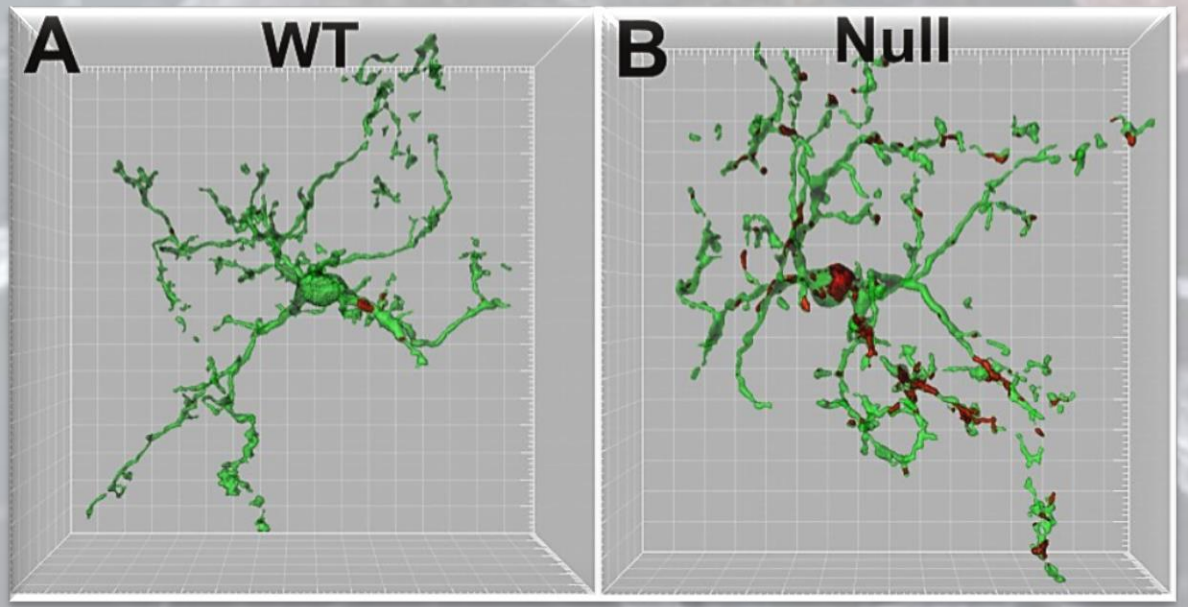
Chahrour and Zoghbi, ***Neuron****, 2007;*
Kilstrup-Nielsen et al., Neural Plast, 2012;
De Filippis R et al., Clin Genet. 2012;
Sala and Pizzorusso, Dev Neurobiol, 2013

RETT SYNDROME

Microglia contribute to circuit defects in *Mecp2 null* mice independent of microglia-specific loss of Mecp2 expression

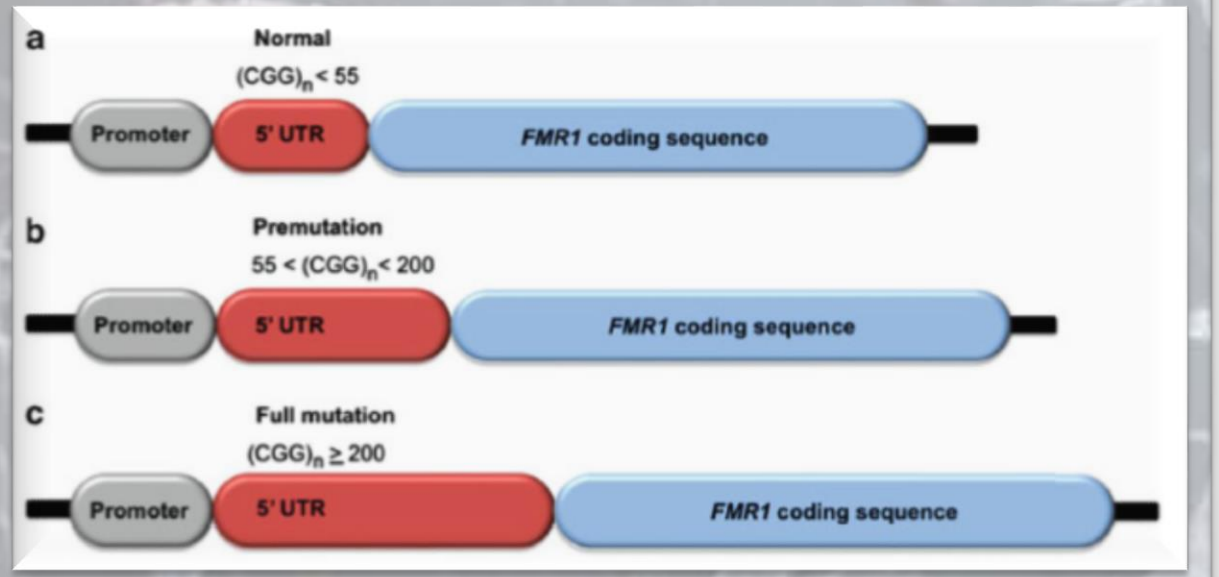
Dorothy P Schafer[1,2]*, Christopher T Heller[1,2], Georgia Gunner[1,2], Molly Heller[1], Christopher Gordon[1], Timothy Hammond[1], Yochai Wolf[3], Steffen Jung[3], Beth Stevens[1,4]

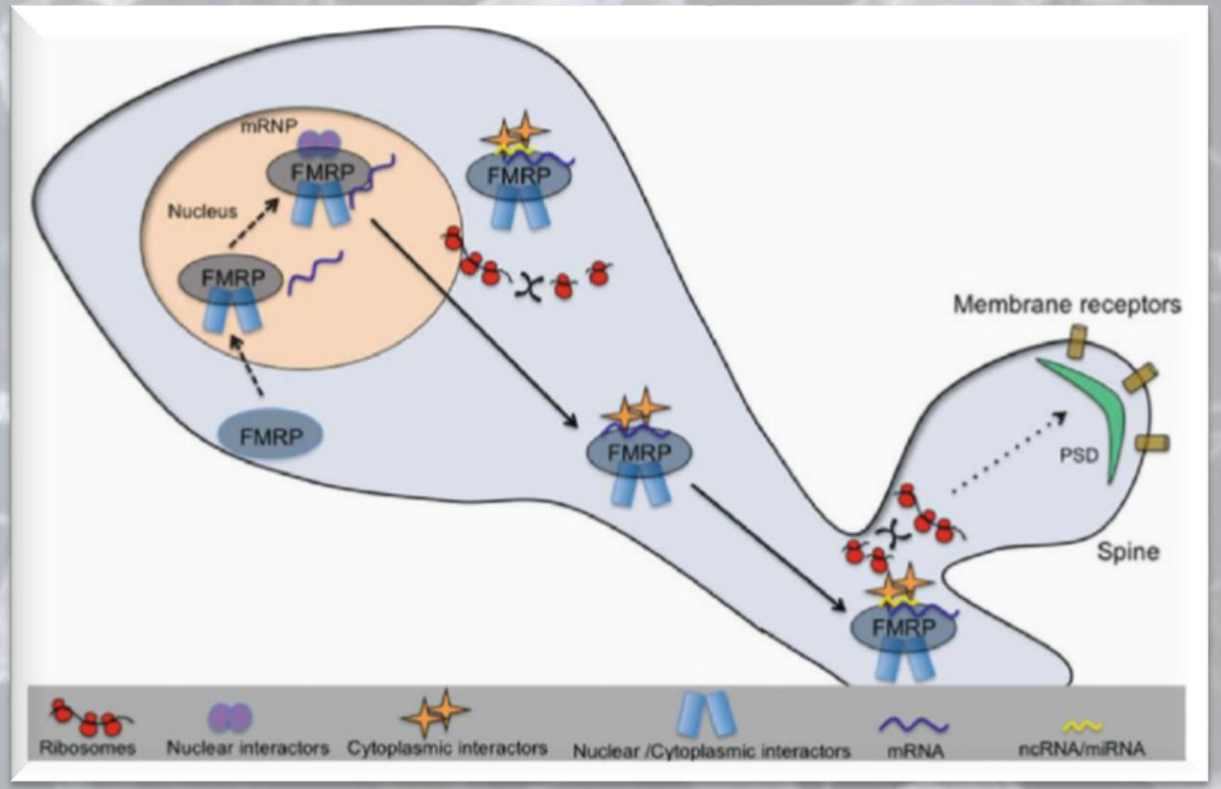




doi: 10.7554/eLife.15224

FRAGILE X SINDROME



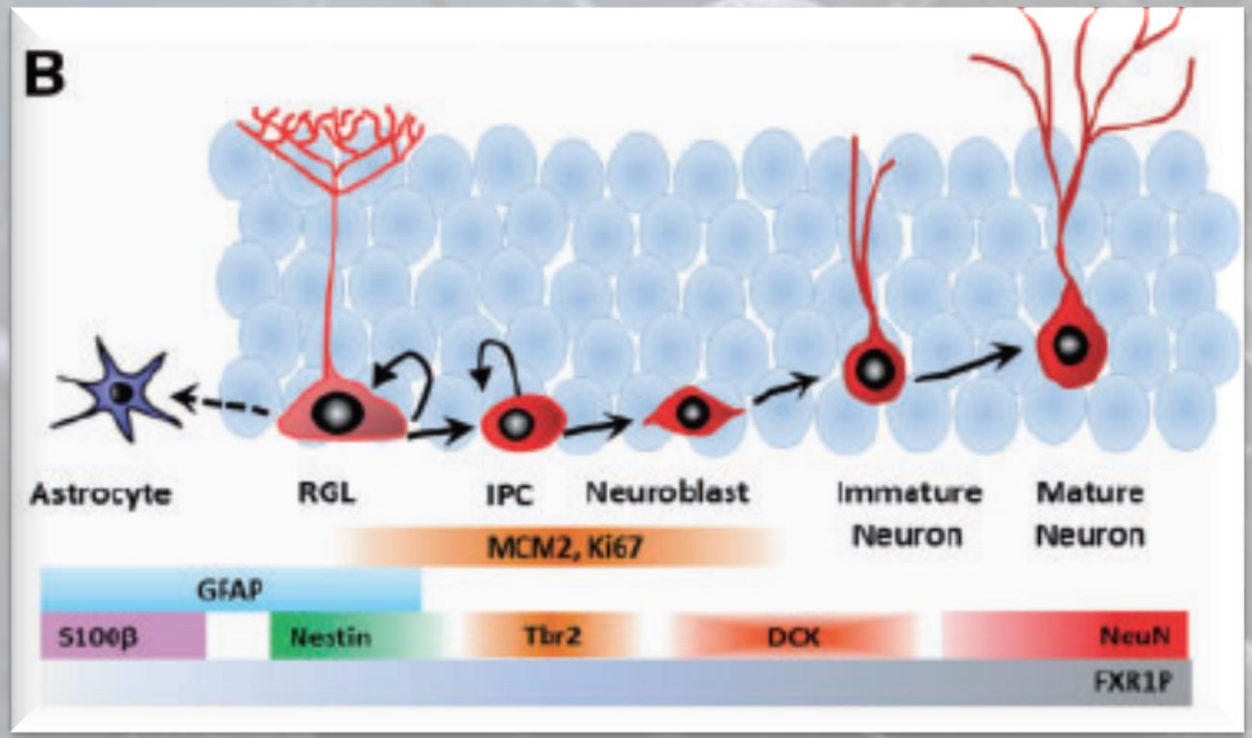


ORIGINAL ARTICLE

Fragile X related protein 1 (FXR1P) regulates proliferation of adult neural stem cells

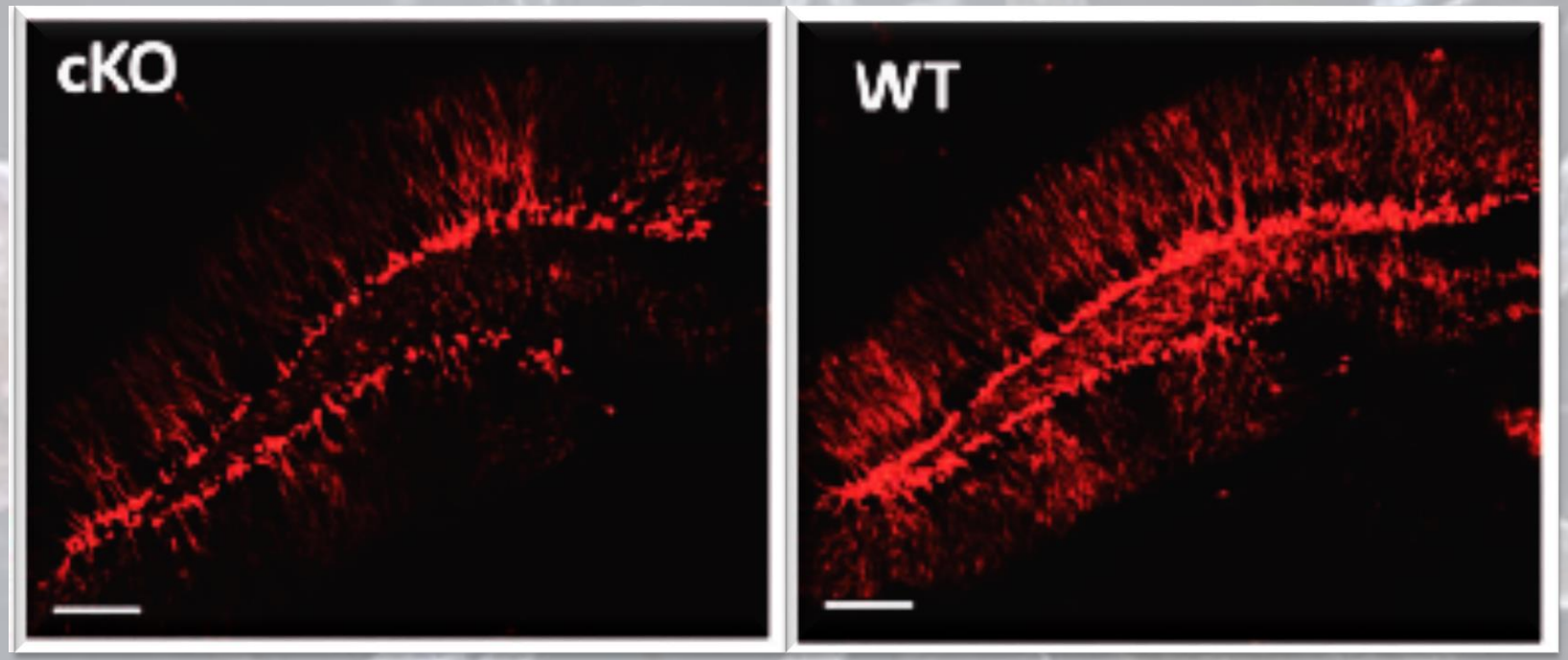
Natalie E. Patzlaff[1,2], Kelsey M. Nemec[1], Sydney G. Malone[1], Yue Li[1] and Xinyu Zhao[1,2,3,*]

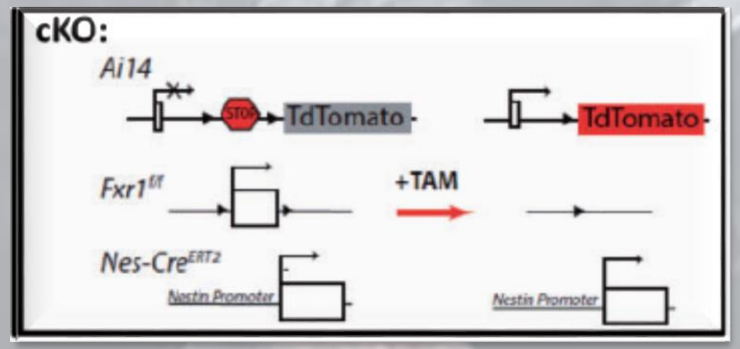
FXR1P expression during adult hippocampal neurogenesis

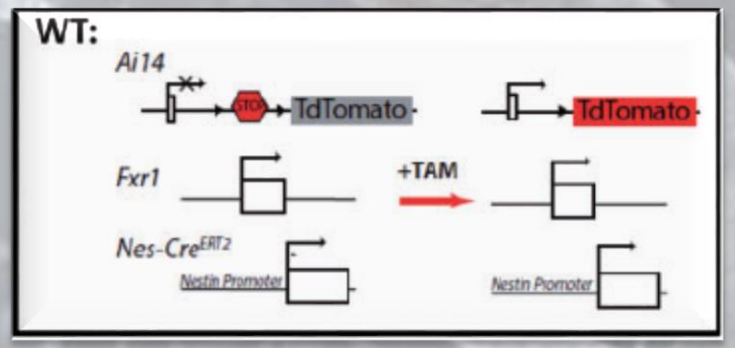


doi: 10.1093/hmg/ddx034

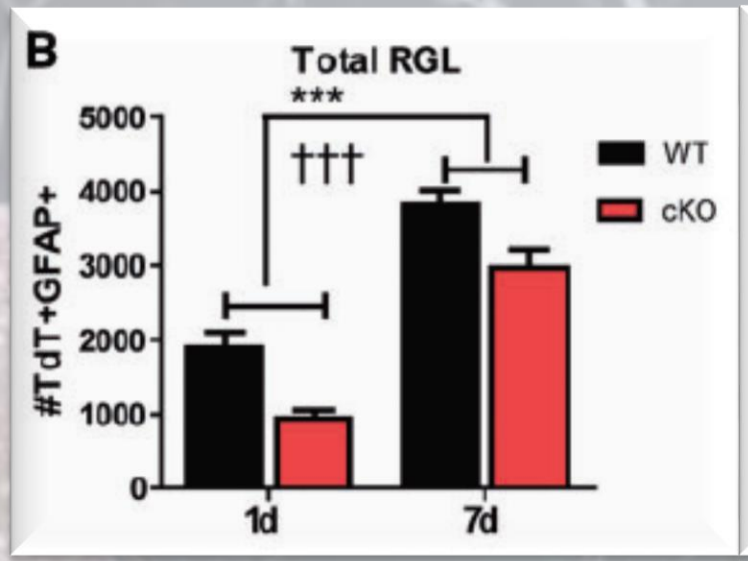
Selective deletion of FXR1P in adult neural stem cells leads to fewer adult-born cells

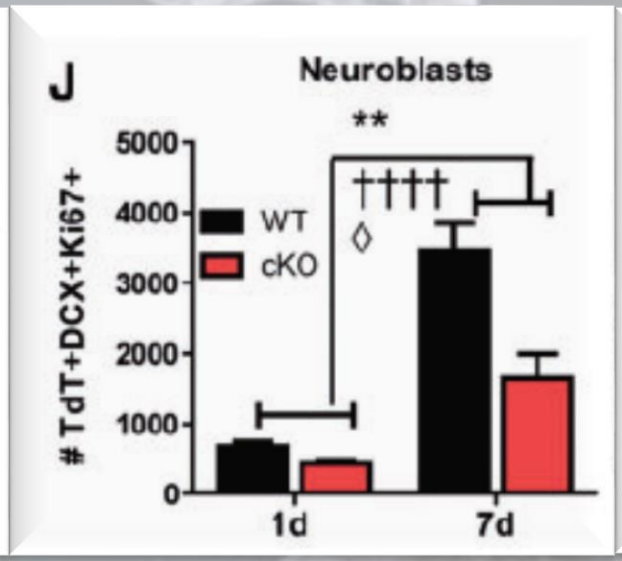


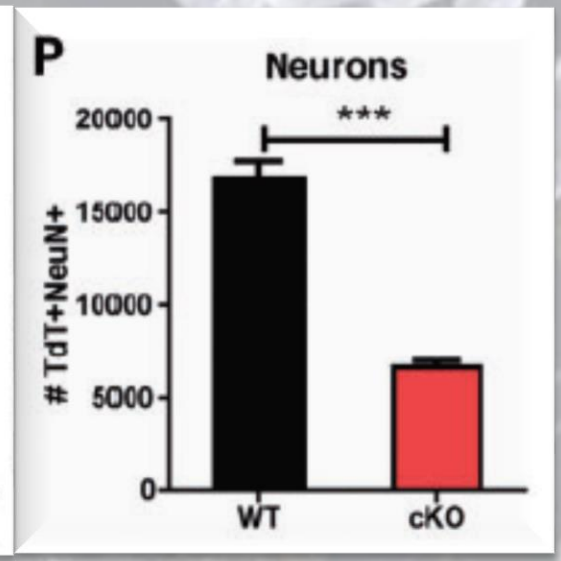


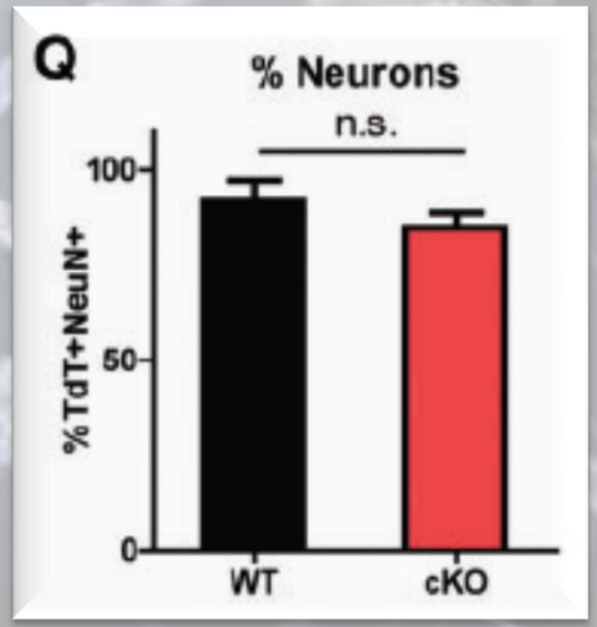


FXR1P lack affects proliferation, but not cell death or differentiation

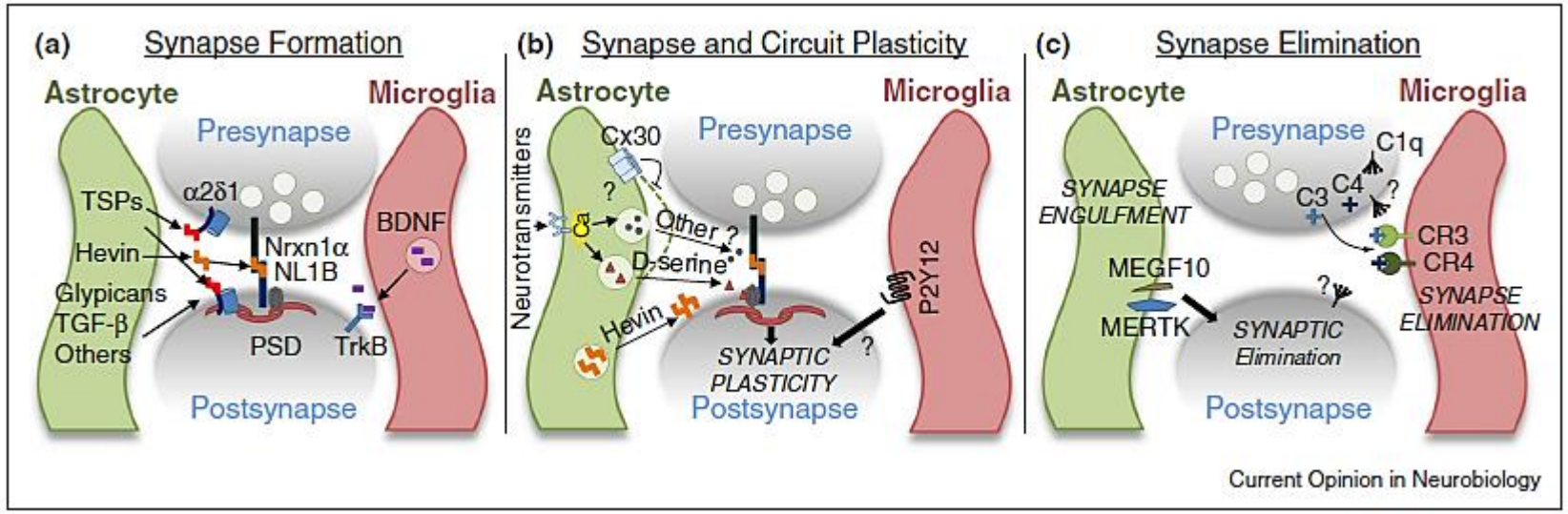








CONCLUSION



Open question…

How do glial cells convert neuronal signals into functional outputs?

Regulation of synaptogenic proteins expression in astrocytes

Communication mechanism among glial cells for synaptic pruning coordination

Microglia role in synaptic response modulation