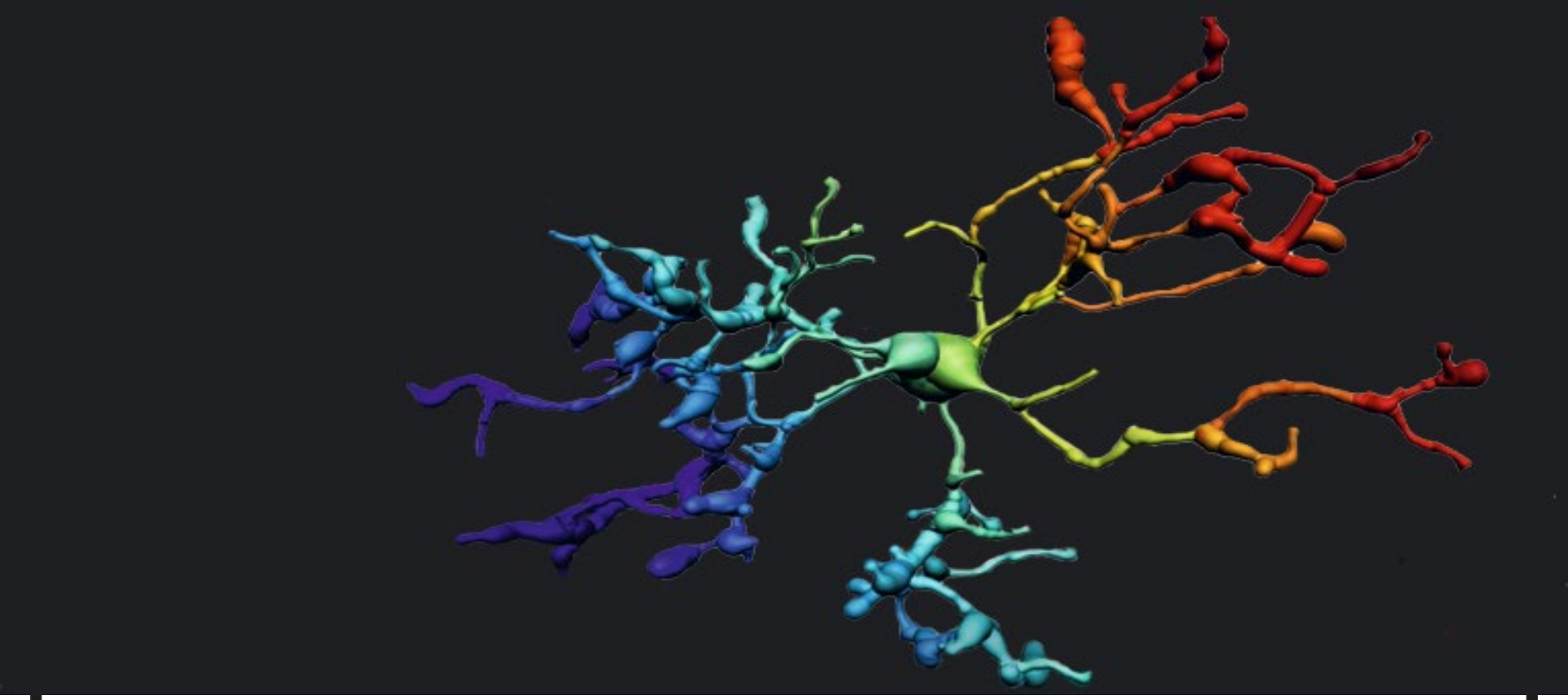

NEUROGLIA

Bert Brône, prof dr

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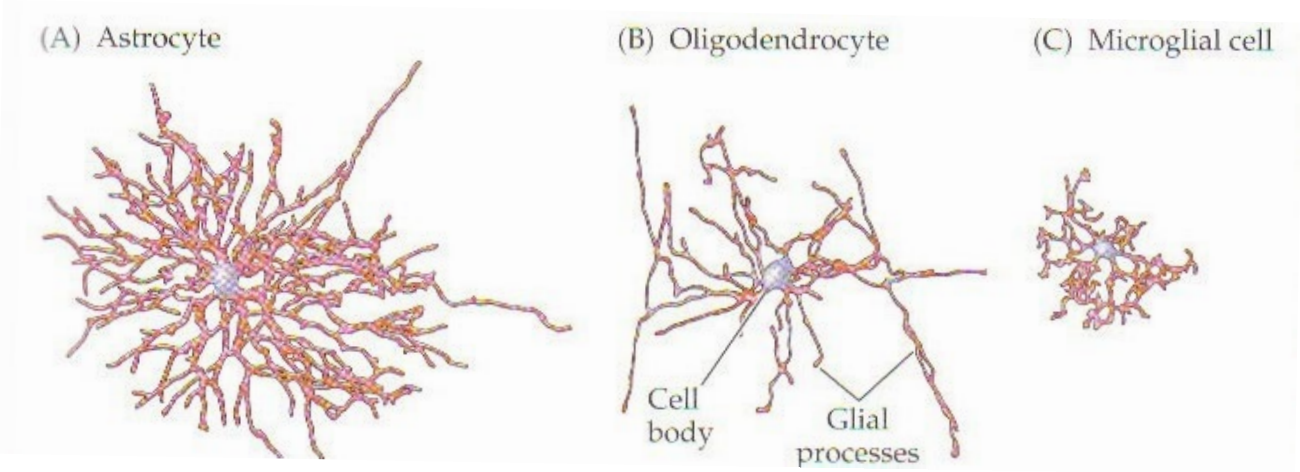
KNOWLEDGE IN ACTION

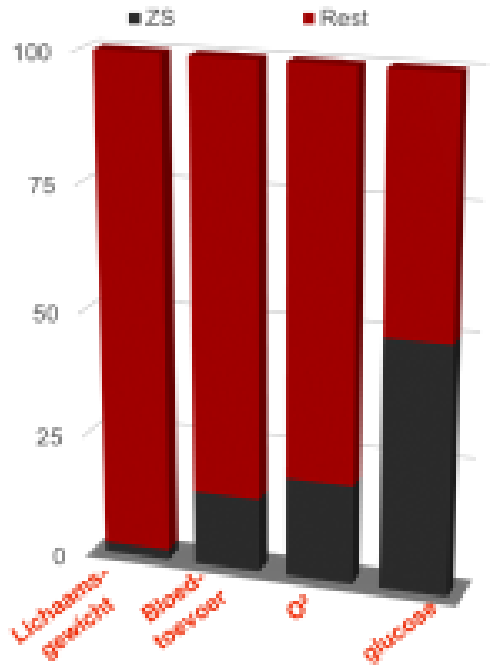
NeuroGlia

	Central Nervous System	Peripheral Nervous System	Enteric Nervous System
Macroglia	Astrocytes		Enteric glia
	Oligodendrocytes	Schwann cells	
	Pericytes		
	NG2 cells		
		Ganglionic glia	
	Microglia	Macrophages	phagocytes



General tasks:
to guard the neuronal microenvironment

- Energy consumption of the brain
- 50% → ion concentration gradients Na^+/K^+ Pump



General tasks:
to guard the neuronal microenvironment

- Ionic concentrations → excitability
- Support conduction of action potentials
- Nutrient concentrations
  - → Amino acids
  - → Signal molecules
  - → Energy supply

Development

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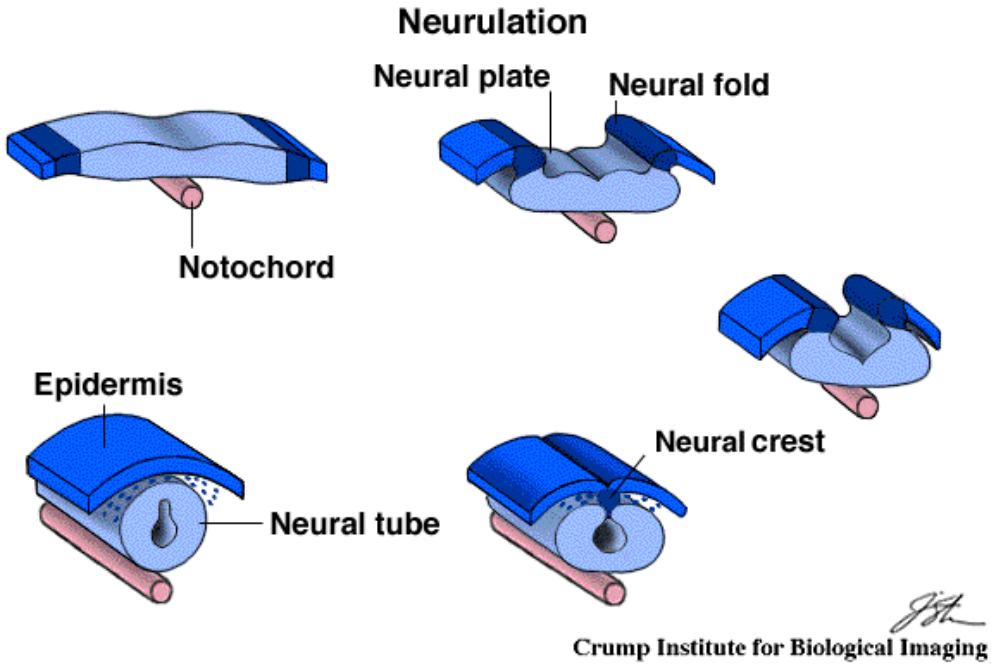
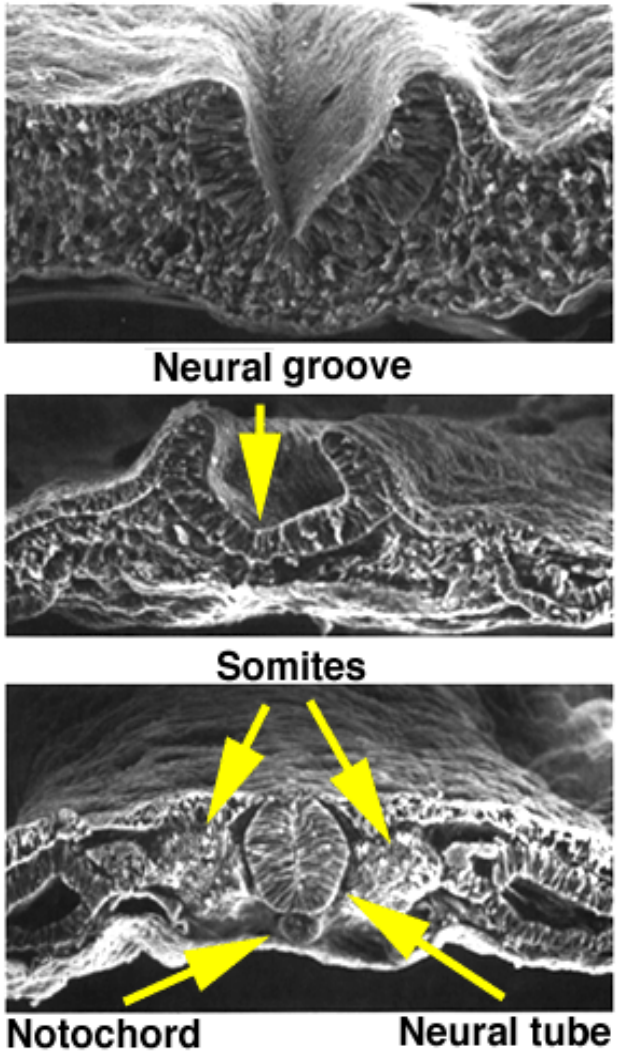
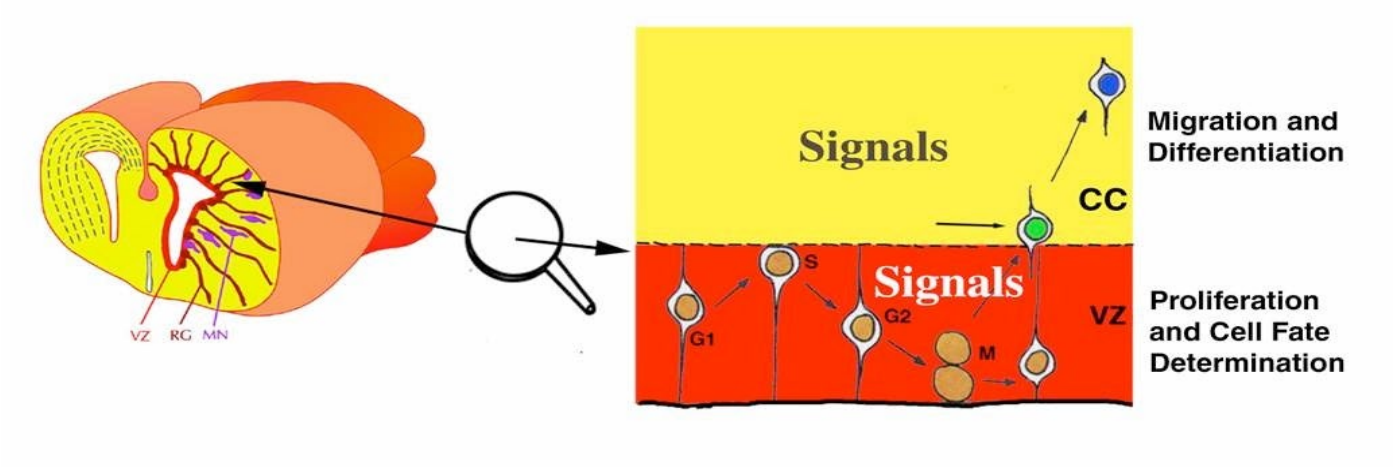
Neurulation





Proliferation

- In humans, neurons are born between E42 and E125 (before MOST glial cells)



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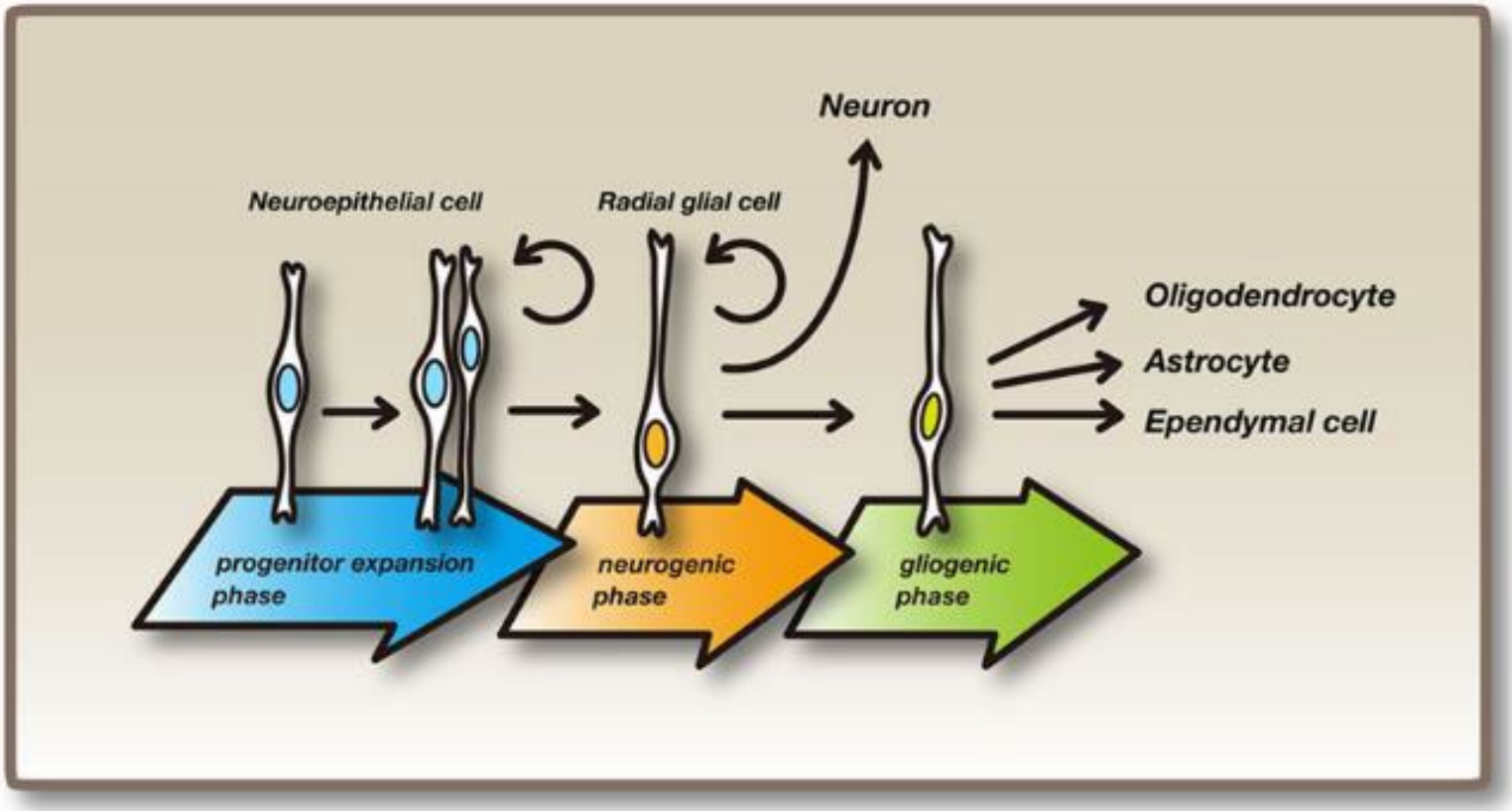
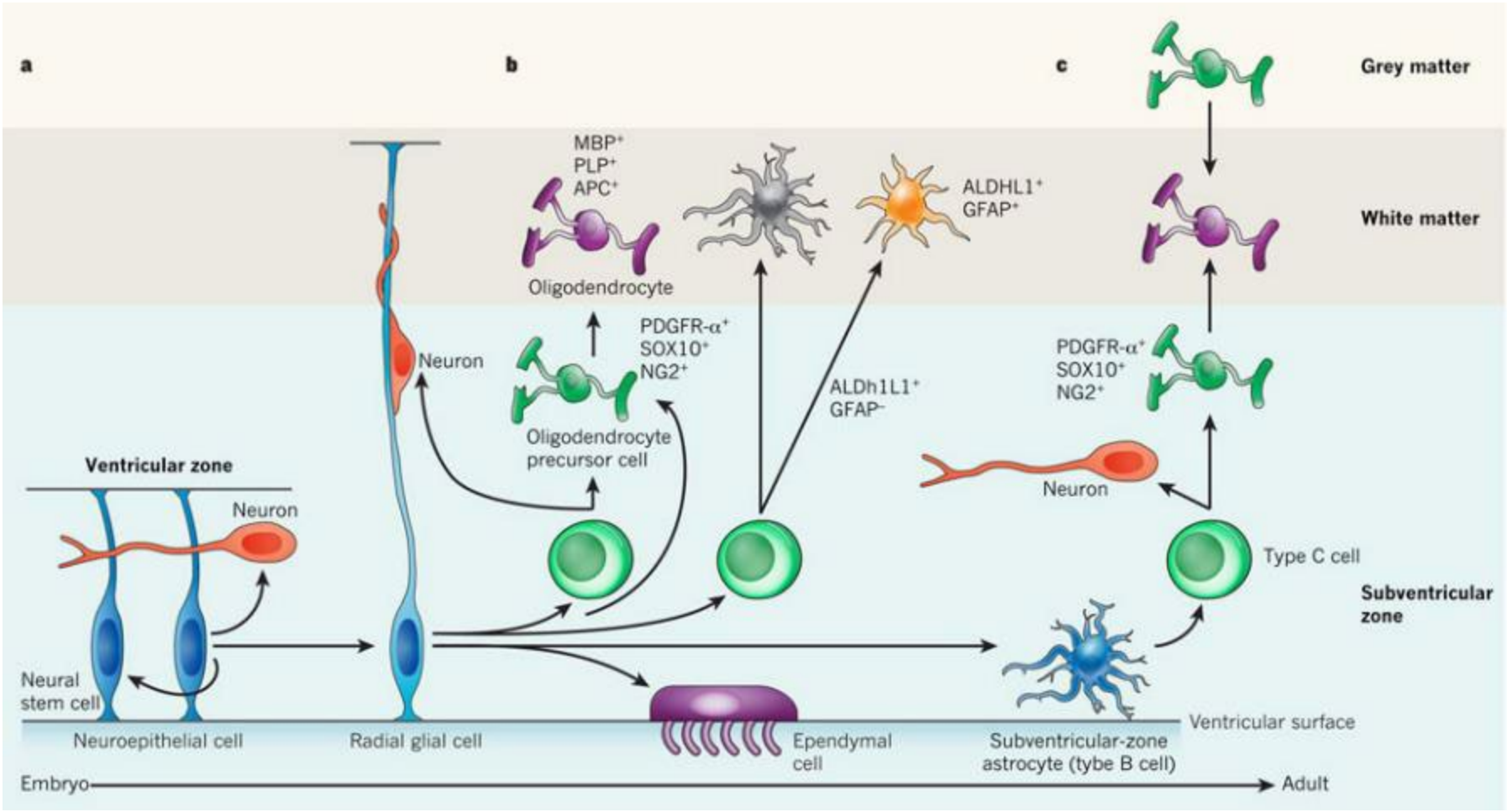


Shimojo 2011



Rowitch and kriegstein 2010

Glial cells

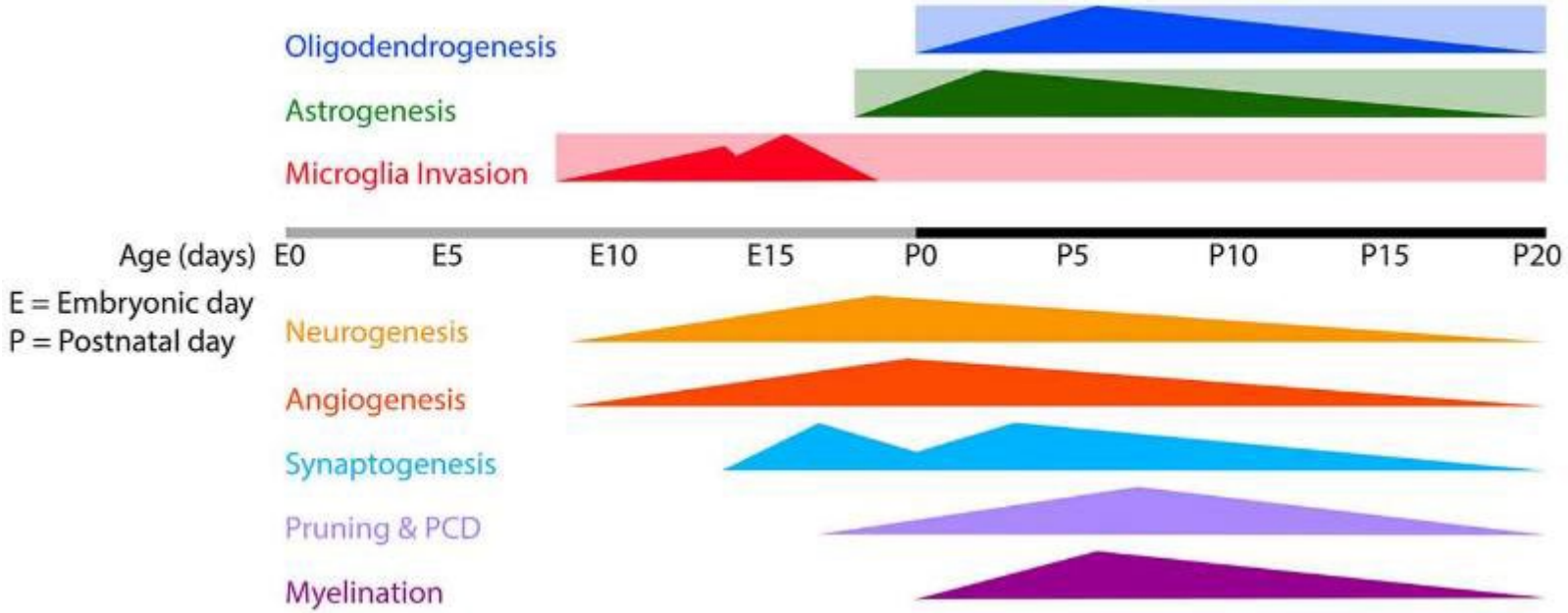
- Originate from embryonic ectoderm
- Intimate morphological association with neurons

  or

  to seperate neuronal elements from mesodermal layers

→MACROGLIA

≠ MICROGLIA



Reemst 2016

Astrocytes

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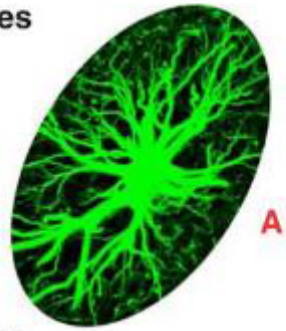
Reactive astrogliosis

Non-reactive astrocytes

In response to e.g. trauma, stroke, epilepsy, neurodegenerative diseases - upregulation of GFAP and hypertrophy of cellular processes are among the hallmarks

Pathophysiological responses
- see Fig 8C

Activation e.g. by TGFα, CNTF, IL-6, LIF, oncostatin M



A defensive reaction aiming at

- handling of acute stress
- limiting tissue damage
- restoring homeostasis

Physiological responses
- see Fig 8C

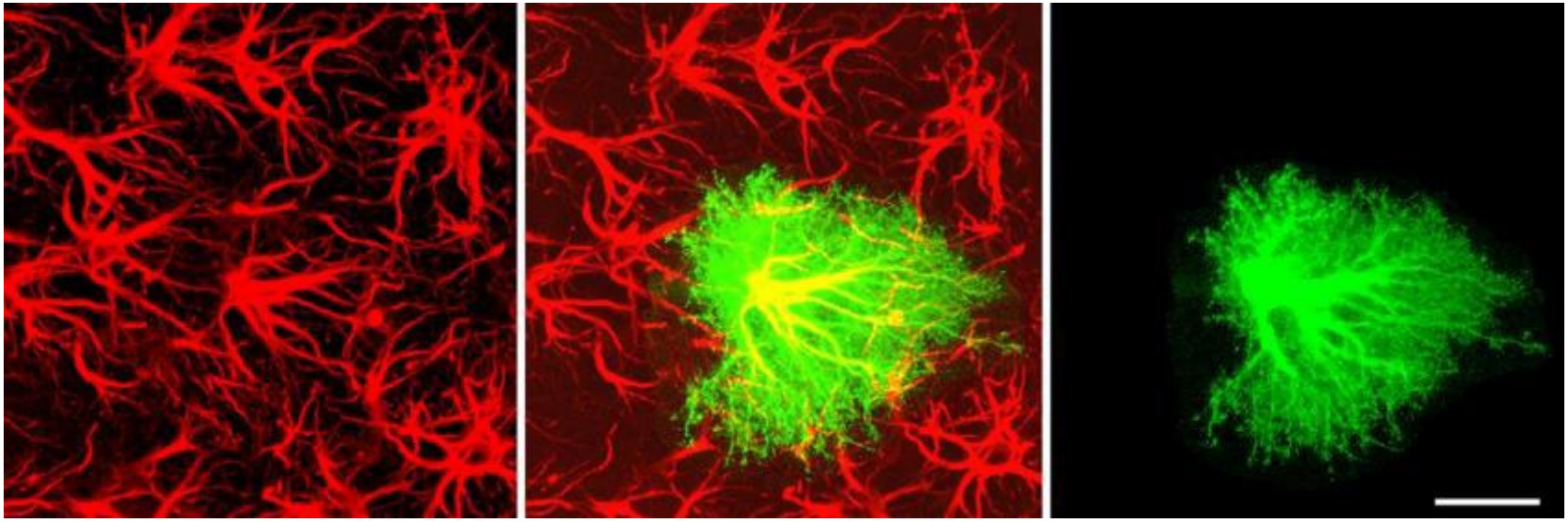
Reactive astrogliosis is

- context (=disease) dependent
- multistage
- region specific
- diffuse or demarcating the lesion
- graded (from mild astrogliosis to a glial scar)

It is adaptive, but when it persists, can turn into maladaptive → *a target for therapeutic intervention*

Pekny, 2014

Astrocyte morphology

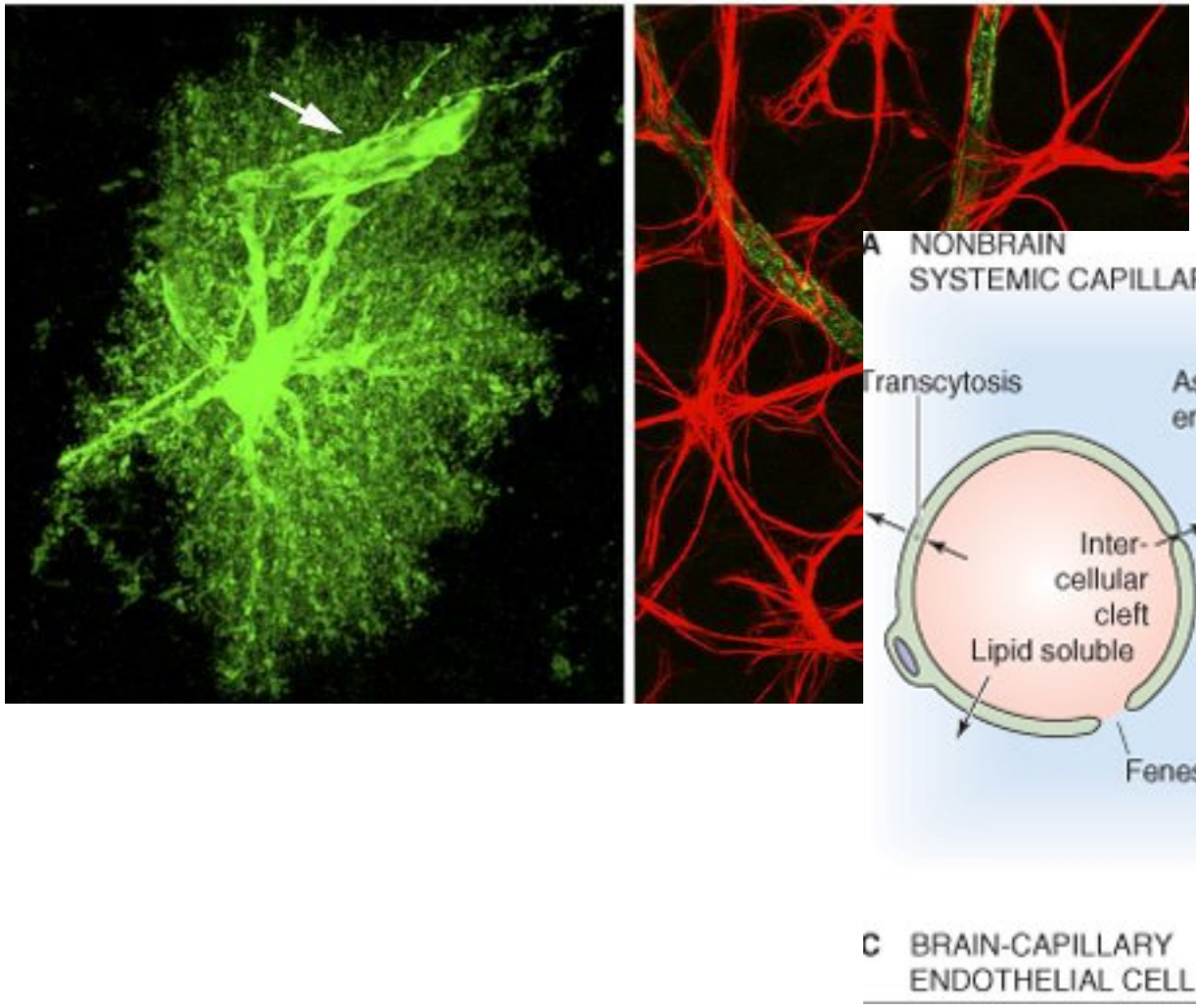


GFAP: Glial fibrillary Acidic Protein = principal intermediate filament (nanofilament) protein of astrocytes

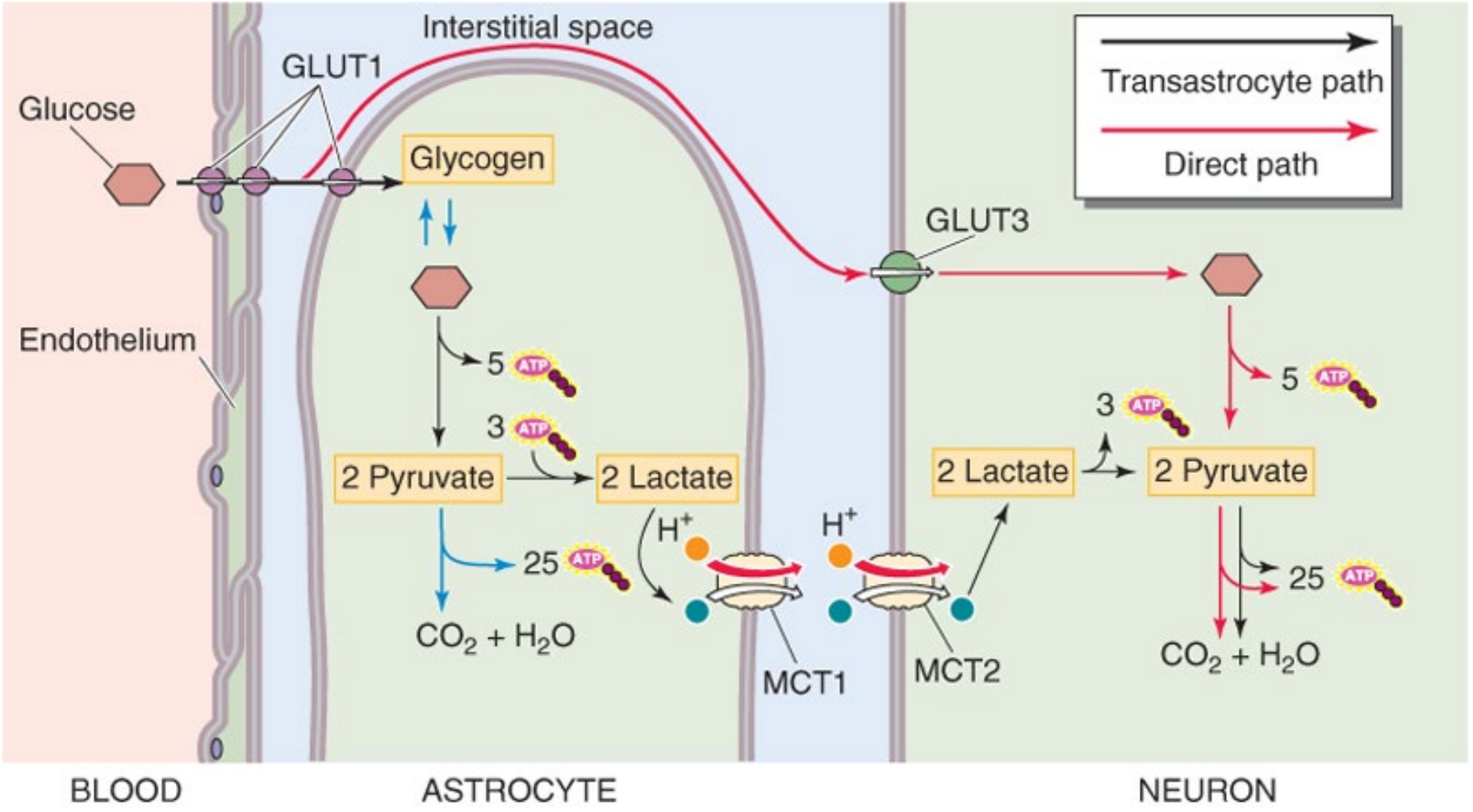
Dye filing → fine branches

Pekny, 2014

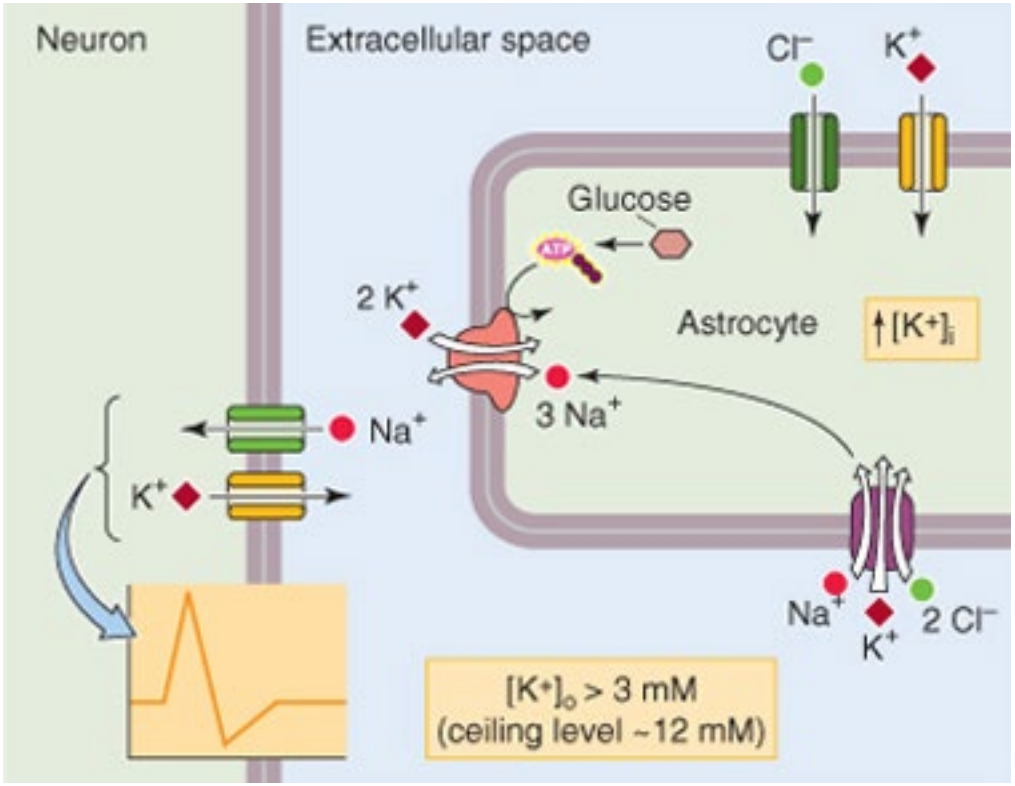
Blood Brain Barrier



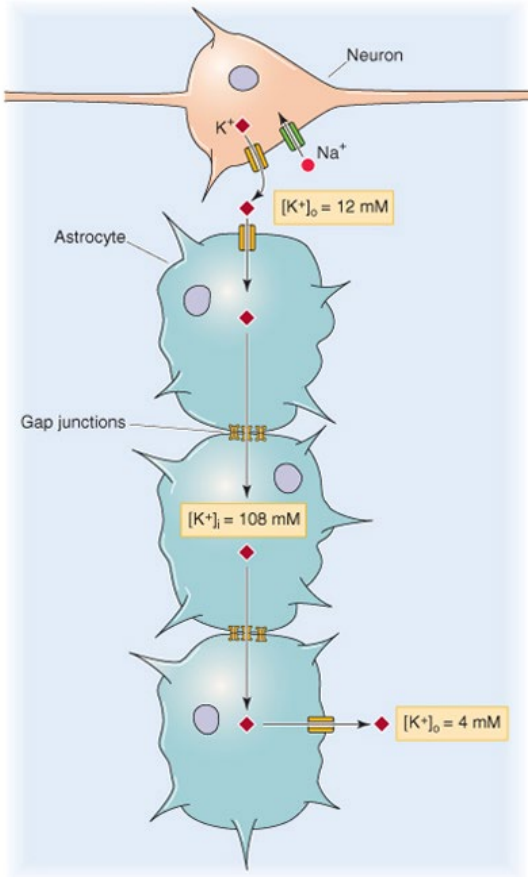
Energy supply



Potassium buffering



Potassium buffering



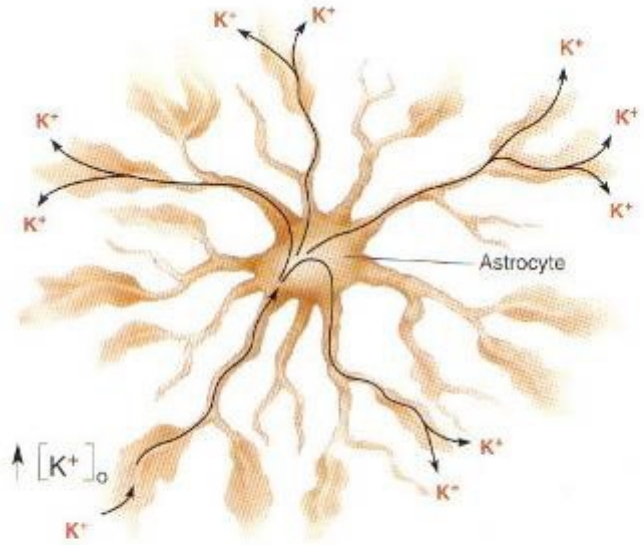
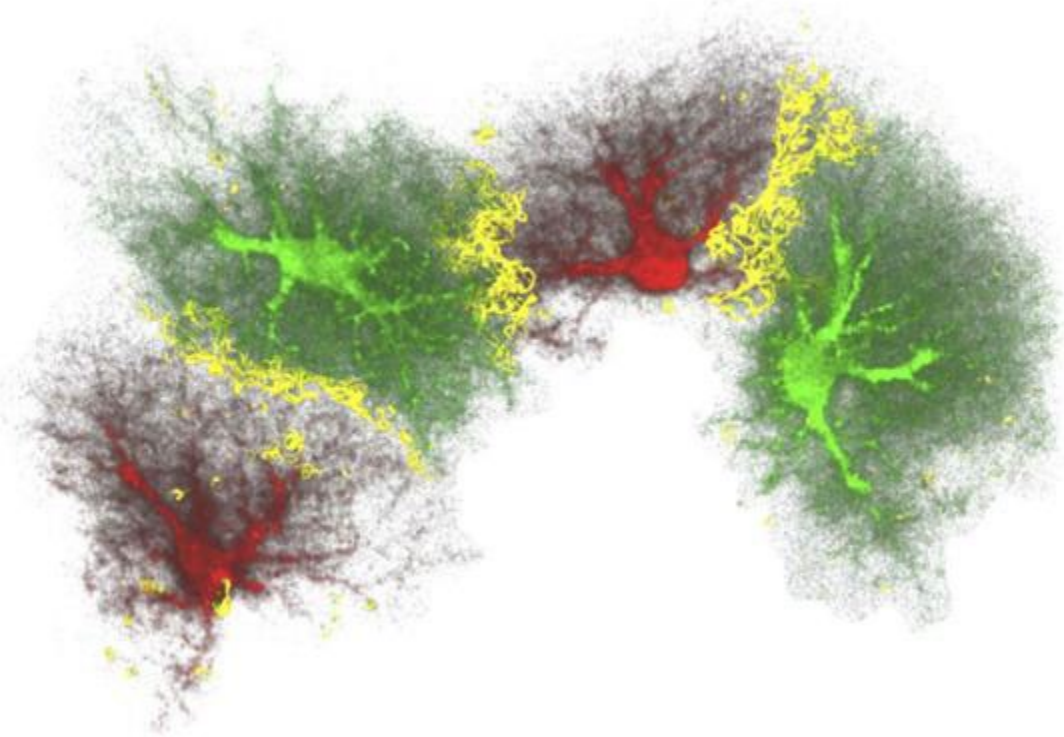
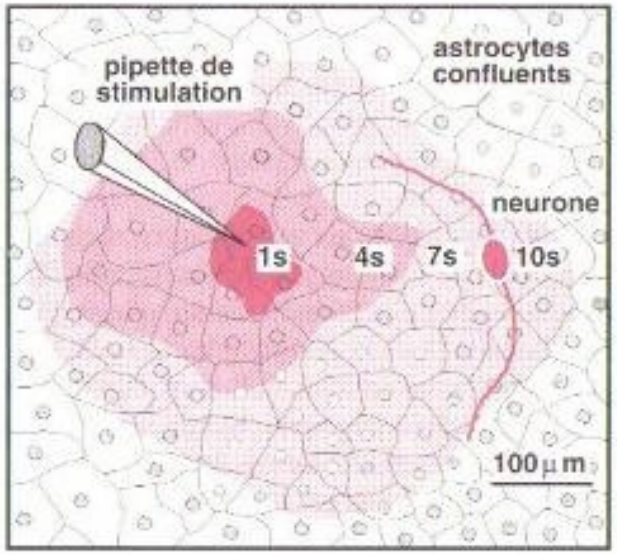


Figure 3.20
Potassium spatial buffering by astrocytes. When brain $[K^+]_o$ increases as a result of local neural activity, K^+ enters astrocytes via membrane channels. The extensive network of astrocytic processes helps dissipate the K^+ over a large area.

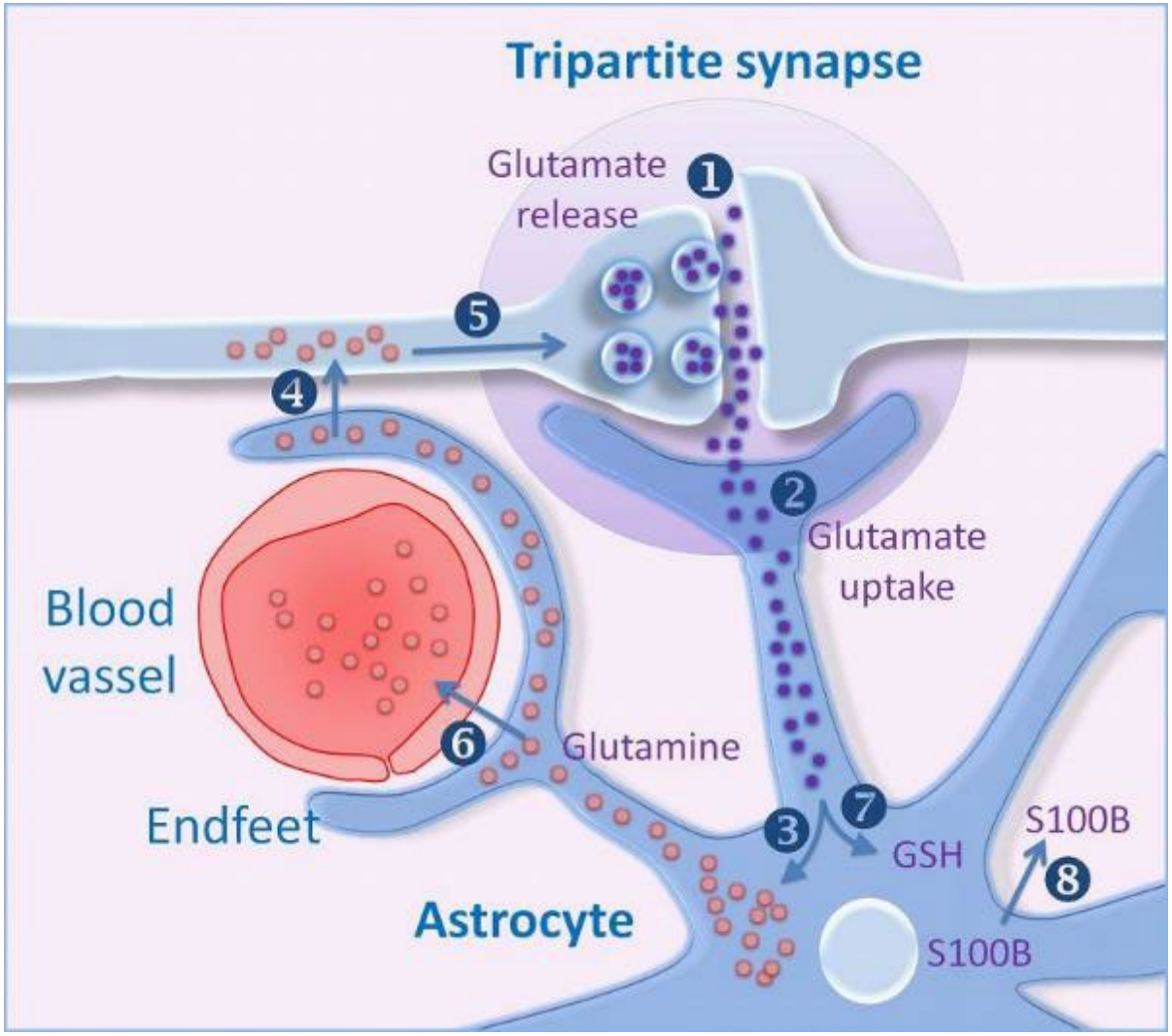
Astrocytic contacts



Pekny, 2014



Tripartite synaps



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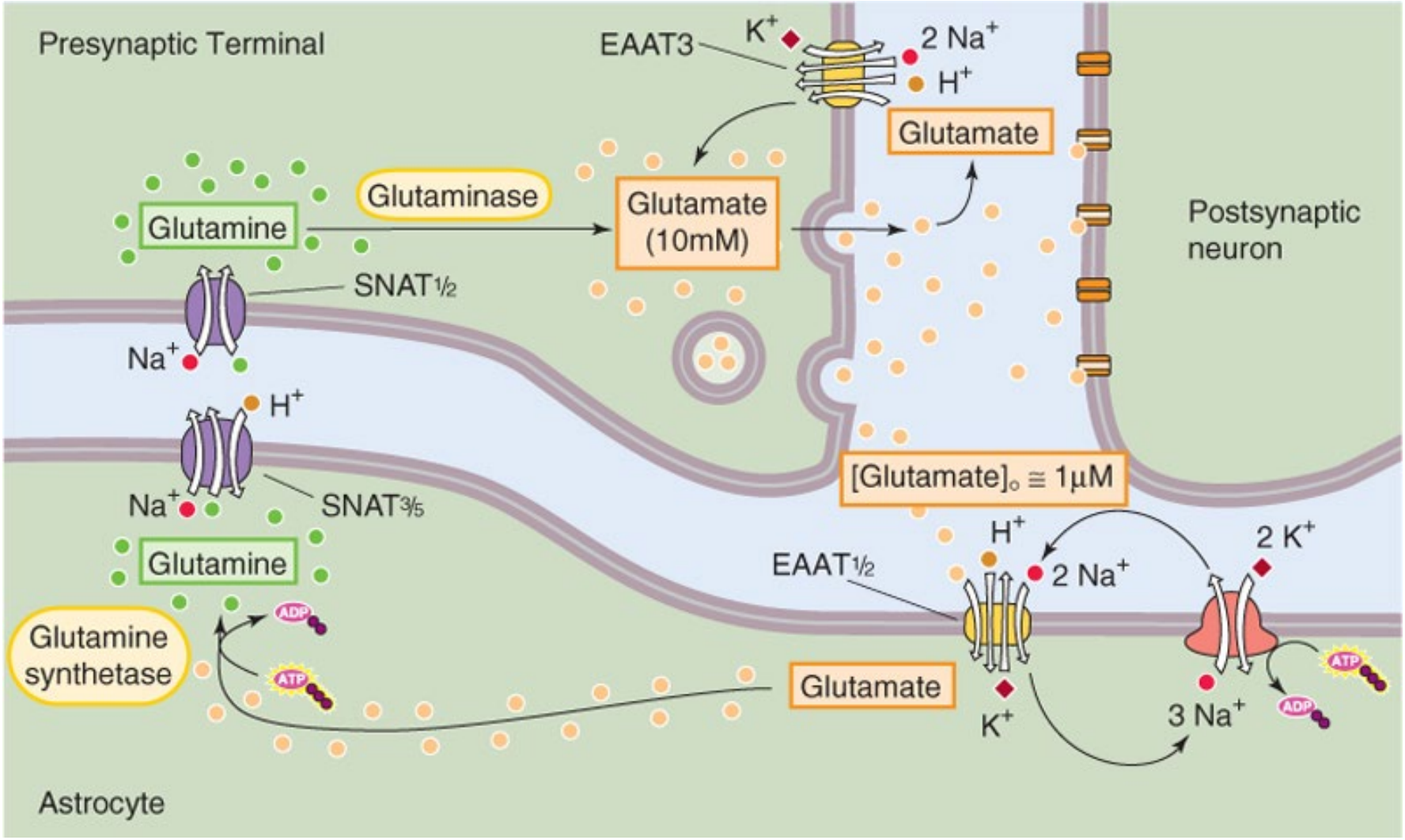
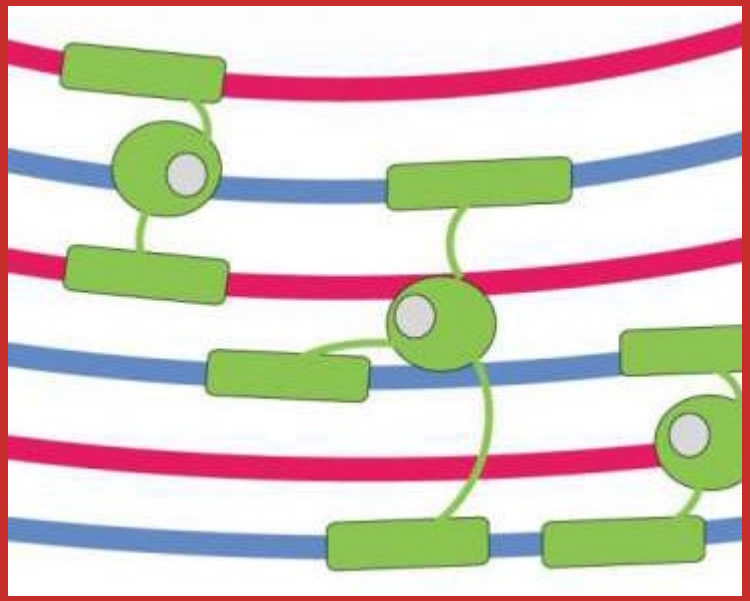
Tripartite synaps



Oligodendrocytes



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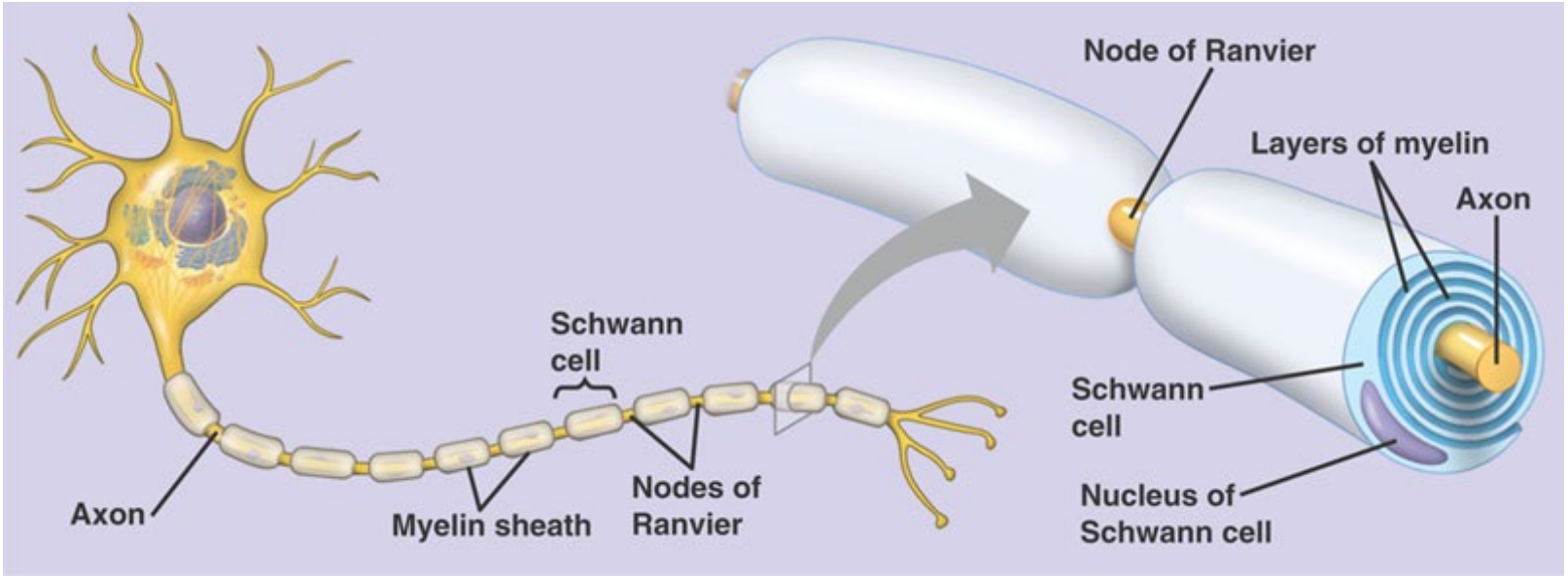
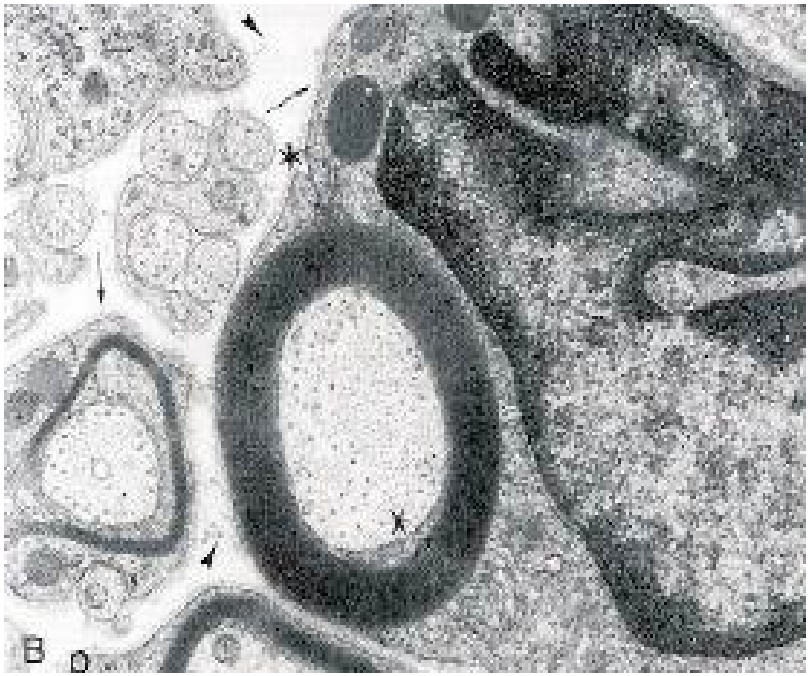
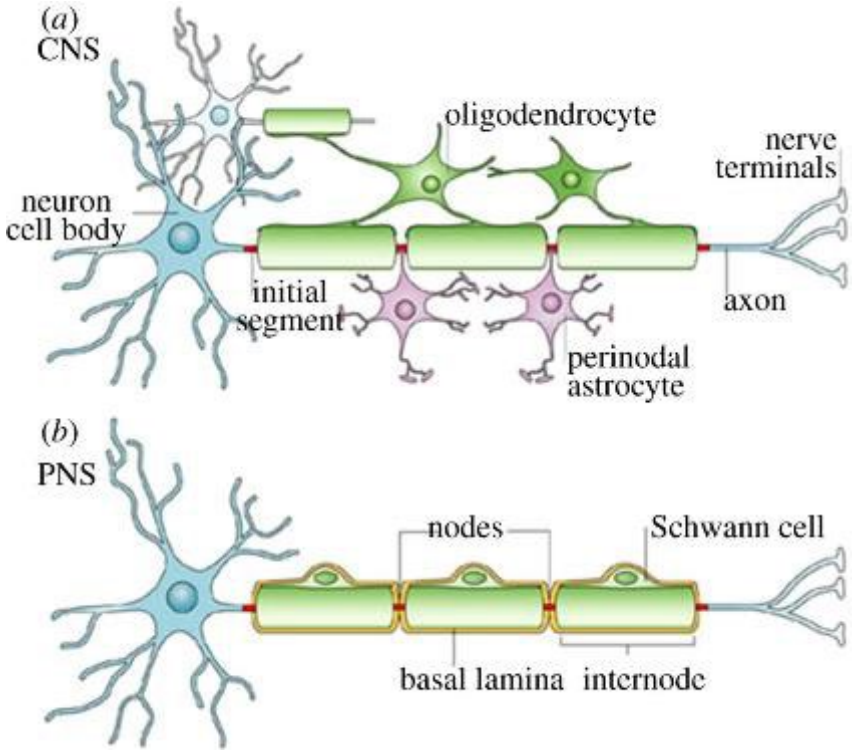
Oligodendrocytes produce myeline

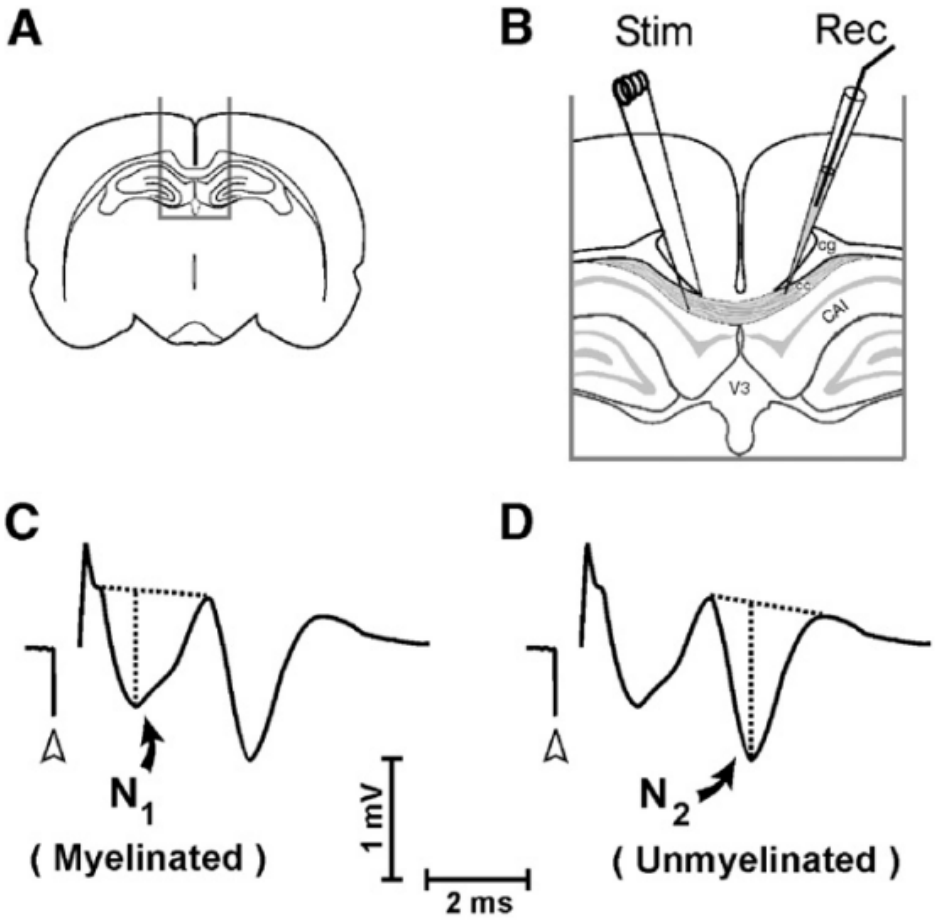


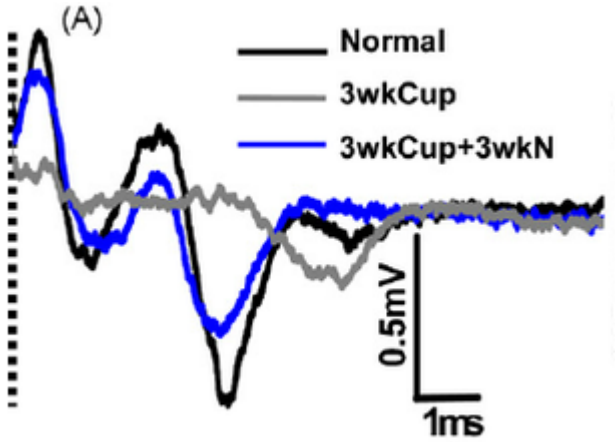
Oligo vs Schwann





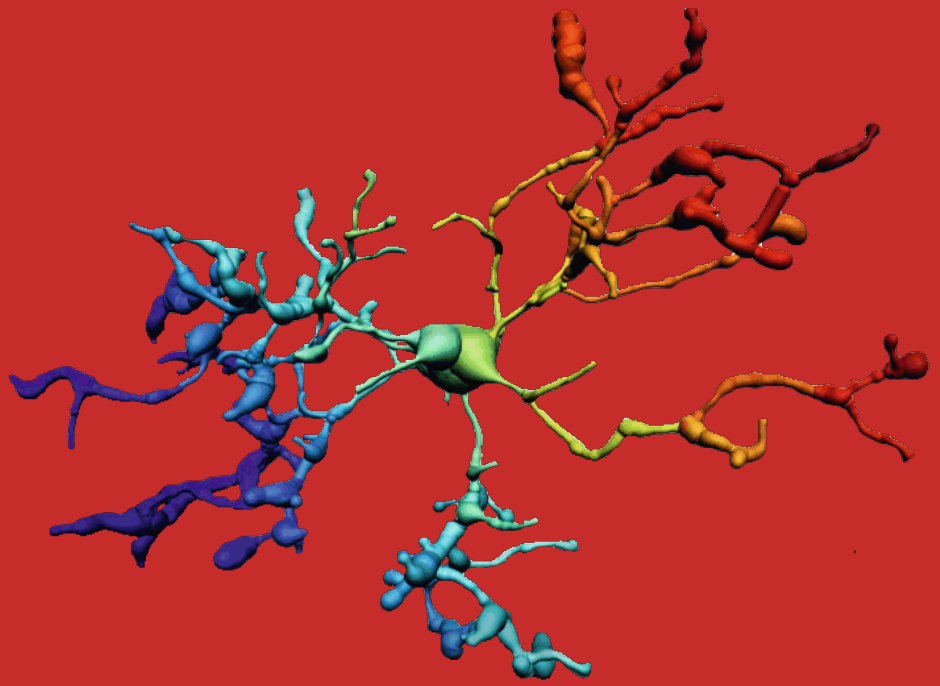
Pathology: Myelin loss





Reeves 2005 ; Crawford 2009

Microglia



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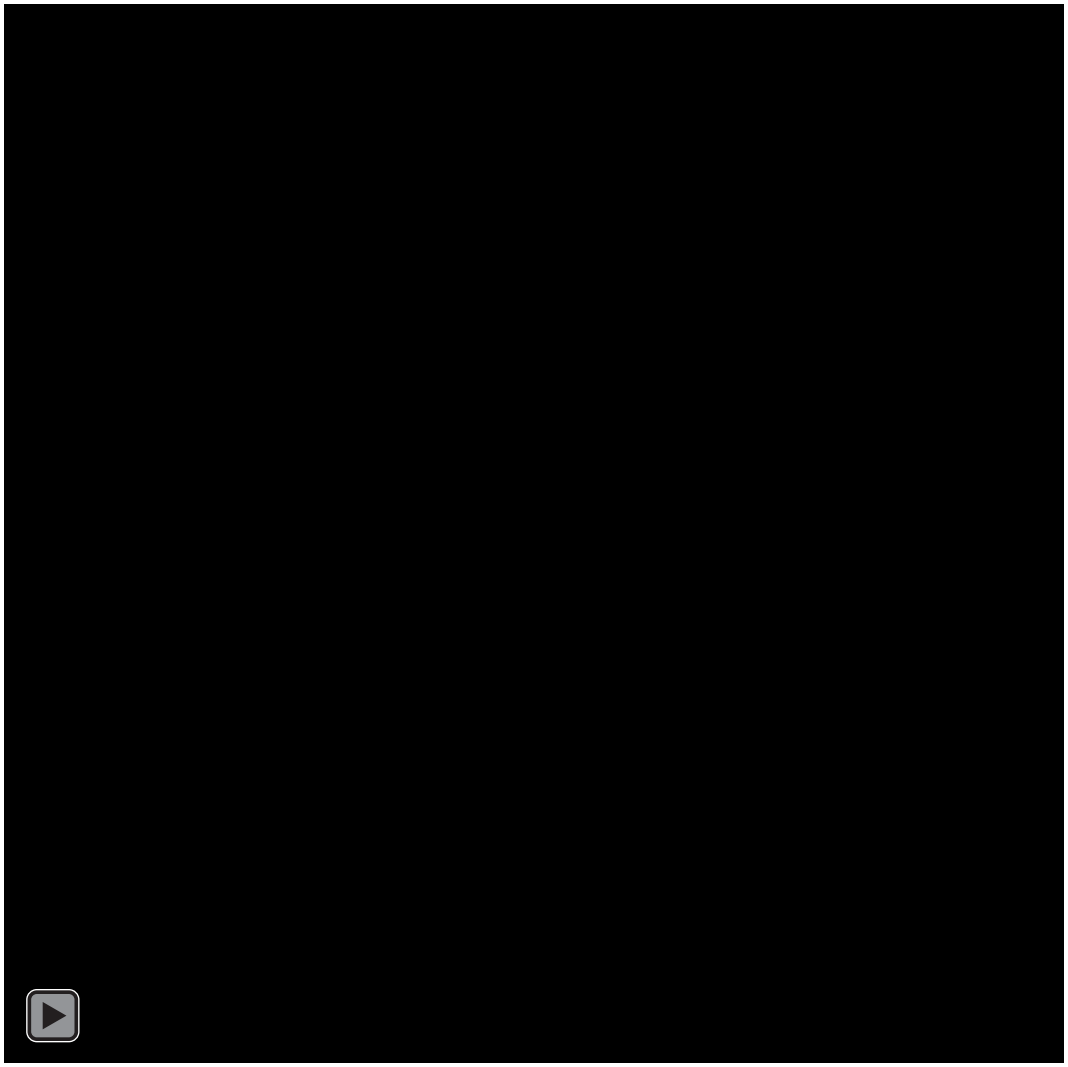
React to brain damage



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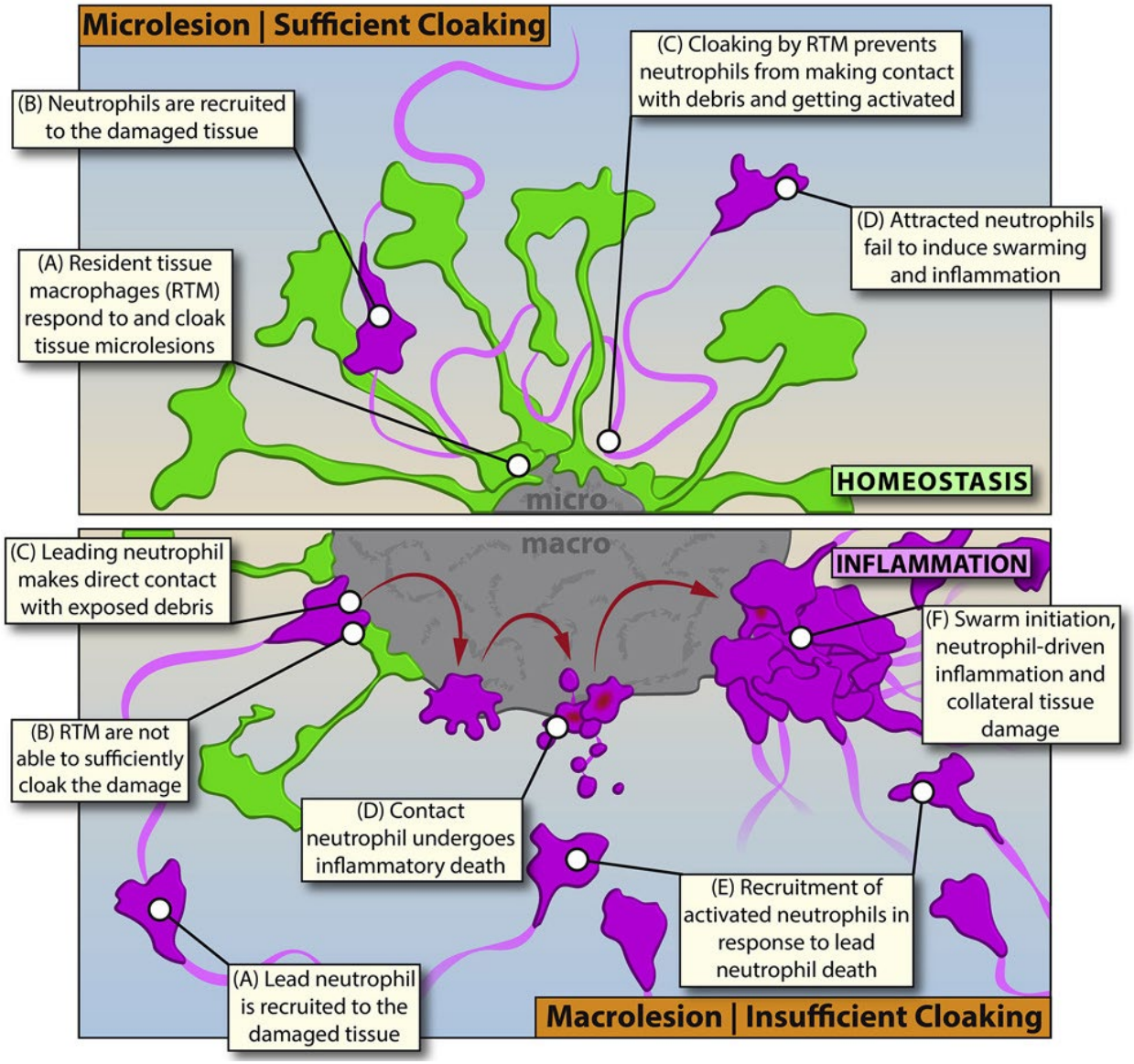
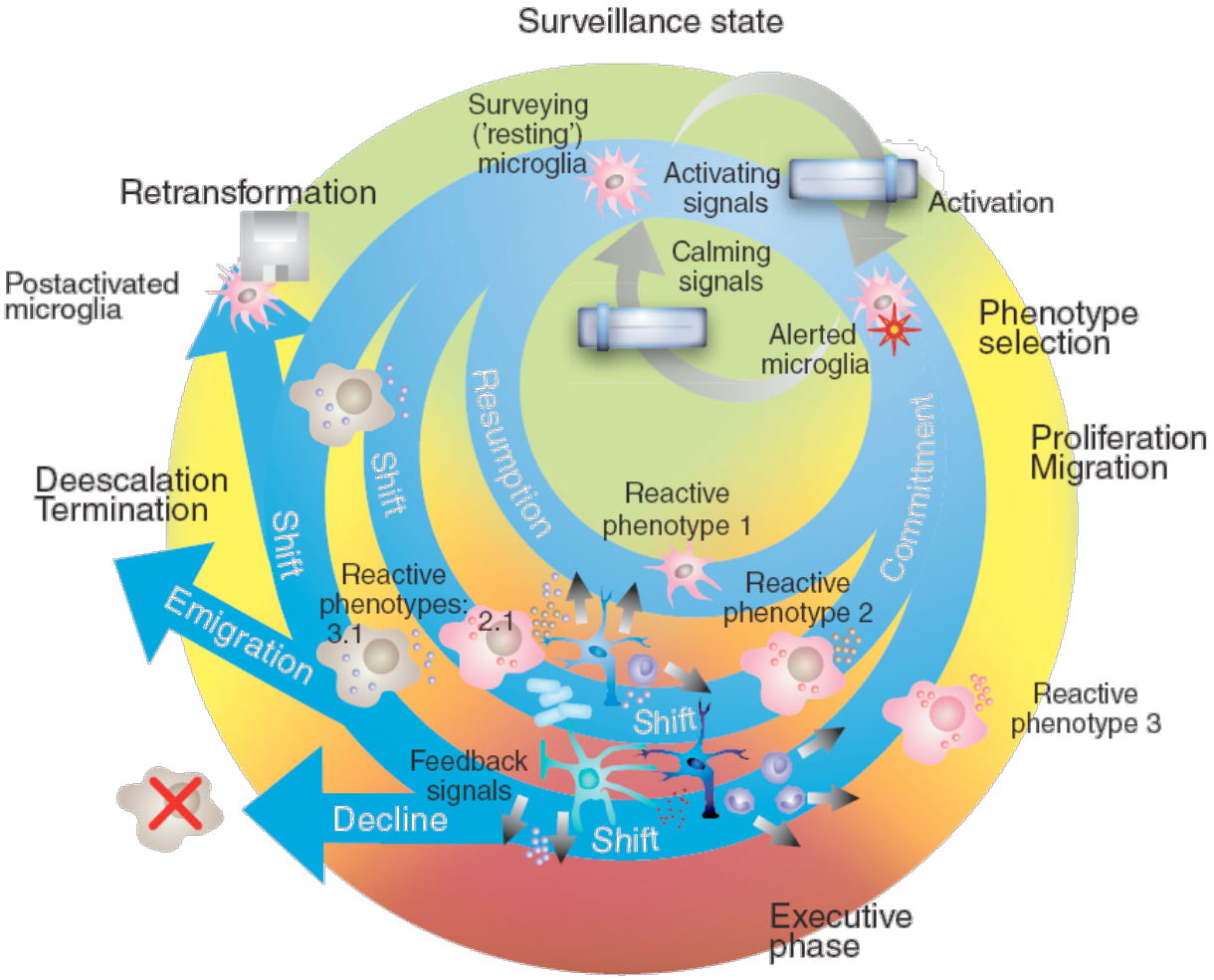
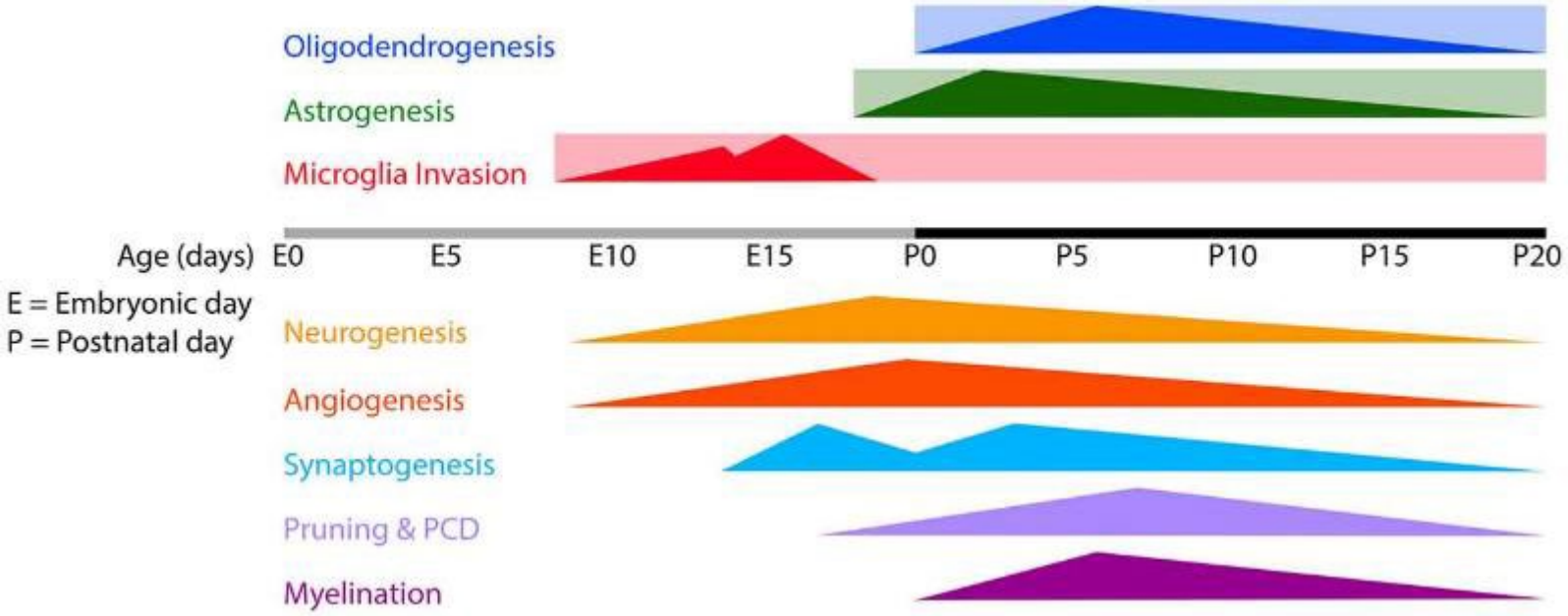


Uderhardt 2019

Resident immune cells of the brain: Activation phenotypes



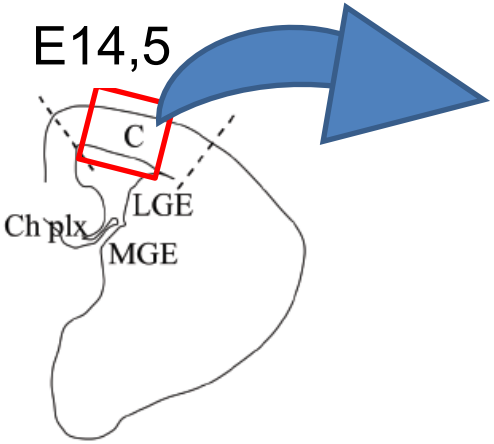
Microglia during development

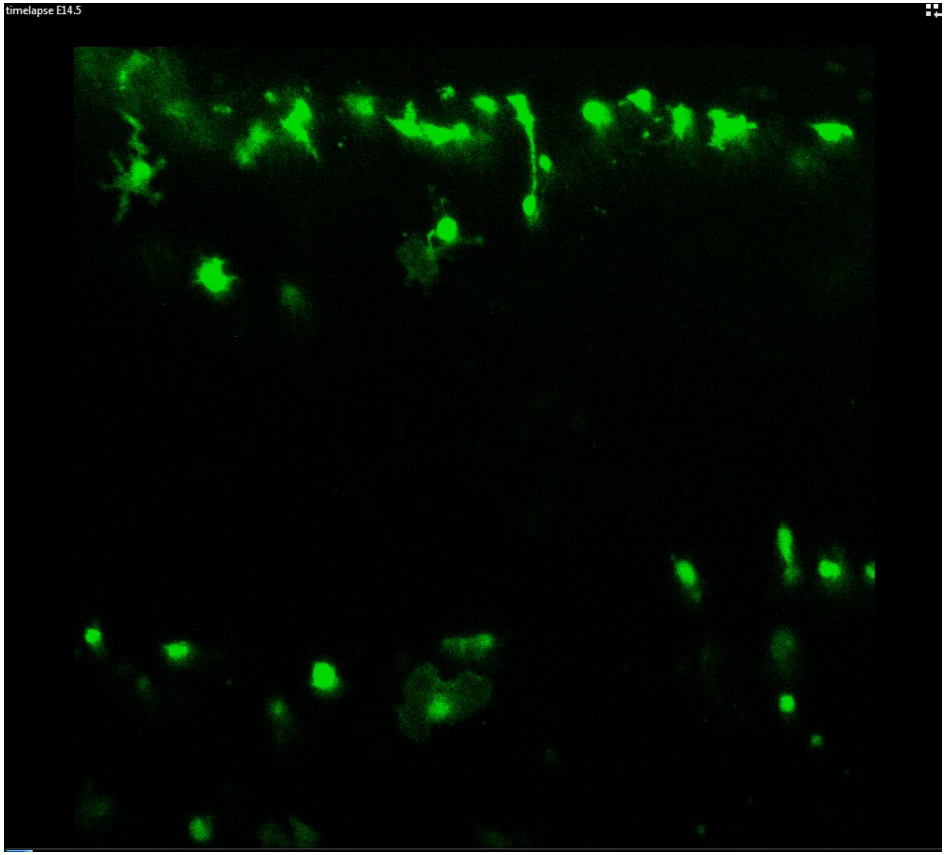


Reemst 2016

How do microglia migrate in the embryonic cortex?

CX3CR1
eGFP $^{+/+}$





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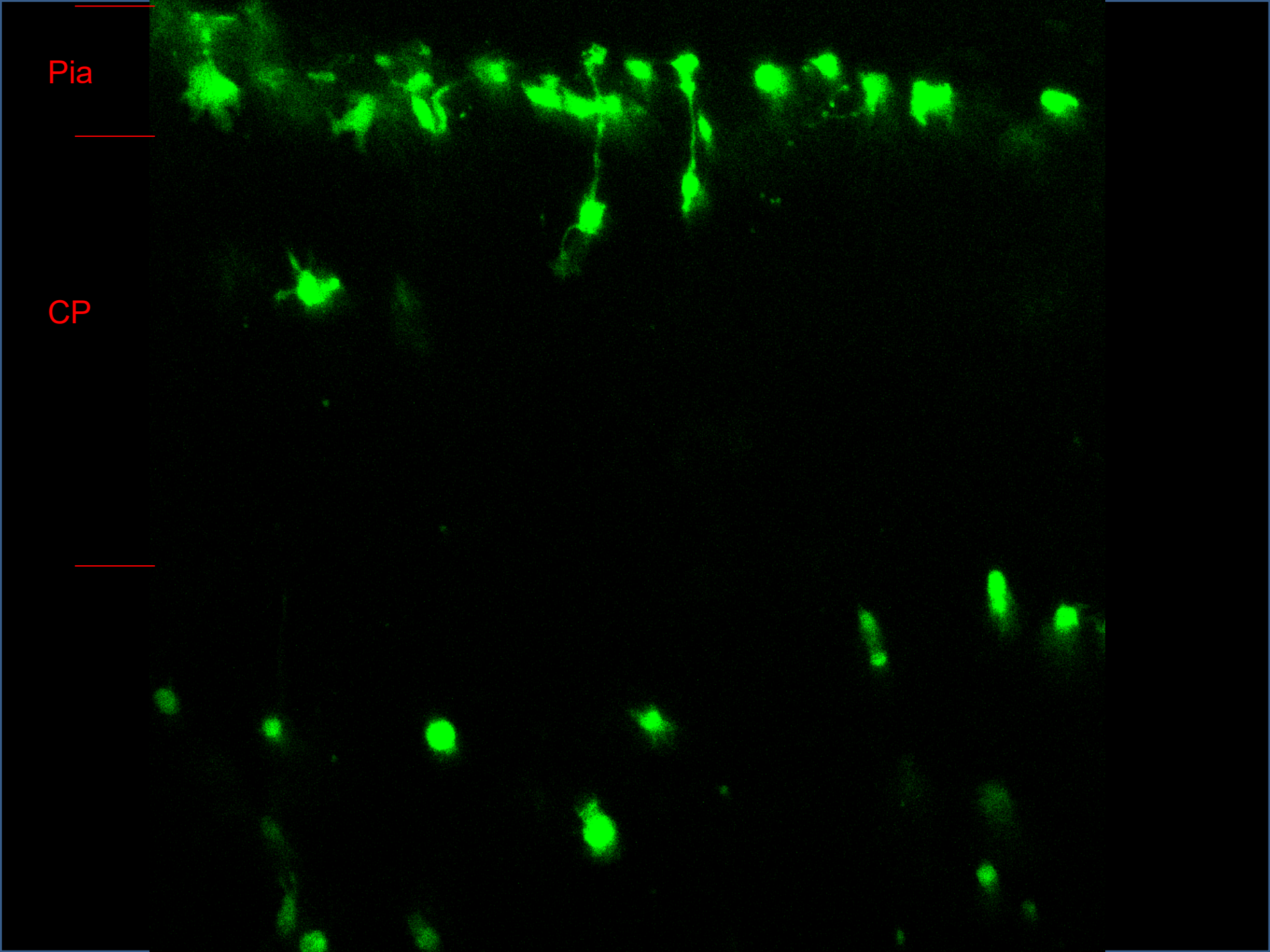
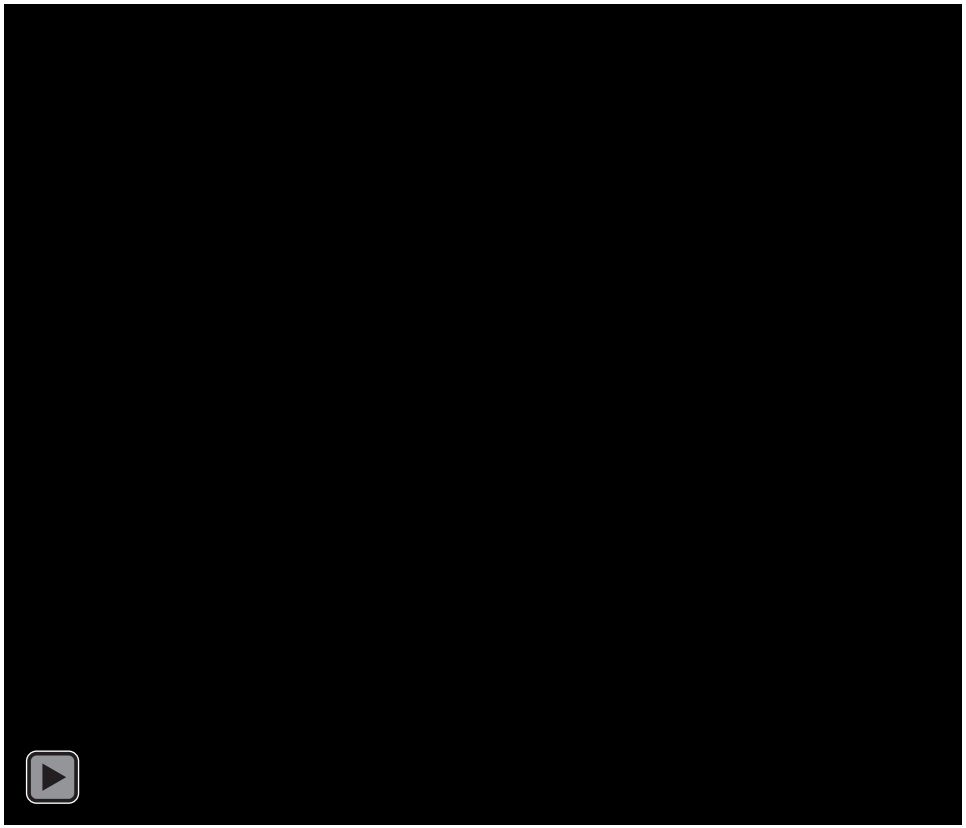

Pia
CP

Microglia tasks: Synaptic remodeling



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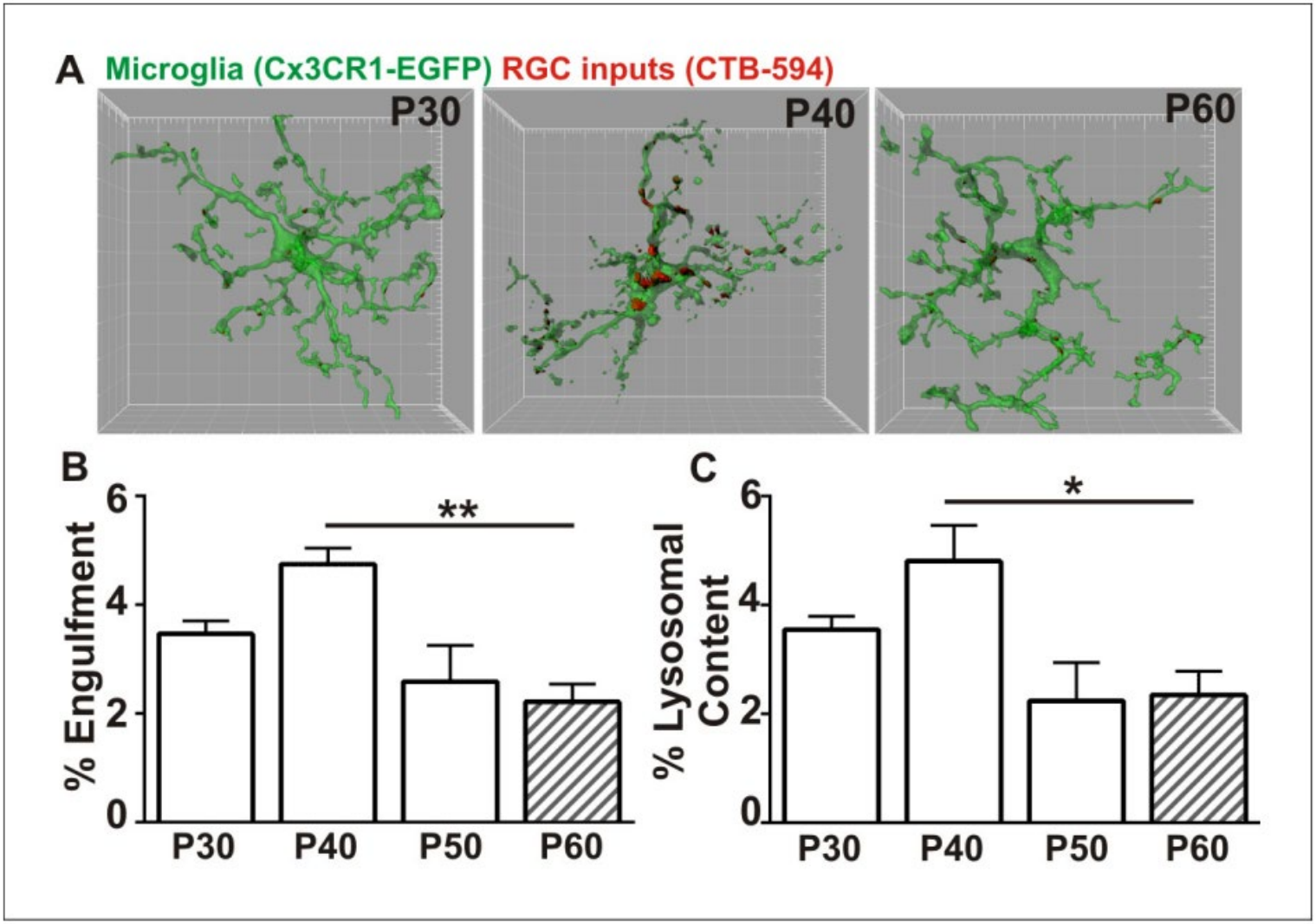
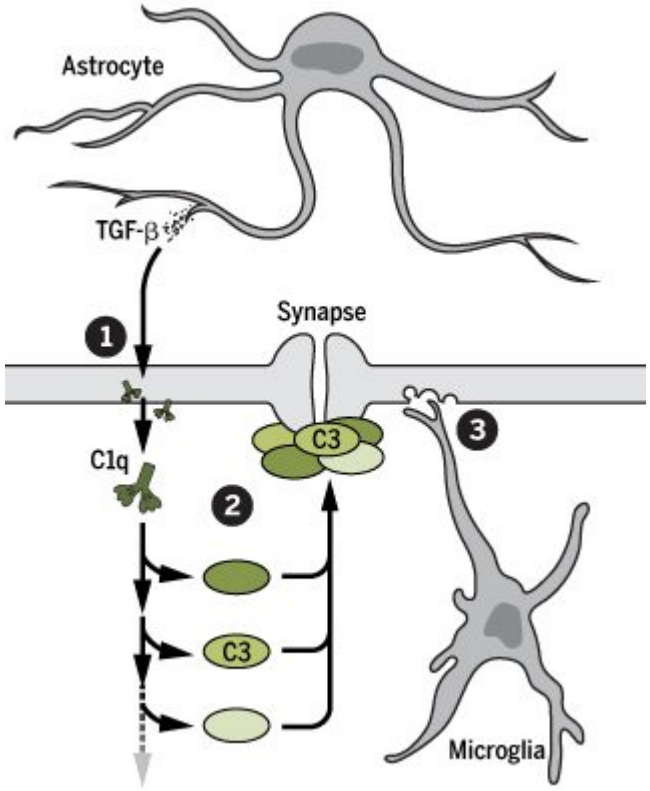
Developmental synaptic pruning



Schafer 2016

Complement dependent synaptic pruning

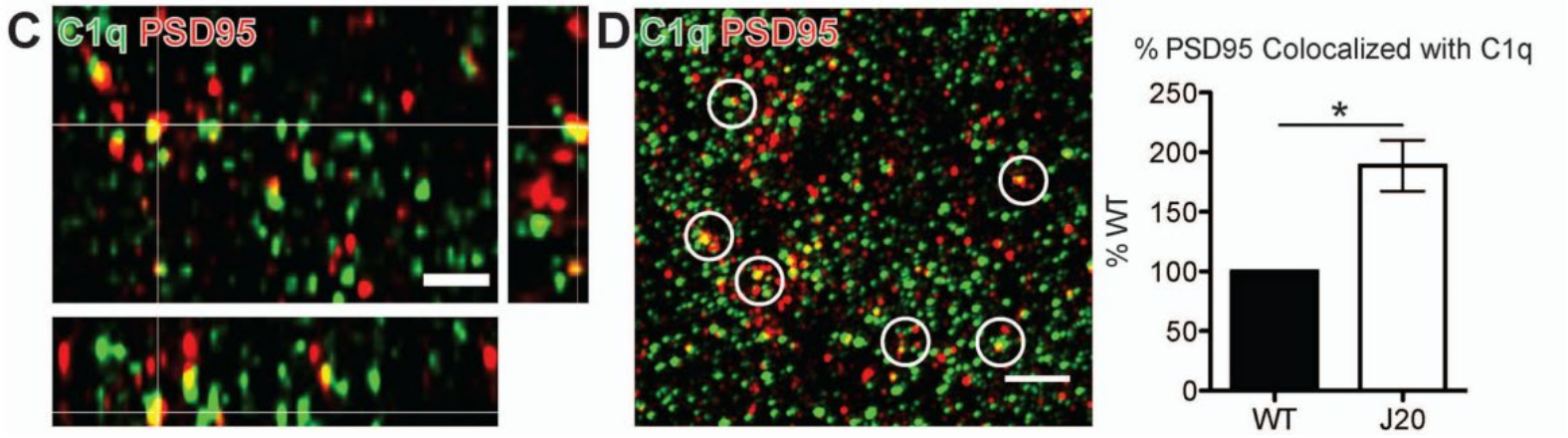


Complement system (C1q C3) marks synapses to be pruned

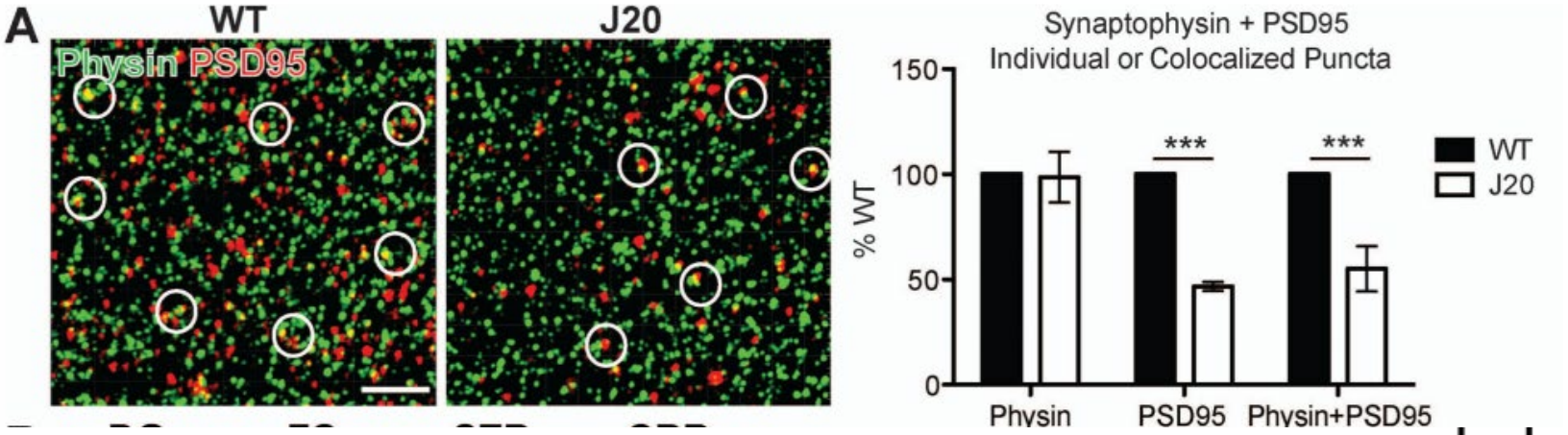
http://www.sciencemag.org/news/2016/08/woman-may-know-secret-saving-brain-s-synapses

Excessive synaptic pruning in disease

Complement marked synapses increased AD mice



Loss of synapses in AD mice



Hong 2016

Glia-Neuron and Glia-Glia cross talk

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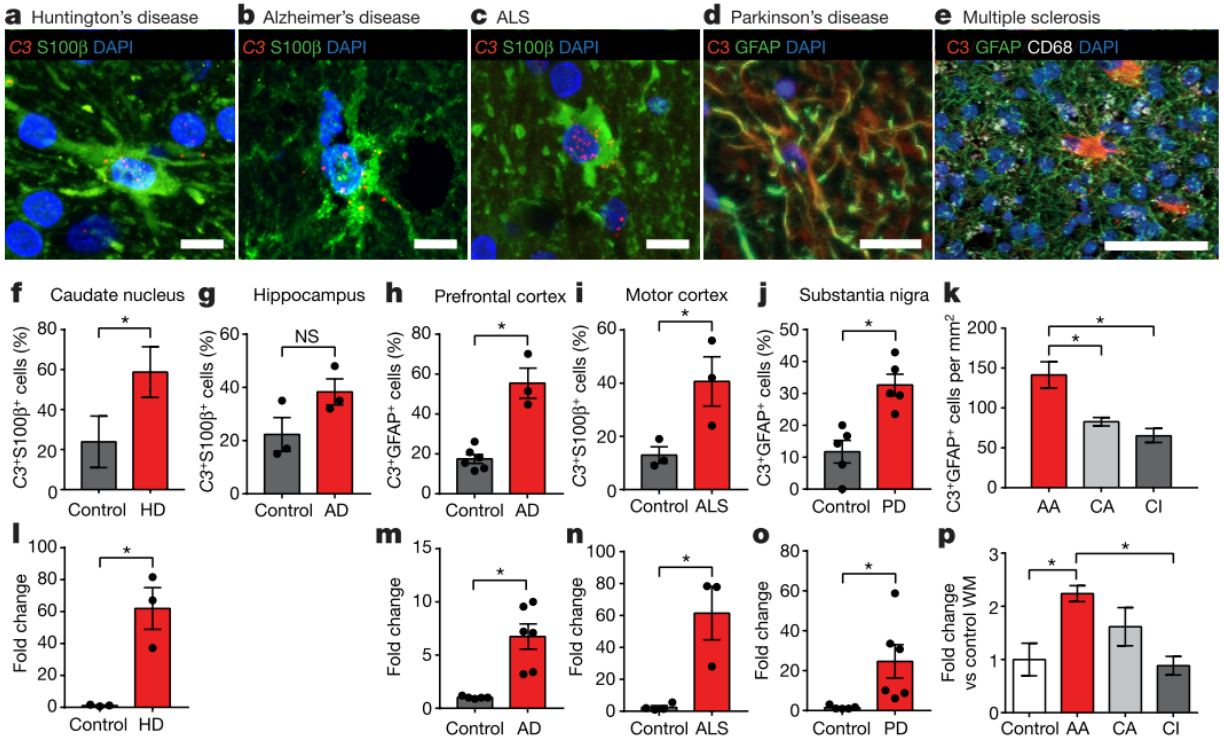
KNOWLEDGE IN ACTION

Microglia-astrocyte cross talk

doi:10.1038/nature21029

Neurotoxic reactive astrocytes are induced by activated microglia

Shane A. Liddelow[1,2], Kevin A. Guttenplan[1], Laura E. Clarke[1], Frederick C. Bennett[1,3], Christopher J. Bohlen[2], Lucas Schirmer[4,5], Mariko L. Bennett[1], Alexandra E. Münch[1], Won-Suk Chung[6], Todd C. Peterson[7], Daniel K. Wilton[8], Arnaud Frouin[8], Brooke A. Napier[9], Nikhil Panicker[10,11,12], Manoj Kumar[10,11,12], Marion S. Buckwalter[7], David H. Rowitch[13,14], Valina L. Dawson[10,11,12,15,16], Ted M. Dawson[10,11,12,16,17], Beth Stevens[8] & Ben A. Barres[1]



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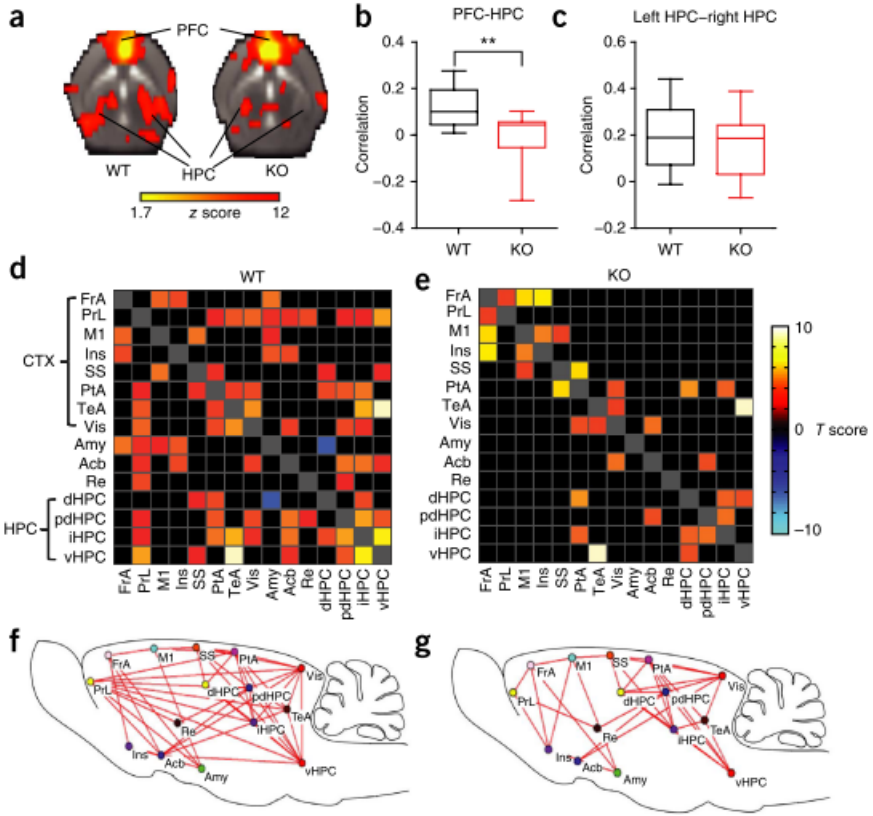
Neuron-microglia cross talk

nature neuroscience

Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior

Yang Zhan[1,8], Rosa C Paolicelli[1,8], Francesco Sforazzini[2,3], Laetitia Weinhard[1], Giulia Bolasco[1], Francesca Pagani[4], Alexei L Vyssotski[5], Angelo Bifone[2], Alessandro Gozzi[2], Davide Ragozzino[6,7] & Cornelius T Gross[1]



CX3CR1 → neuro glia cross talk

CX3CR1 KO
→ reduced synaptic events
→ Reduced fMRI connectivity

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Models to study Glia

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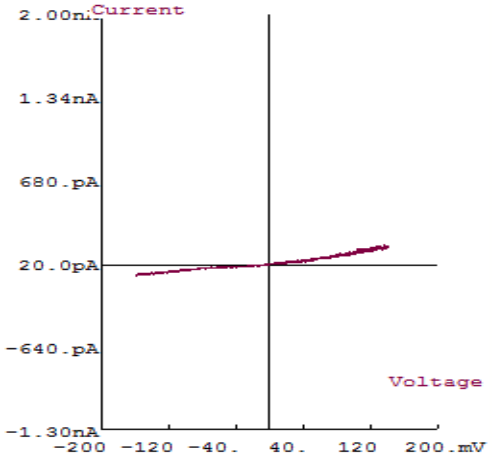
Glial Cell Models

- Cell lines
  - BV2, RBA-2, CG-4…
- Primary cell cultures
  - Shake off technique
  - FACS, MACS,…
- iPSC derived cells

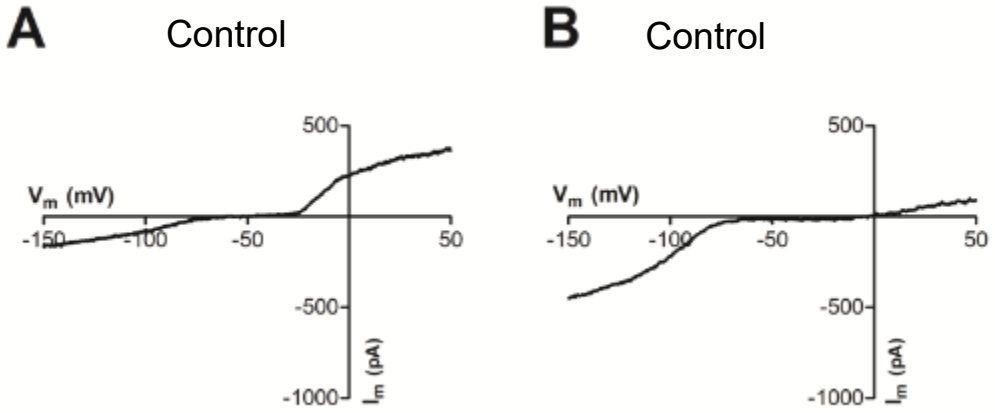
RELEVANCE???

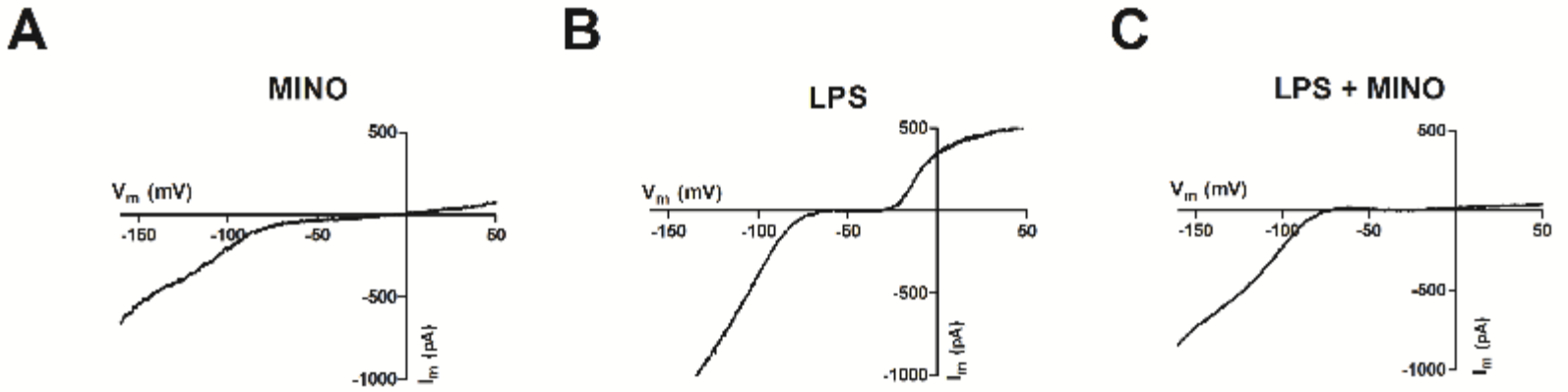
Primary cultured microglial cells

Brain slice



Primary cultured microglia





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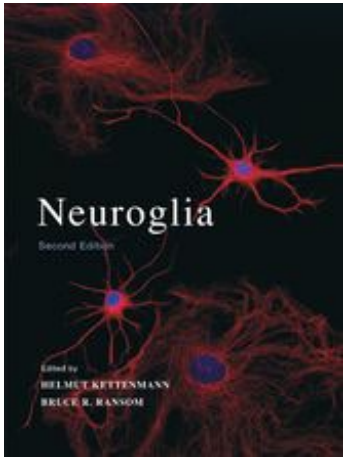
Glial Mouse Models

- Mouse reporter lines
  - Microglia: CX3CR1-eGFP, fmp
  - Astrocytes: GFAP-CFP
  - Oligodendrocytes: CNP-GFP
- IHC/markers
  - Microglia: Iba-1, TMEM119, CSF1R, Sal1, P2Y12
  - Astrocytes: GFAP, S100β, CD144
  - Oligodendrocytes: NG2, O4, MBP, PLP (different.)
- Depletion models
  - Microglia: Difteria tox, CSF1R AB, PU1 KO, clodronate, PLX compounds
  - Astrocytes: GFAP Cre?
  - Oligodendrocytes: cuprisone model,…

Literature



- "Neuroglia"
  - Helmut Kettenmann and Bruce R. Ransom
- "Reactive astrocyte nomenclature, definitions, and future directions." Escartin et al Nat Neurosci. 2021
- "Defining Microglial States and Nomenclature: A Roadmap to 2030" *Cell 'Sneak Peek' P*aolicelli et al

Questions? → bert.brone@uhasselt.be