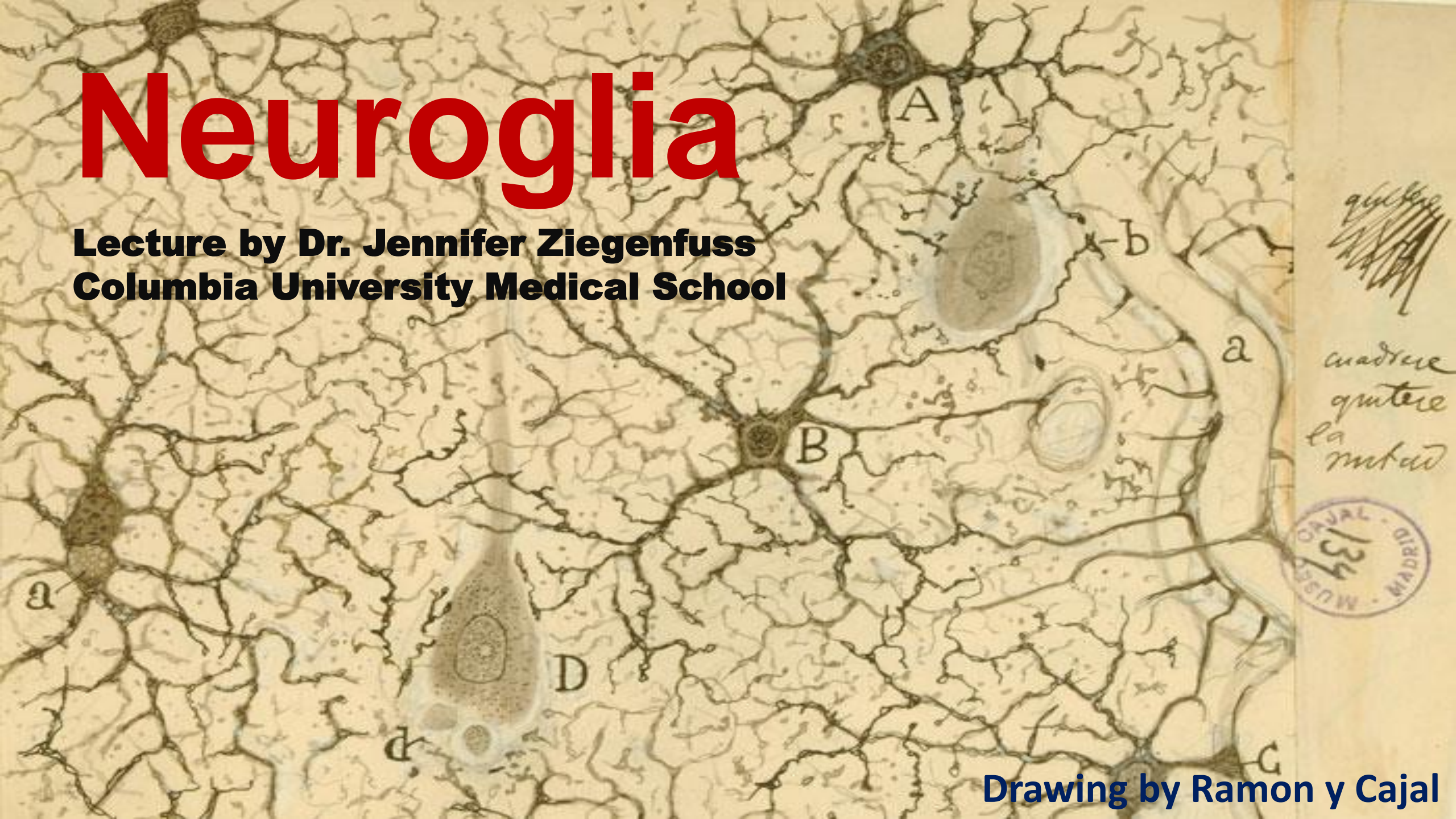


# Neuroglia

Lecture by Dr. Jennifer Ziegenfuss  
Columbia University Medical School

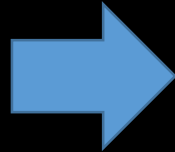
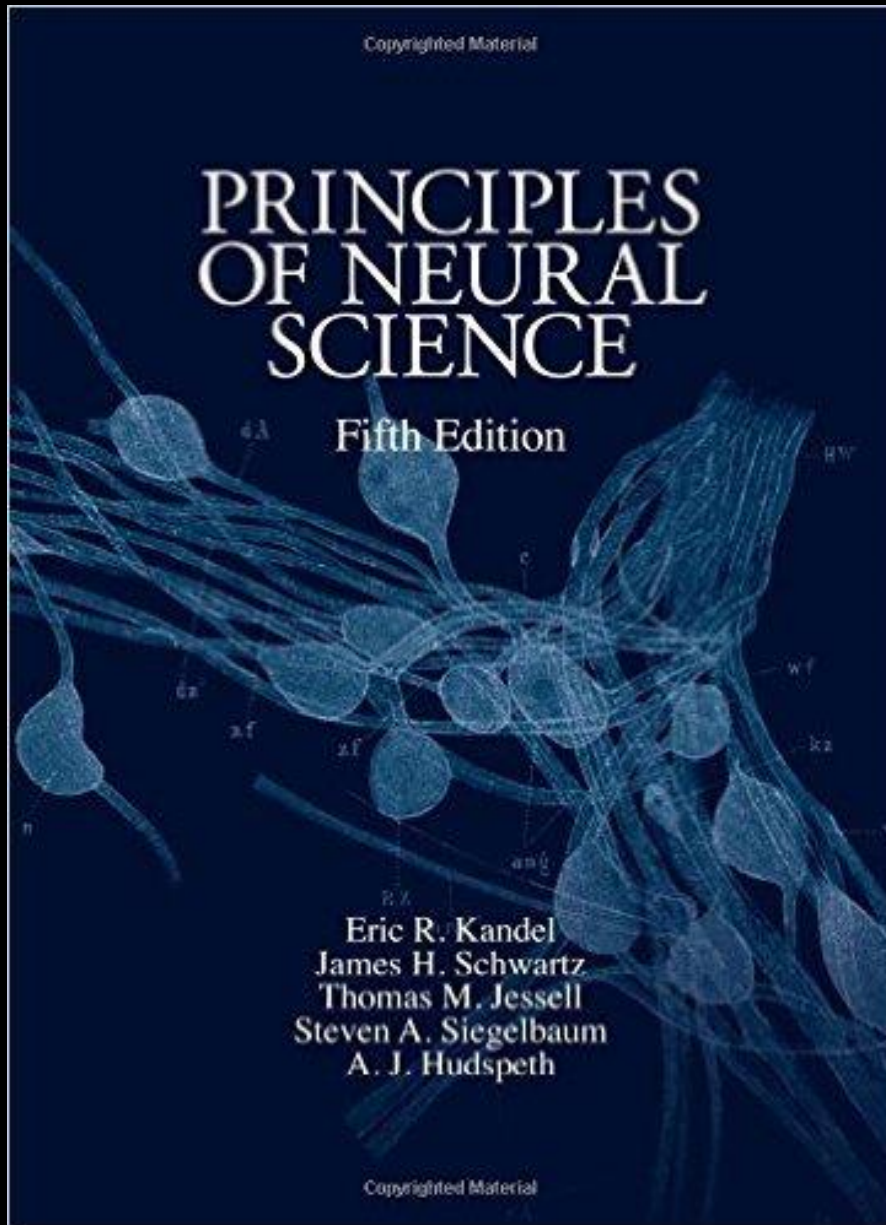


Drawing by Ramon y Cajal





441 pages long.....



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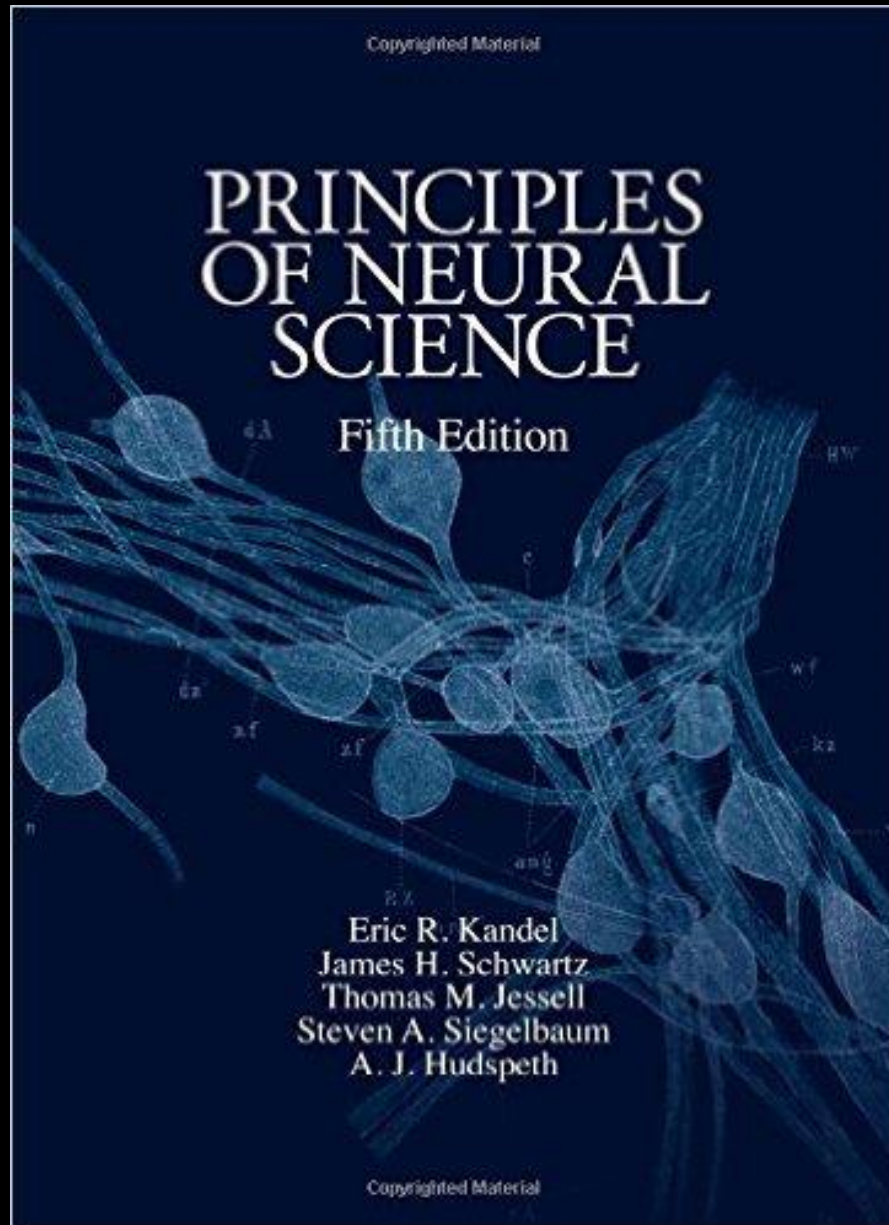
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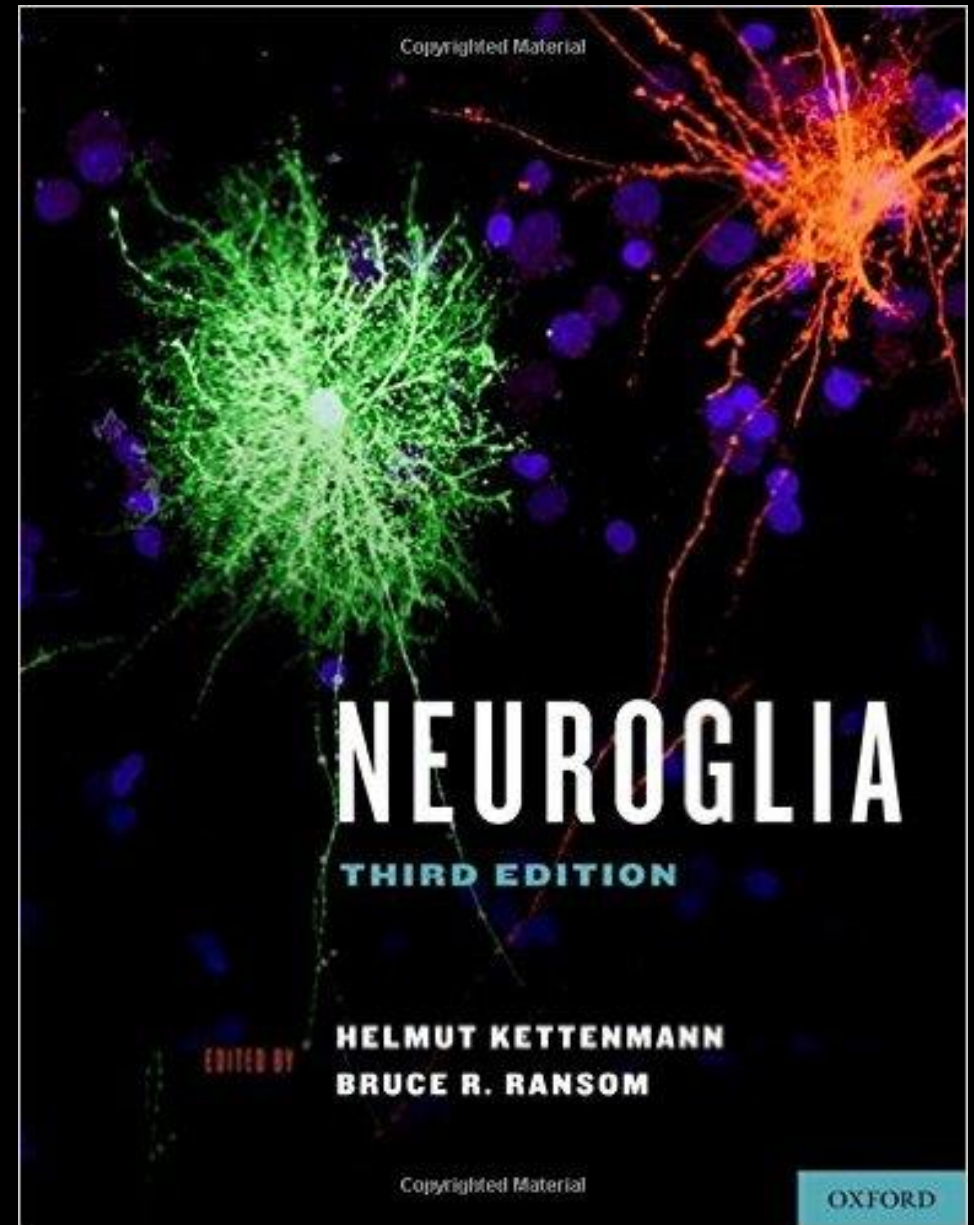
Copyrighted M

But only **THREE** pages dedicated to glial cells.

441 pages long....



599 pages long....

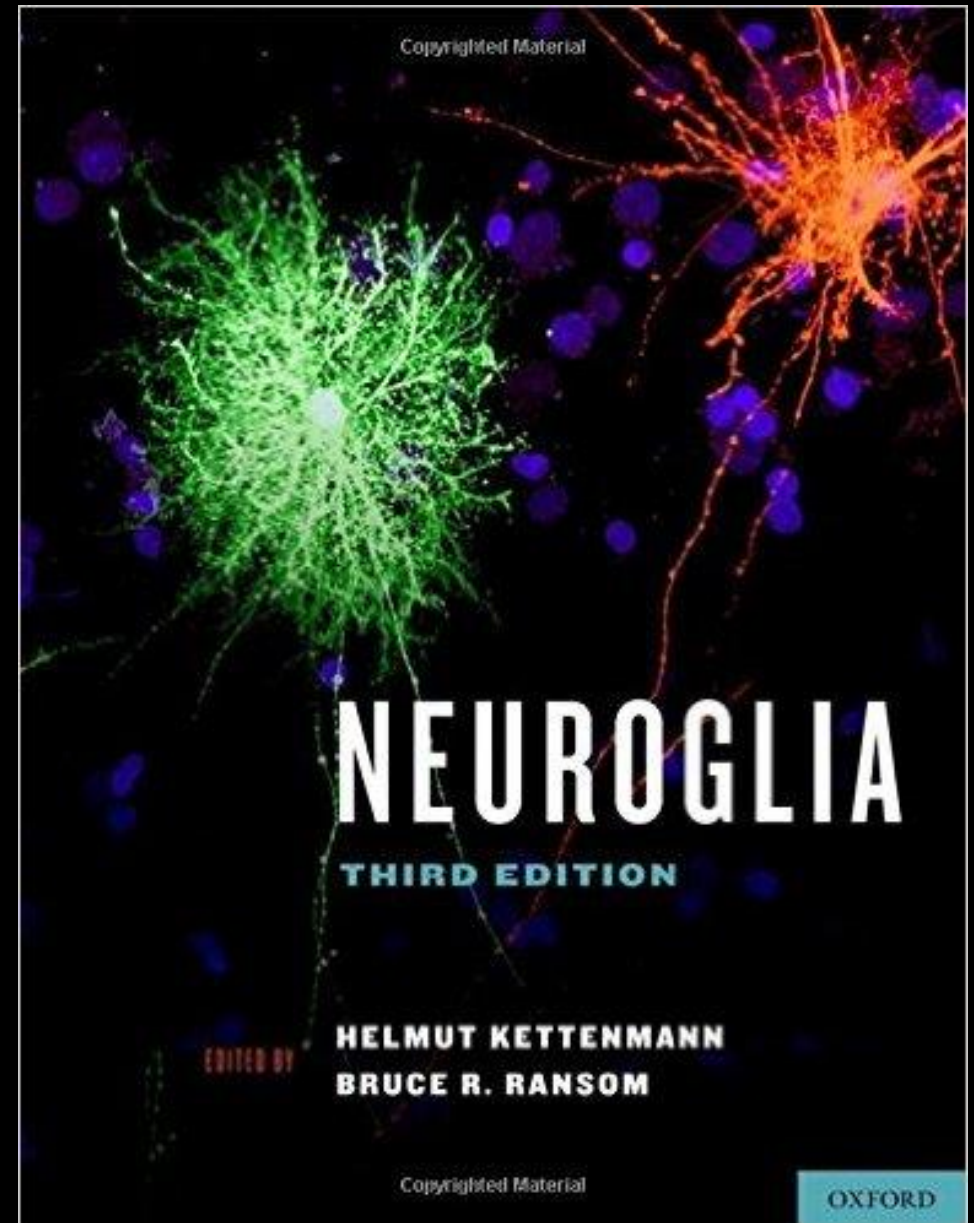
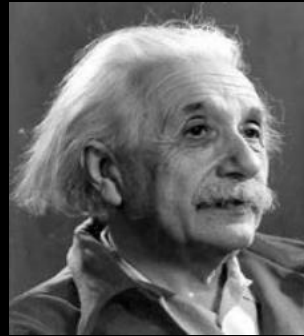




599 pages long.....

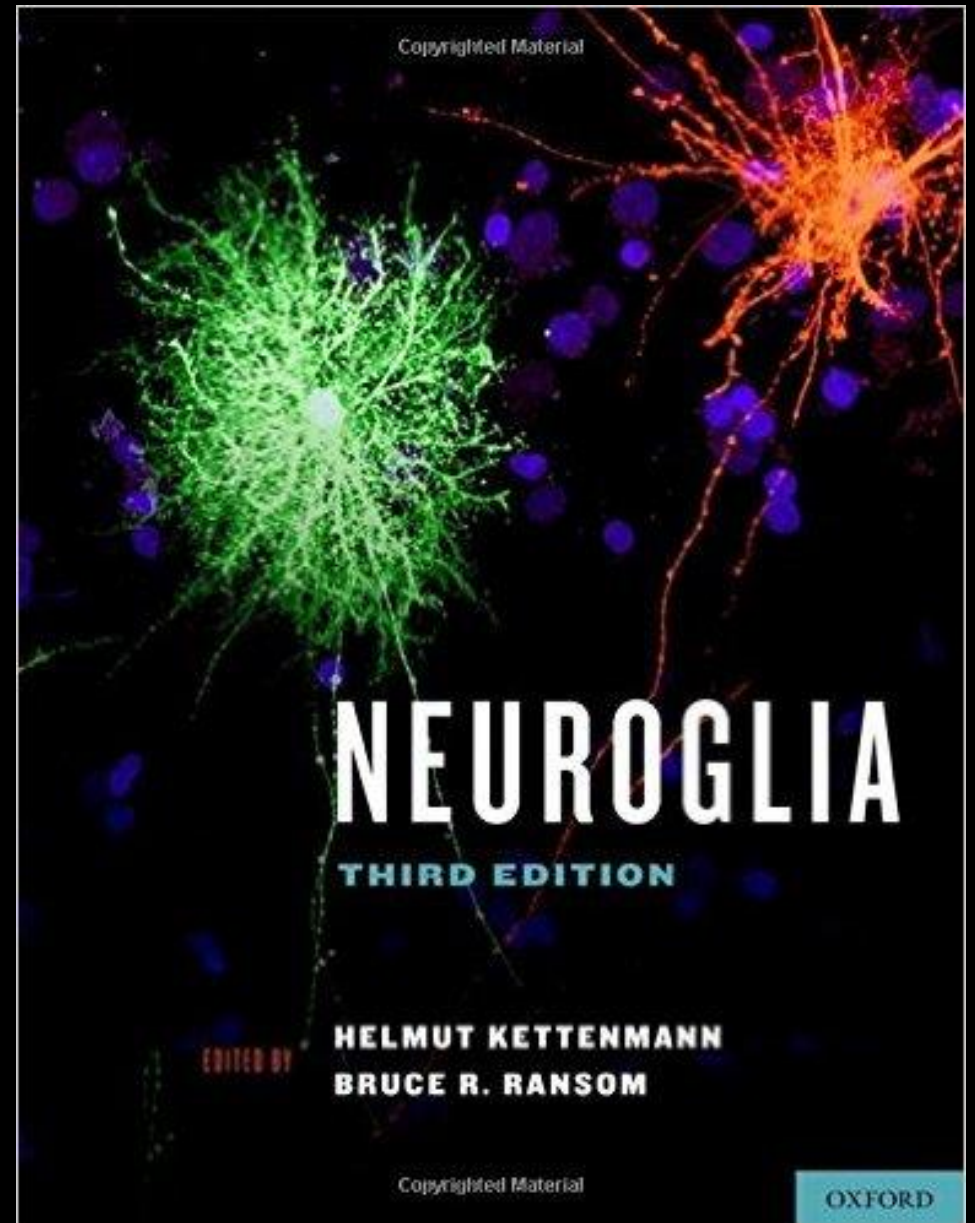
## Why so long?

- There are roughly equal number of neurons and glia in the CNS:
  - 98 billion neurons to 96 billion glia (+ or – 9 billion cells)
  - This guy on the right had an abnormally higher amount of glia than typical.
- There are SIX different glial subtypes.
  - 4 in CNS
  - 2 in PNS
- They do way more than just act as “glue”.

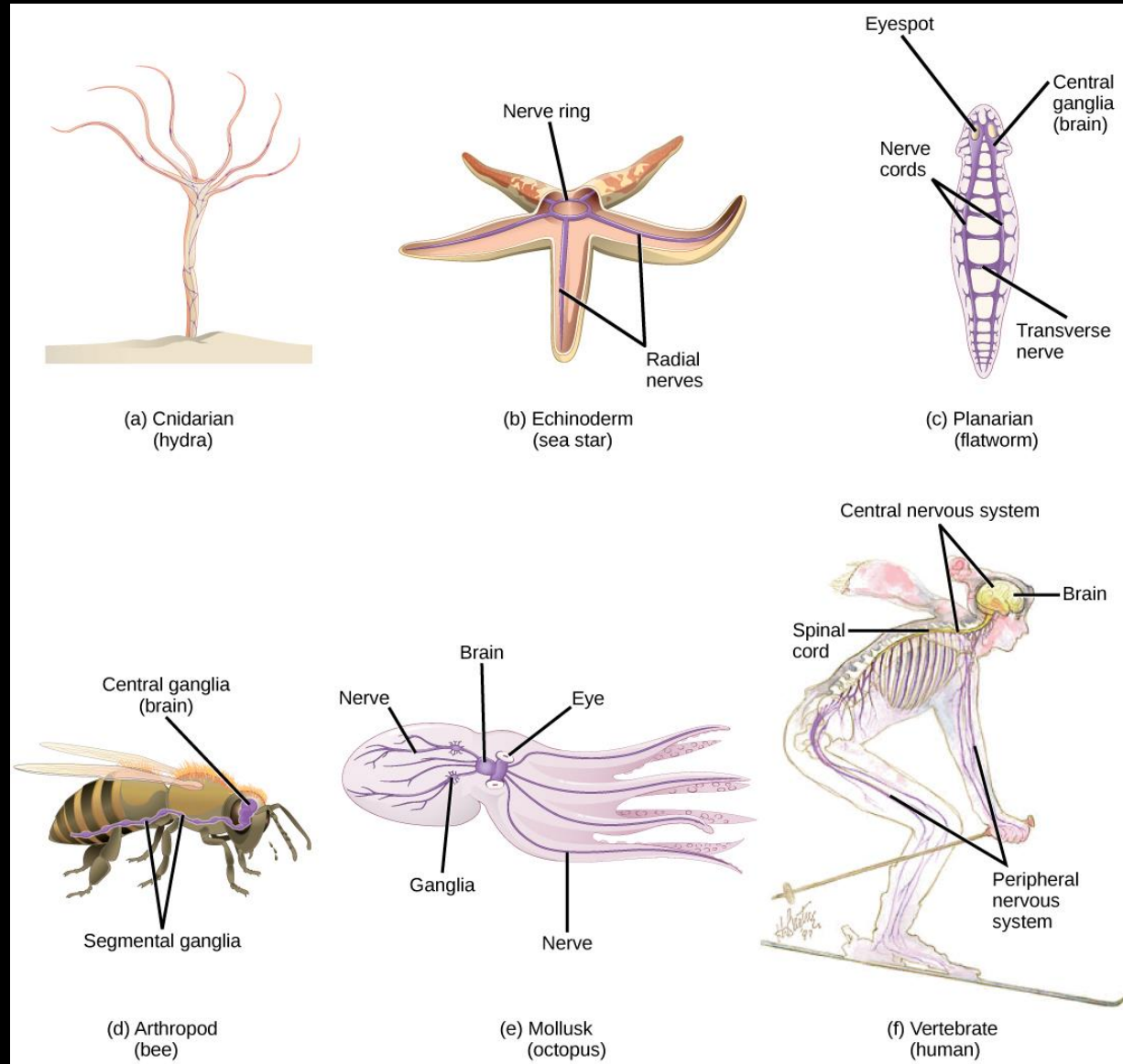


599 pages long.....

I think it's about  
time to become  
“glia-evangelized”



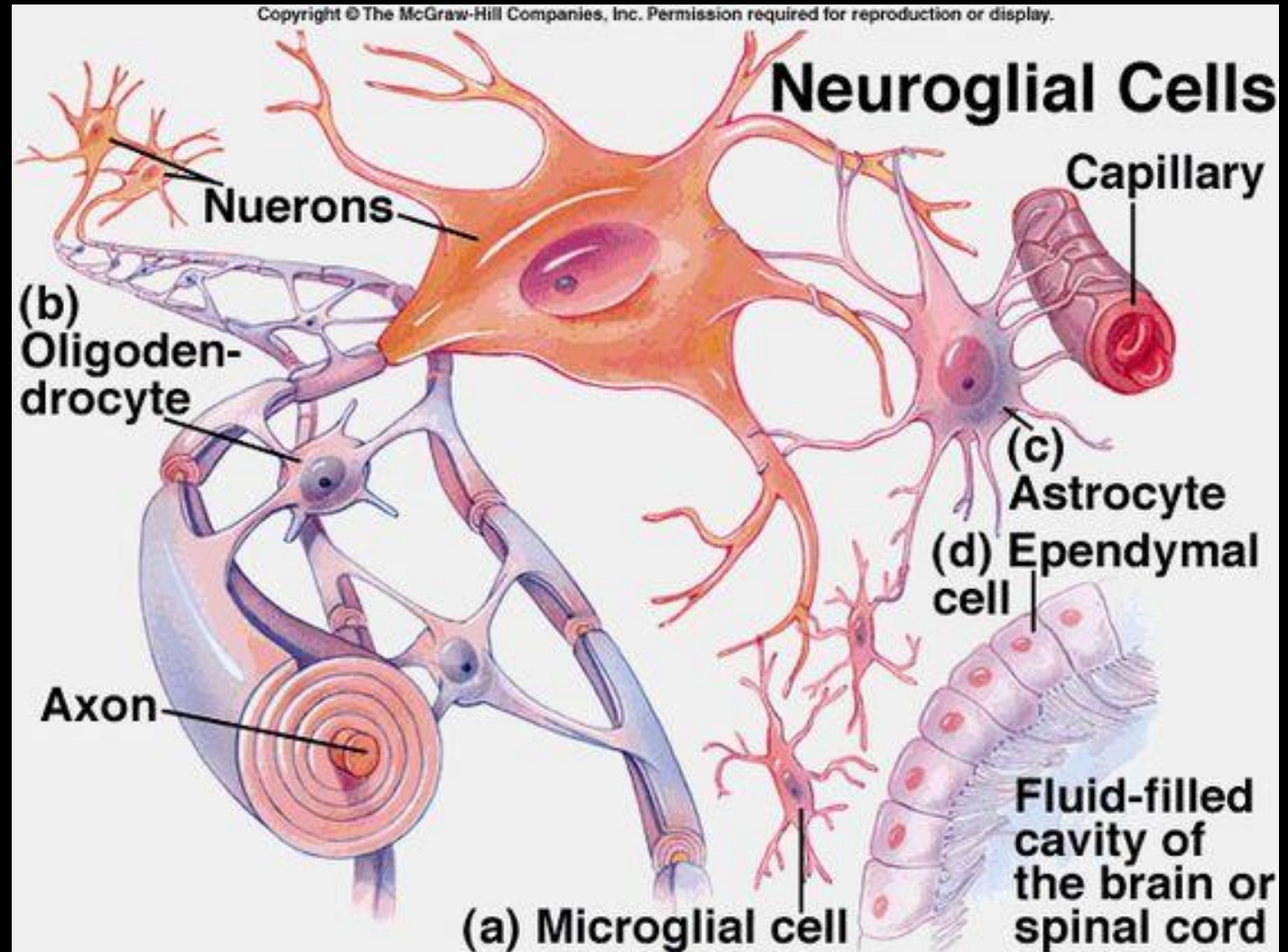
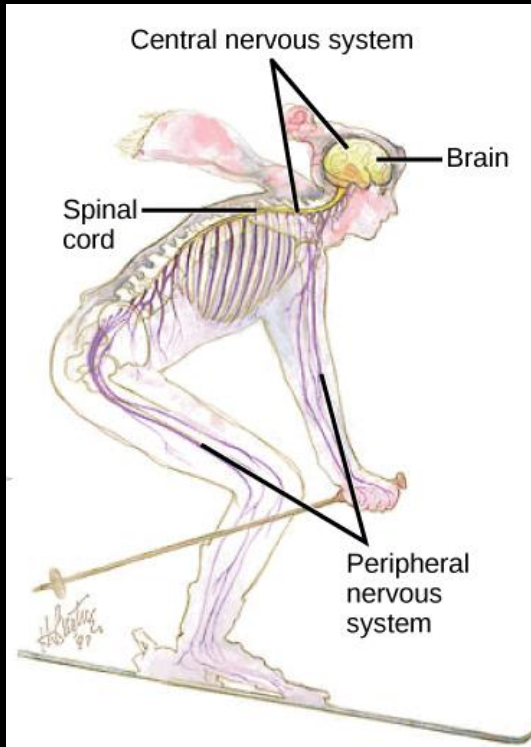
# Every living creature has “signaling cells” but not as many have “brains”



# Neuroglia roles in nervous system function



# What are the glia in the human CNS?

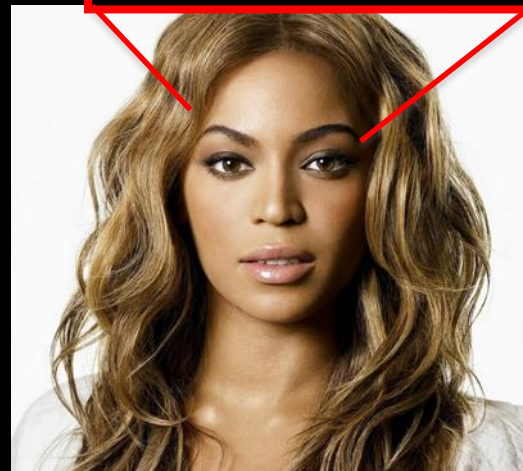
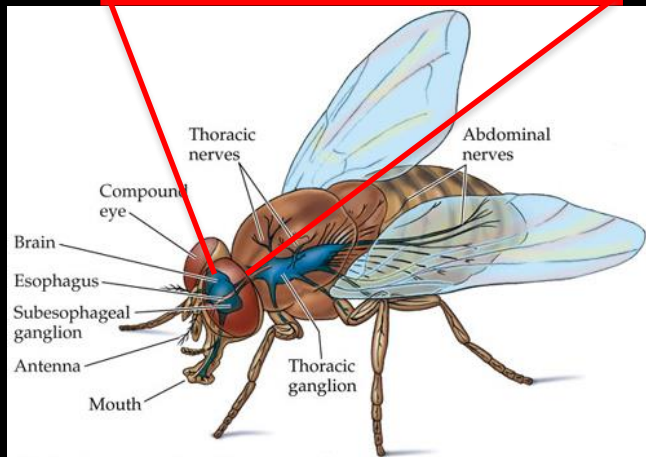
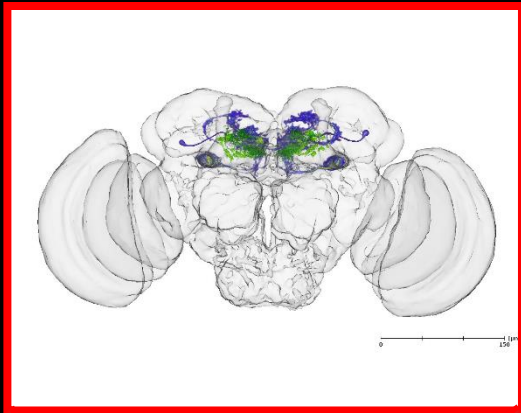


# Using fruit flies to study glia?

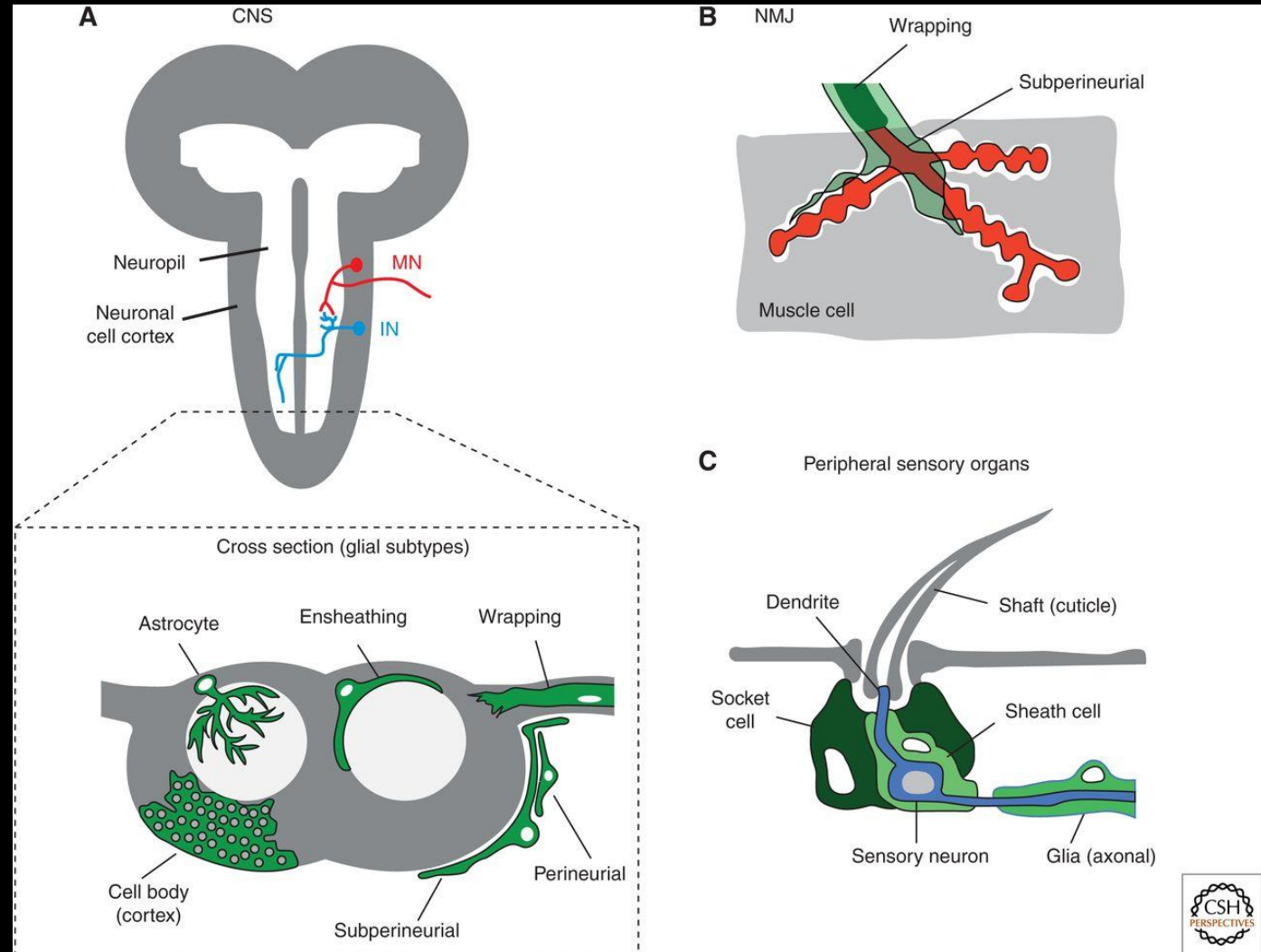
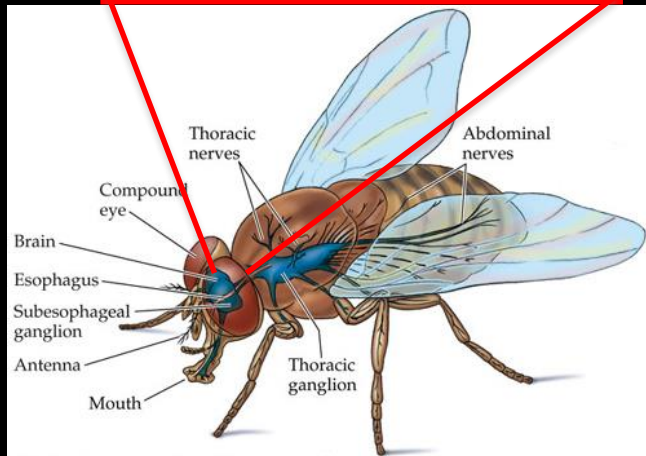
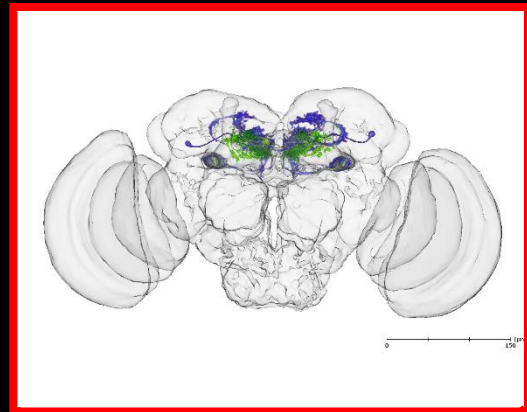
100,000 neurons  
(30% all brain cells are glia)  
14,000 genes

~100 billion neurons  
(50% all brain cells are glia)  
24,000 genes

- Fruit flies share 60% of its DNA with humans.
- 75% of all human disease-causing genes in humans are also found in fruit flies.
- Fruit flies have roughly same glia subtypes as mammals/humans

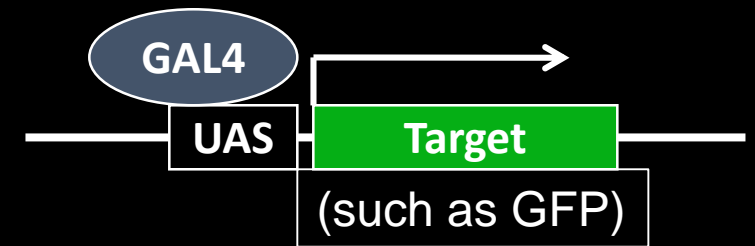
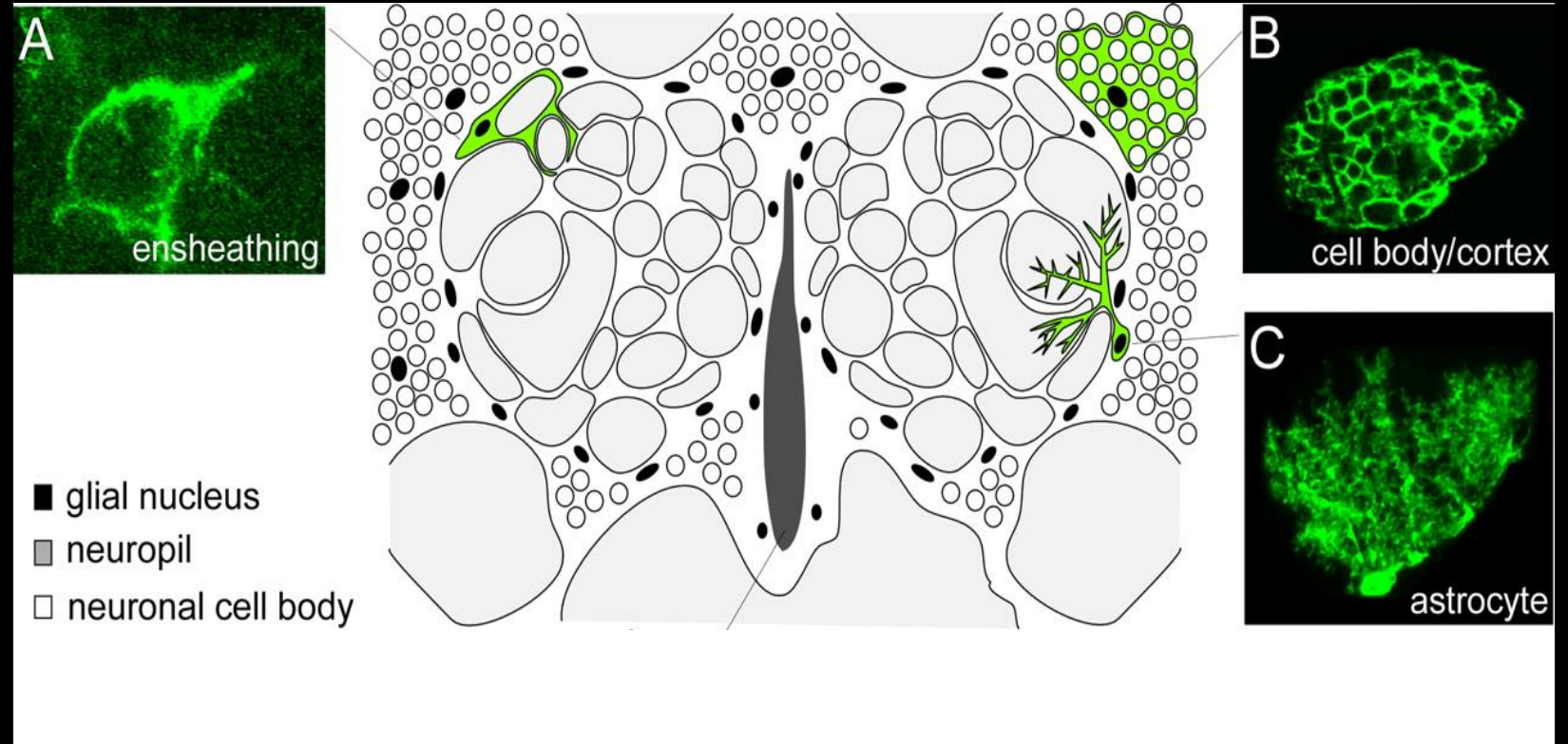
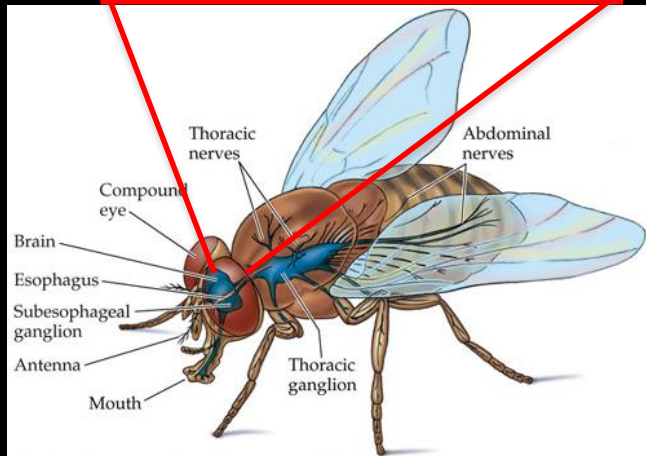
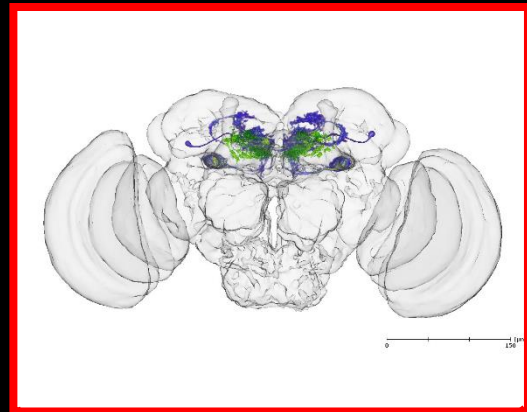


# Types of glia in the fruit fly



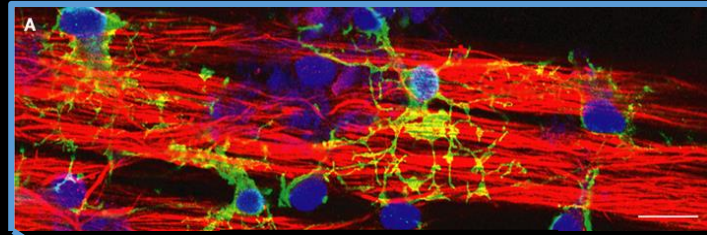


# Types of glia in the fruit fly

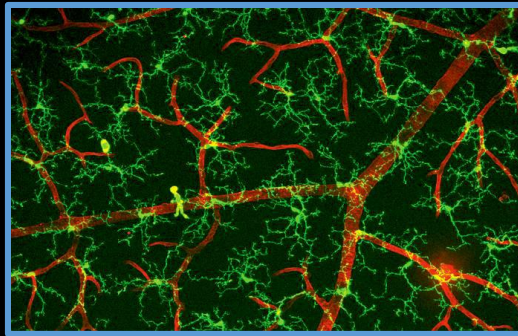


# Glia and the brain

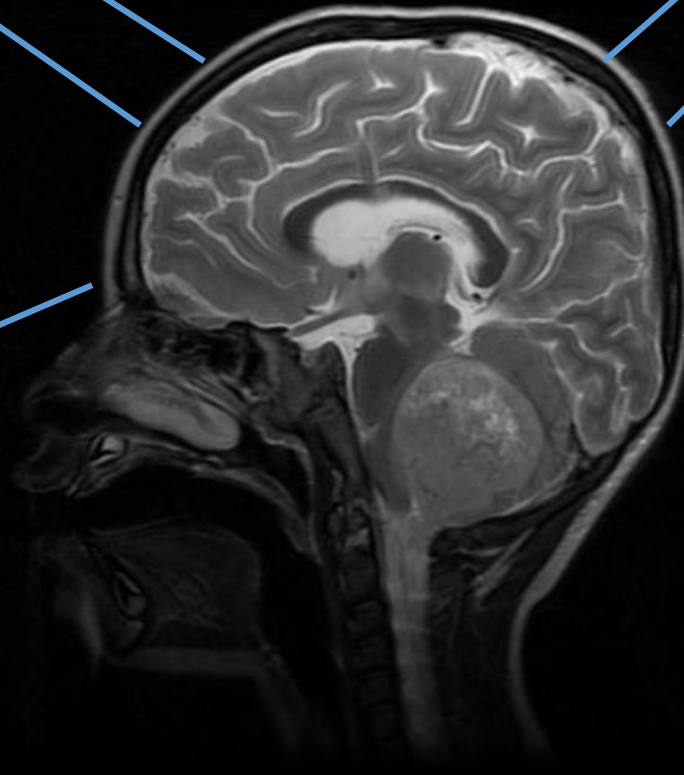
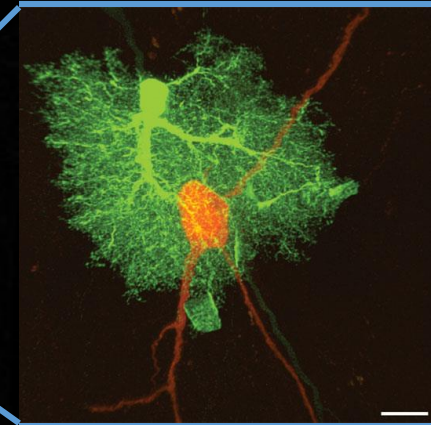
oligodendrocytes



microglia



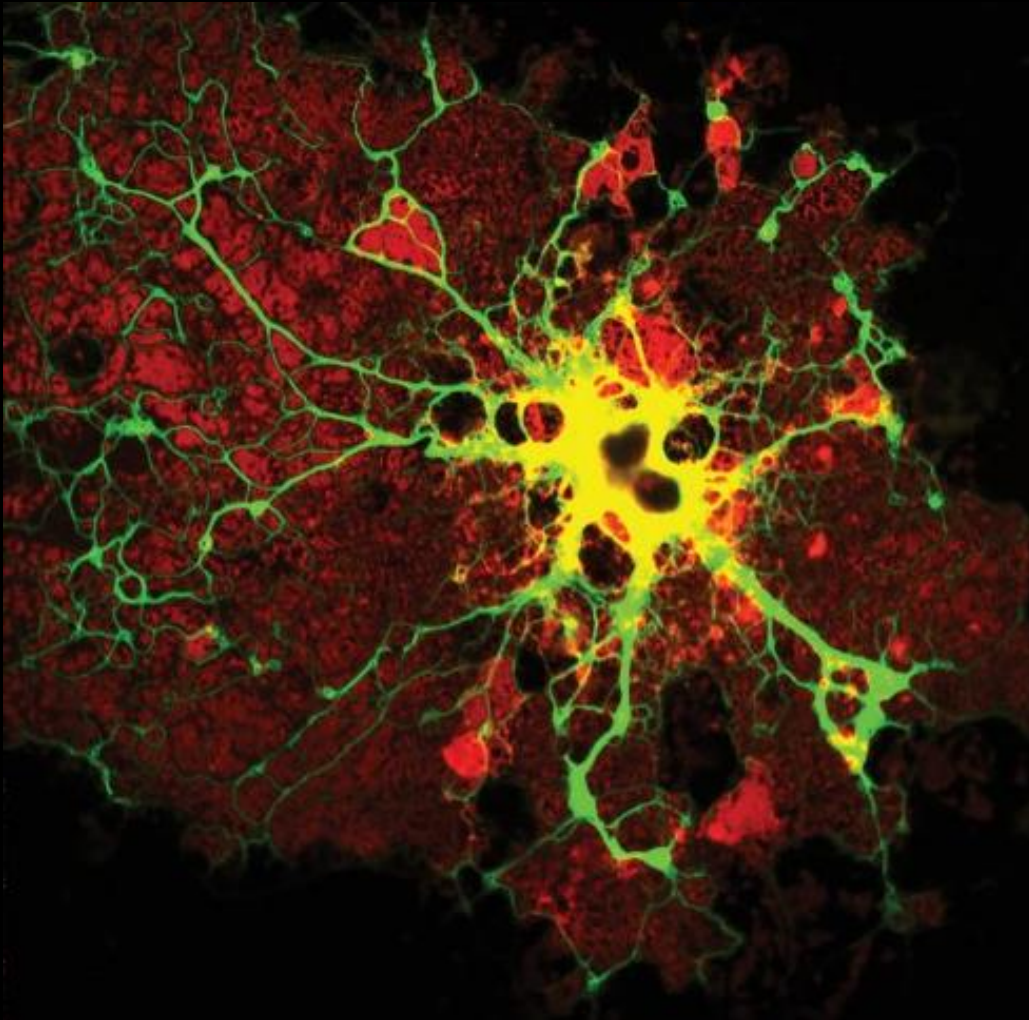
astrocytes



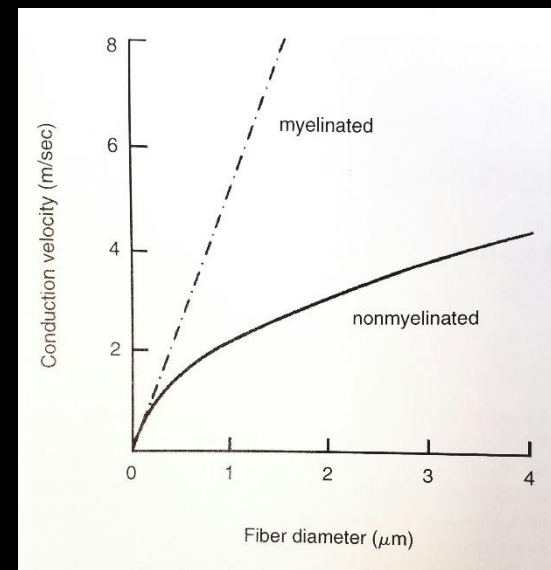
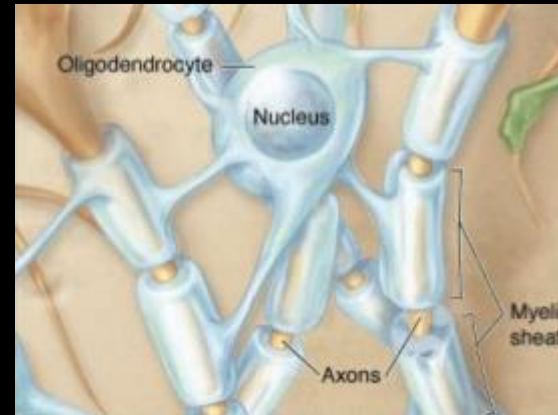


# Oligodendrocytes

- Oligodendrocytes, which are continuously remodeling the myelin, and thus finely tuning axonal conduction velocity, in response to neuronal activity.



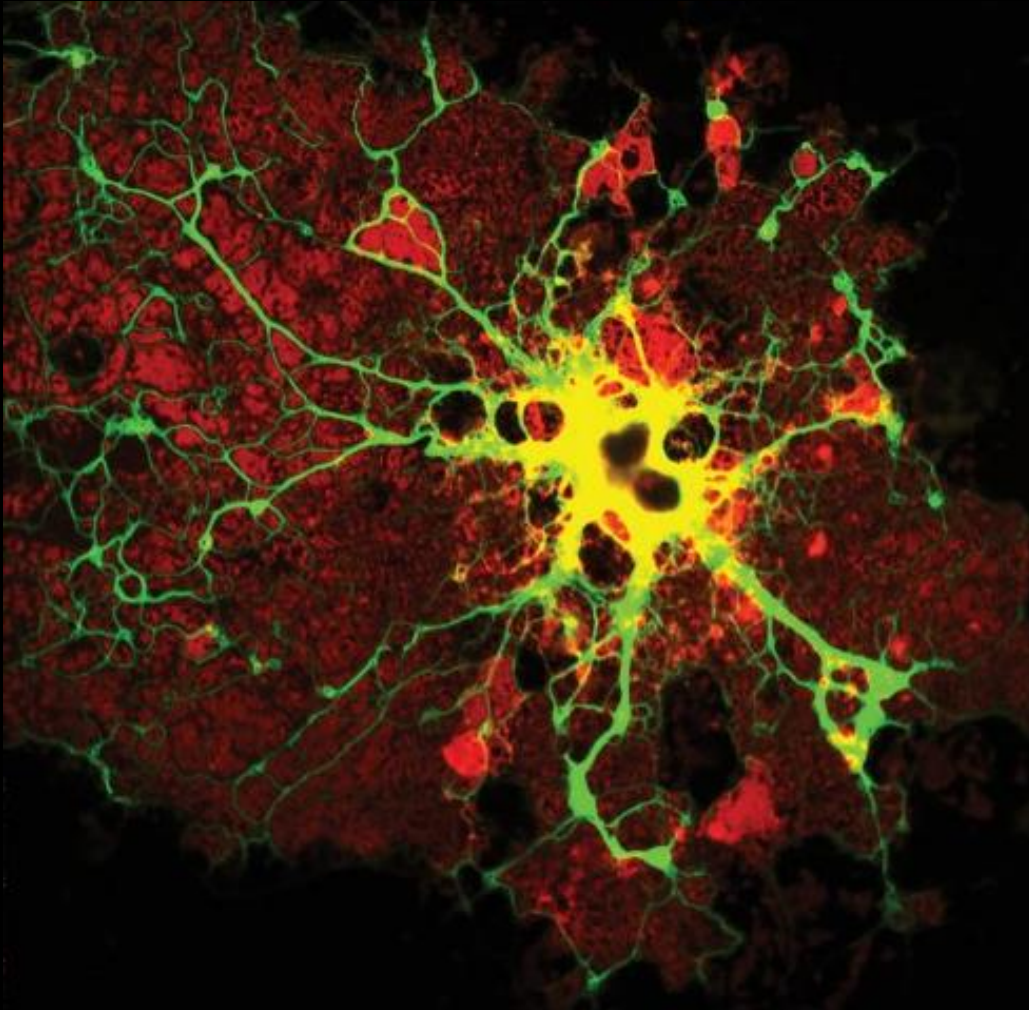
oligodendrocytes



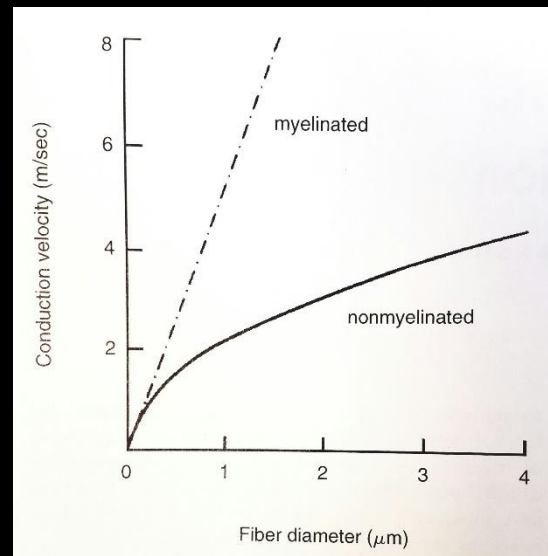
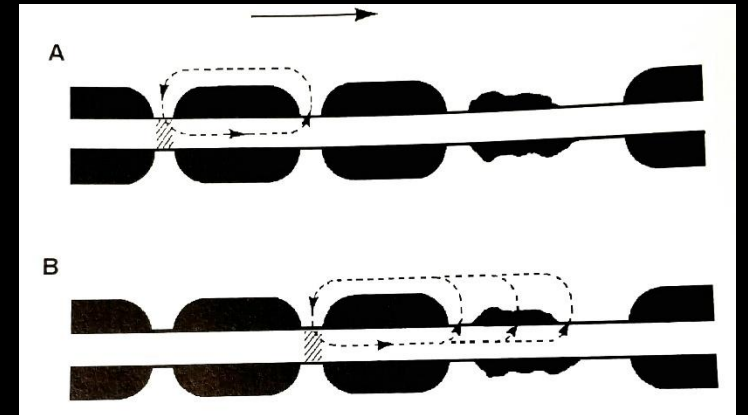
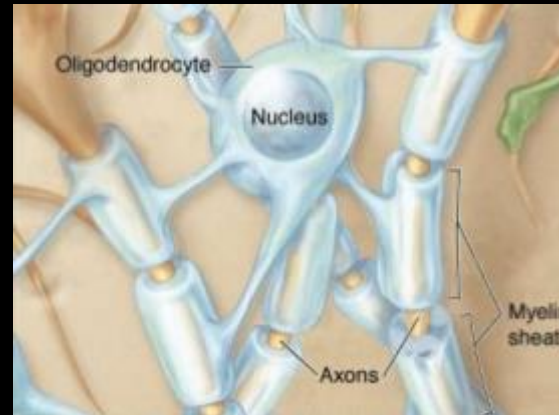


# Oligodendrocytes (this is also the same for peripheral Schwann cells)

- Oligodendrocytes, which are continuously remodeling the myelin, and thus finely tuning axonal conduction velocity, in response to neuronal activity.

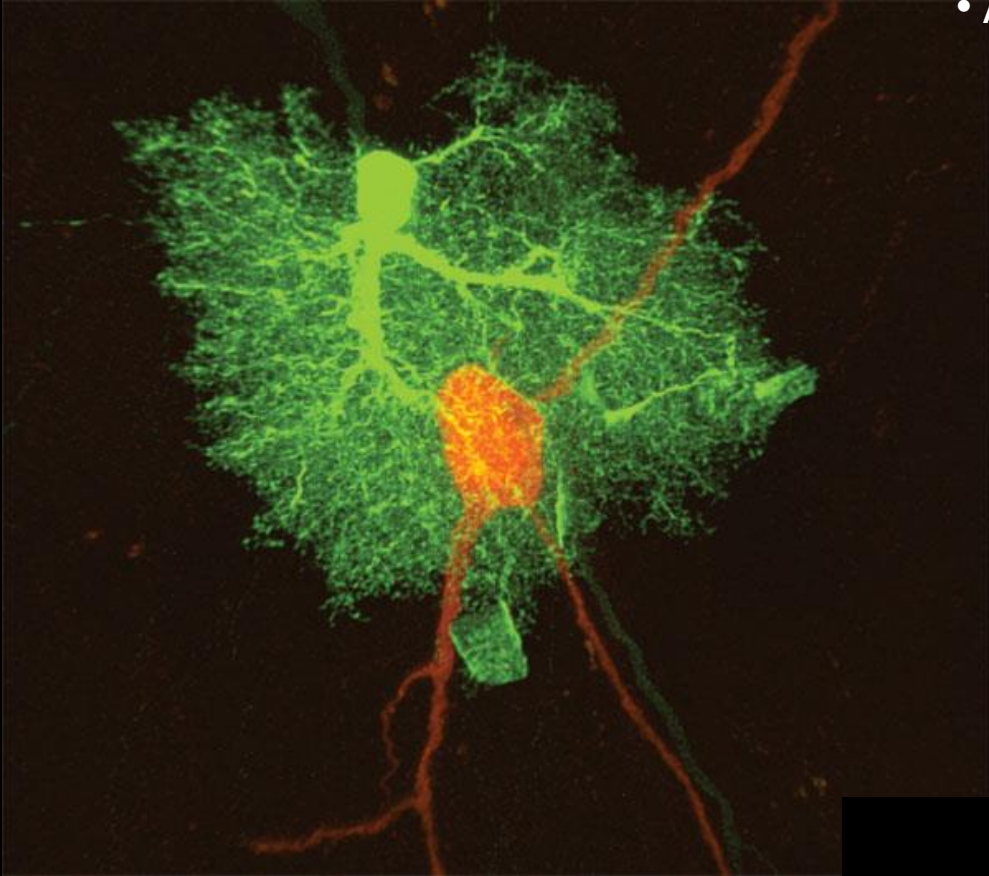


Oligodendrocyte - mouse

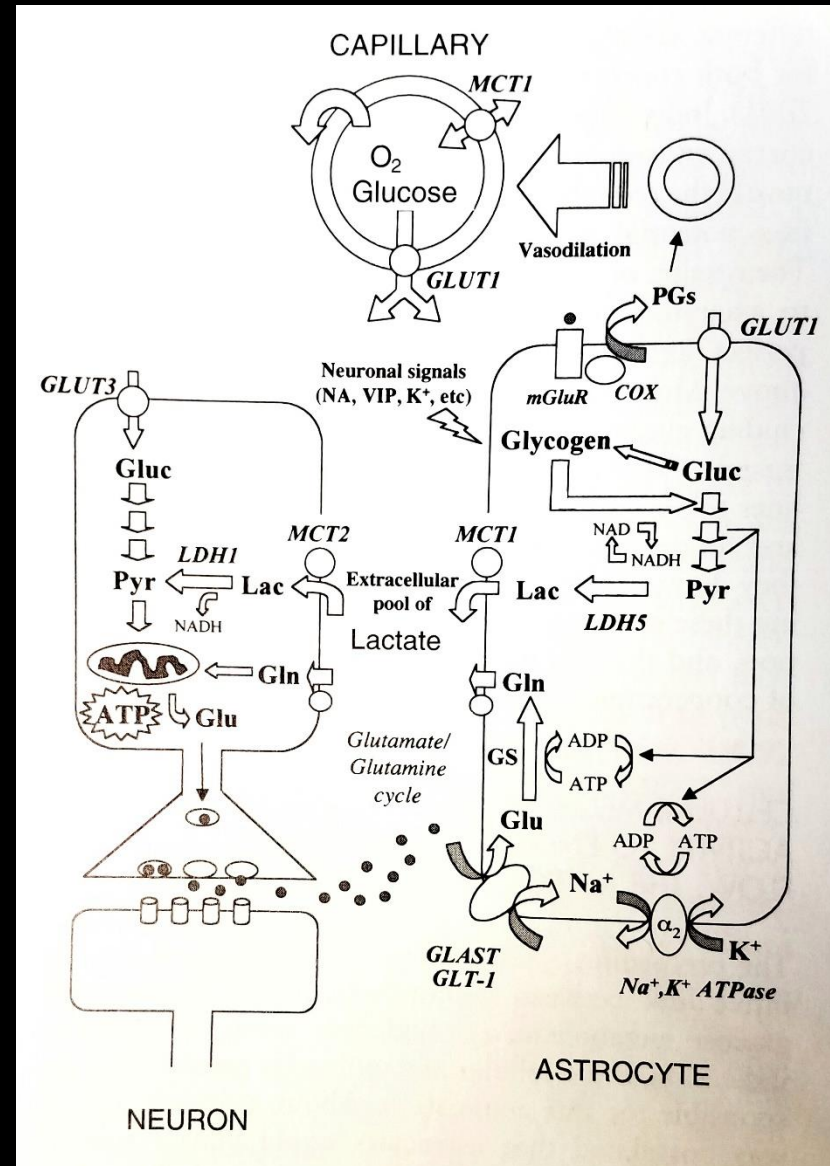


# Astrocytes (I)

- Astrocytes – help provide energy to neurons



astrocyte - mouse



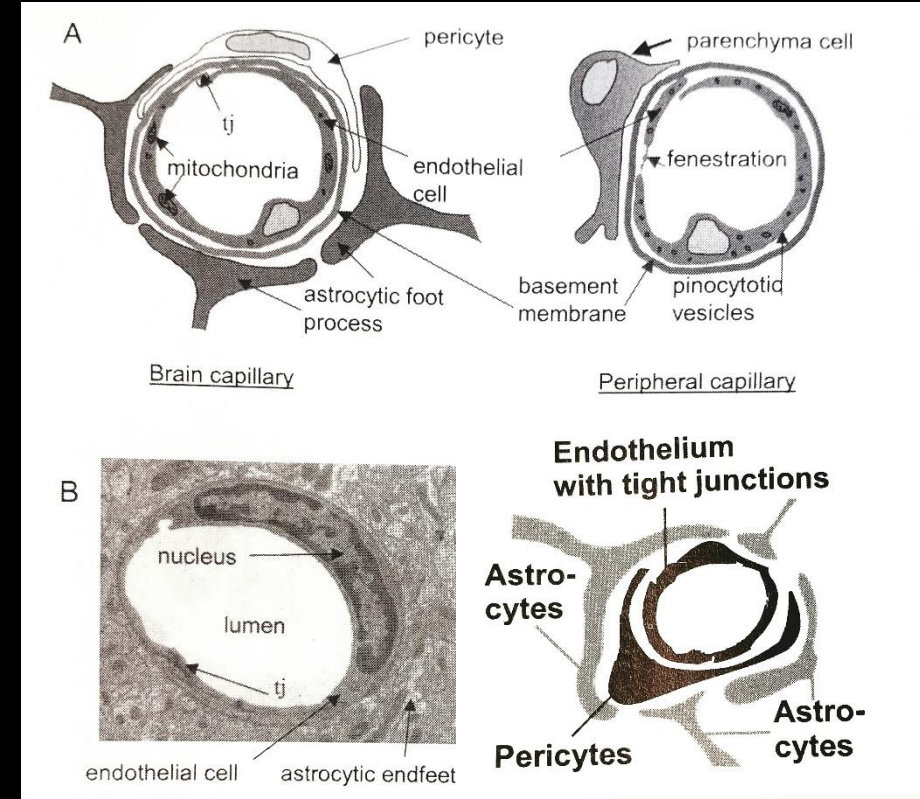
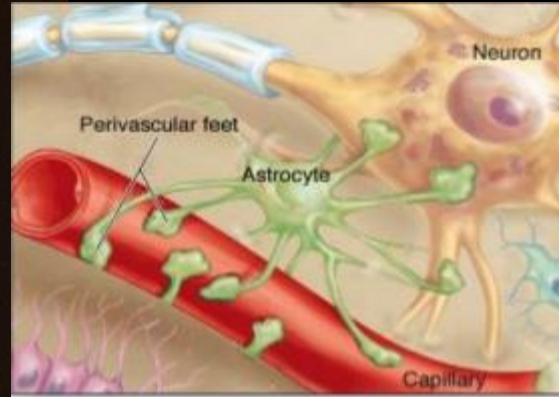


# Astrocytes (II)

- Astrocytes have multiple processes and form perivascular feet that completely enclose all capillaries and ensure blood-brain barrier intact.



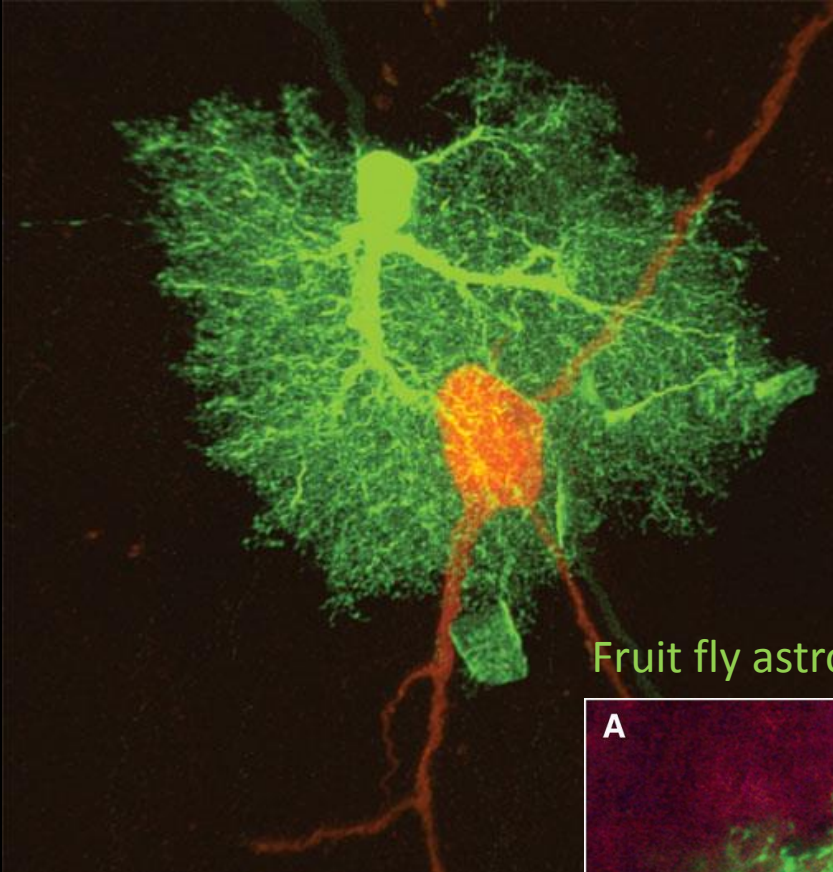
astrocyte - mouse



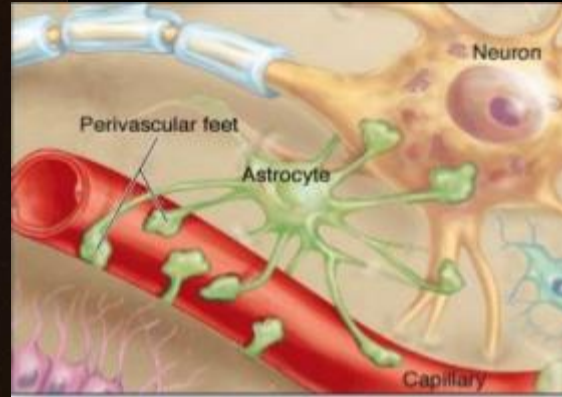


# Astrocytes (II)

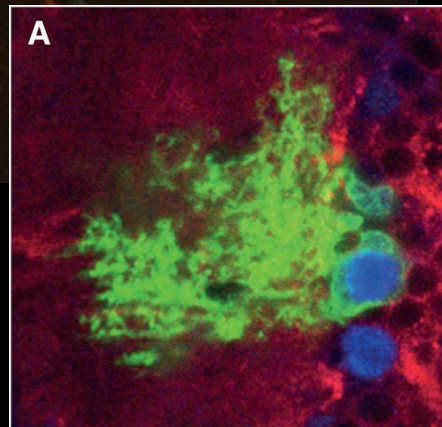
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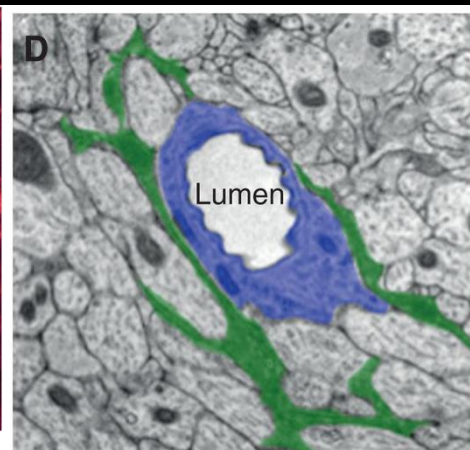
astrocyte - mouse



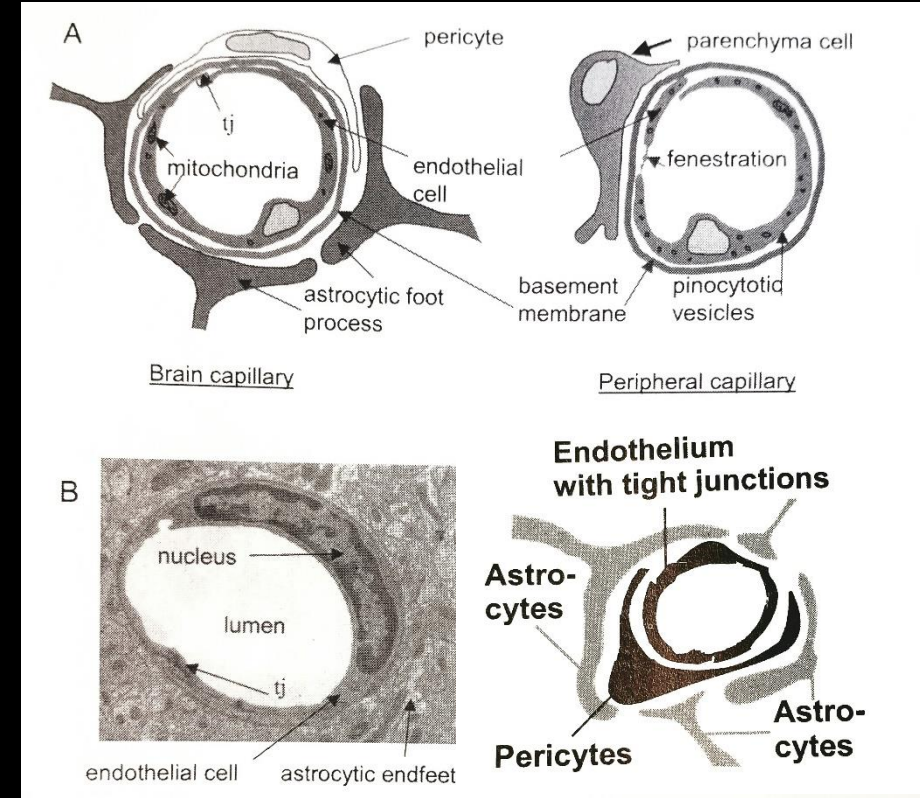
Fruit fly astrocytes



Astro membranes/astro nucleus/neurons



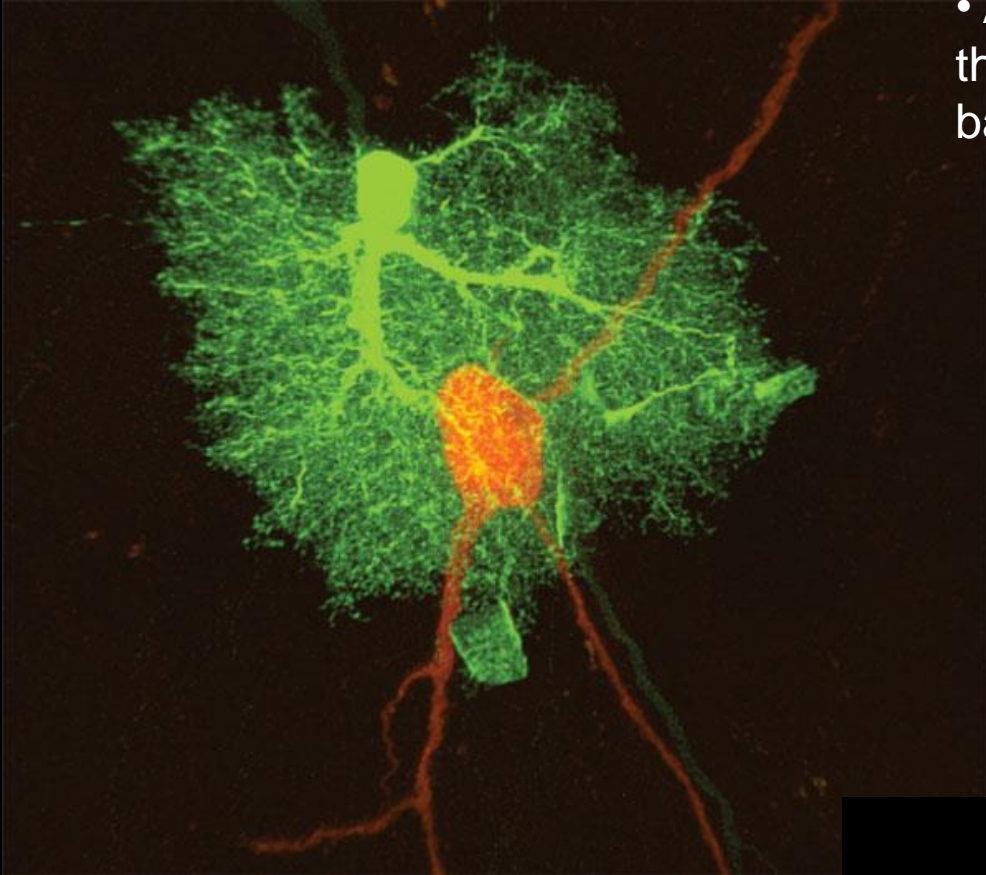
Astro membranes/tracheal cell



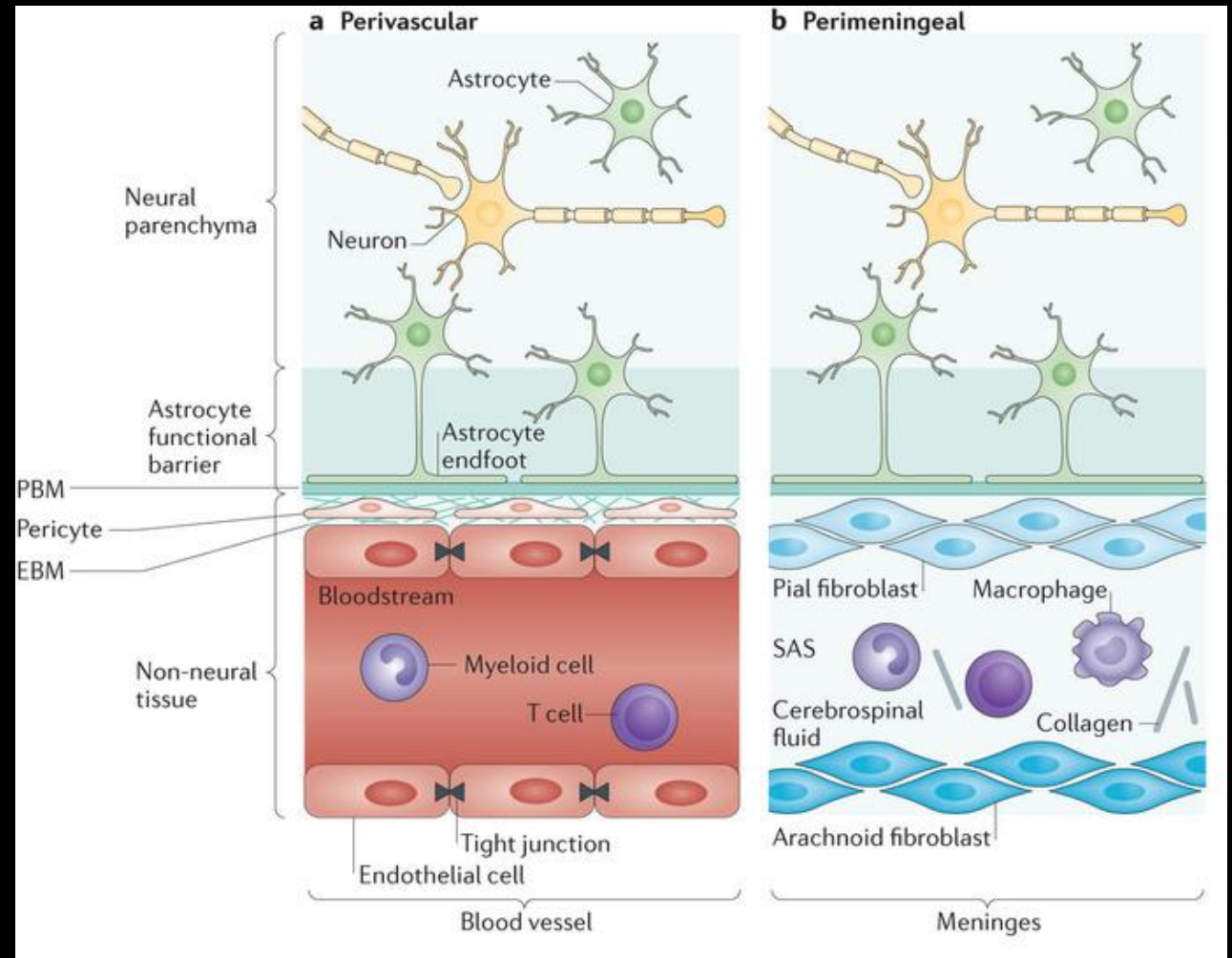


# Astrocytes (II)

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astrocyte - mouse





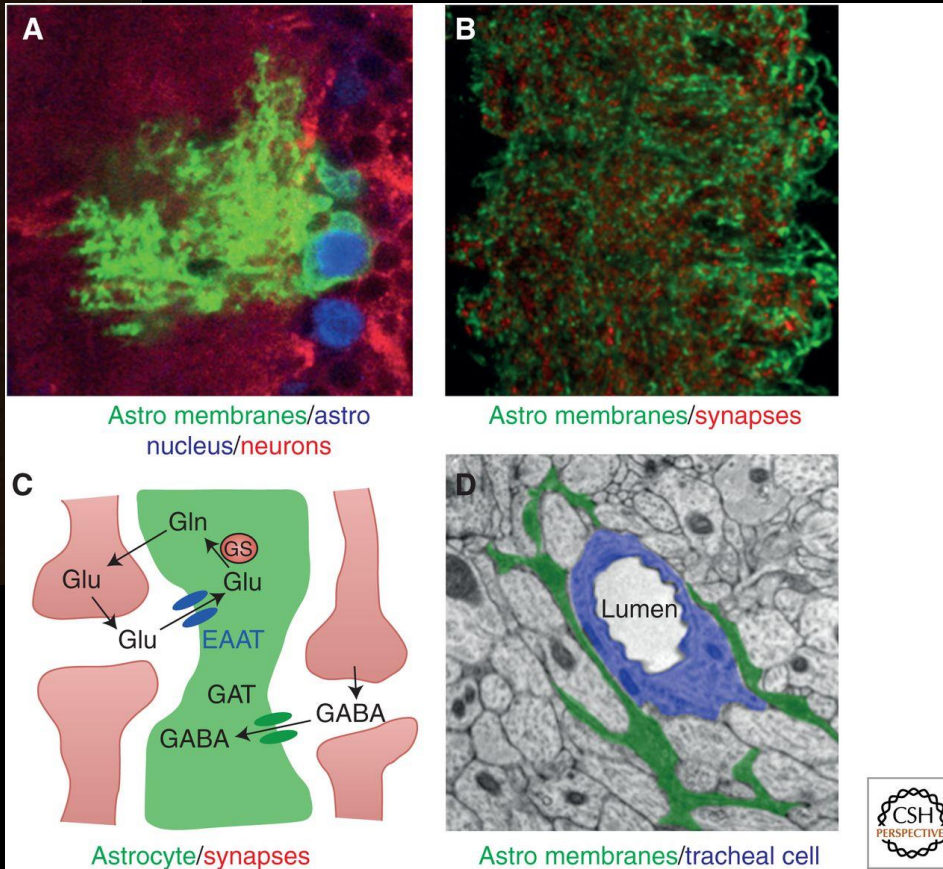
# Astrocytes (III)

- Astrocytes, which are communicating across vast distances in the brain and spinal cord to shape neural activity via extra-synaptic means.

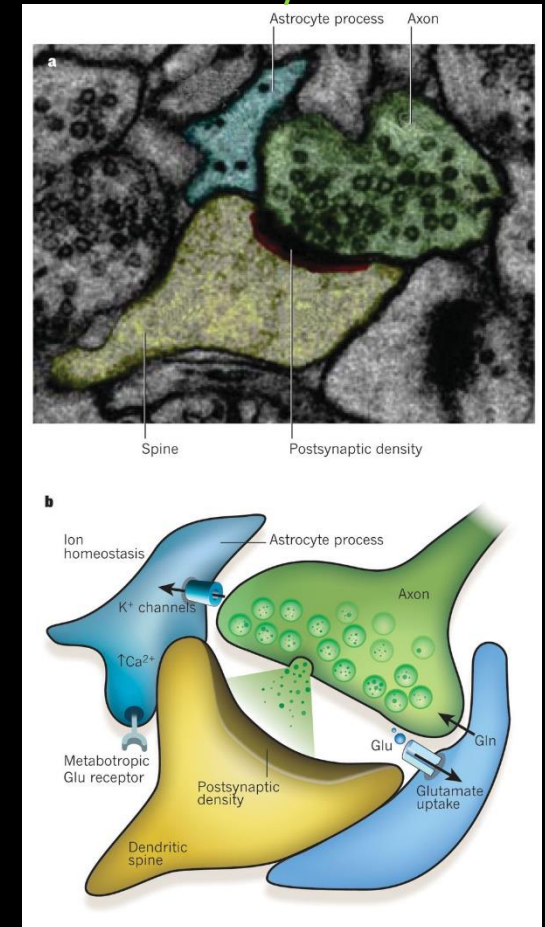


astrocyte - mouse

## Fruit fly astrocytes



## Mouse astrocytes



M.R. Freeman, Cold Spring Harb Perspect Biol, 2015

Eroglu and Barres, Nature reviews, 2010

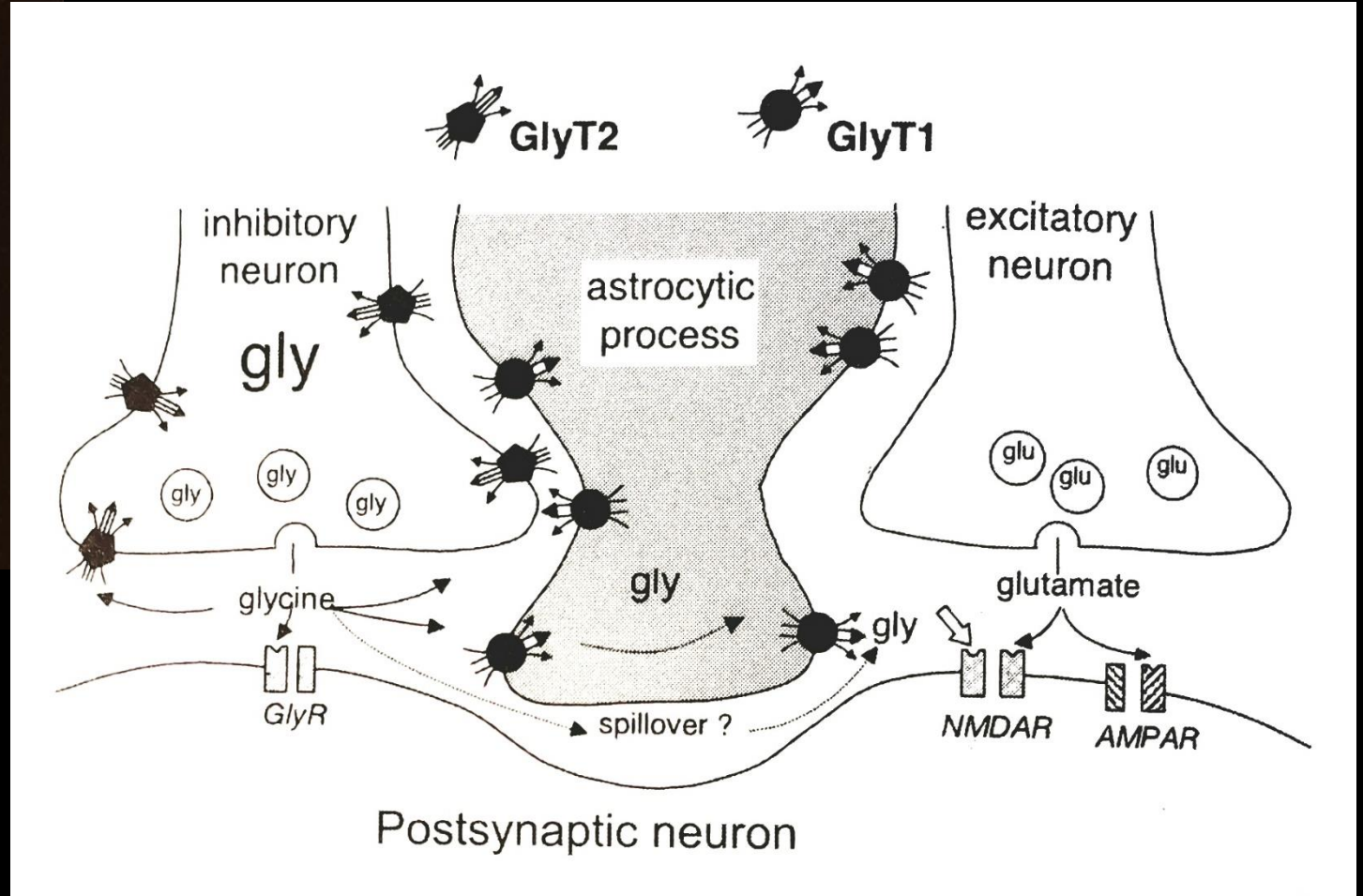


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astrocyte - mouse



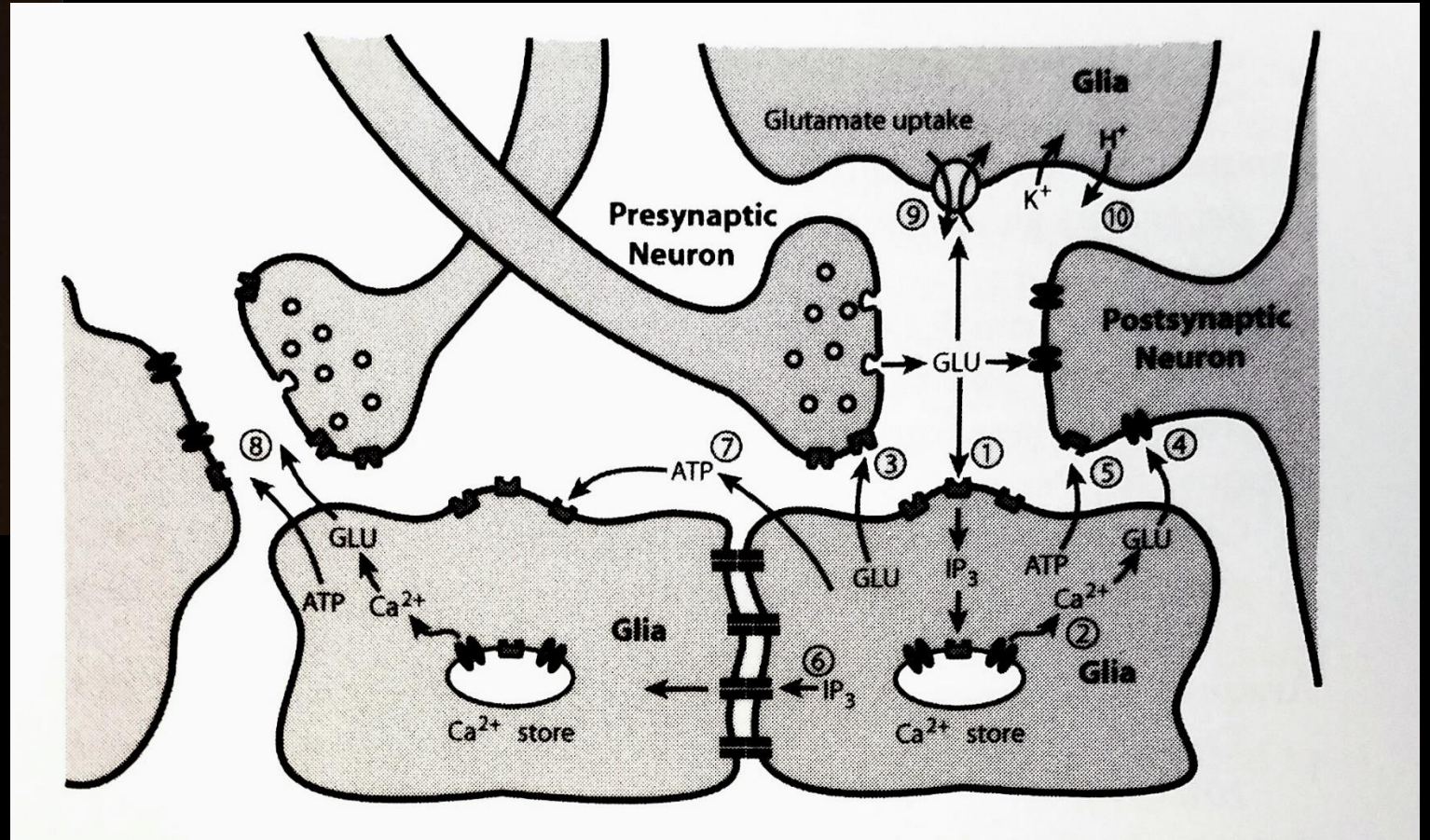


# Astrocytes (III)

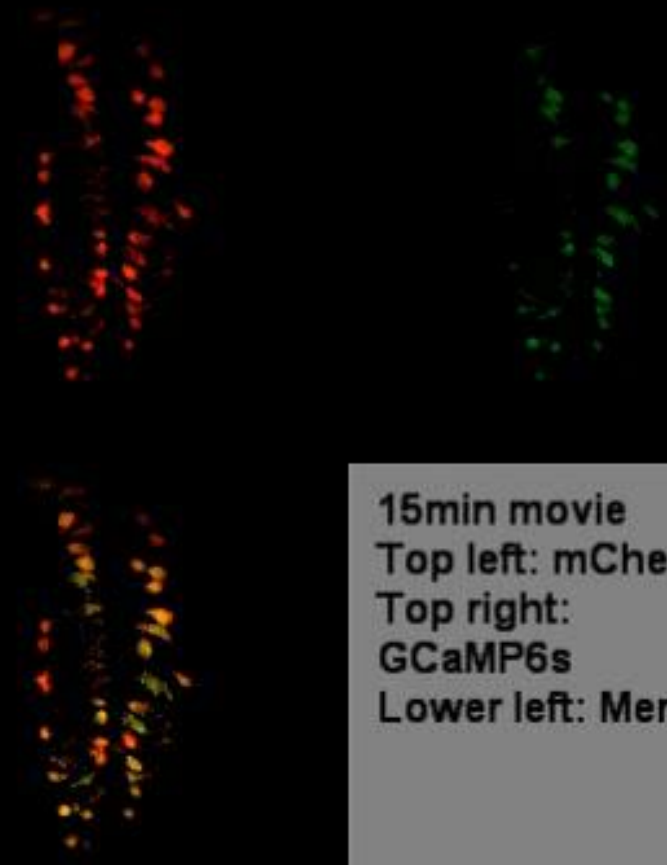
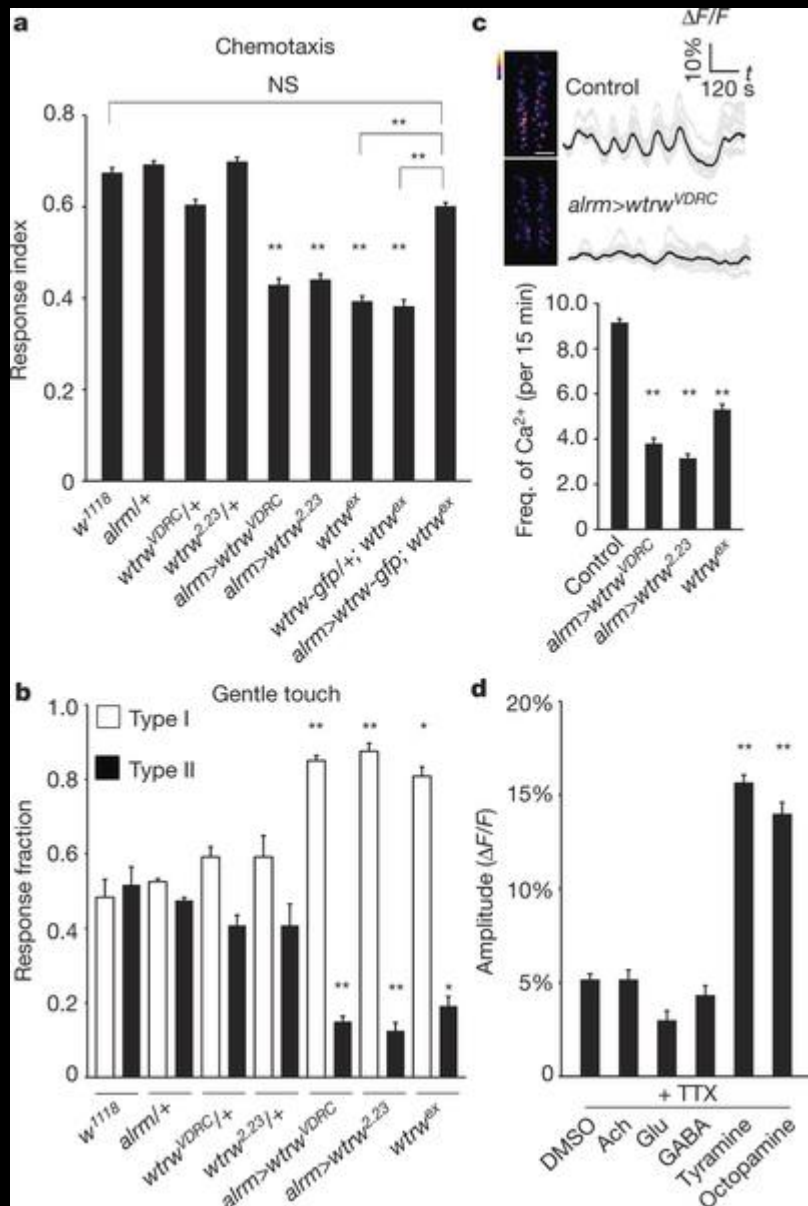
- Astrocytes, which are communicating across vast distances in the brain and spinal cord to shape neural activity via extra-synaptic means.



astrocyte - mouse



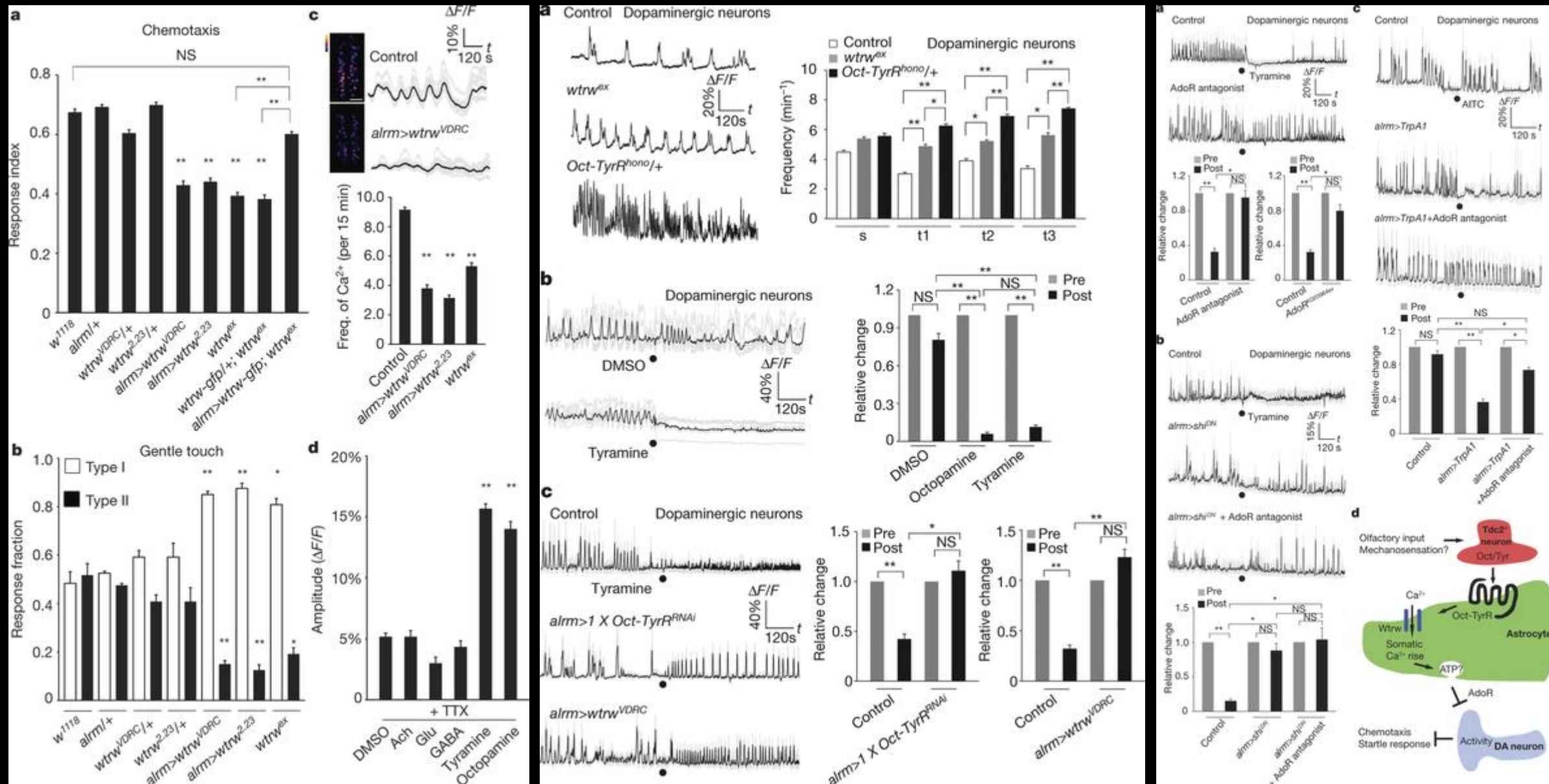
# Neuromodulators utilize astrocyte calcium waves to alter circuit activity and behavior



15min movie  
 Top left: mCherry  
 Top right: GCaMP6s  
 Lower left: Merge

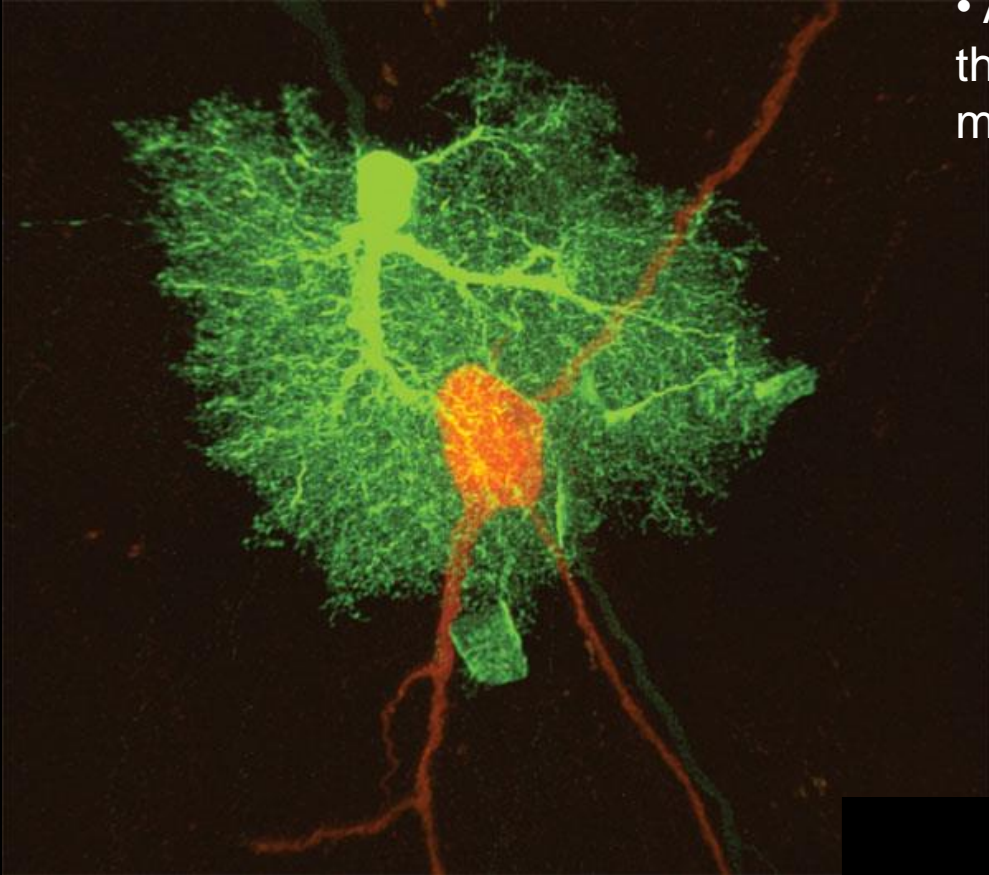


# Neuromodulators utilize astrocyte calcium waves to alter circuit activity and behavior



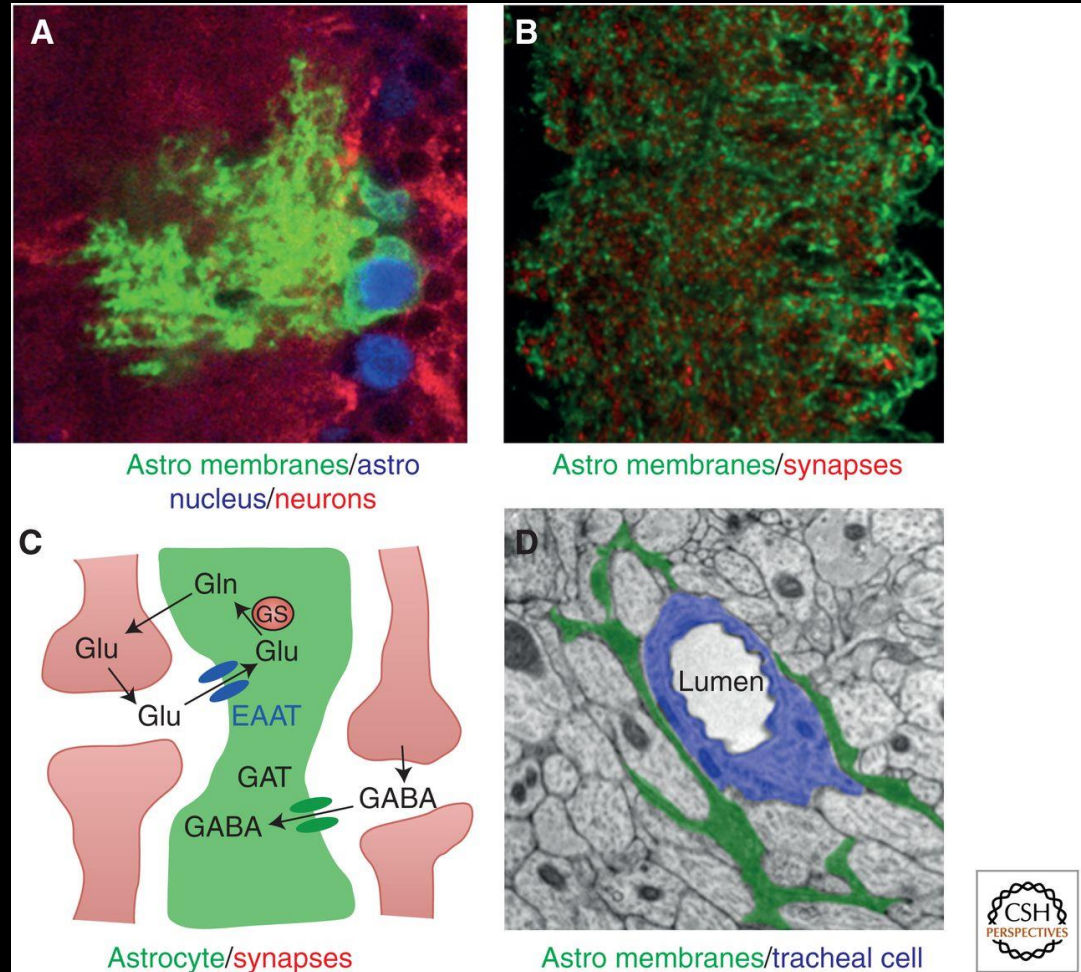
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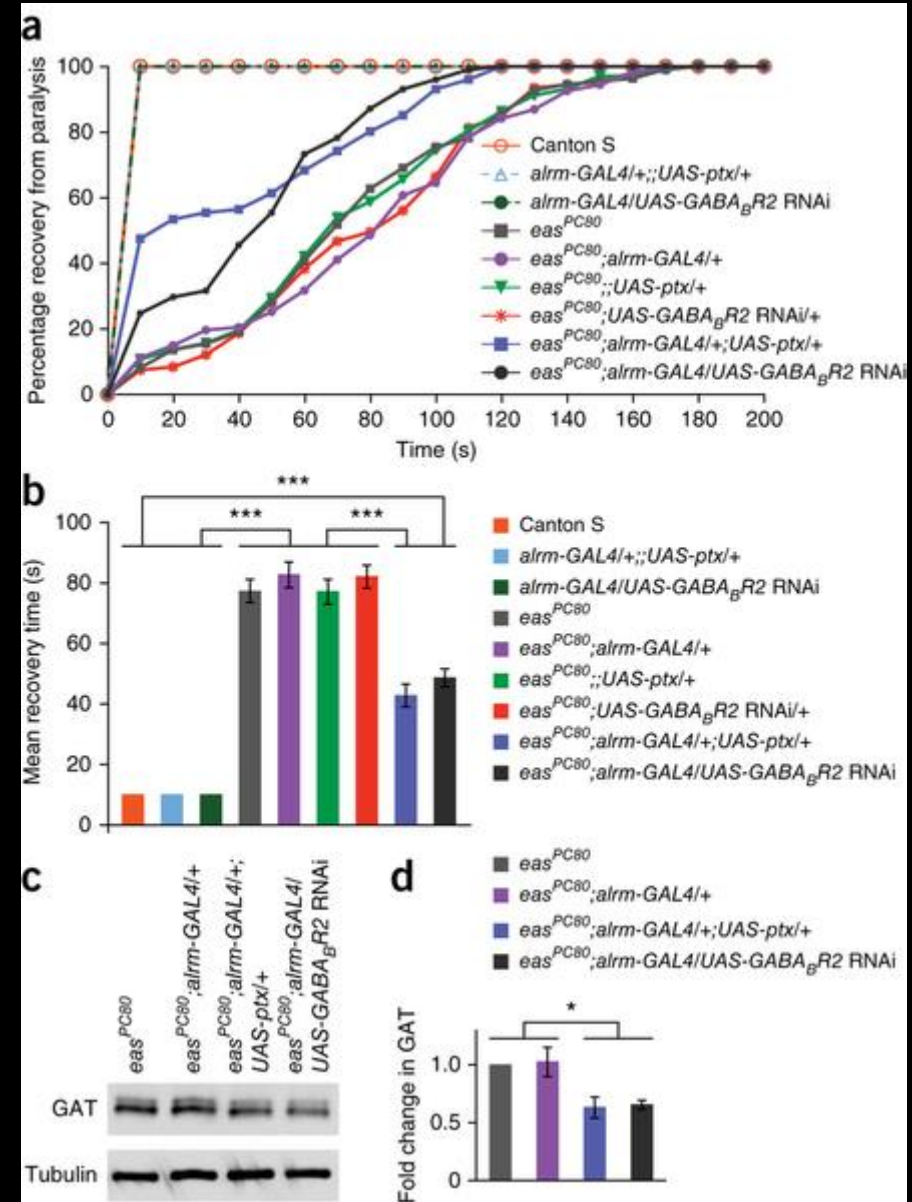
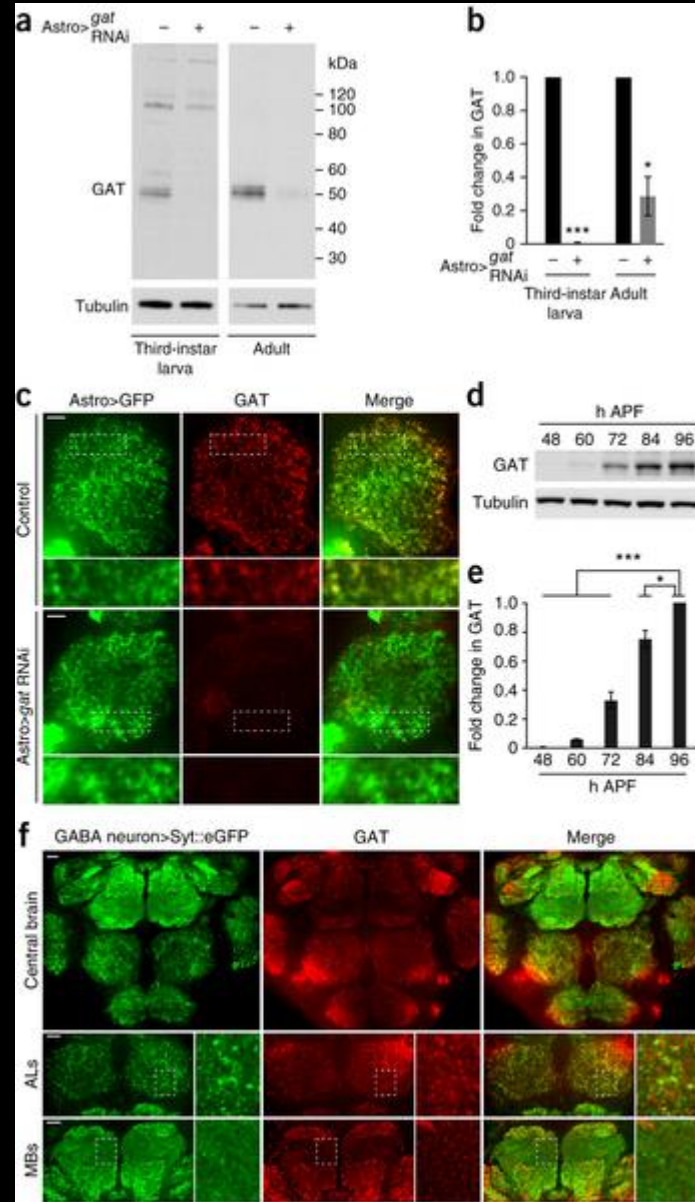
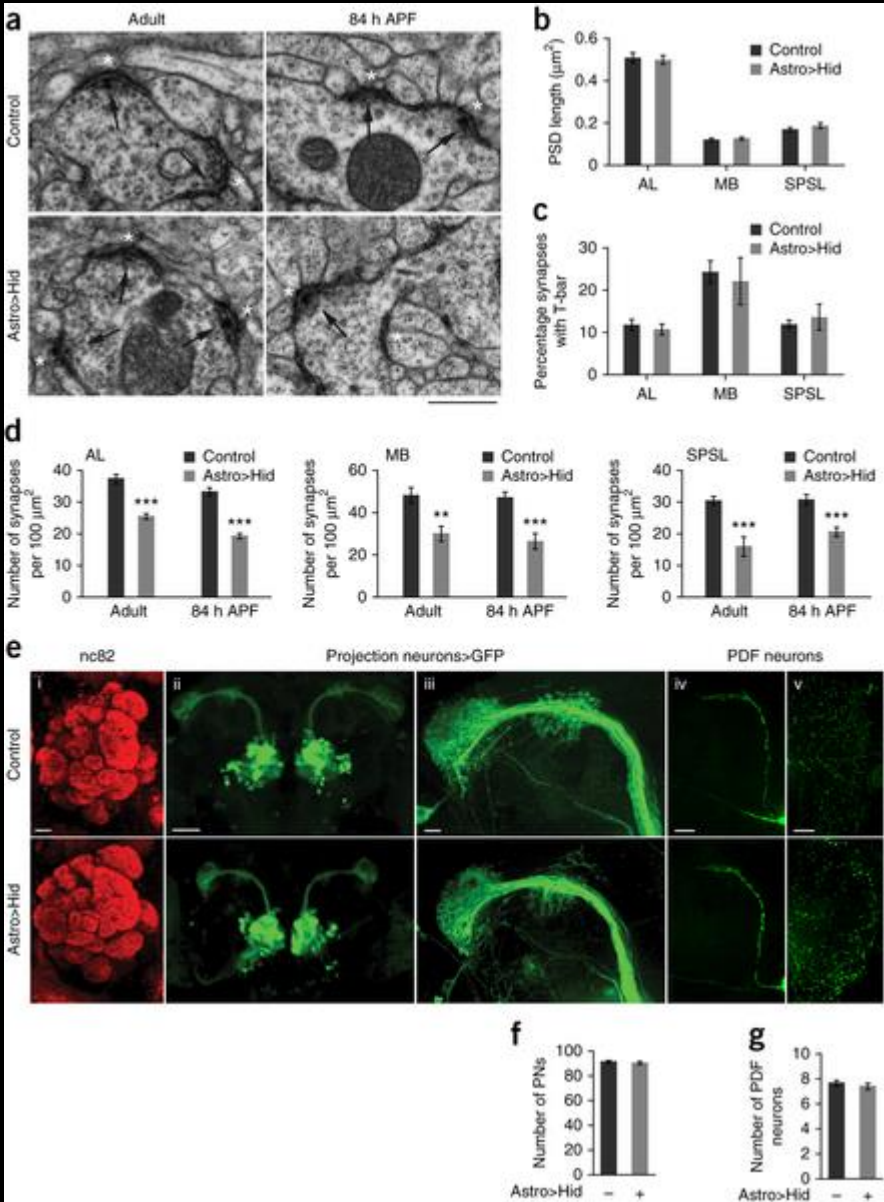
astrocyte - mouse

## Fruit fly astrocytes



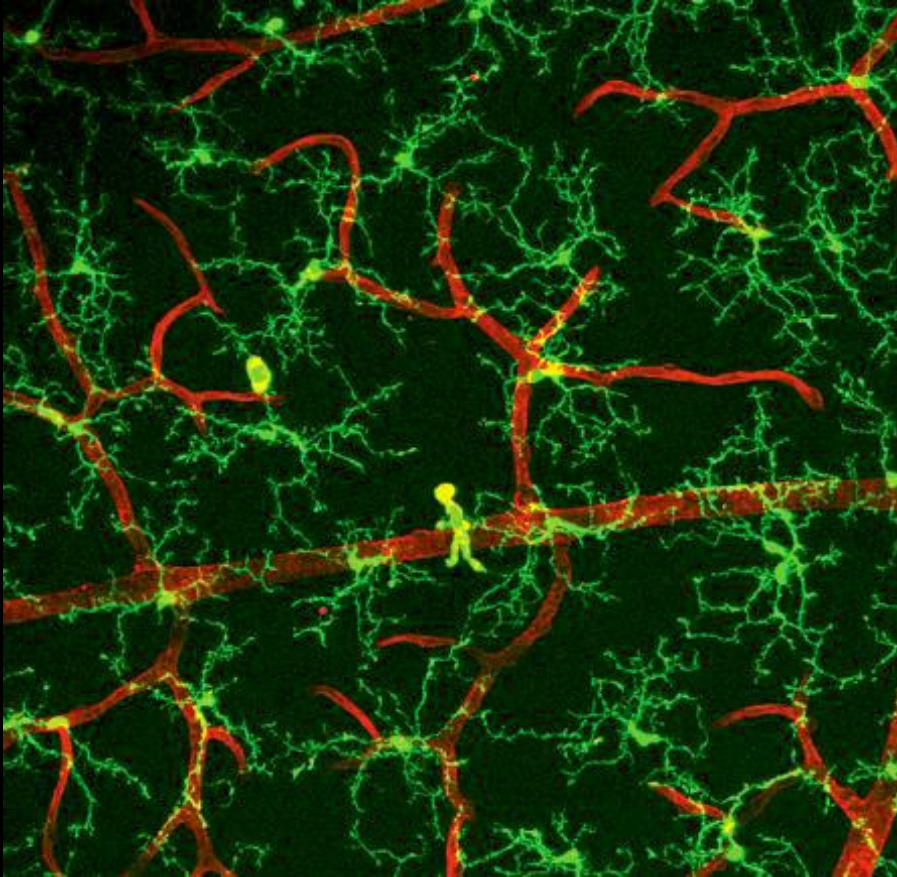


# Astrocyte regulation of synaptogenesis and modulation of inhibitory synaptic signaling



# Microglia (I)

- Microglia, which play important roles in synaptic pruning during development, and have a protective phagocytic immune-related function.



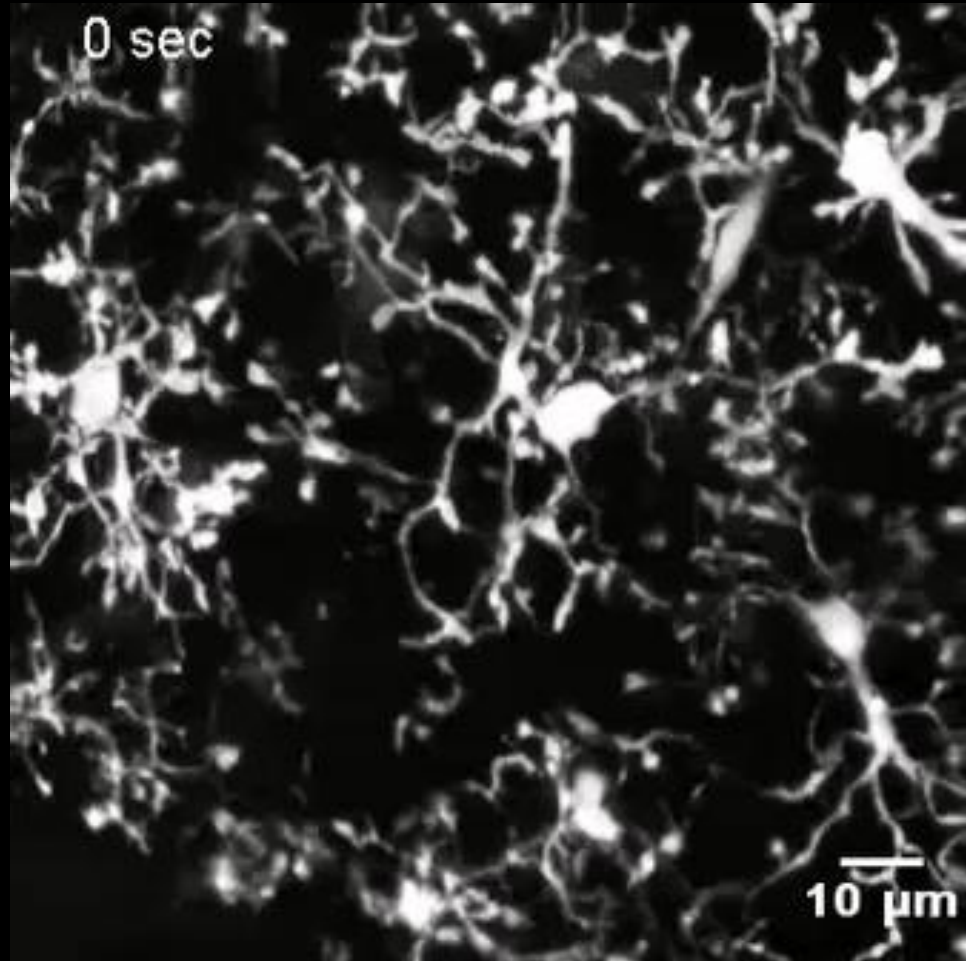
microglia



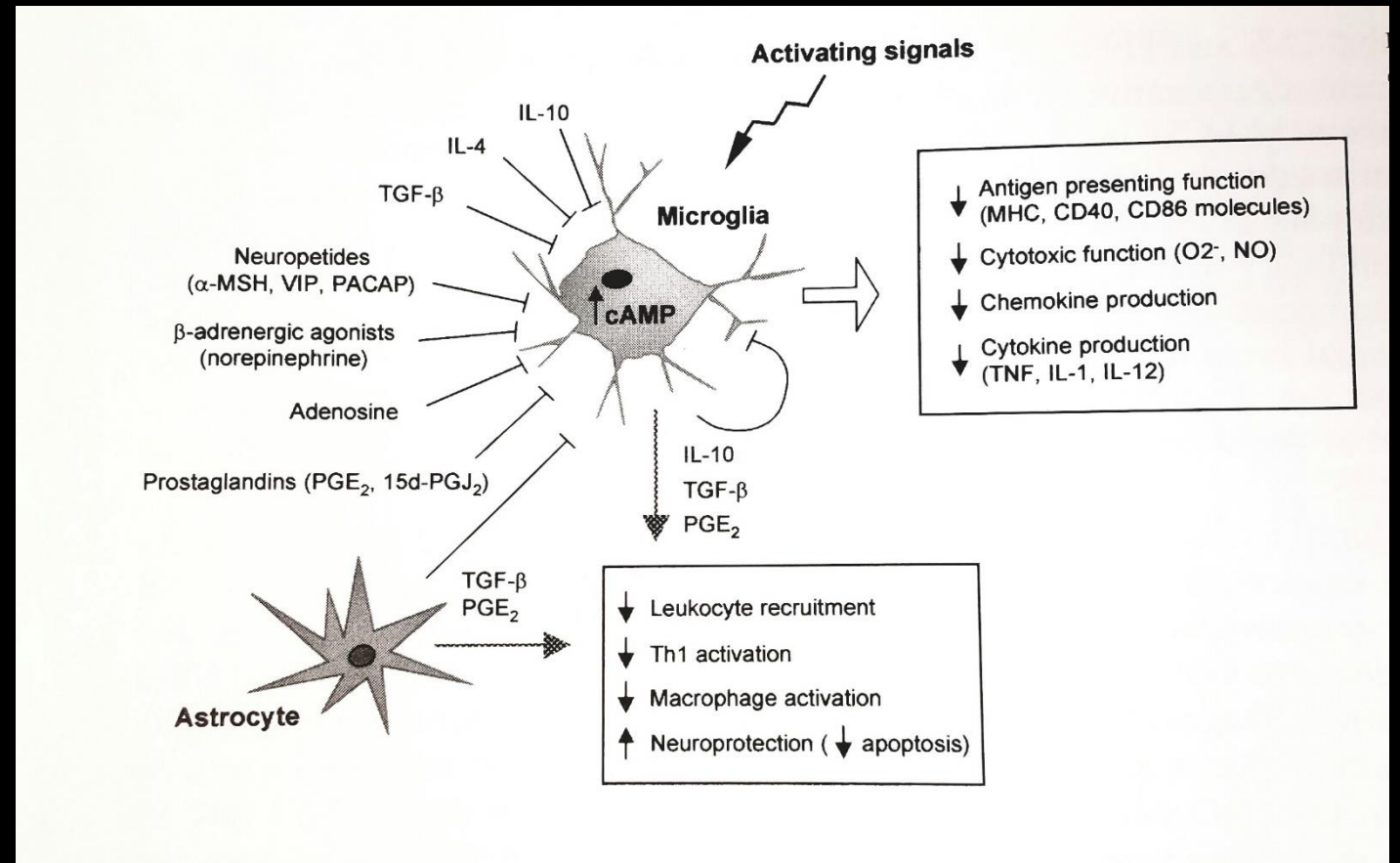


# Microglia (I)

Microglia in resting brain



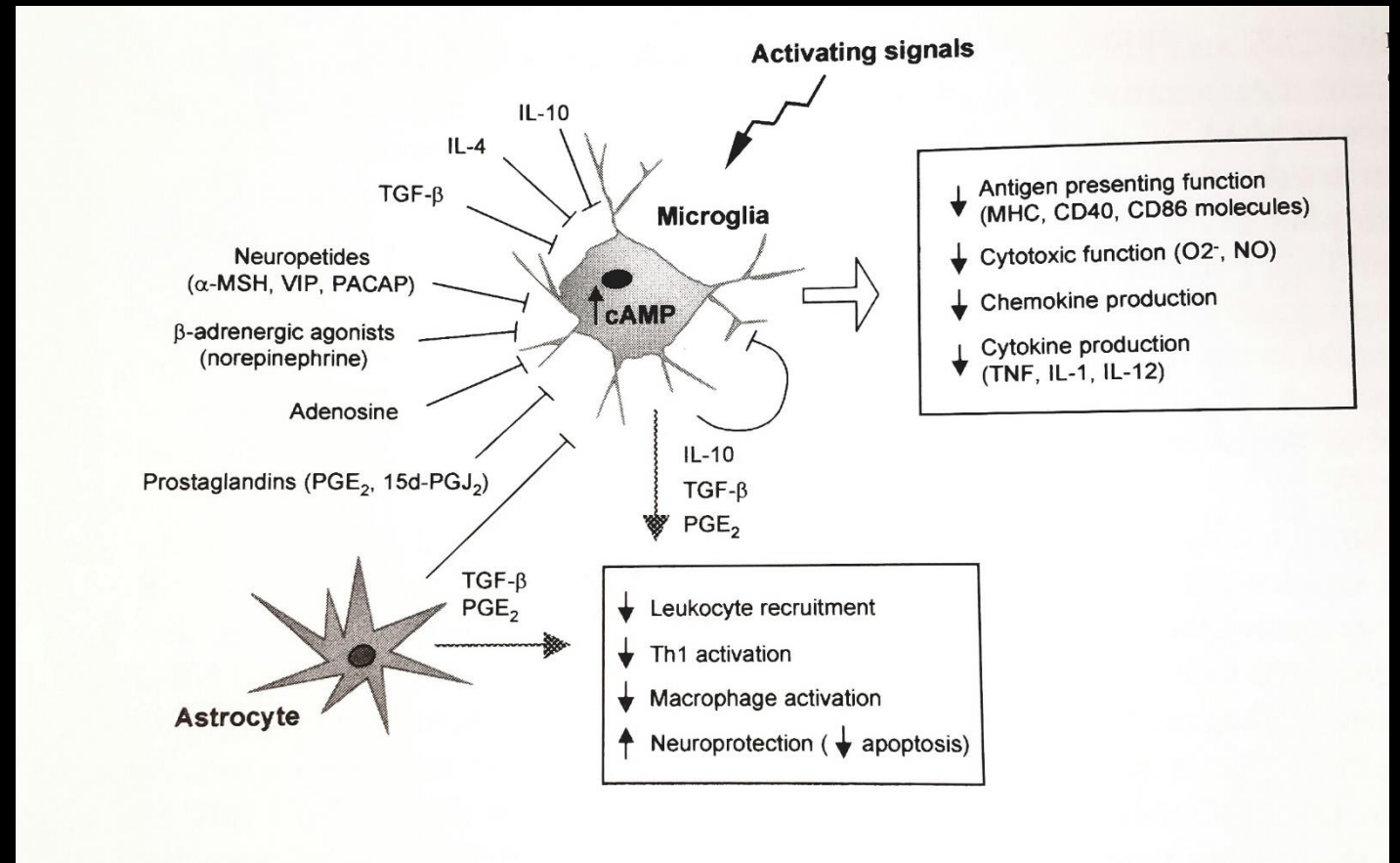
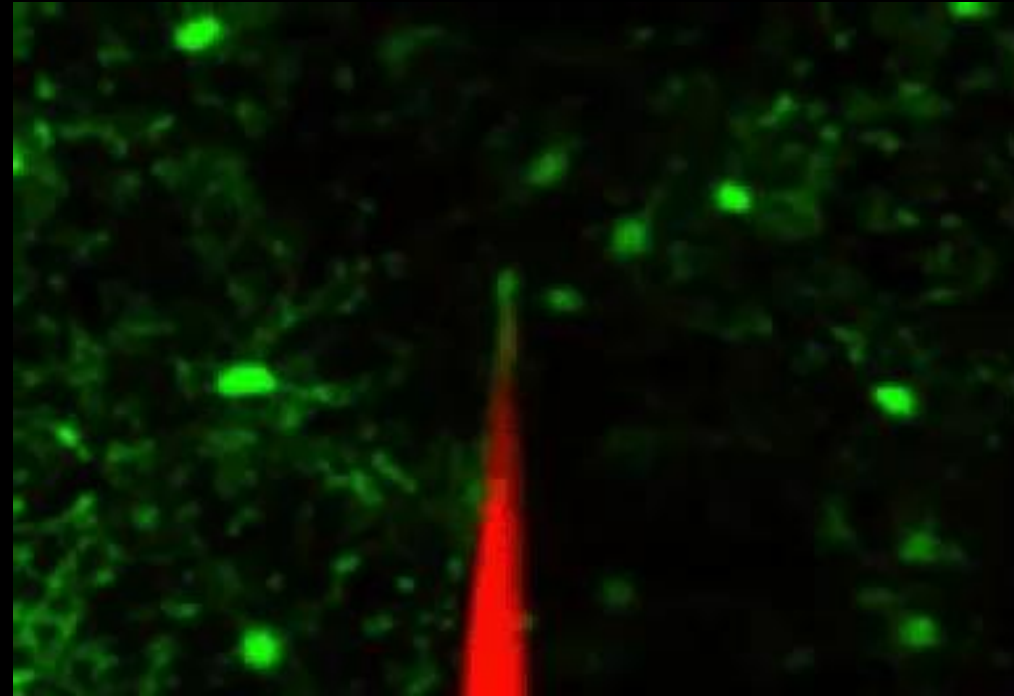
- Microglia, which play important roles in synaptic pruning during development, and have a protective phagocytic immune-related function.



# Microglia (I)

## Microglia + LPS application

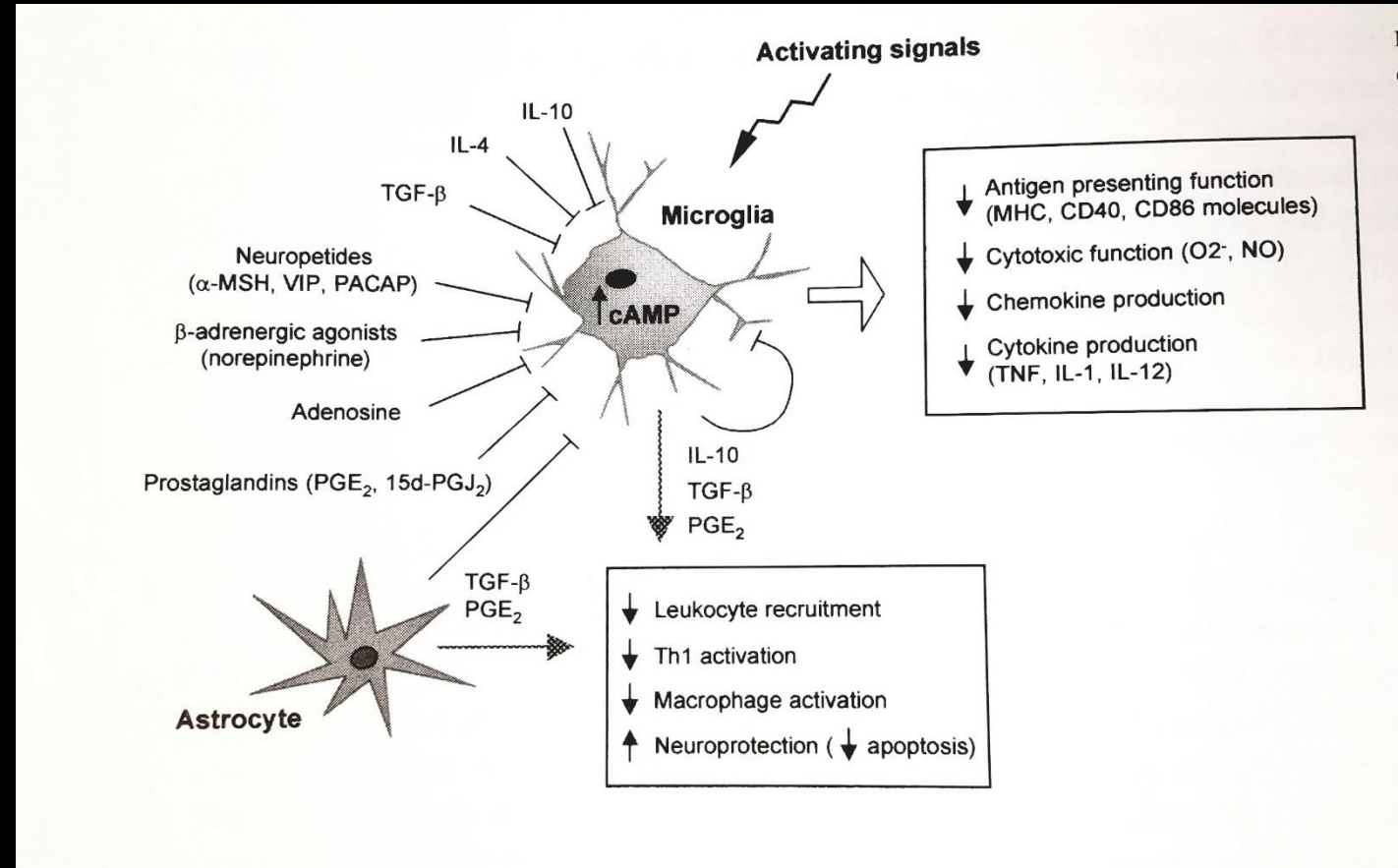
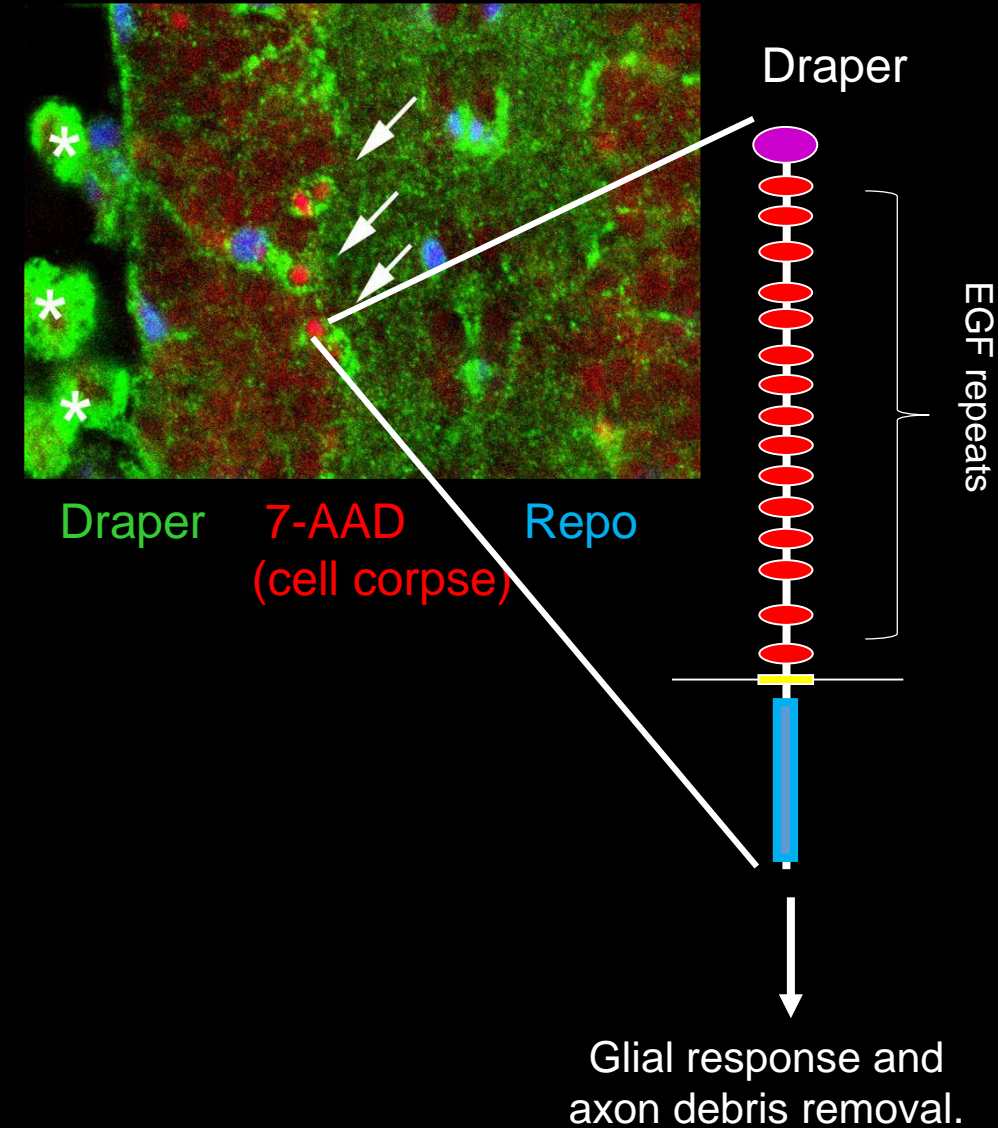
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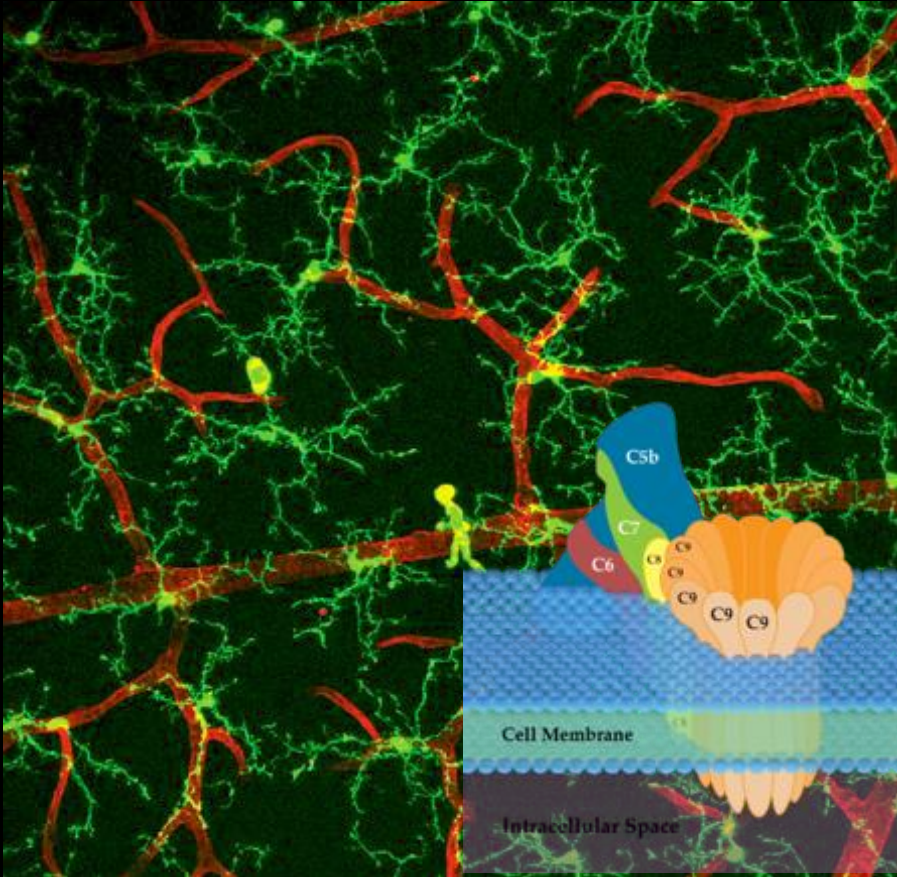
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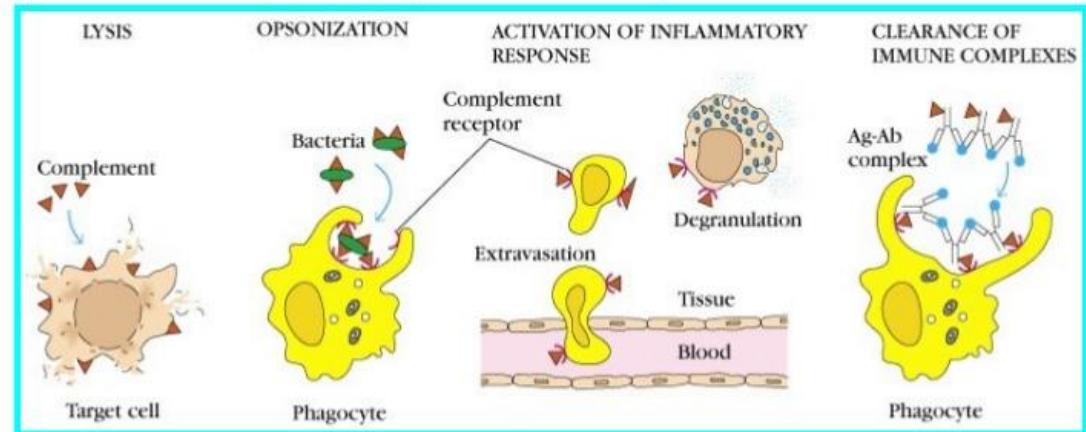
## Microglia (II)

- Microglia, which play important roles in synaptic pruning during development, and have a protective phagocytic immune-related function.



microglia

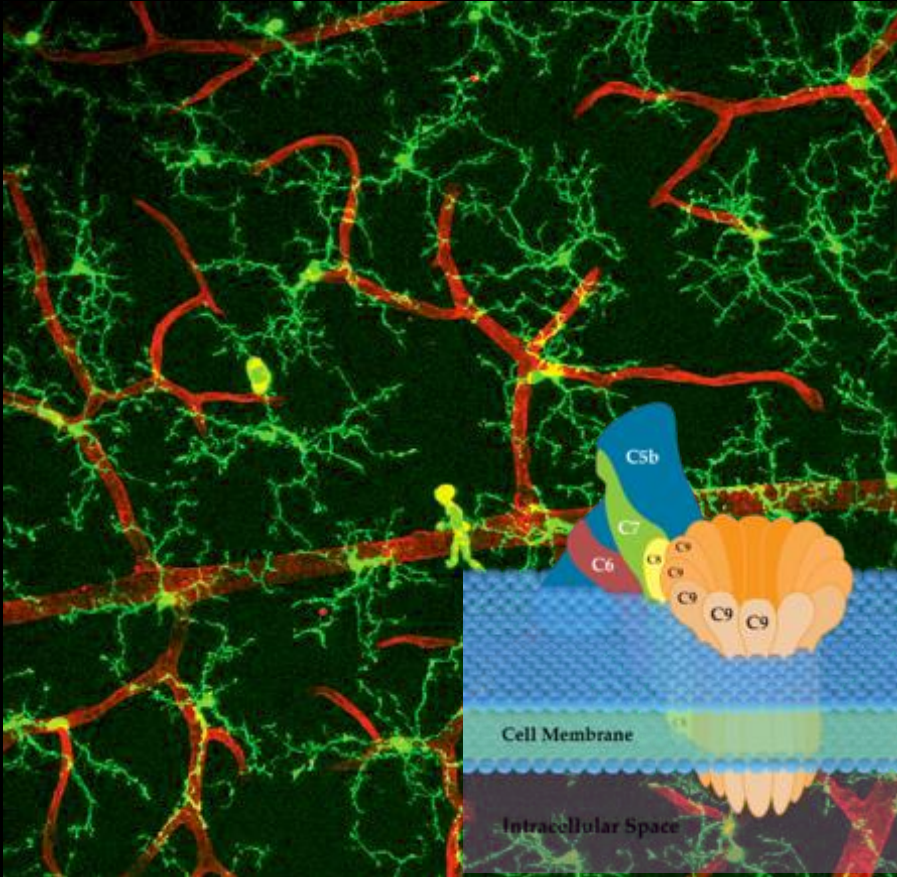
### The Multiple Activities of the Complement System



Serum complement proteins and membrane-bound complement receptors partake in a number of immune activities: lysis of foreign cells by antibody-dependent or antibody-independent pathways; opsonization or uptake of particulate antigens including bacteria, by phagocytosis; activation of inflammatory responses; and clearance of circulating immune complexes by cells in the liver and spleen. Soluble complement proteins are schematically indicated by a triangle and receptors by a semicircle; no attempt is made to differentiate among individual components of the complement system here.

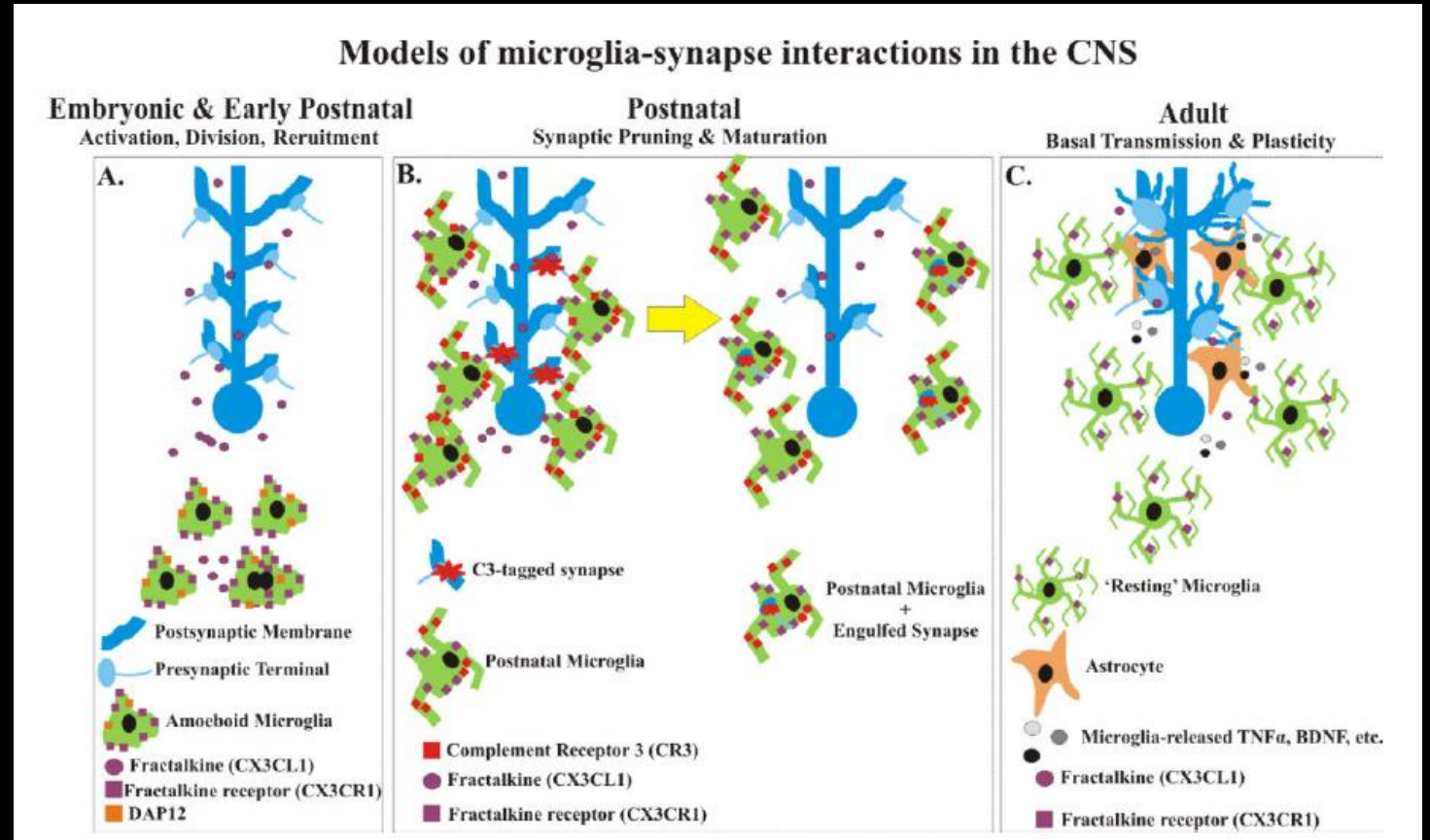


# Microglia (II)

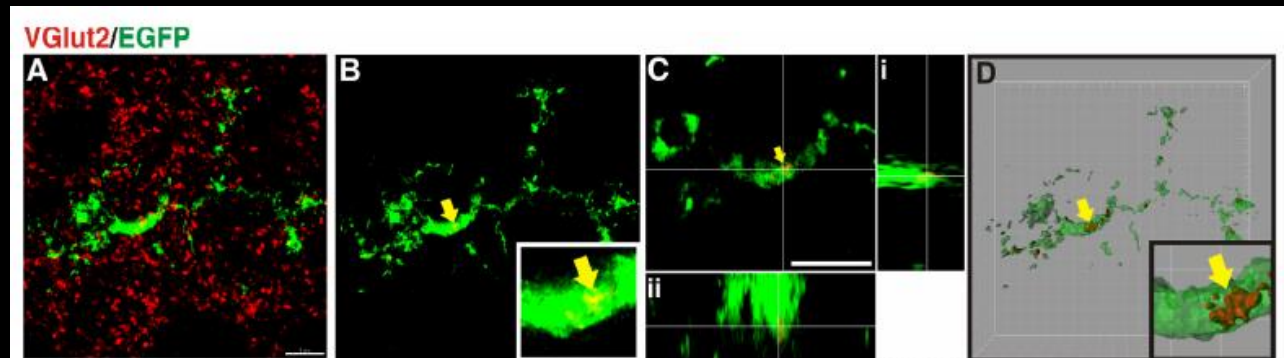
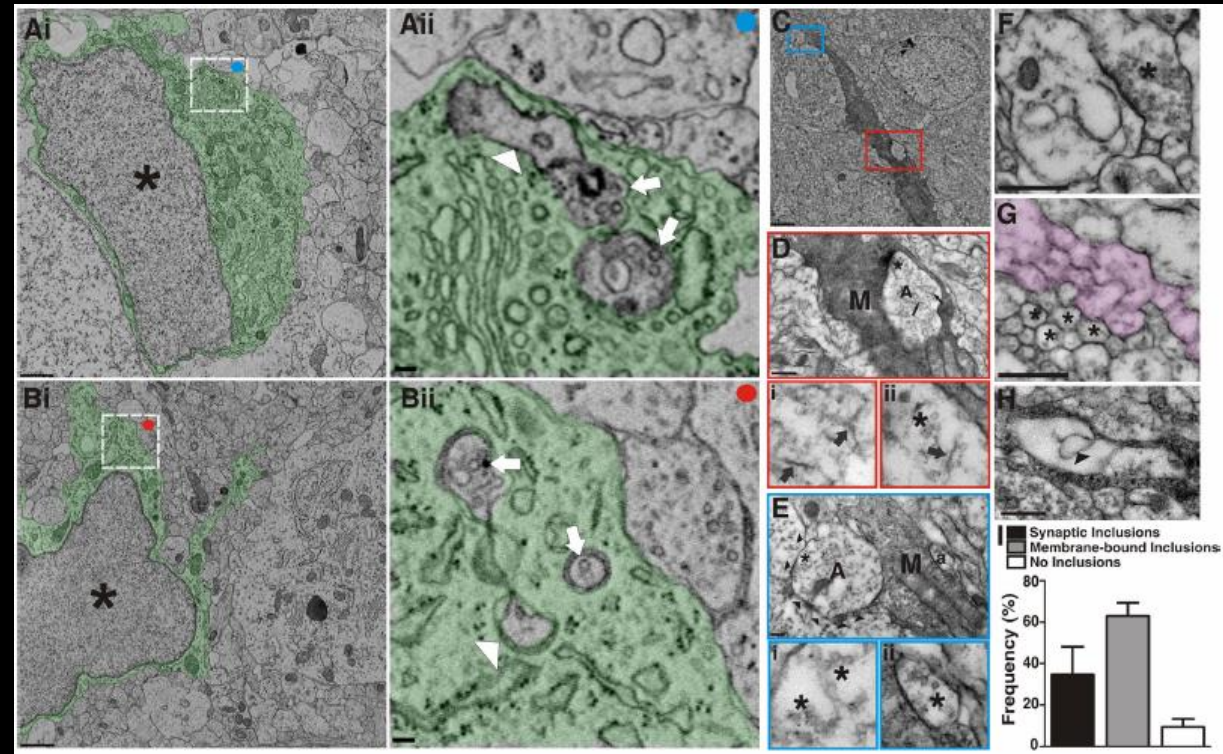


microglia

- Microglia, which play important roles in synaptic pruning during development, and have a protective phagocytic immune-related function.

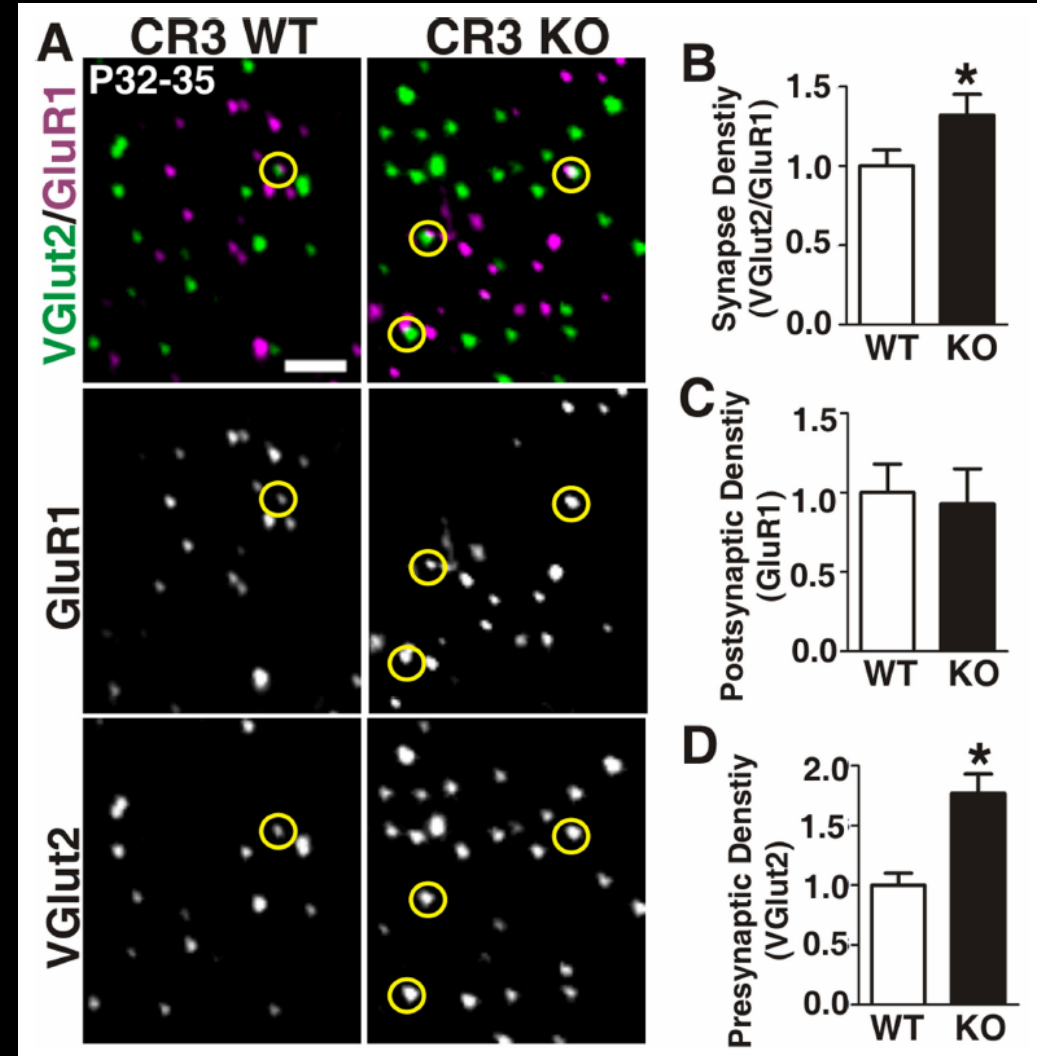
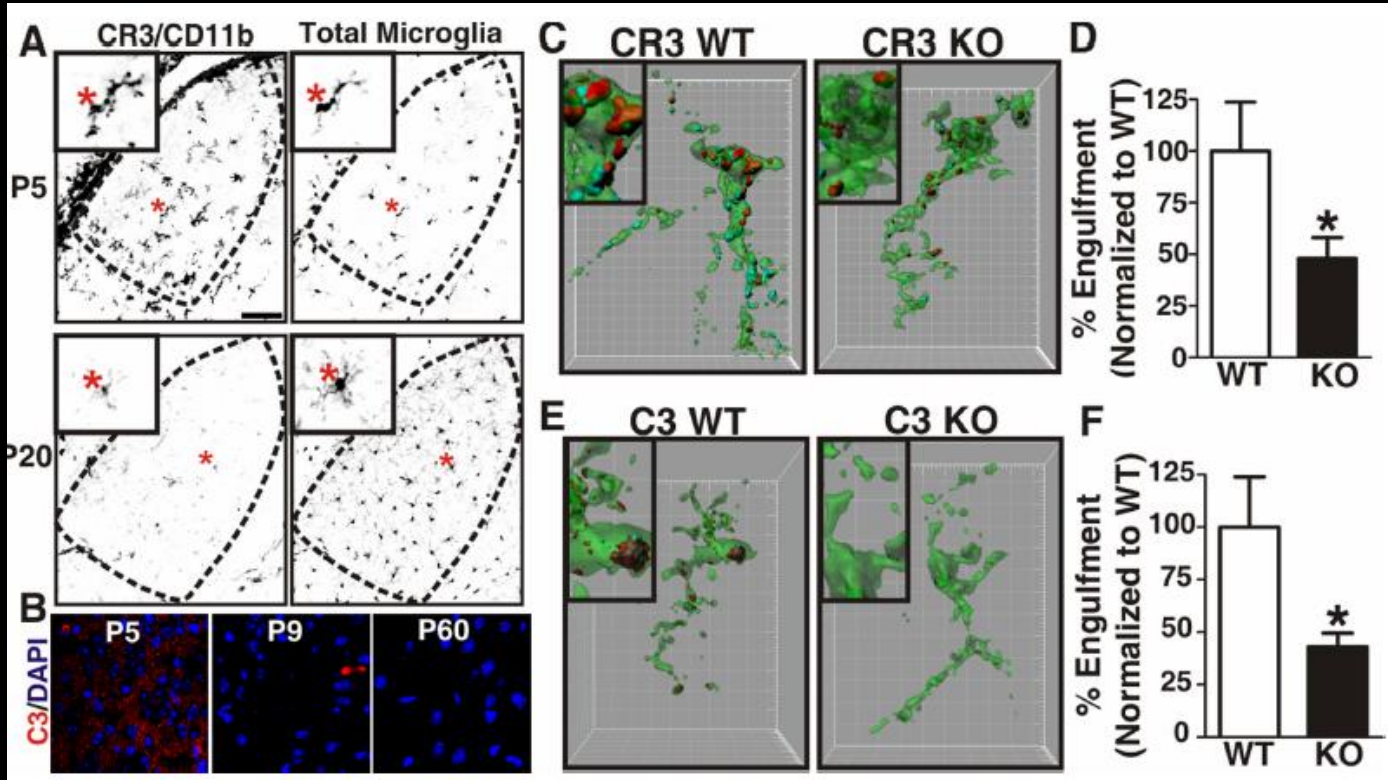


# Microglia engulf presynaptic elements undergoing active synaptic pruning



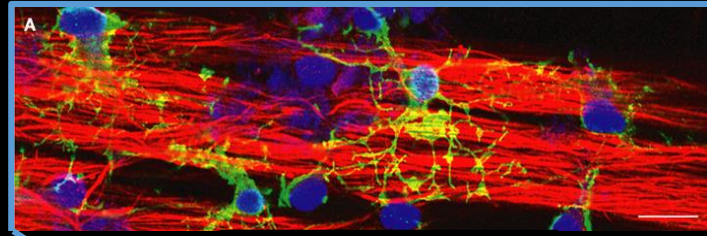


# CR3/C3-dependent signaling regulates engulfment of synaptic inputs by microglia

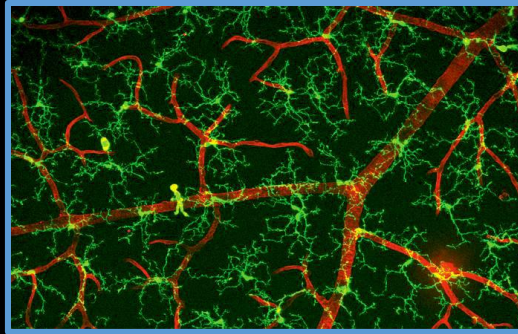


# Glia and the brain

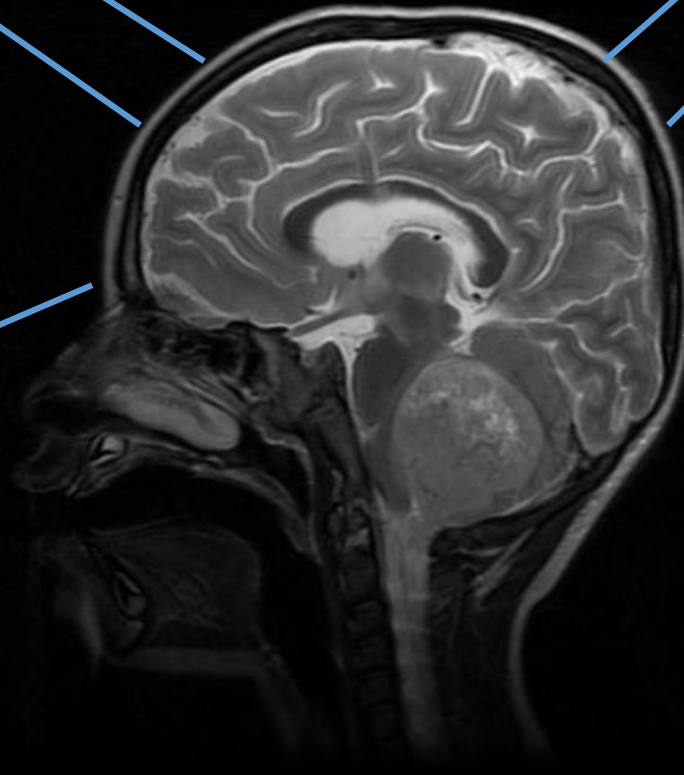
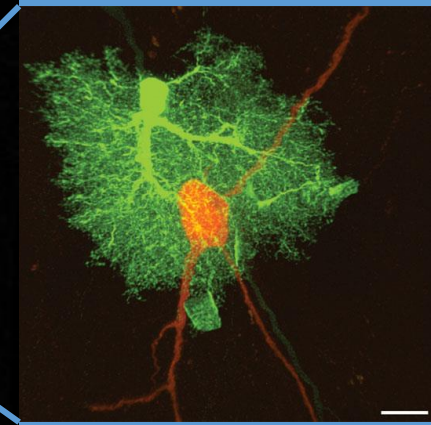
oligodendrocytes



microglia

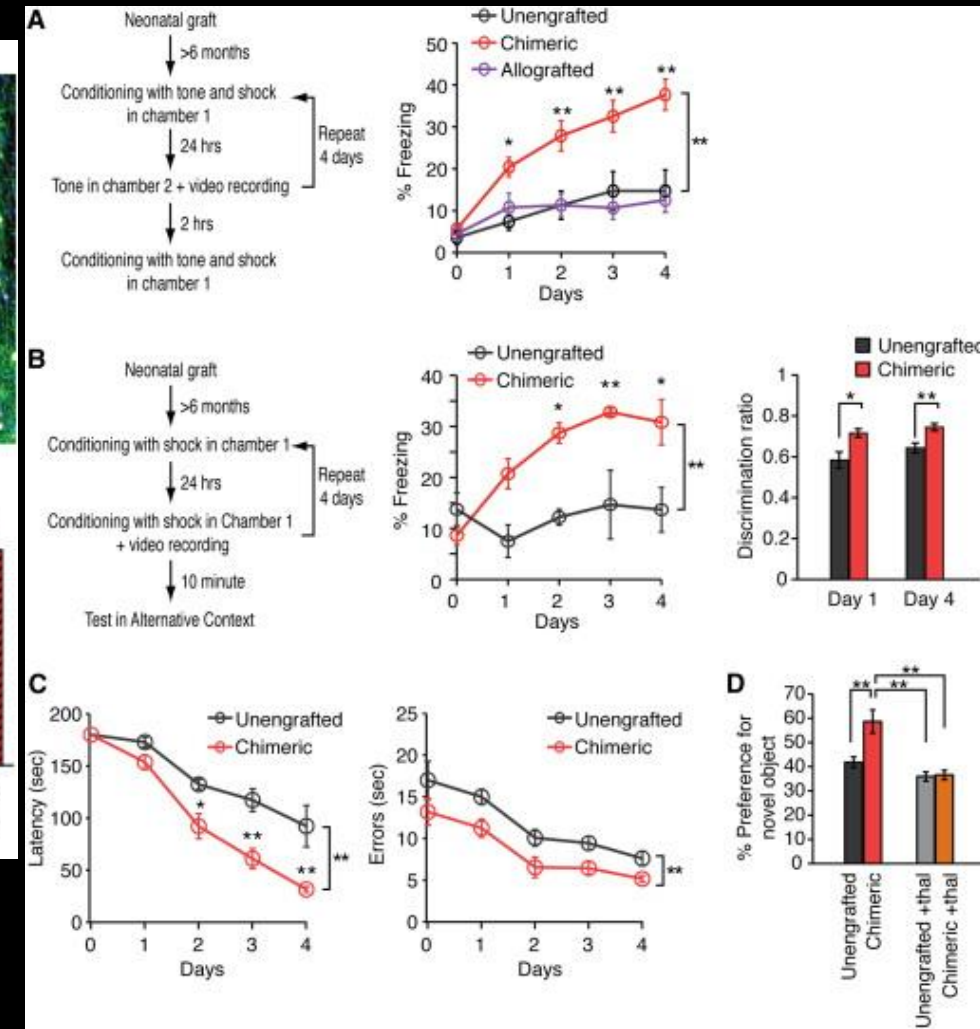
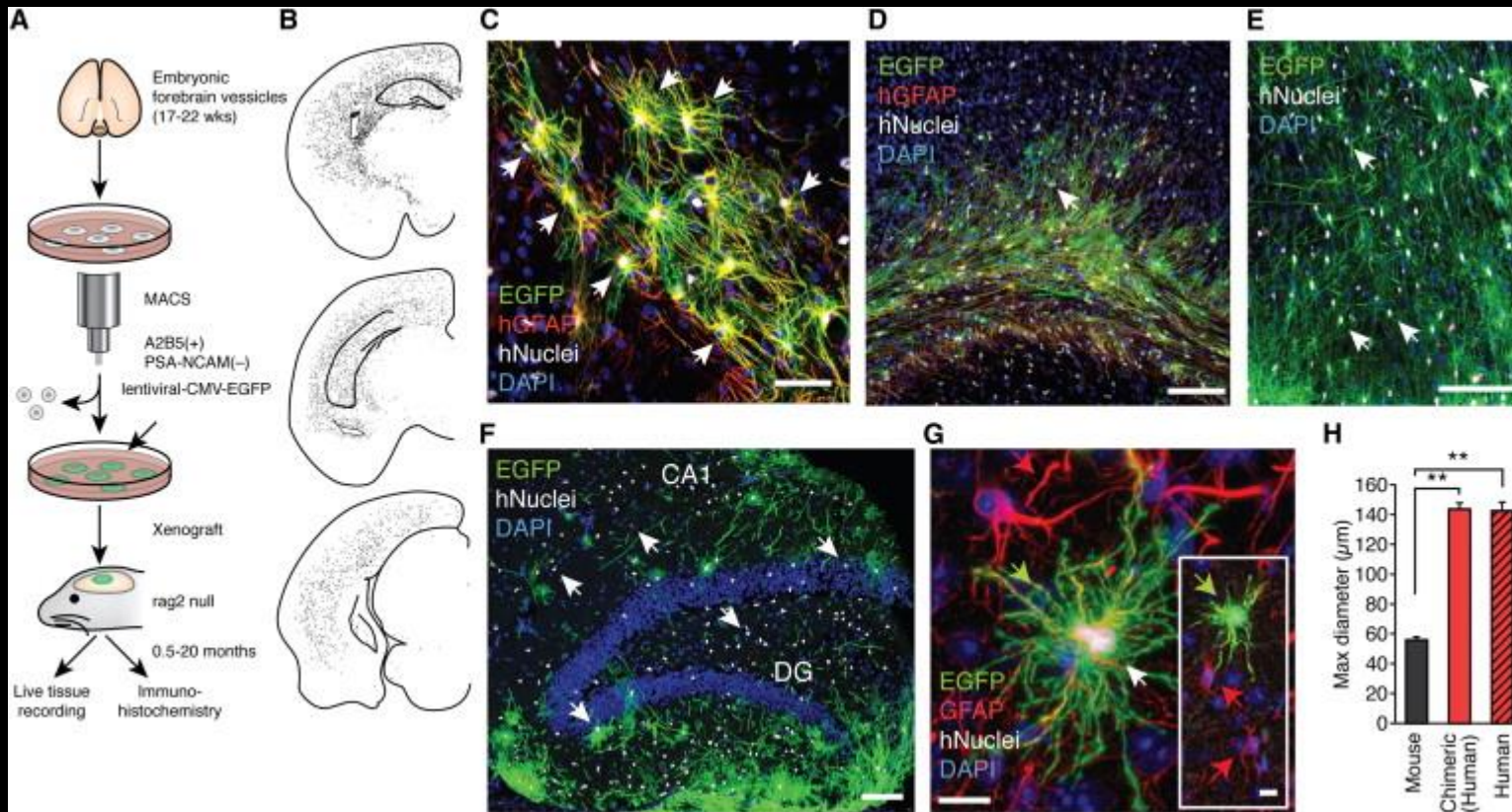


astrocytes





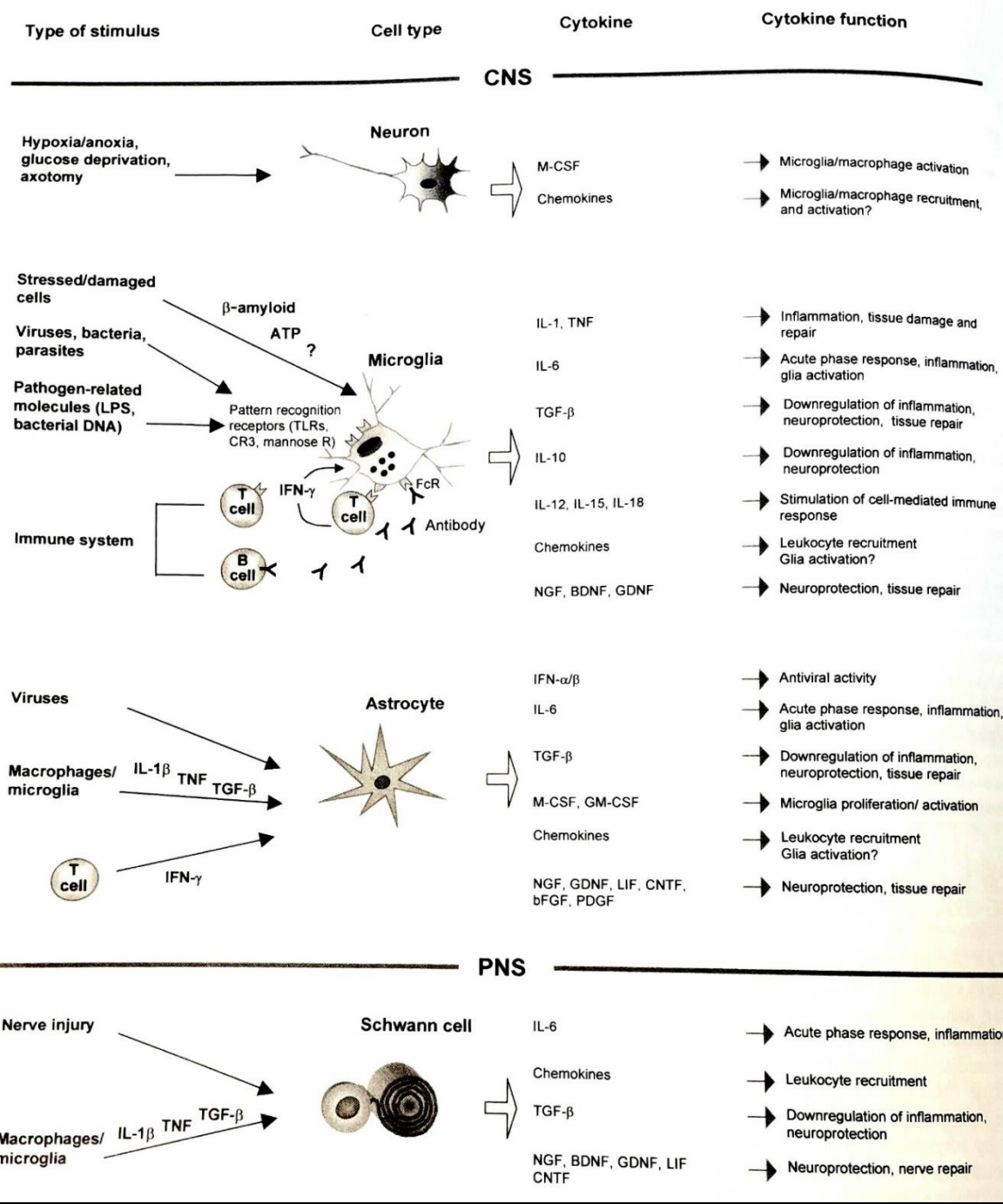
# Forebrain Engraftment by Human Glial Progenitor Cells Enhances Synaptic Plasticity and Learning in Adult Mice



Break

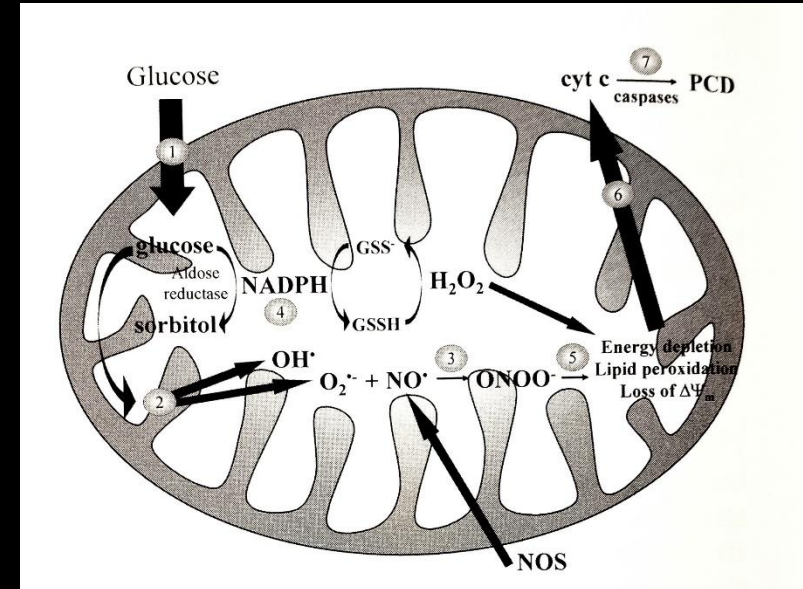
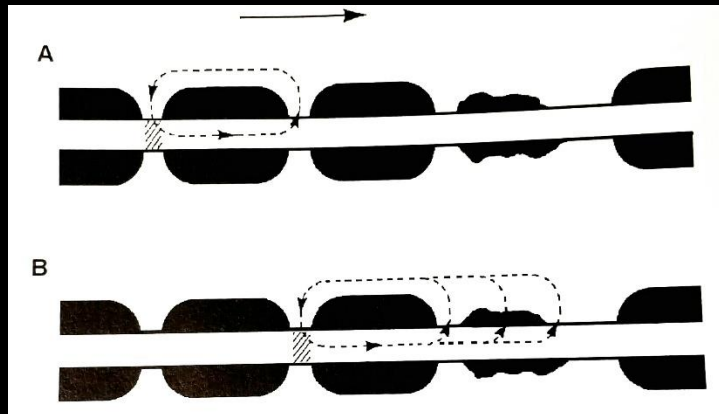
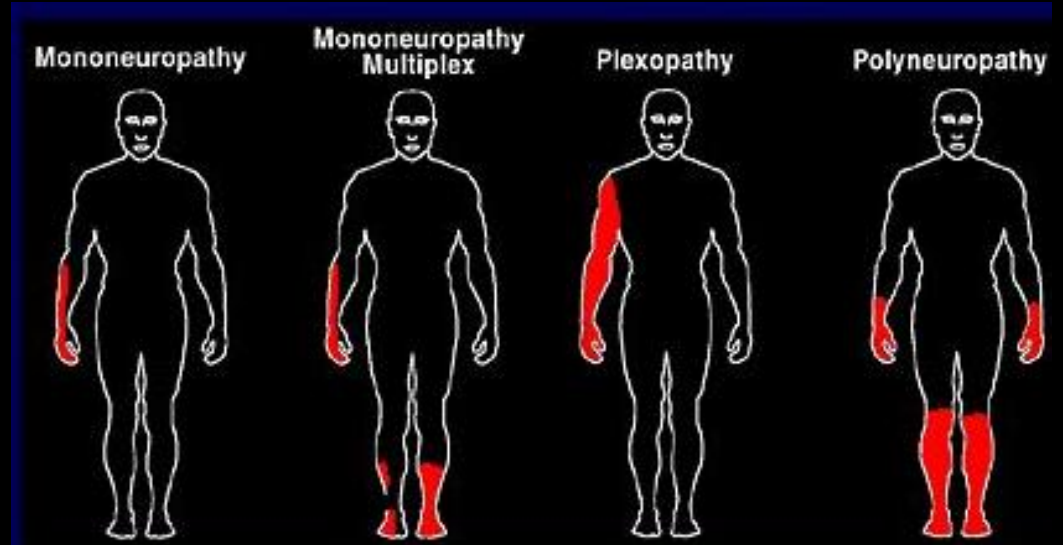
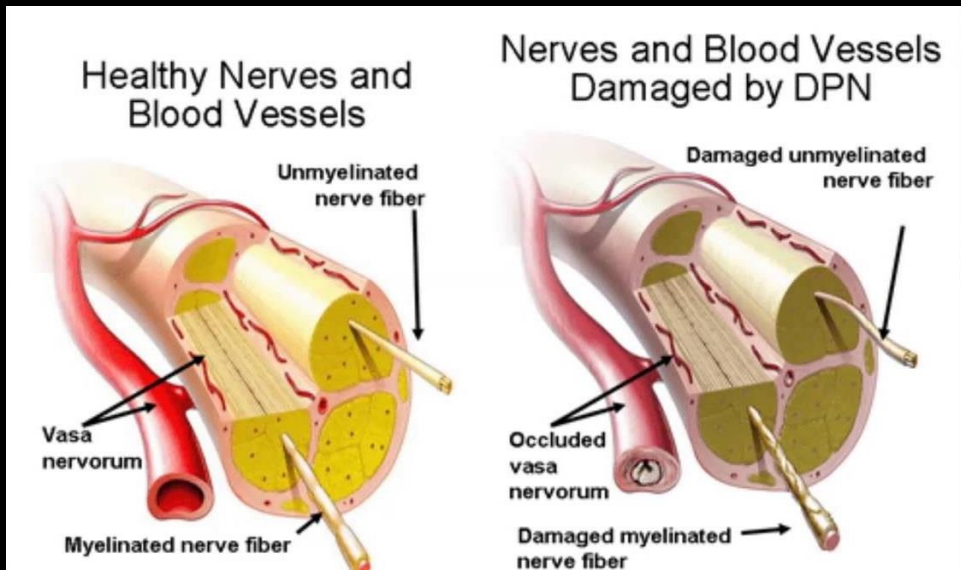


Neuroglia roles in  
nervous system, disease,  
and degeneration

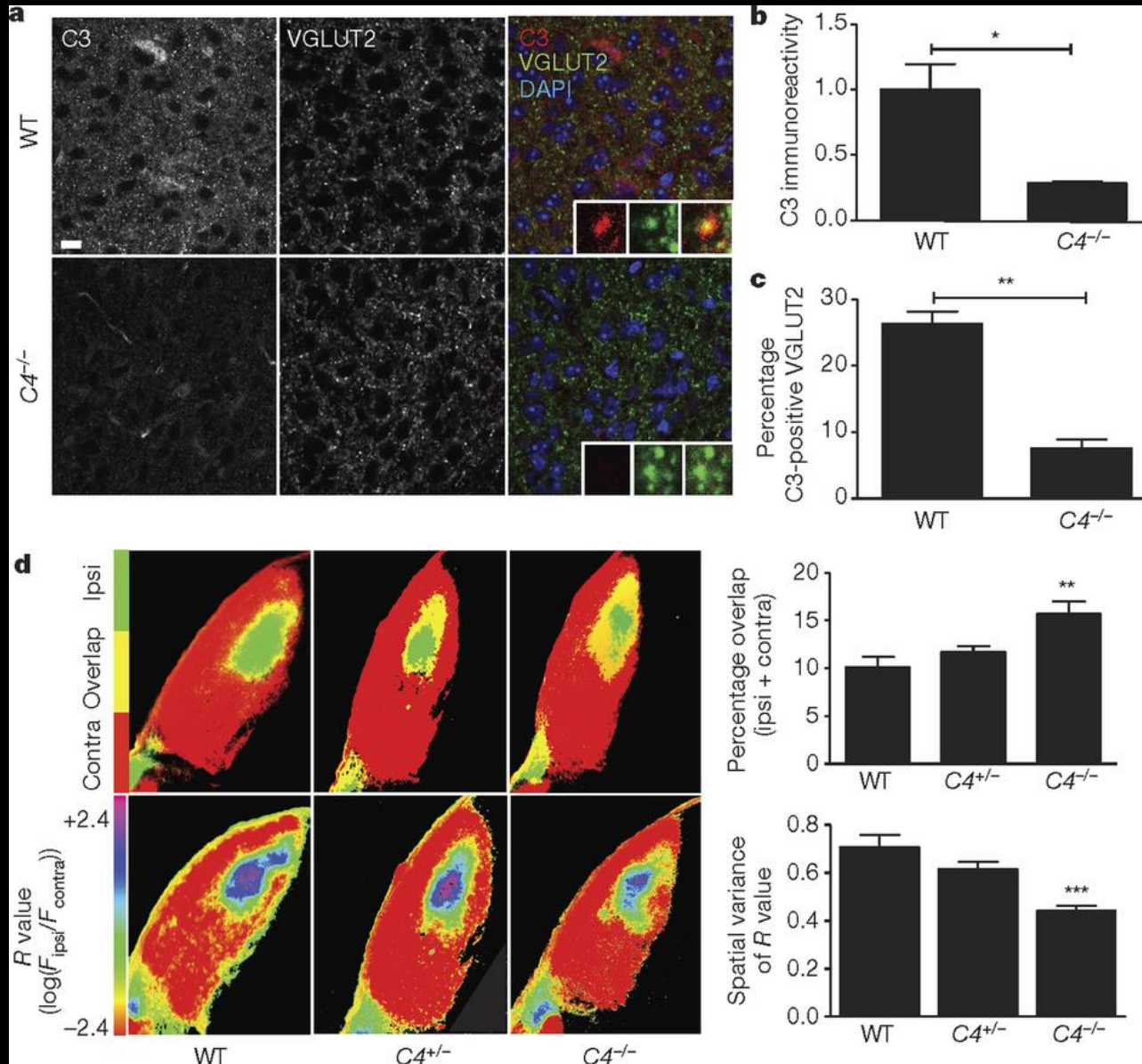




# Diabetes: diabetic peripheral neuropathy disorder

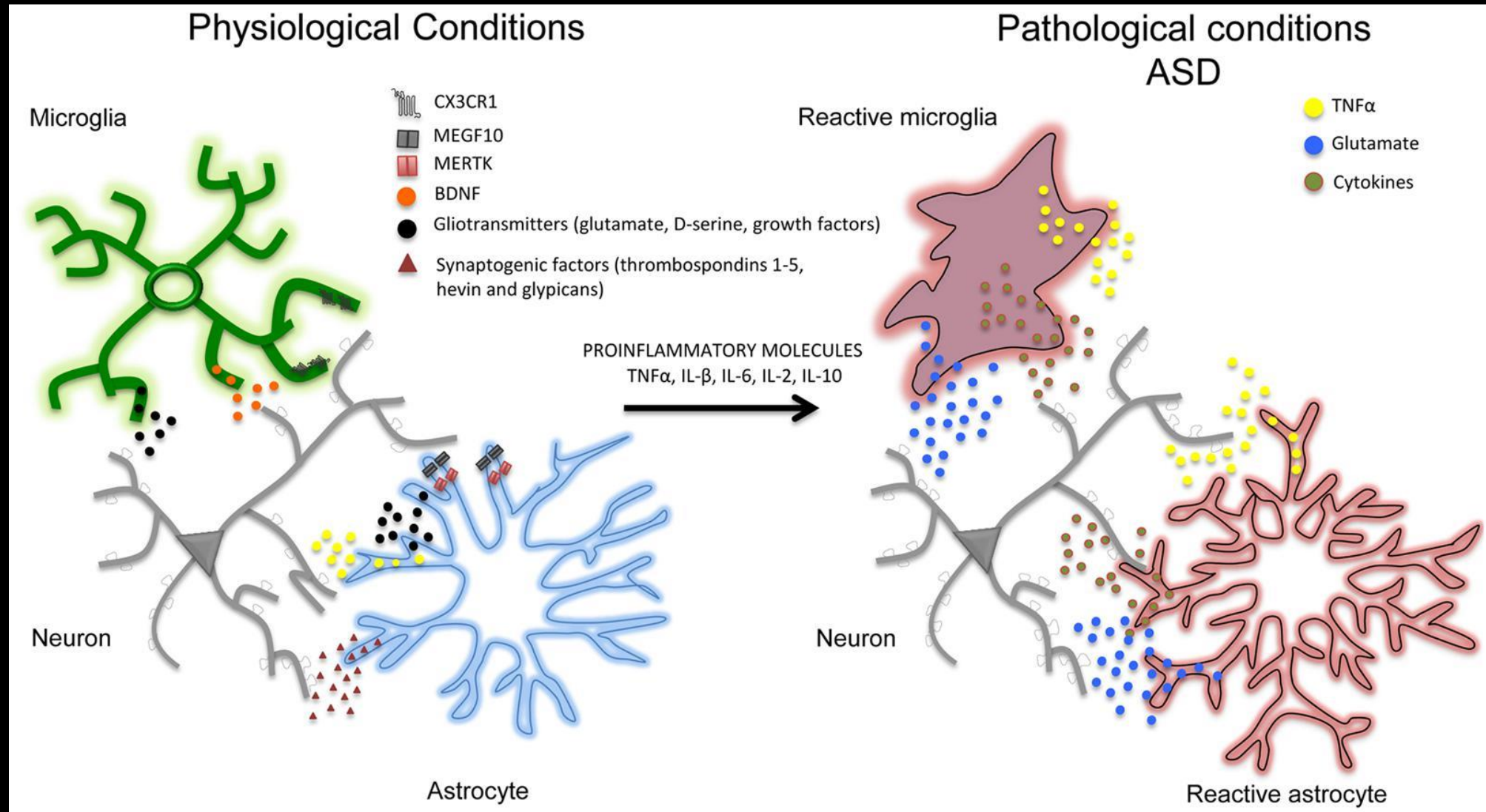


# Schizophrenia

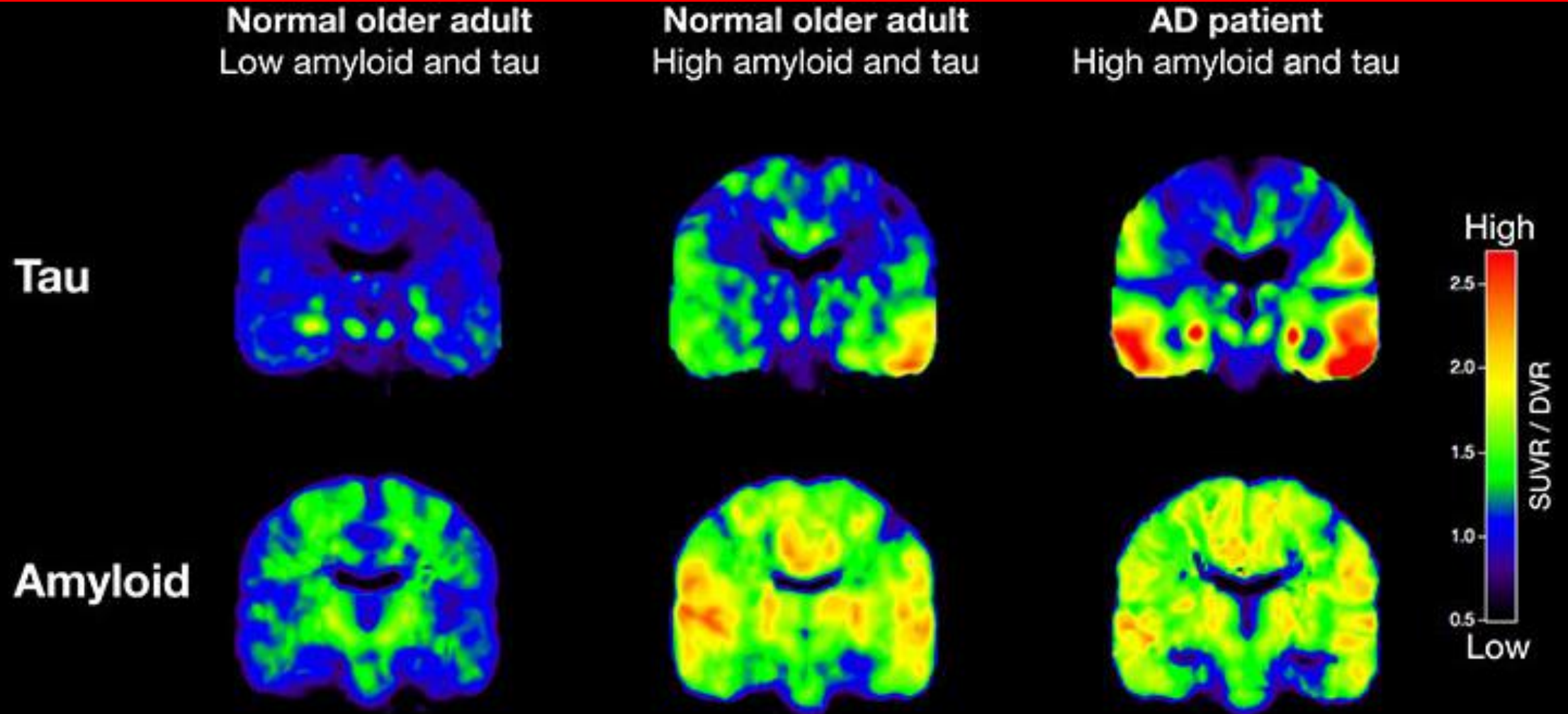




# Autism Spectrum Disorders (ASD)



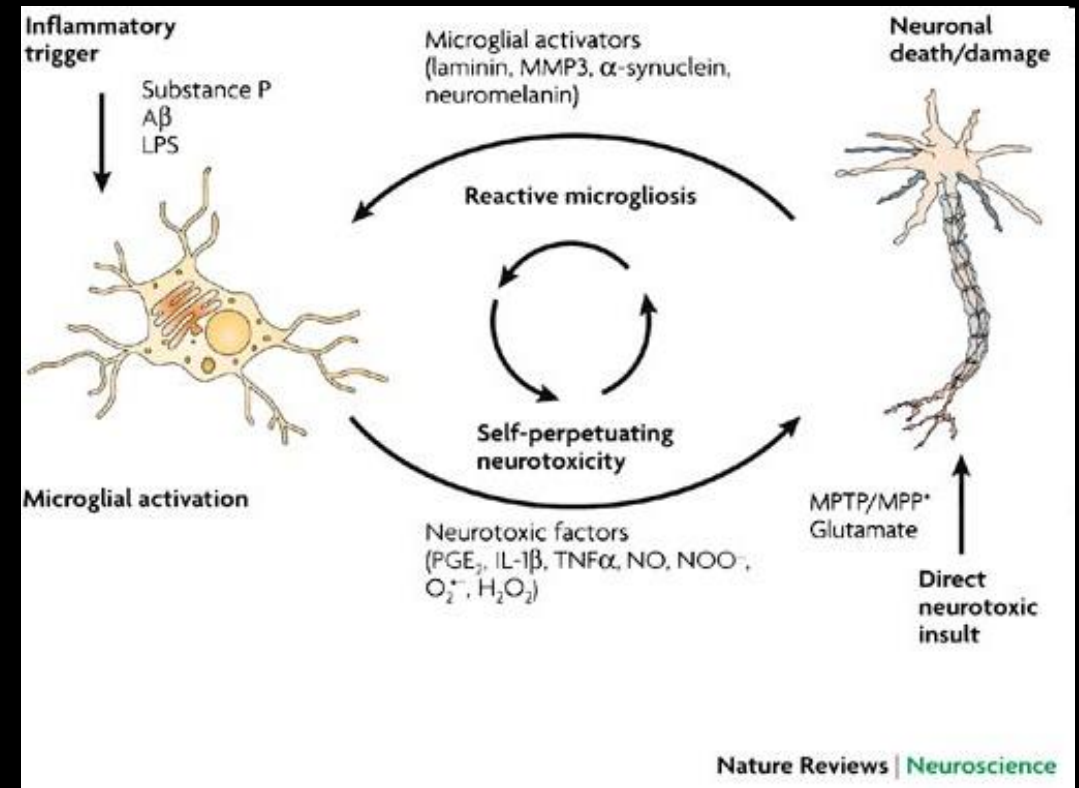
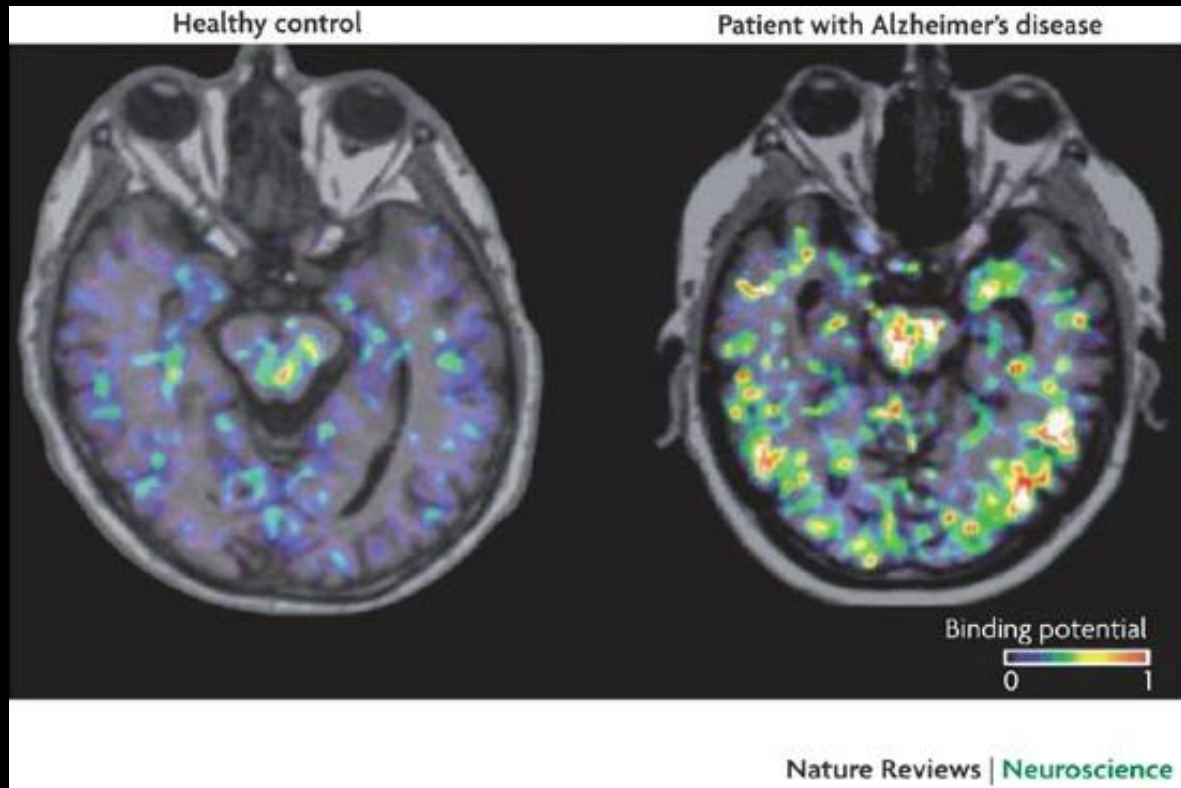
# Alzheimer's disease



Shown are PET scans that track tau (top row) and beta-amyloid from two normal older people and one patient with Alzheimer's disease (AD). The normal older adult on the left has no brain amyloid deposition and minimal tau in the medial temporal lobe. In the normal older adult in the middle, amyloid deposition is present throughout the brain, and tau has spread out into the temporal cortex. In the AD patient, both amyloid and tau are spread through the brain. (Image by Michael Schöll)

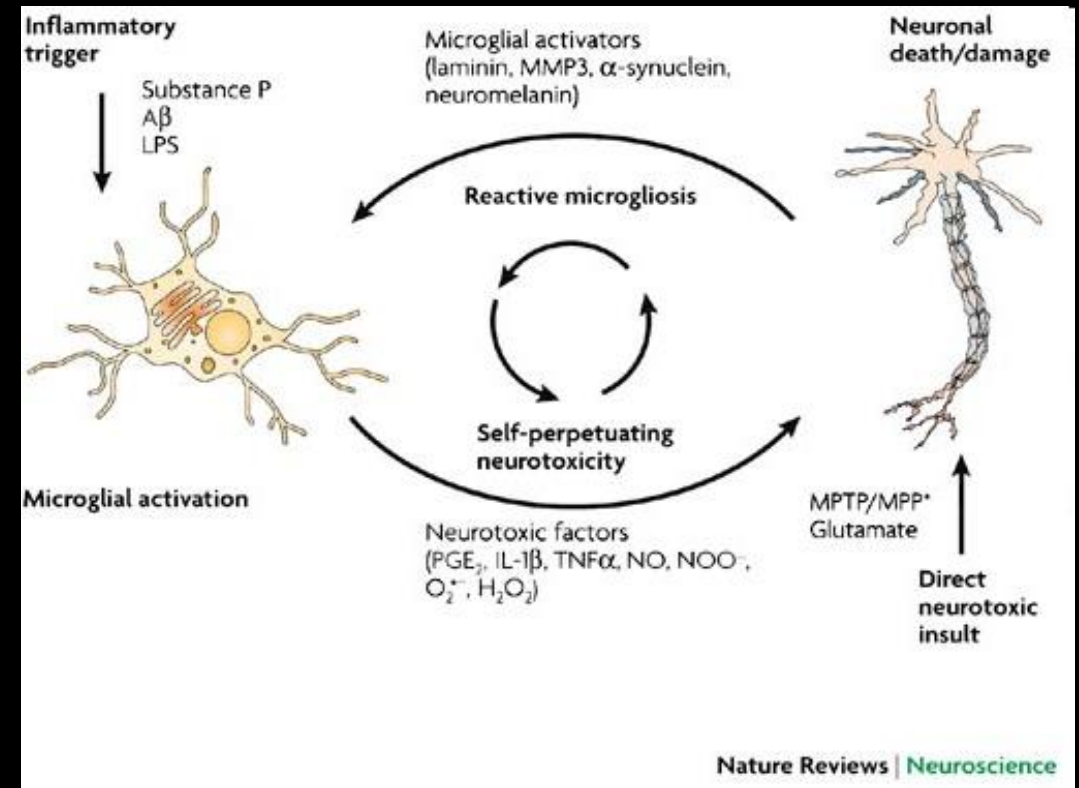
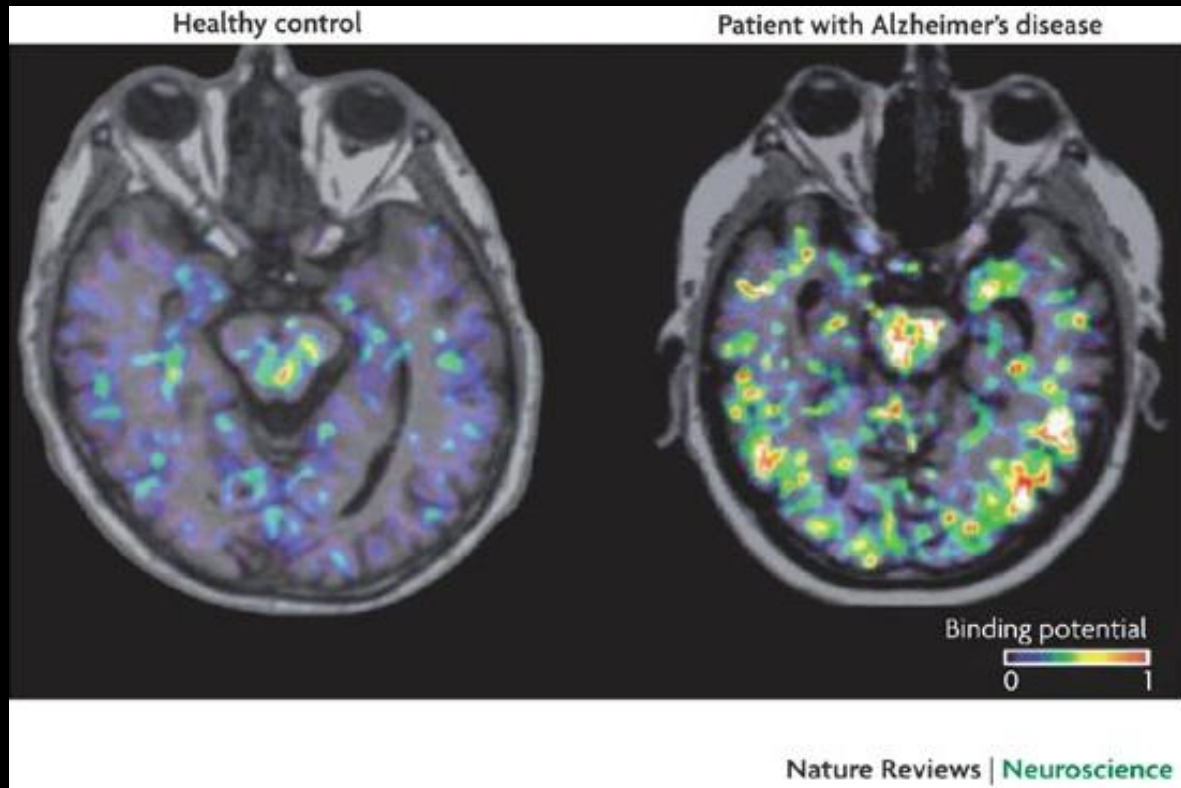


# Alzheimer's disease



Activated microglia (radiolabeled peripheral benzodiazepine receptor)

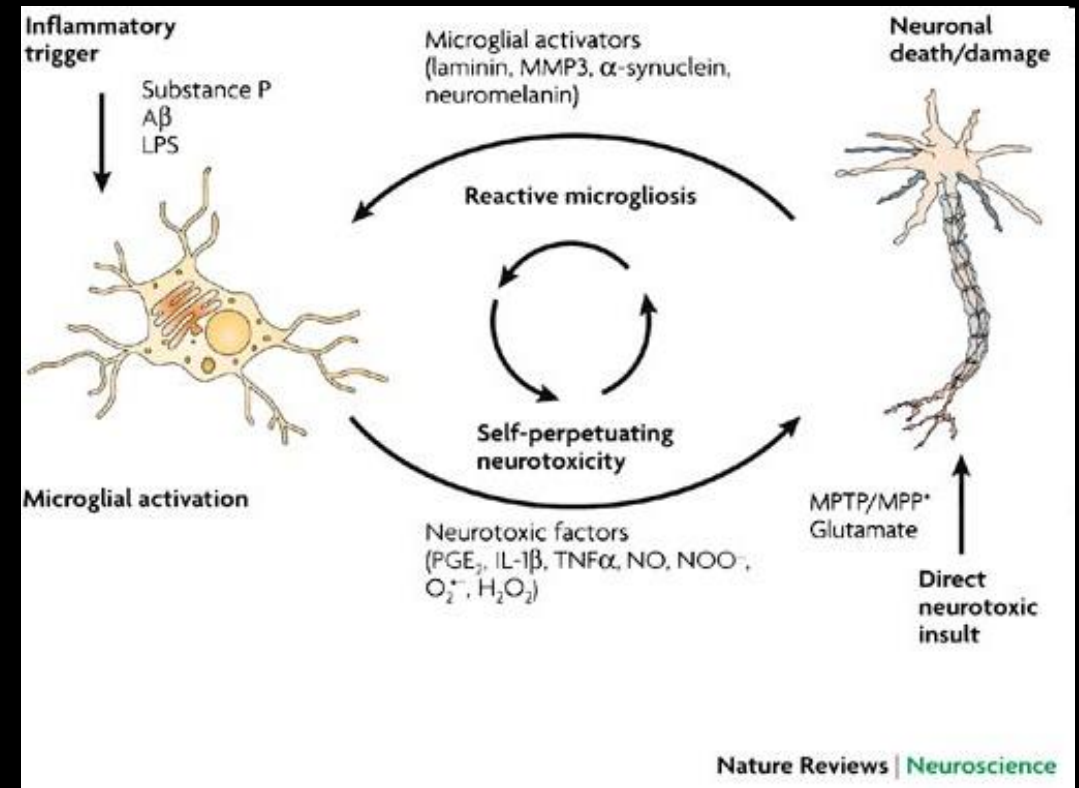
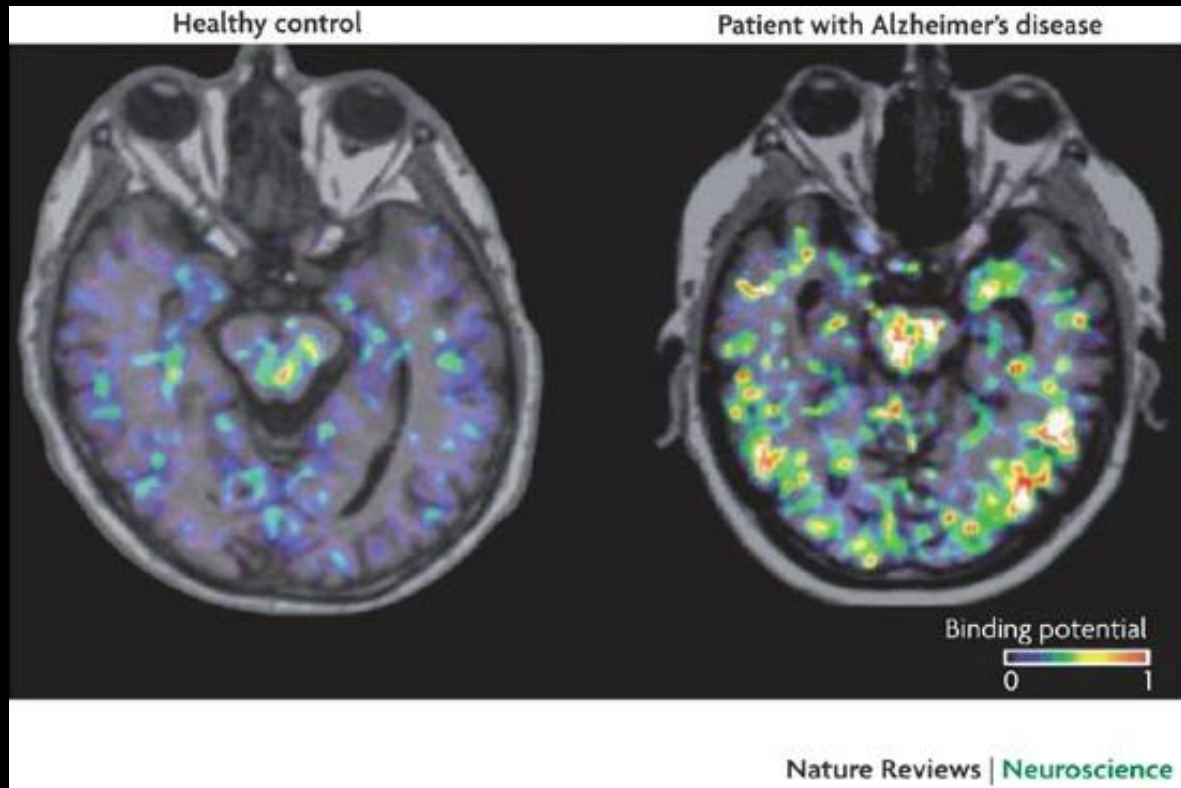
# Alzheimer's disease



Activated microglia (radiolabeled peripheral benzodiazepine receptor)

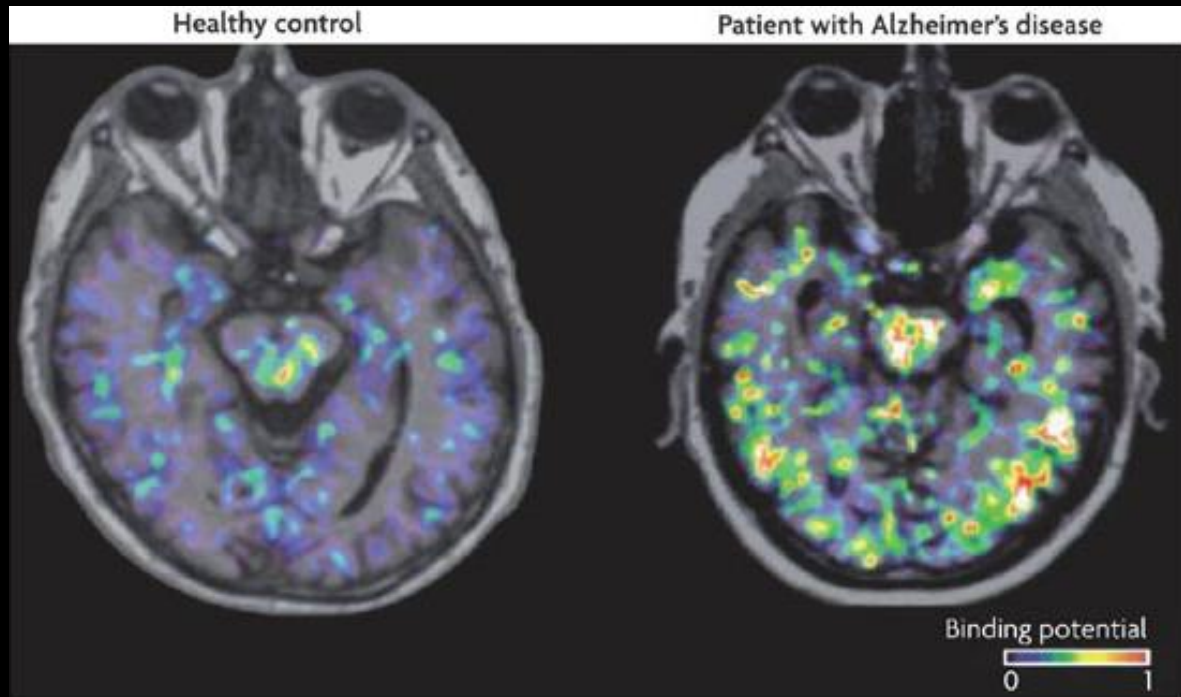


# Alzheimer's disease

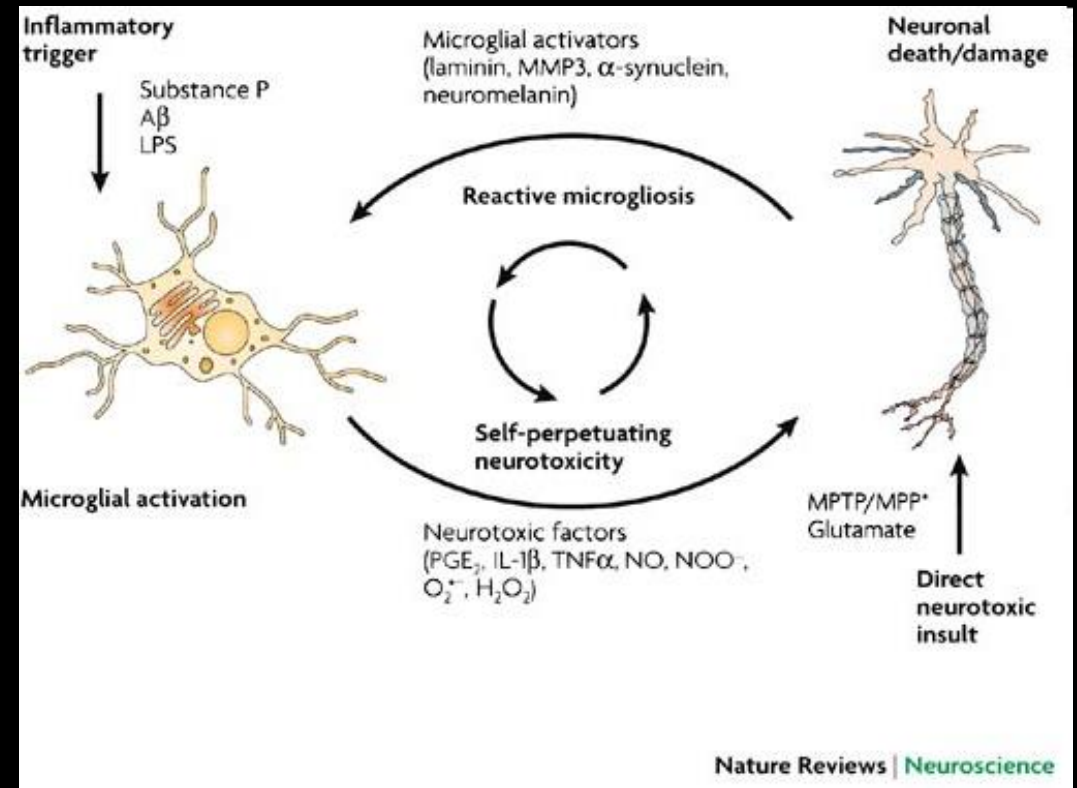


Activated microglia (radiolabeled peripheral benzodiazepine receptor)

# Alzheimer's disease



Nature Reviews | Neuroscience

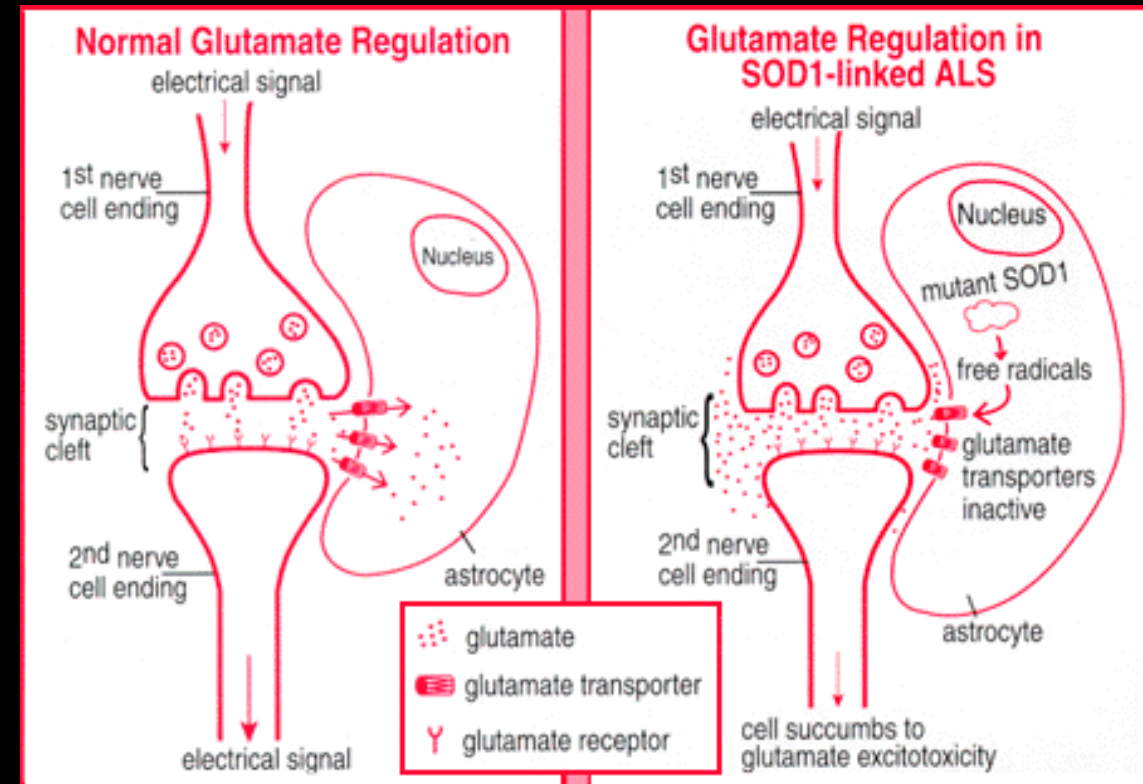
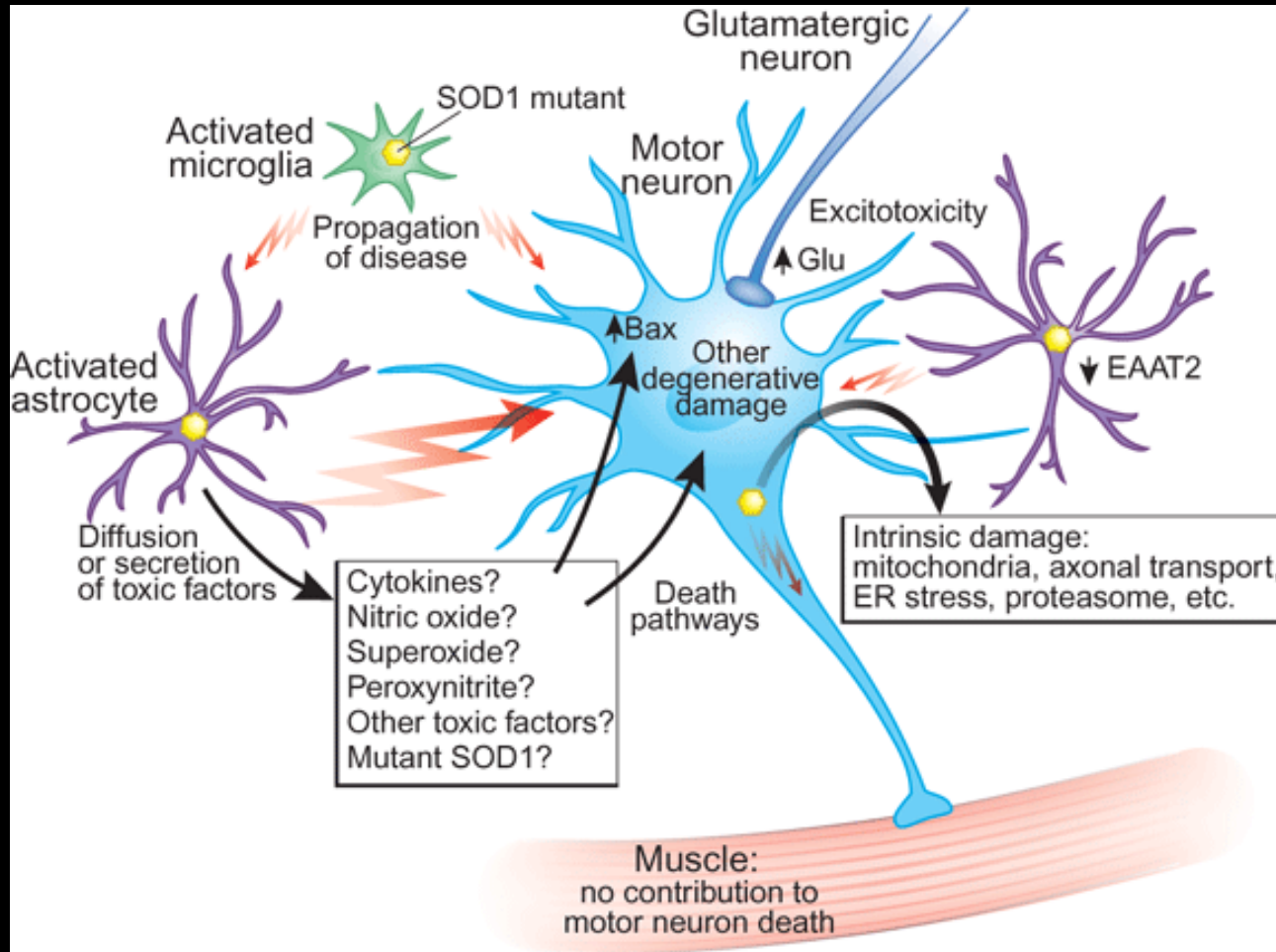


Nature Reviews | Neuroscience

Activated microglia (radiolabeled peripheral benzodiazepine receptor)



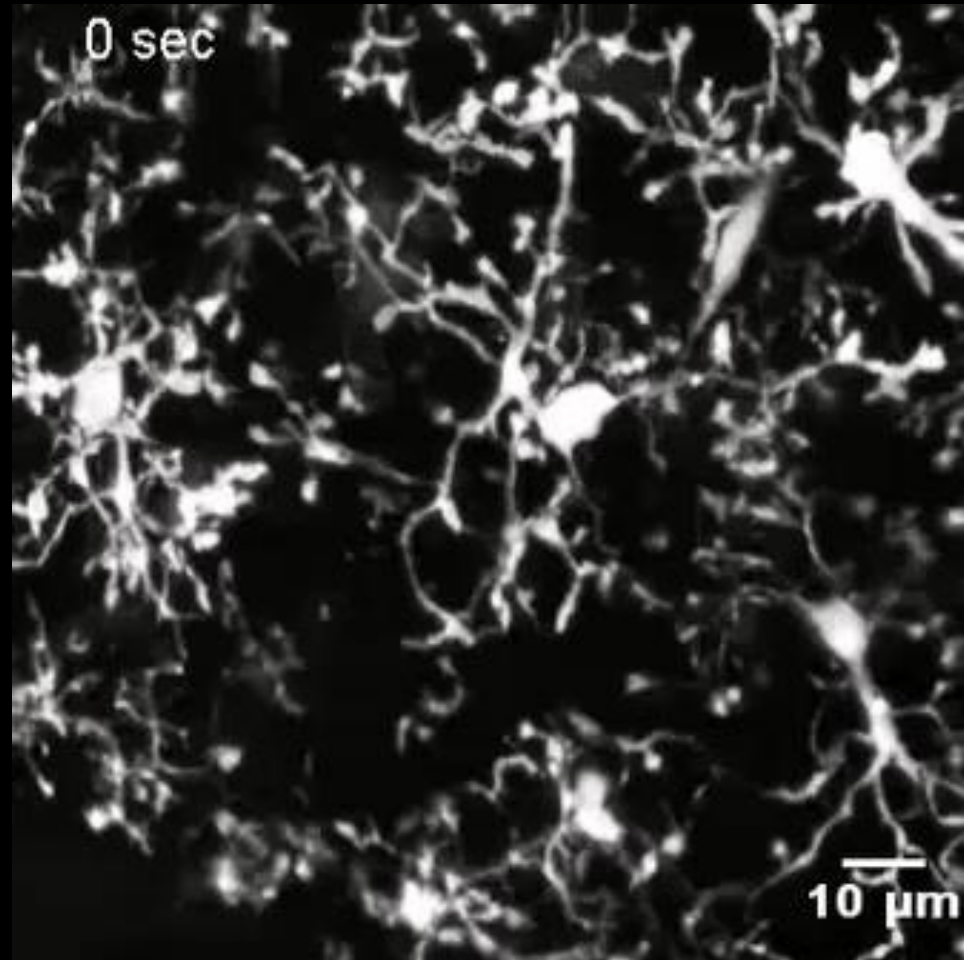
# ALS- Amyotrophic Lateral Sclerosis



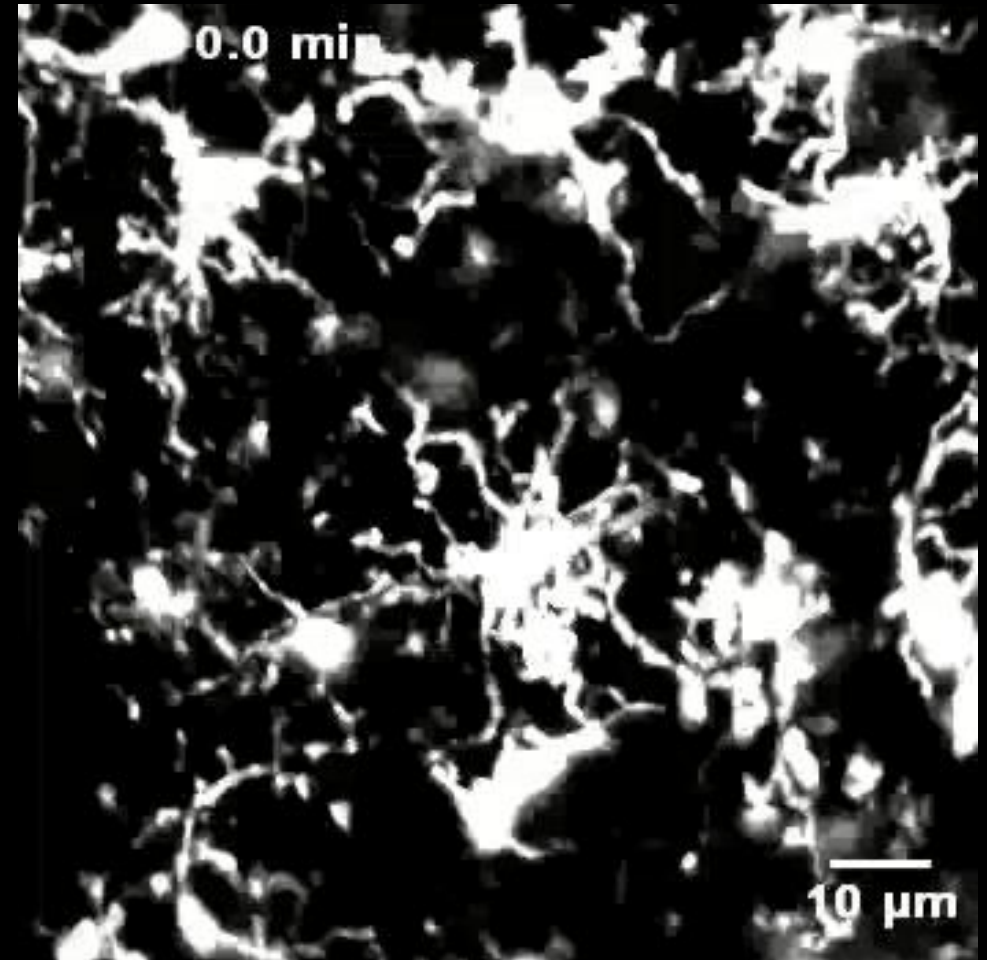
## Microglia respond to traumatic brain injury

Microglia show rapid response in the adult mouse CNS after a laser kills neurons at the surface of the brain

Microglia in resting brain



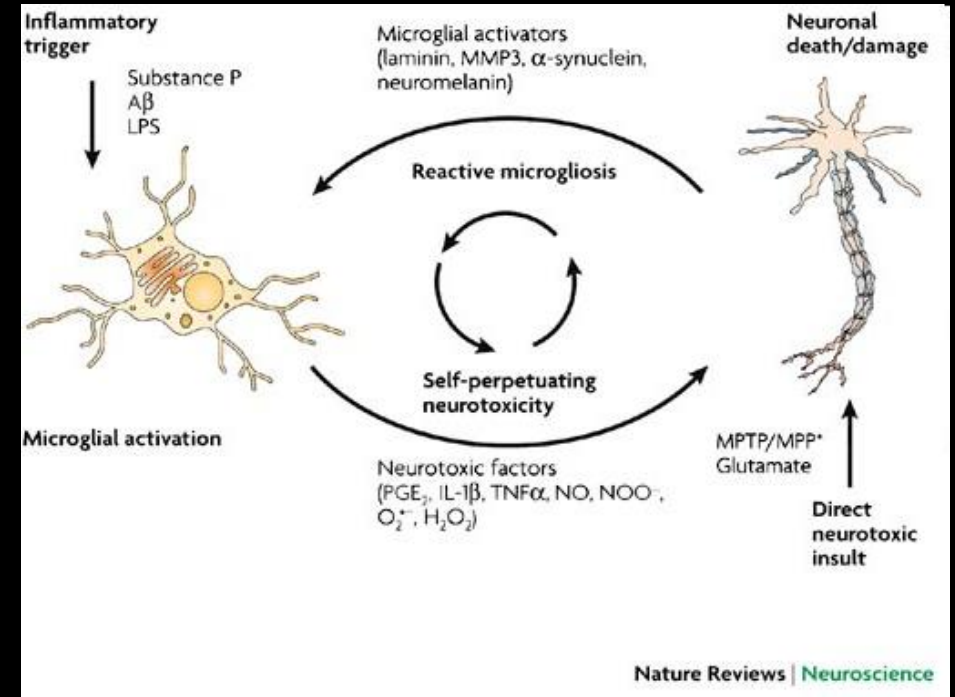
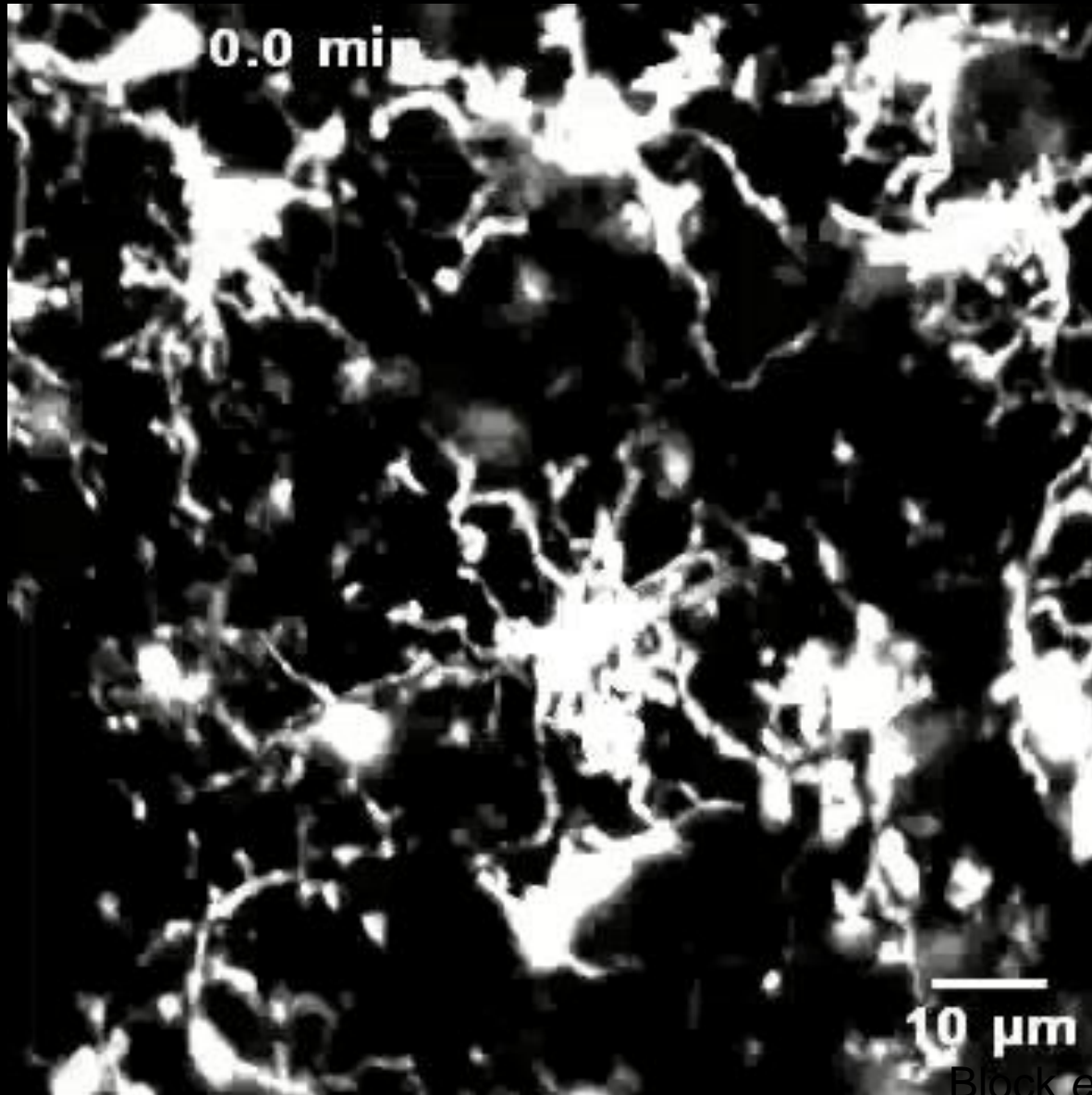
Microglia after laser injury





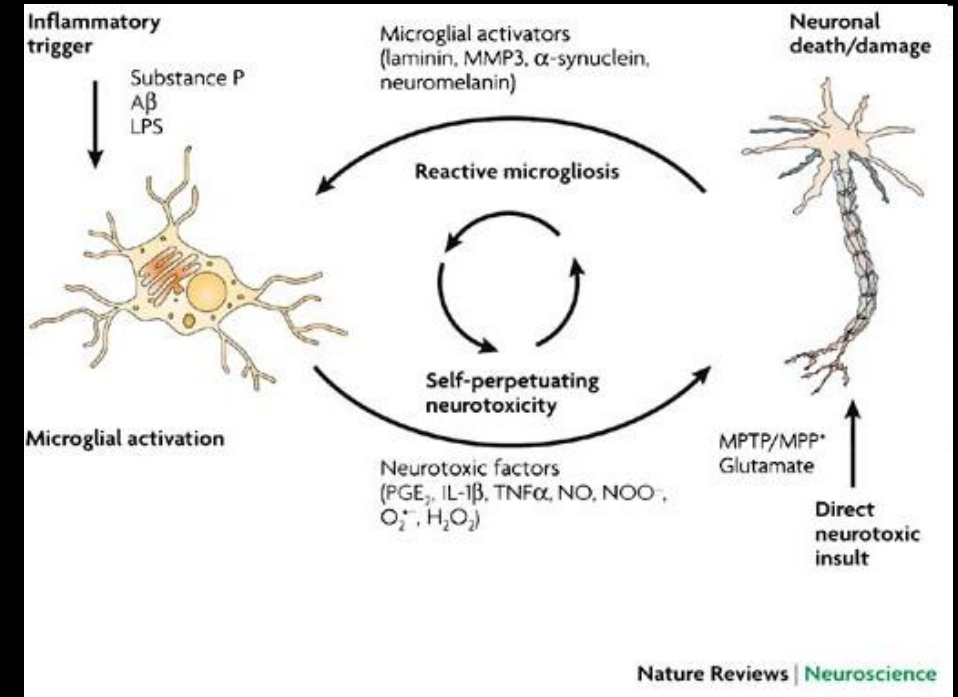
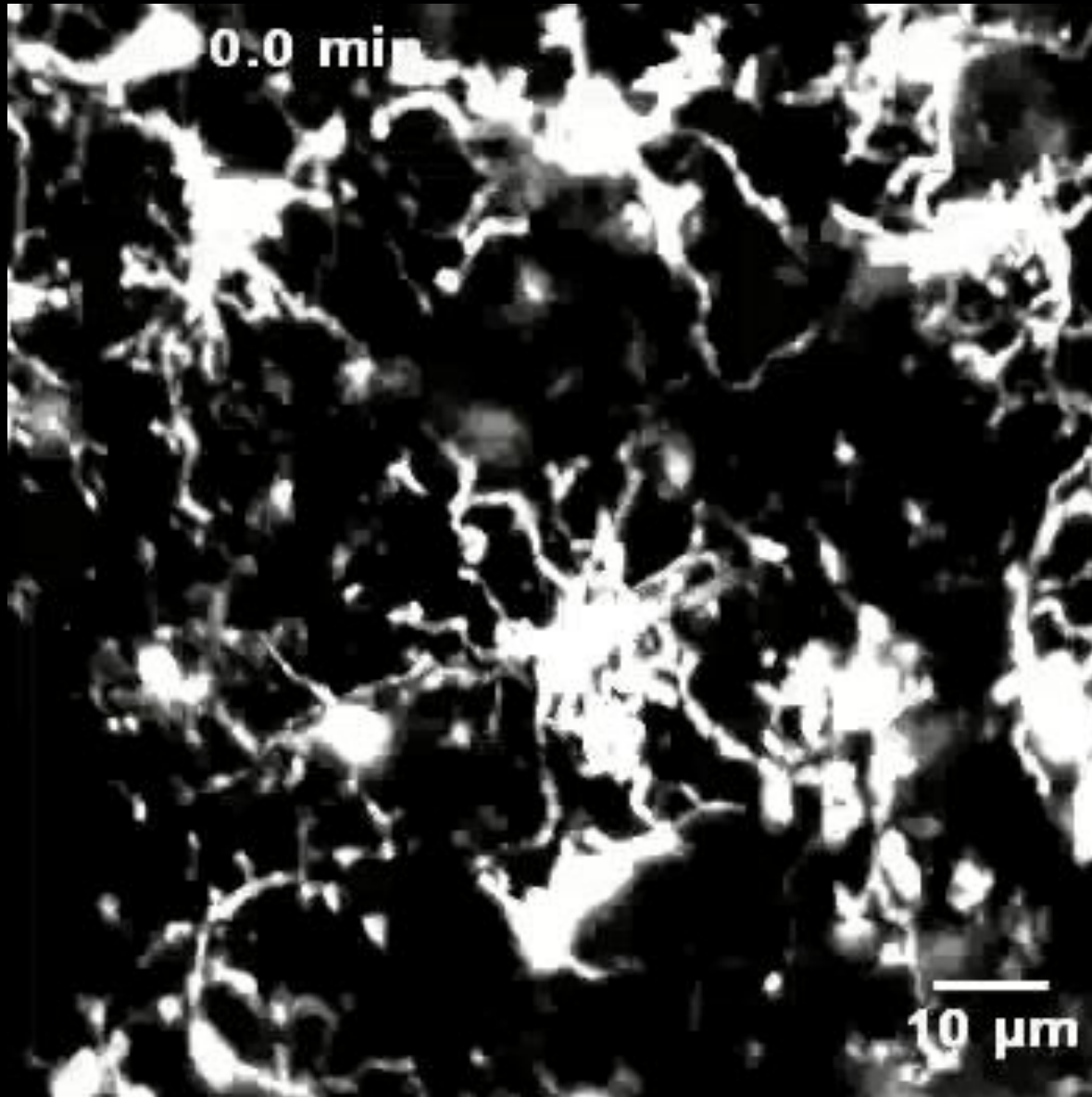
# Microgliosis induces secondary wave of degeneration after injury

Microglia after laser injury



# Microgliosis induces secondary wave of degeneration after injury

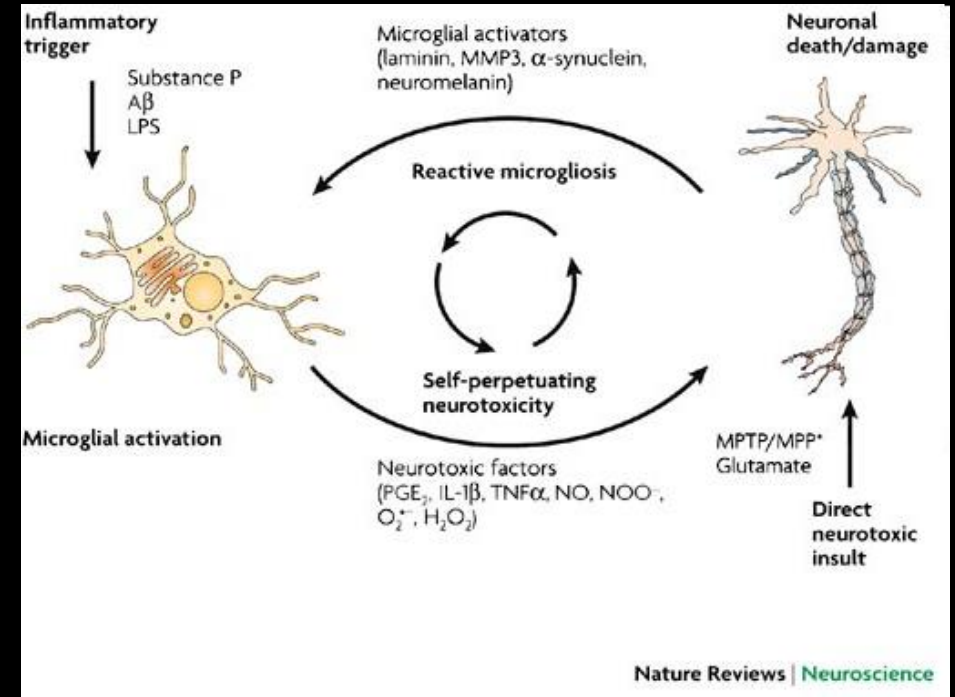
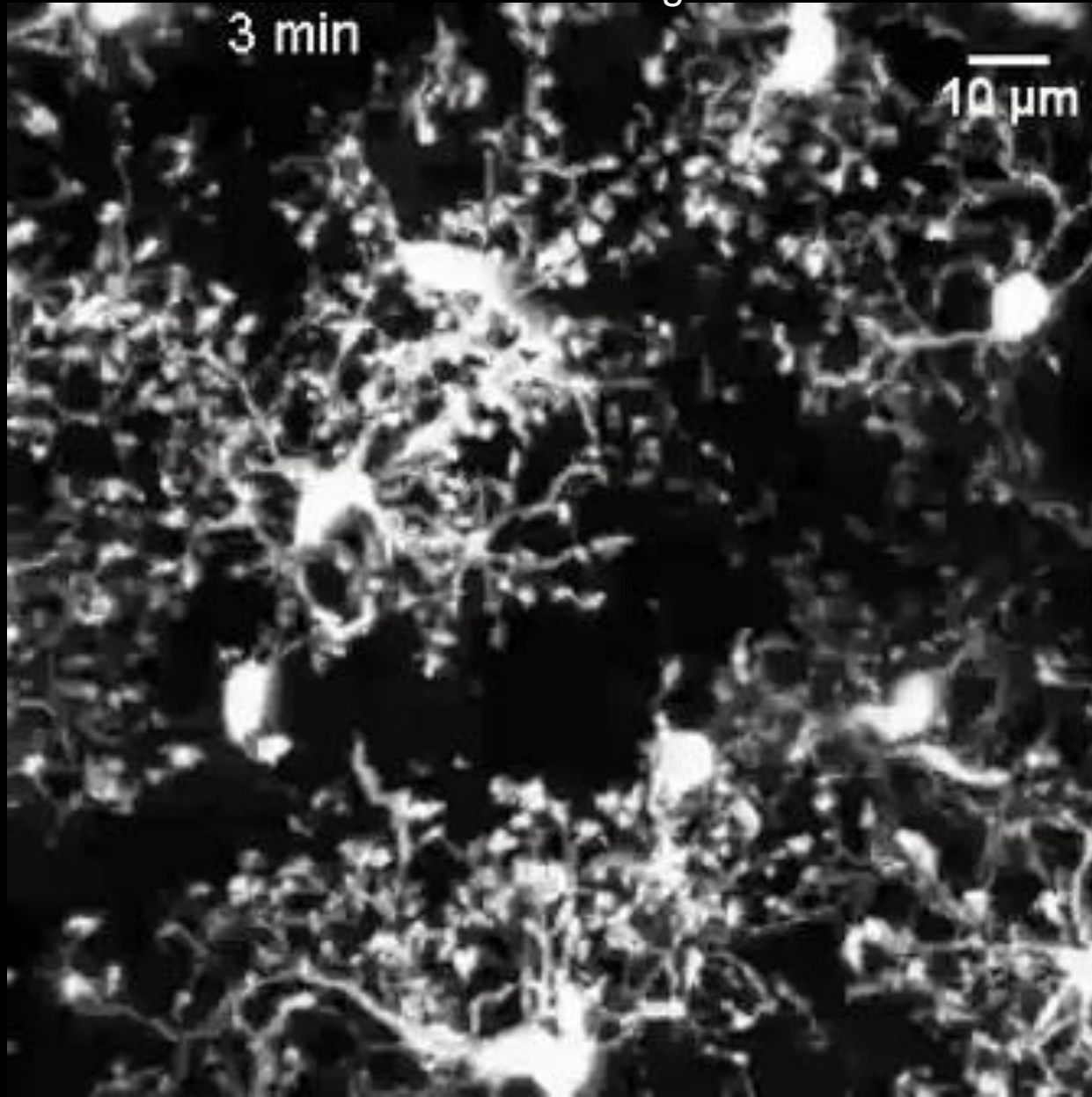
Microglia after laser injury





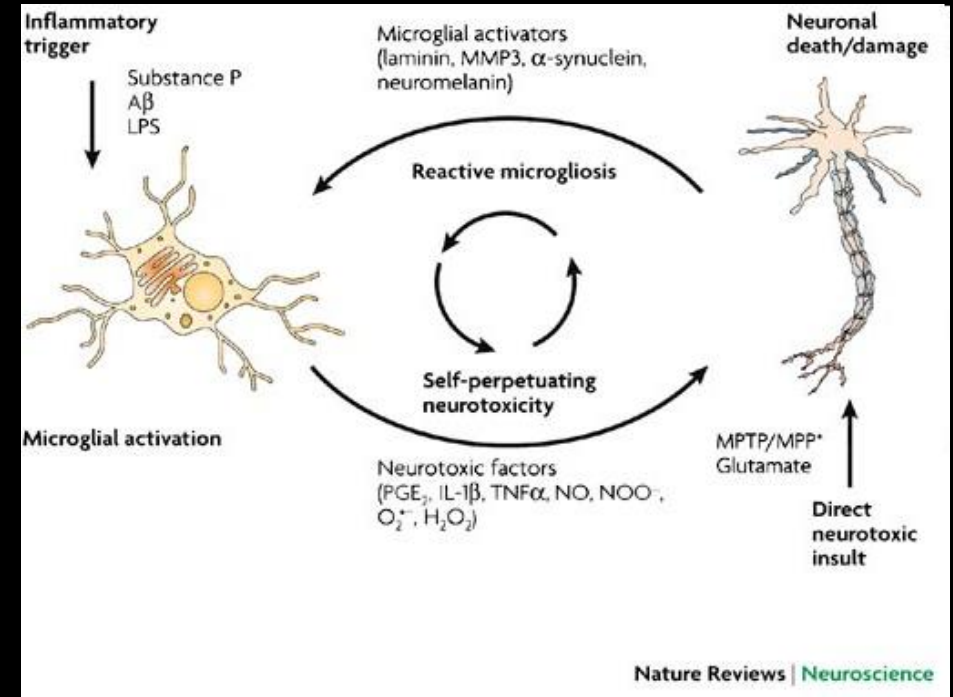
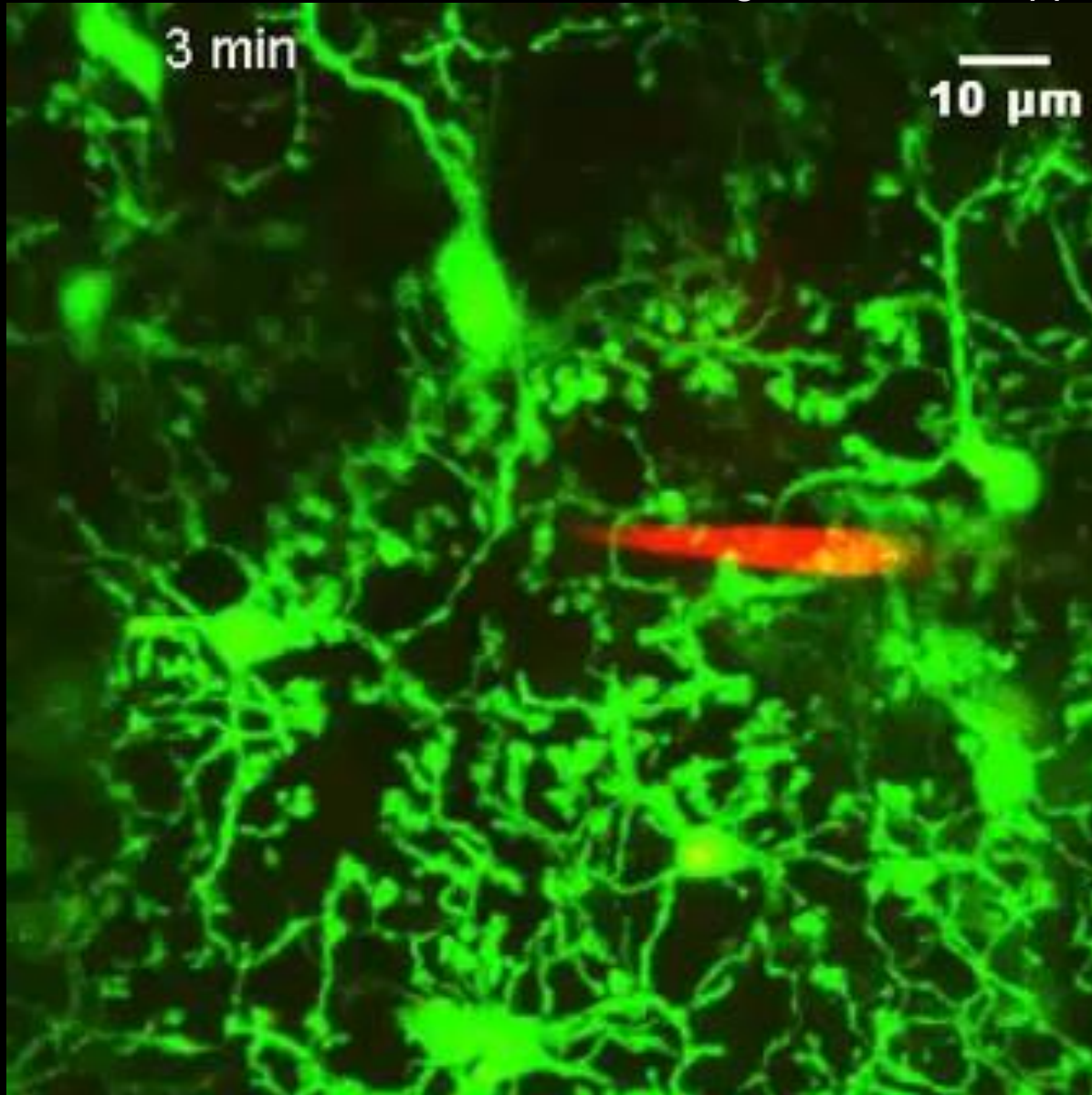
# Microgliosis induces secondary wave of degeneration after injury

Microglia after mechanical injury



# Microgliosis is induced by ATP

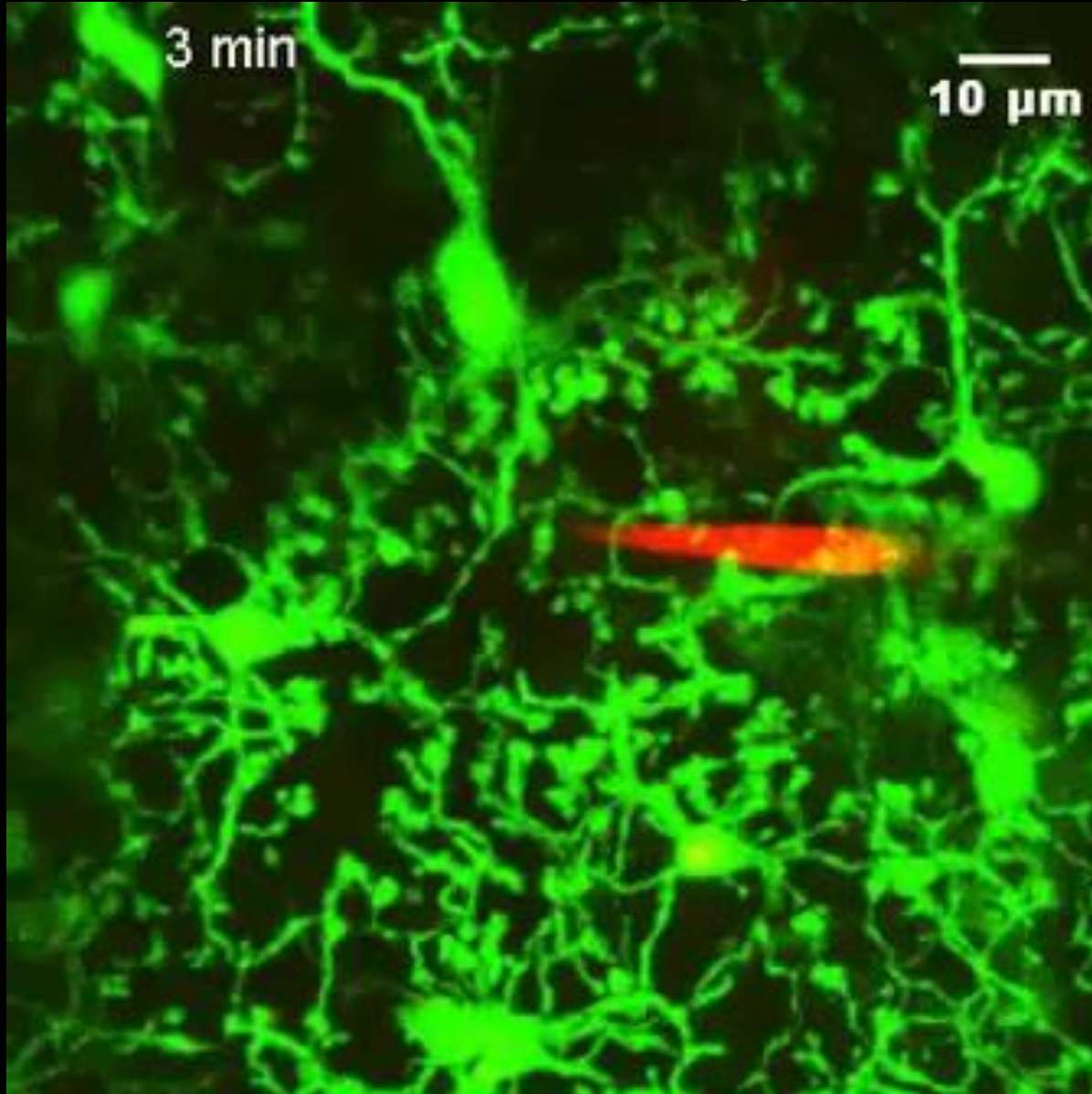
Microglia after ATP application





# Microgliosis is induced by ATP

Microglia after ATP application

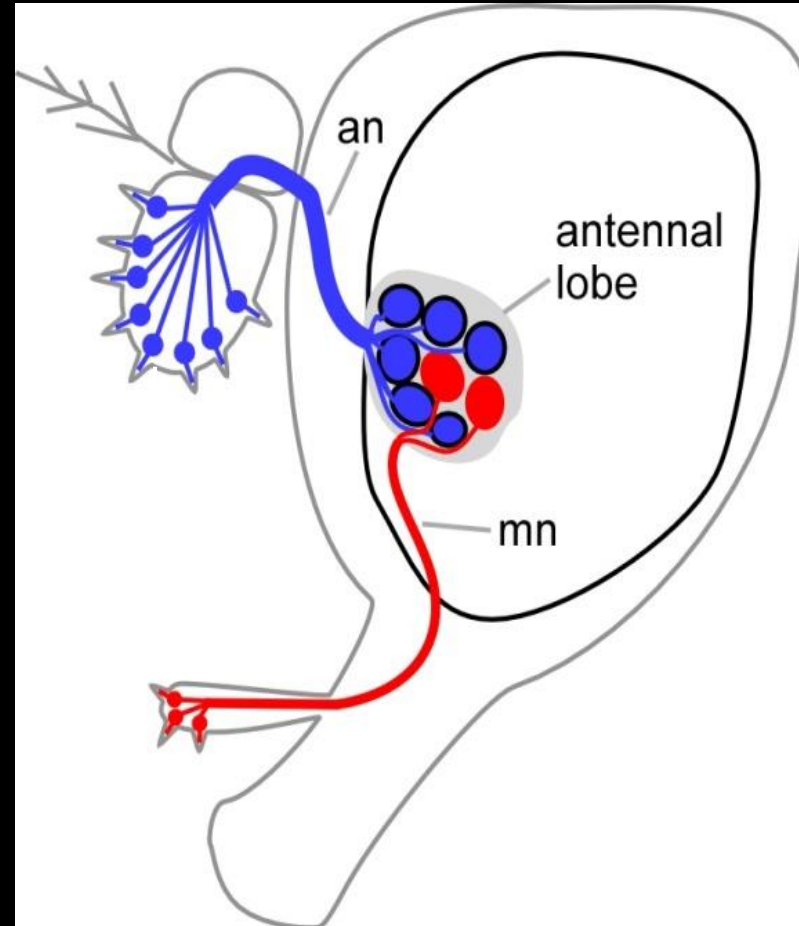


- Where is the balance between beneficial and detrimental glial activation?



- Where is the balance between beneficial and detrimental glial activation?
- What is the basic biology behind glial activation?

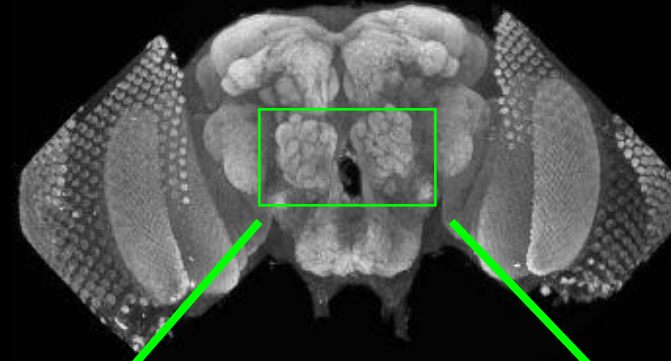
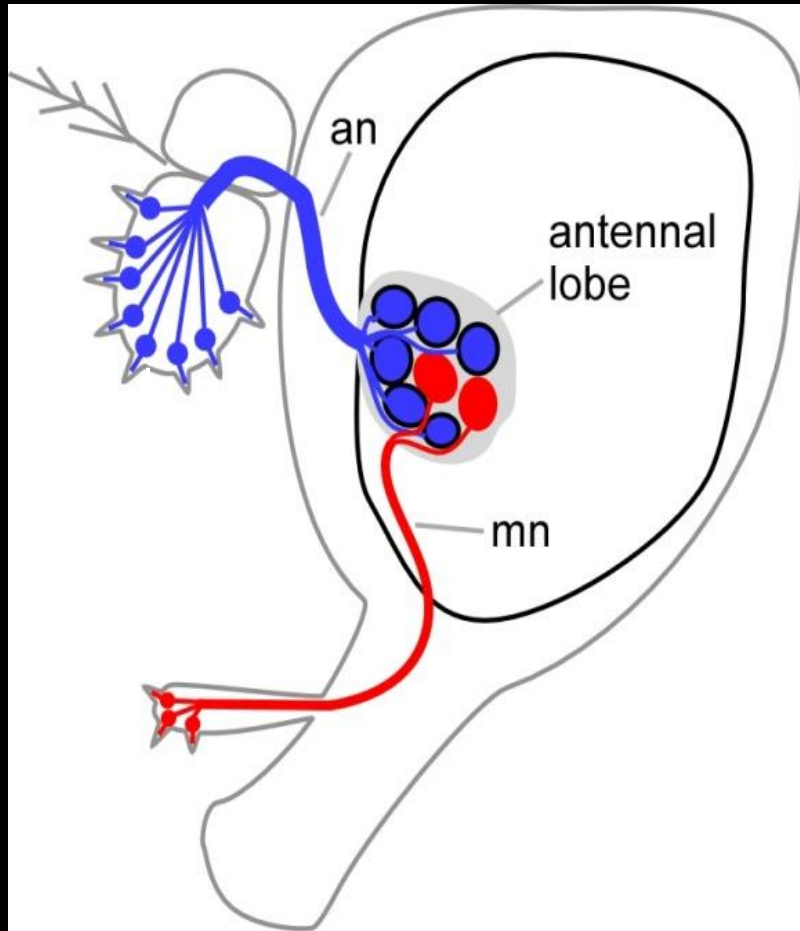
## Activating engulfment function in *Drosophila*



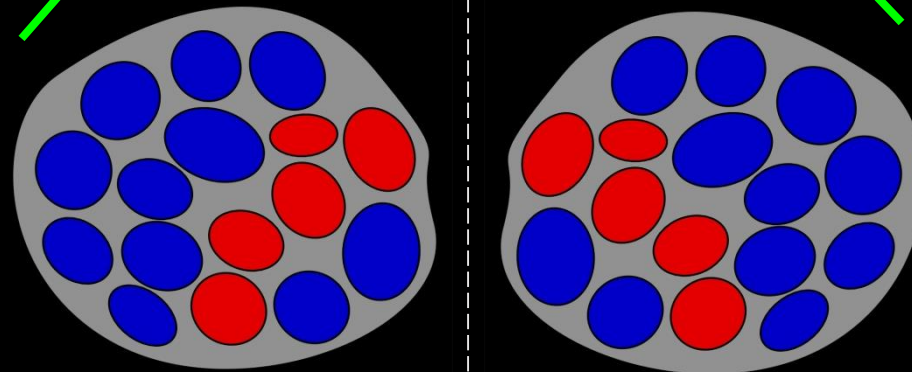


# Antennal and maxillary palp ORNs innervate distinct glomeruli

Curtsey of Dr. Xuejun Sun



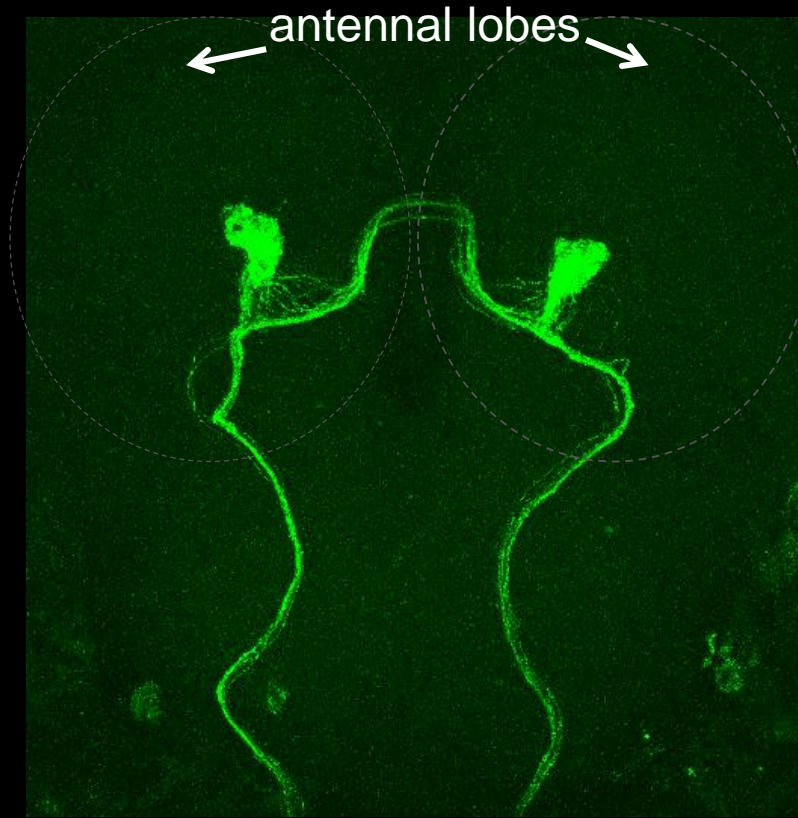
~44 antennal ORN innervated  
~6 maxillary palp ORN innervated



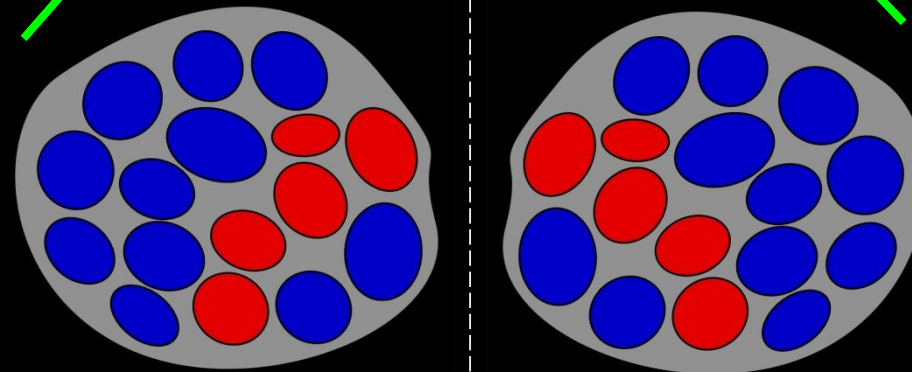
adult antennal lobes: home of the olfactory system

# Antennal and maxillary palp ORNs innervate distinct glomeruli

Curtsey of Dr. Xuejun Sun

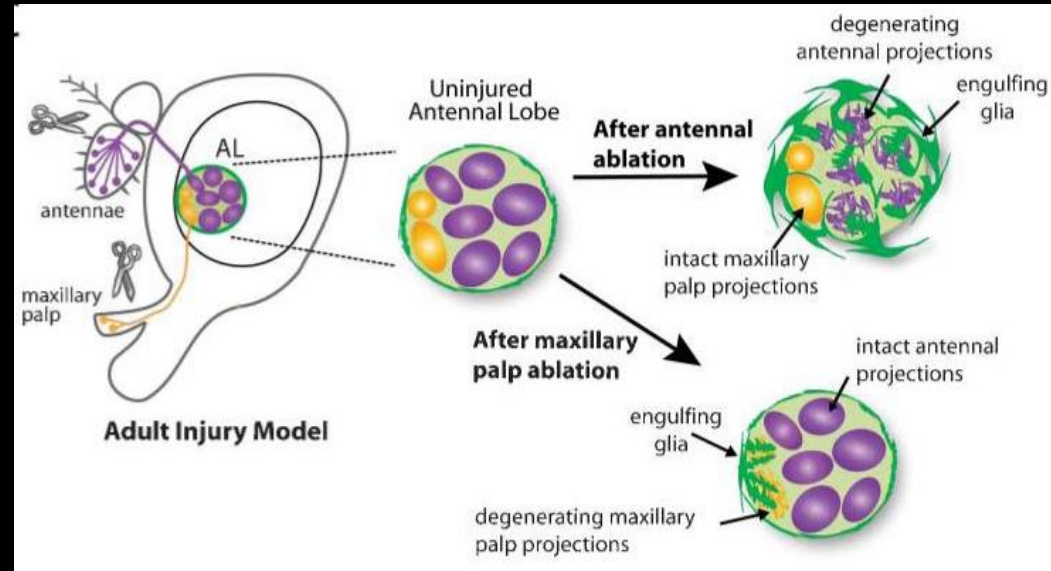


~44 antennal ORN innervated  
~6 maxillary palp ORN innervated



adult antennal lobes: home of the olfactory system

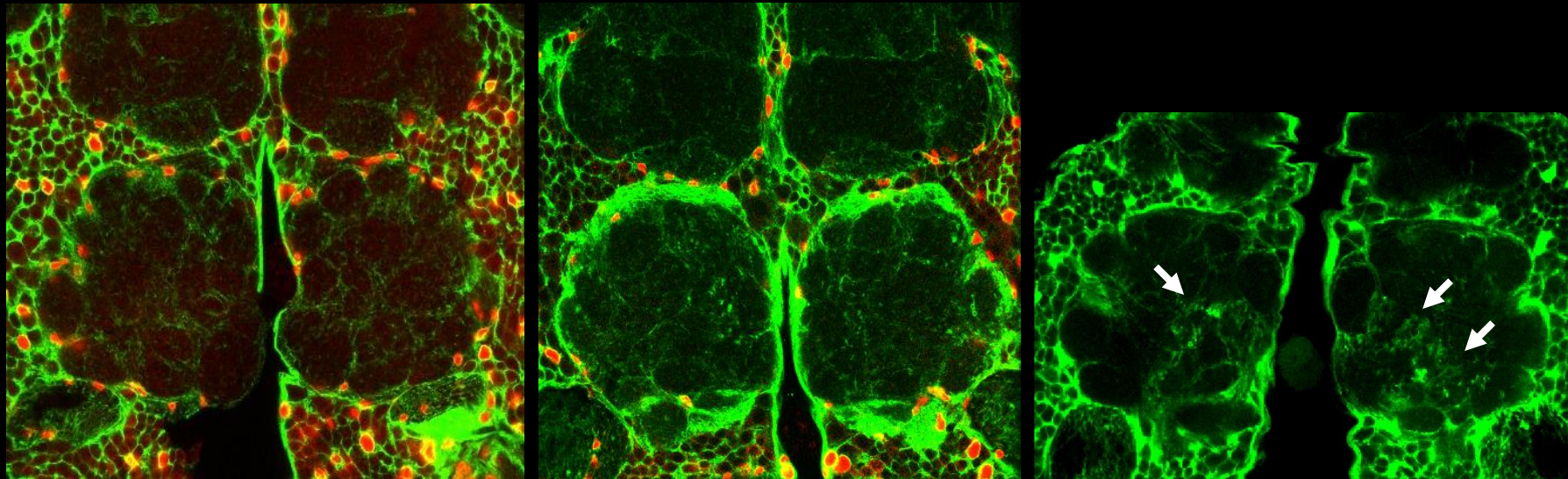
# *Drosophila* glia respond morphologically to ORN axon injury



control

1 day after antennal ablation

1 day after maxillary palp ablation

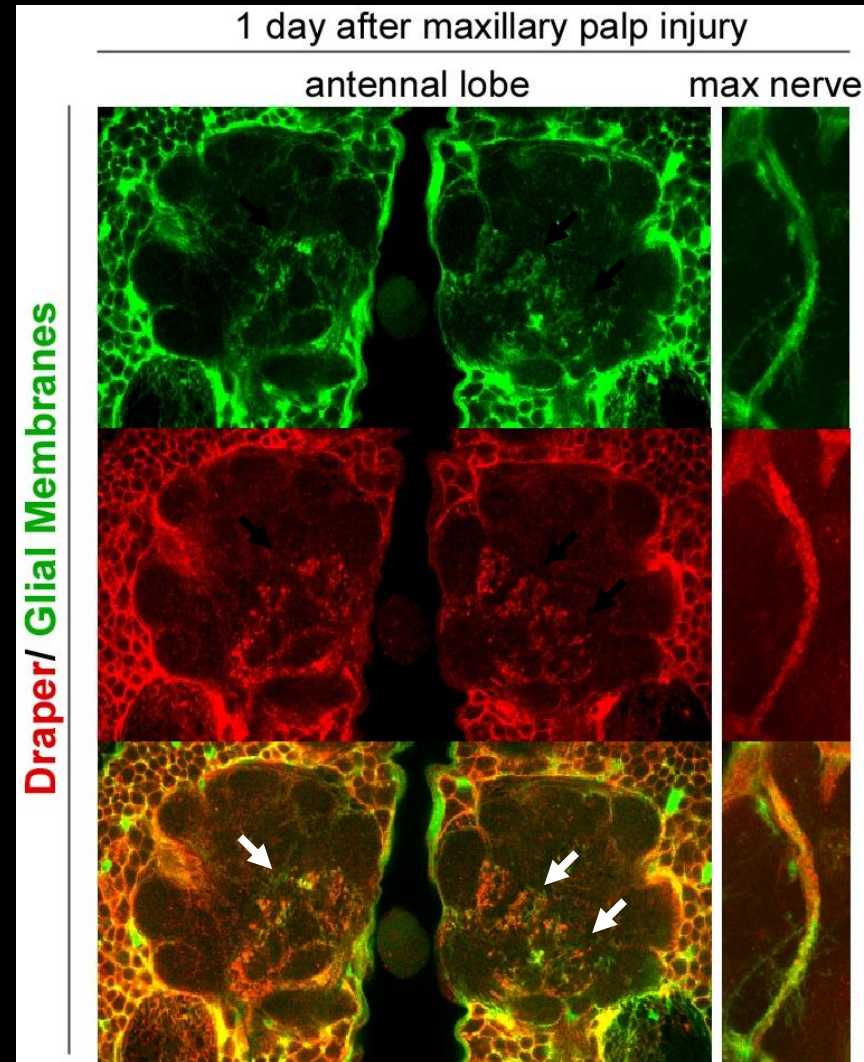




Glia and Draper both localize precisely to severed axons after injury

ORN injury results in Draper localizing to severed axons

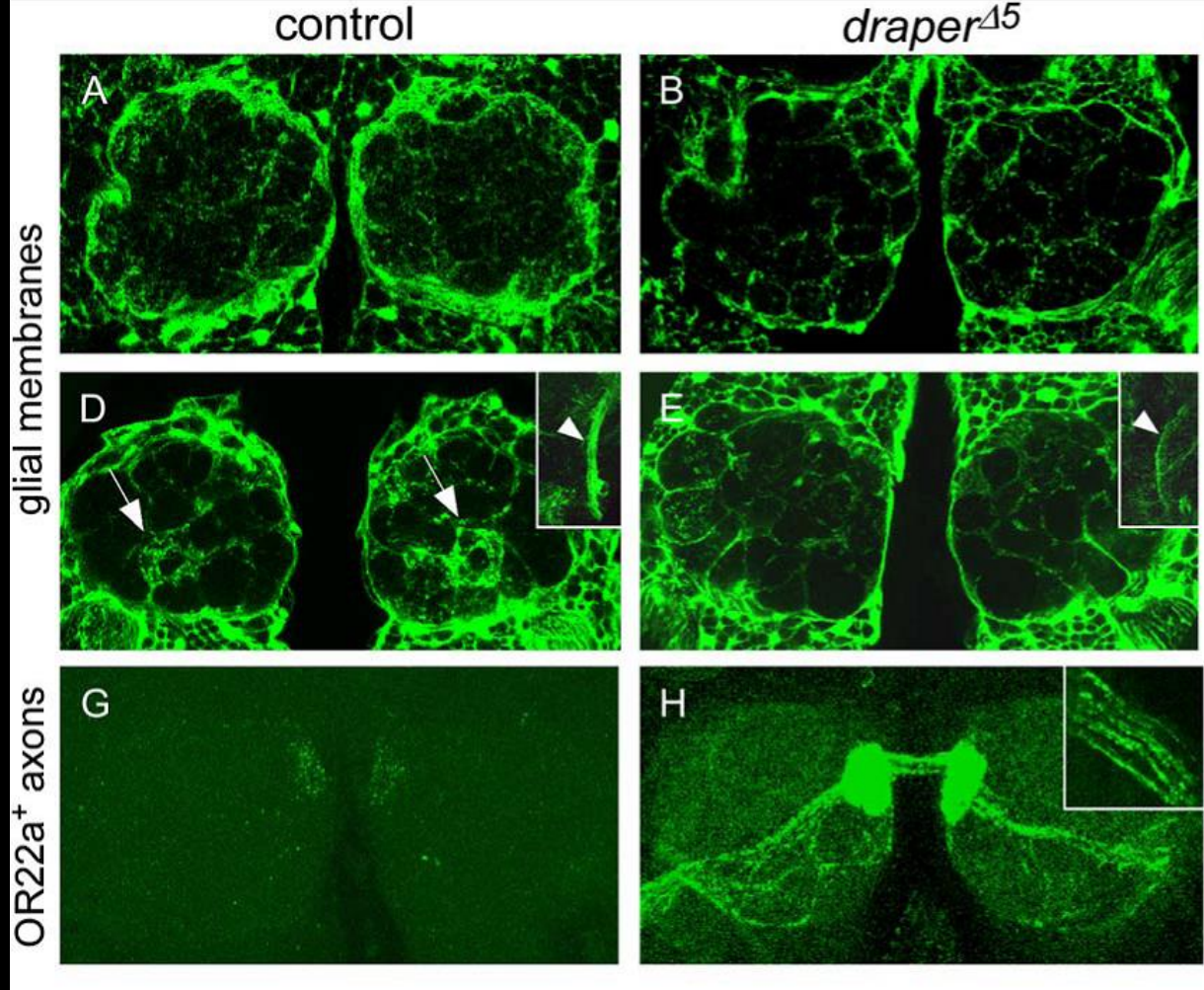
Draper co-localizes with glial membranes responding to severed axons



# Glial Draper essential for glial response and engulfment of axon debris

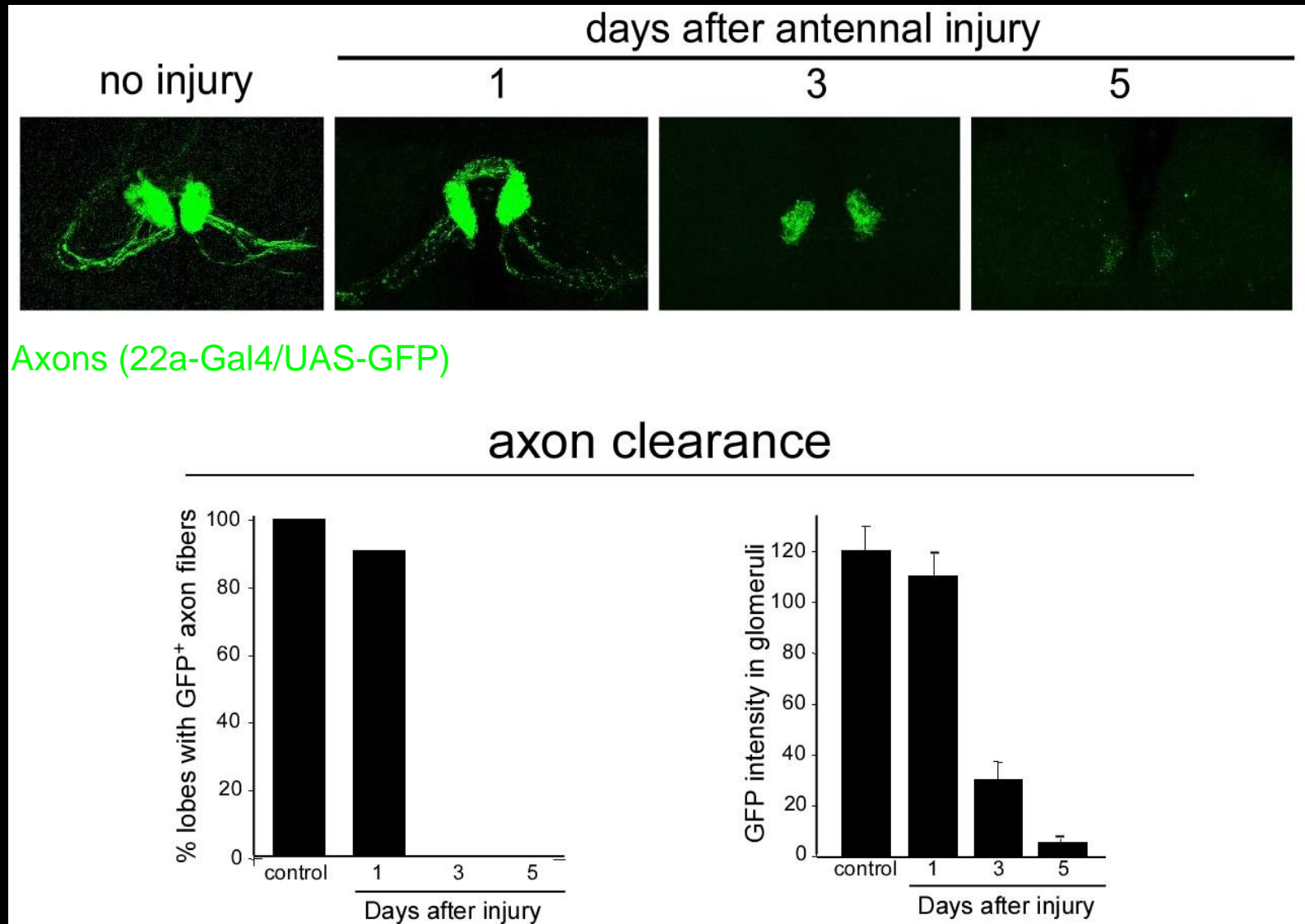
Days after maxillary palp injury

1



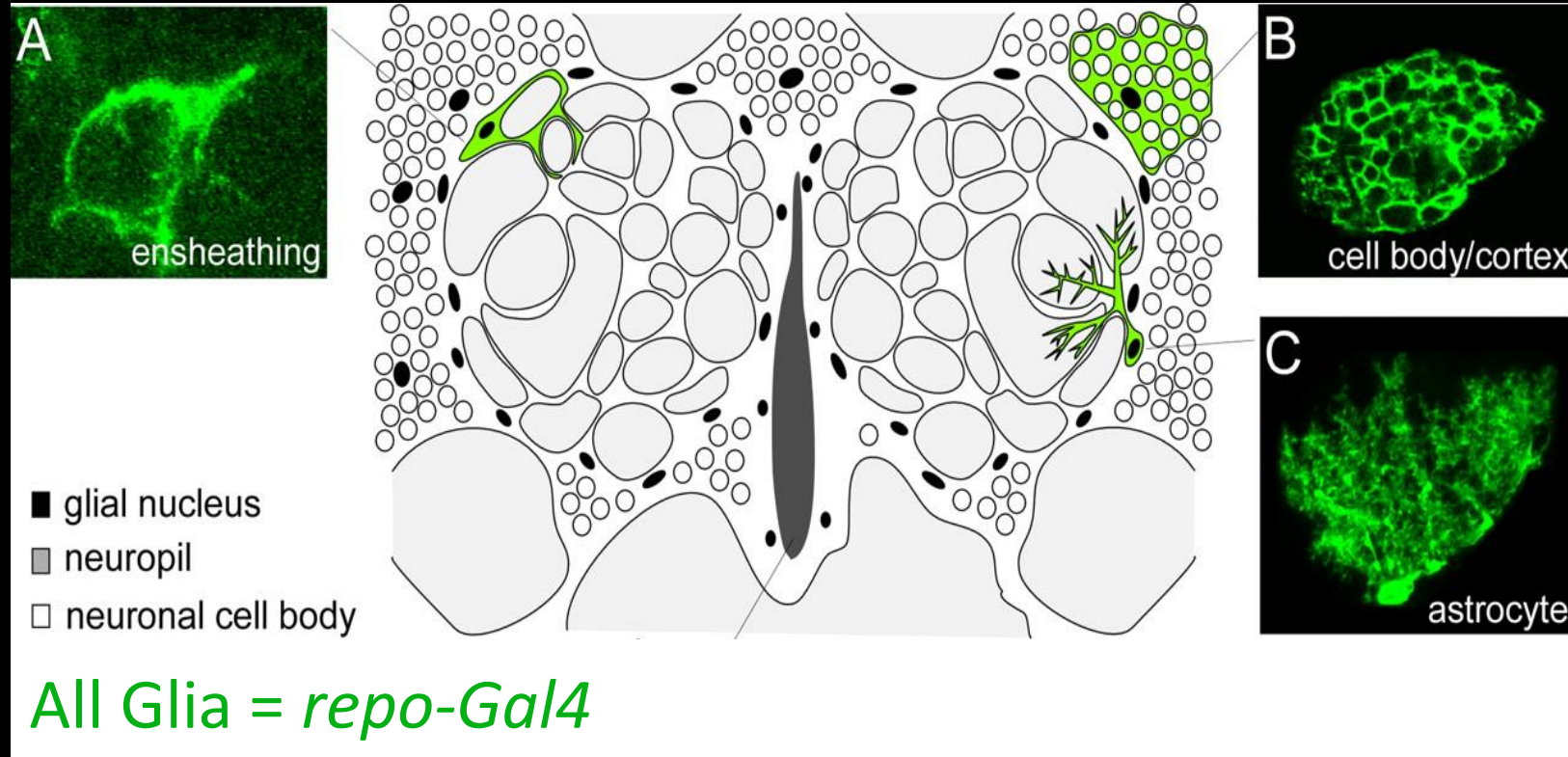
5

# Severed ORN axons are cleared from the CNS within 5 days





# *Drosophila* CNS glia surround and invade glomeruli

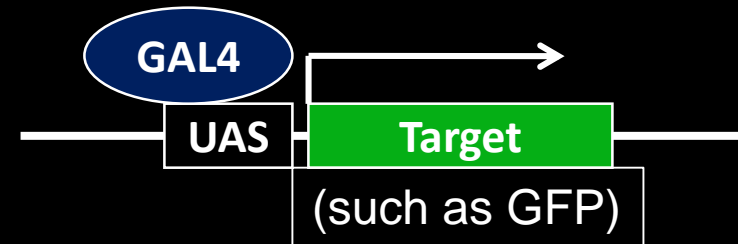


All Glia = *repo-Gal4*

Ensheathing glia =

*MZ0709-Gal4* or *TIFR-Gal4*

Astrocytic glia = *alrm-Gal4*



# Steps for successful axon engulfment by glia

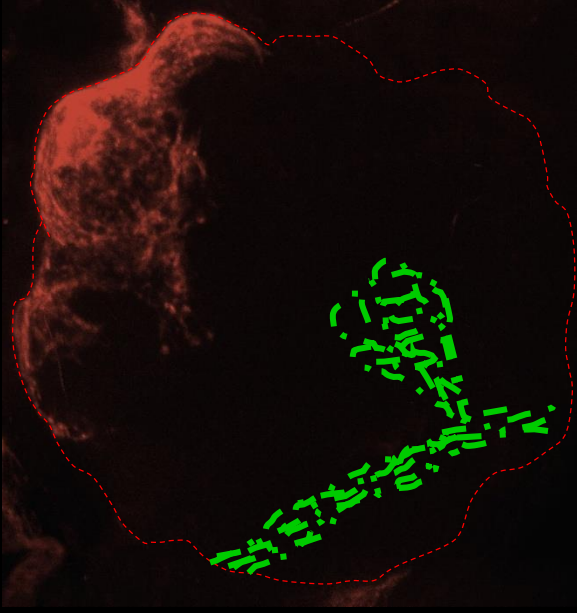
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# Engulfment Steps: Glial Activation

---

~ 1 hour



Step 1:  
Glial Activation

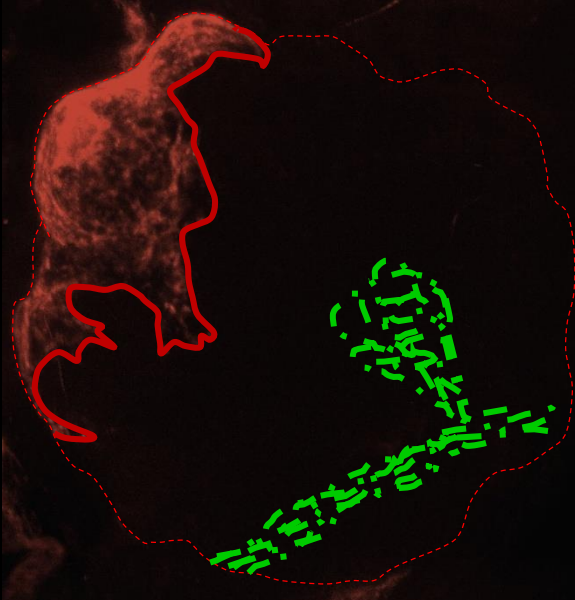
- Recognition



# Engulfment Steps: Glial Activation

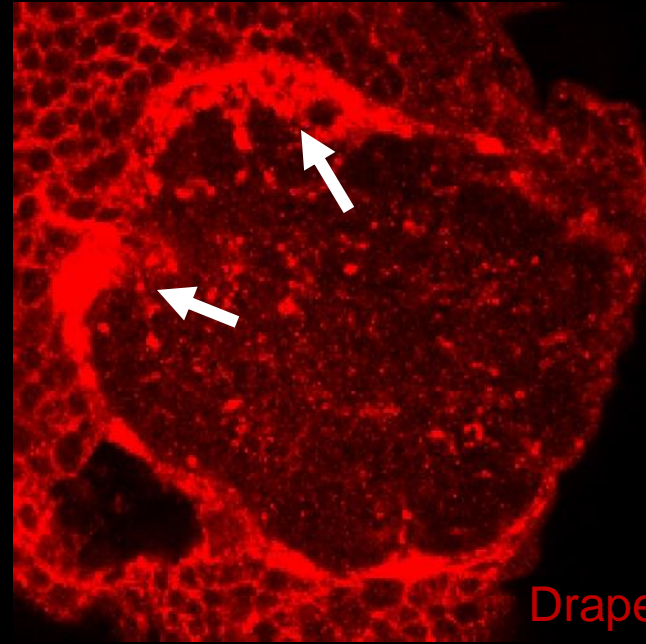
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~ 6-12 hours



**Step 1:  
Glial Activation**

- Recognition
- Up-regulate engulfment proteins

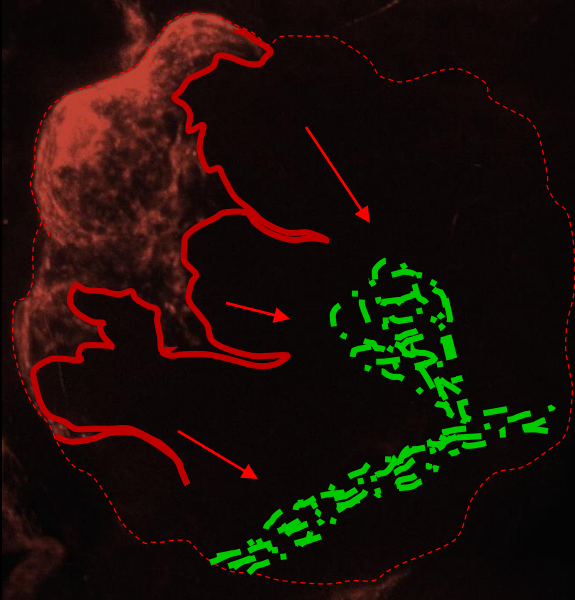


Draper

# Engulfment Steps: Glial Activation

---

~ 6-12 hours

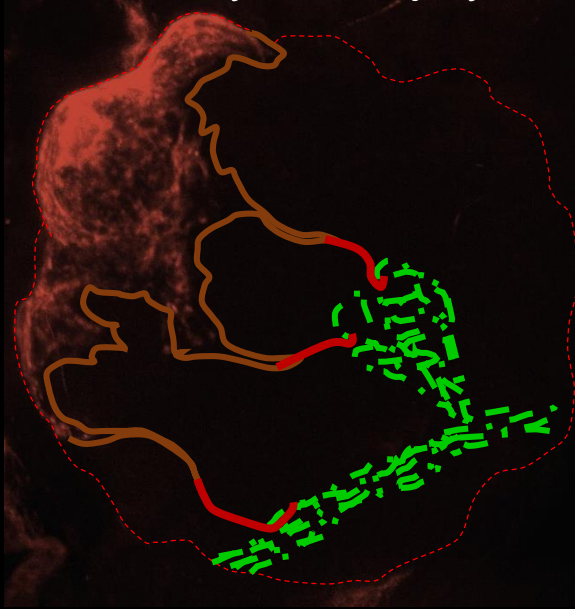


## Step 1: Glial Activation

- Recognition
- Up-regulate engulfment proteins
- Change morphology

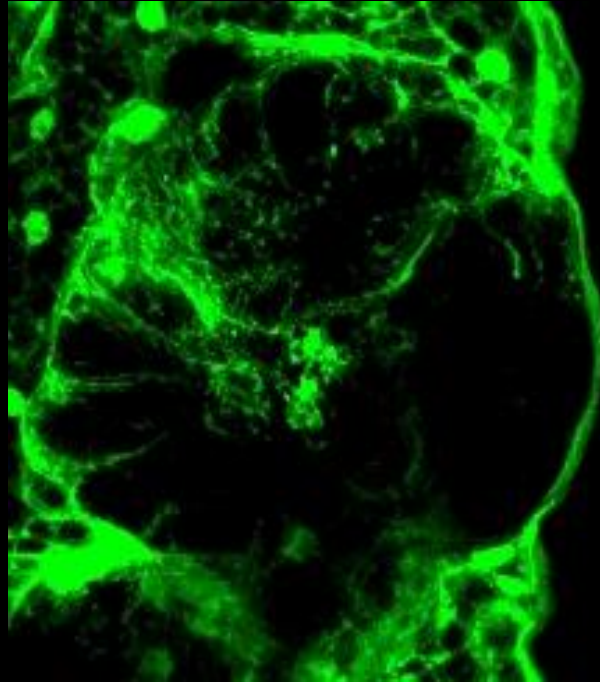
# Engulfment Steps: Glial Activation

1 day after injury

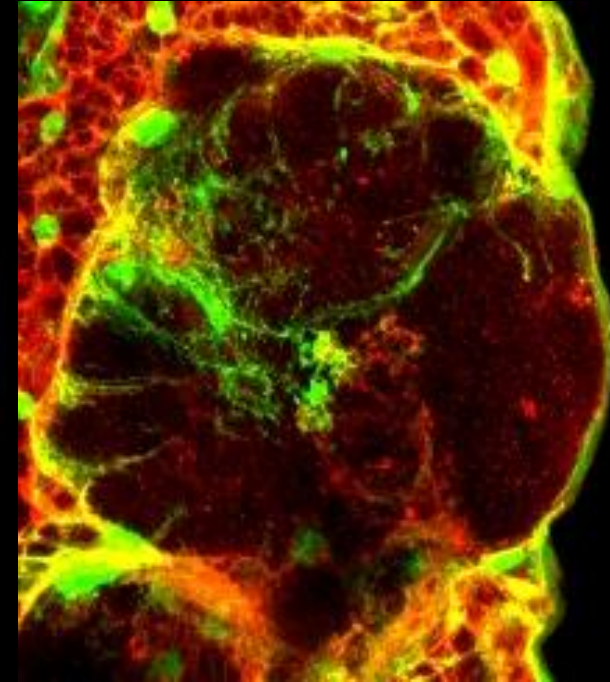


**Step 1:  
Glial Activation**

- Recognition
- Up-regulate engulfment proteins
- Change morphology



Glia membranes

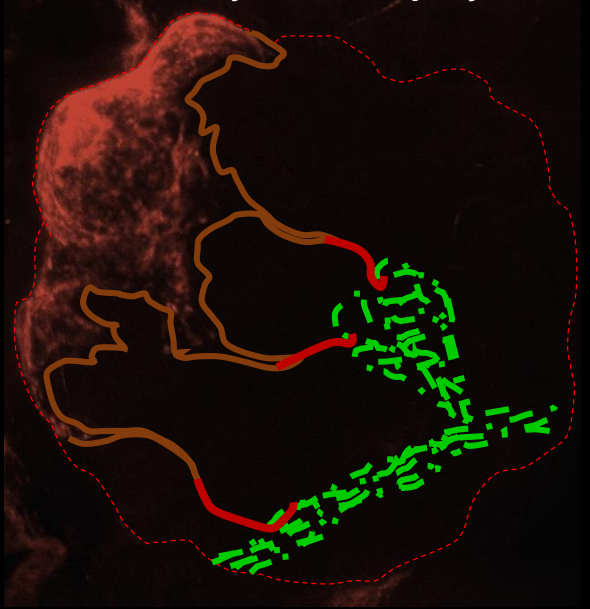


Glia membranes  
Draper



# Engulfment Steps: Phagocytosis

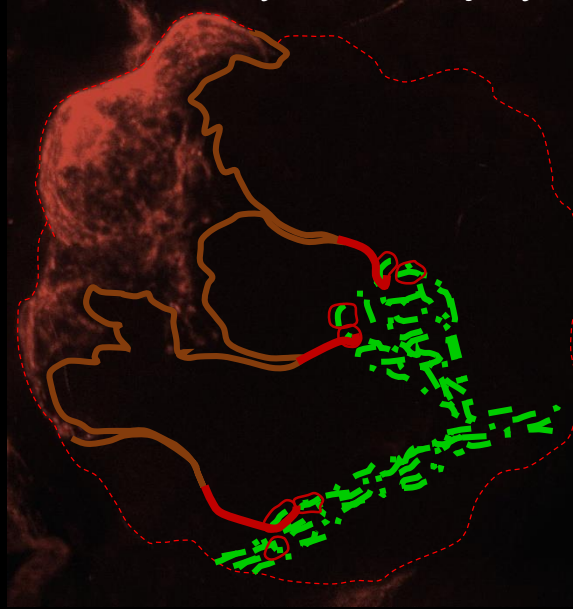
1 day after injury



**Step 1:  
Glial Activation**

- Recognition
- Up-regulate engulfment proteins
- Change morphology

1-5 days after injury



**Step 2:  
Phagocytosis**

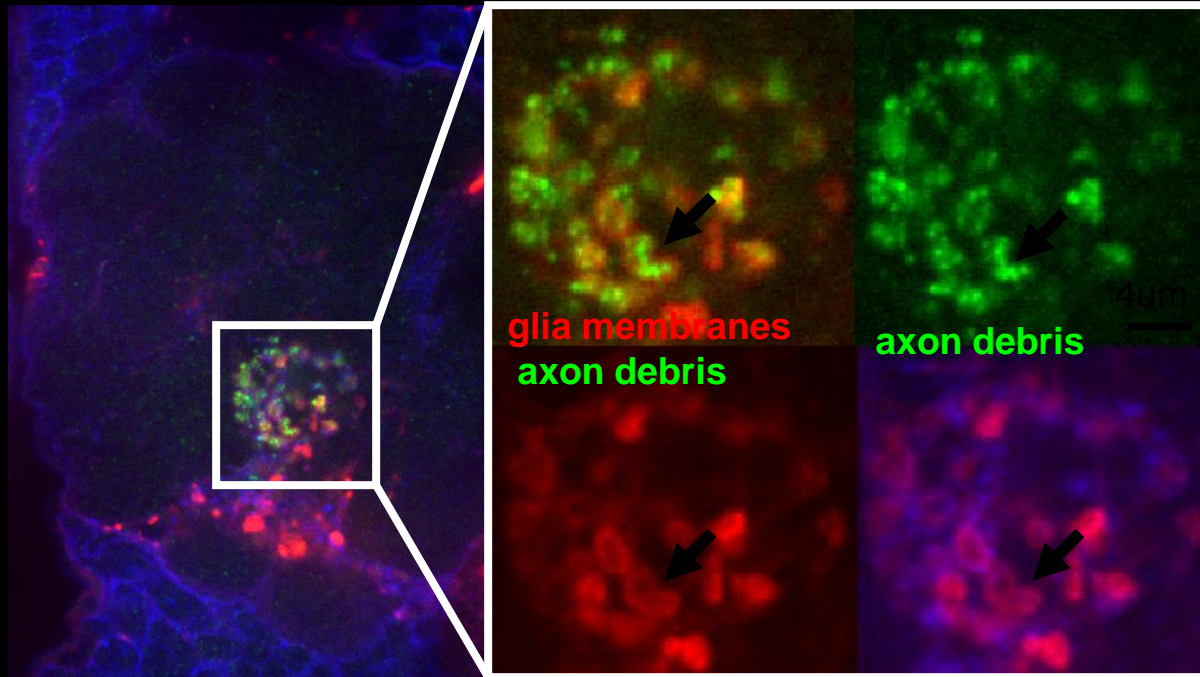
- Internalize debris

# Engulfment Steps: Phagocytosis



Step 2:  
Phagocytosis

- Internalize debris



glia membranes  
axon debris  
Draper

glia membranes

glia membranes  
Draper

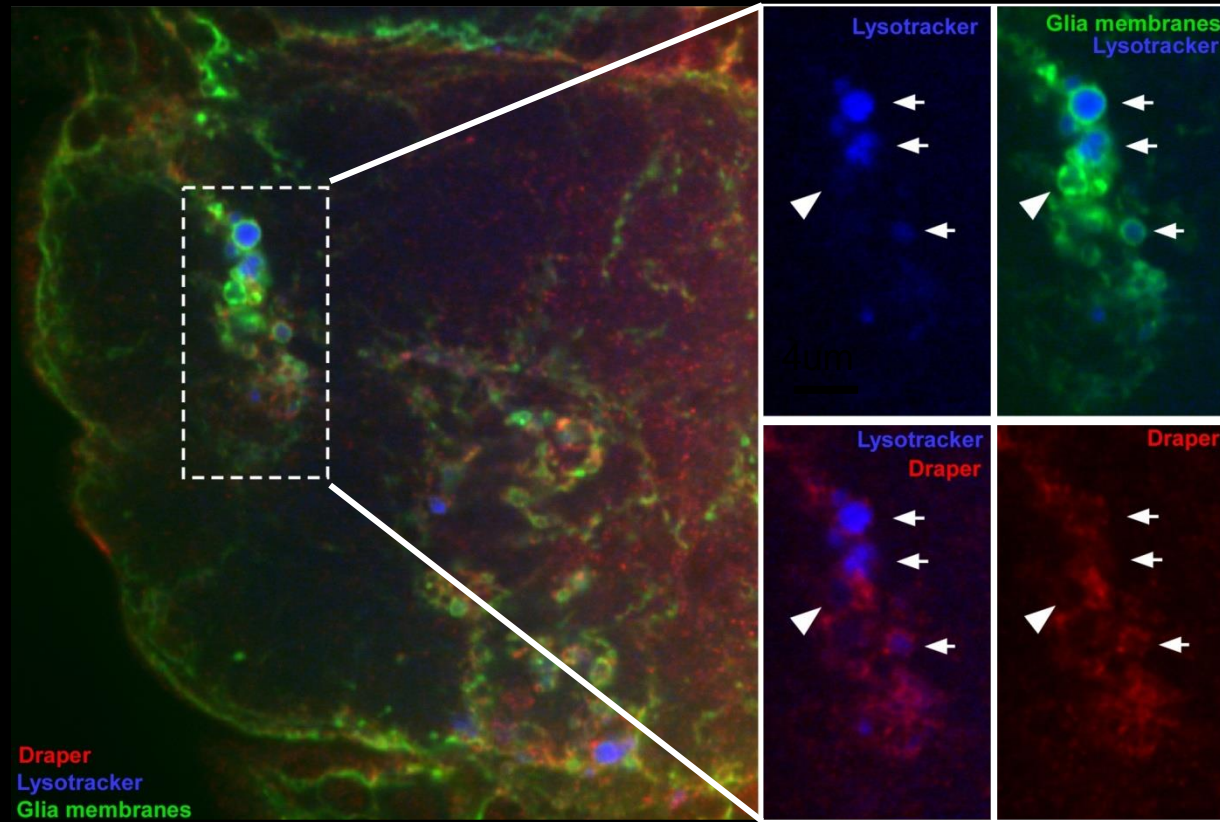
OR85e-mcd8GFP *TIFR-gal4* > UASmcd4::tdTomato

# Engulfment Steps: Phagocytosis



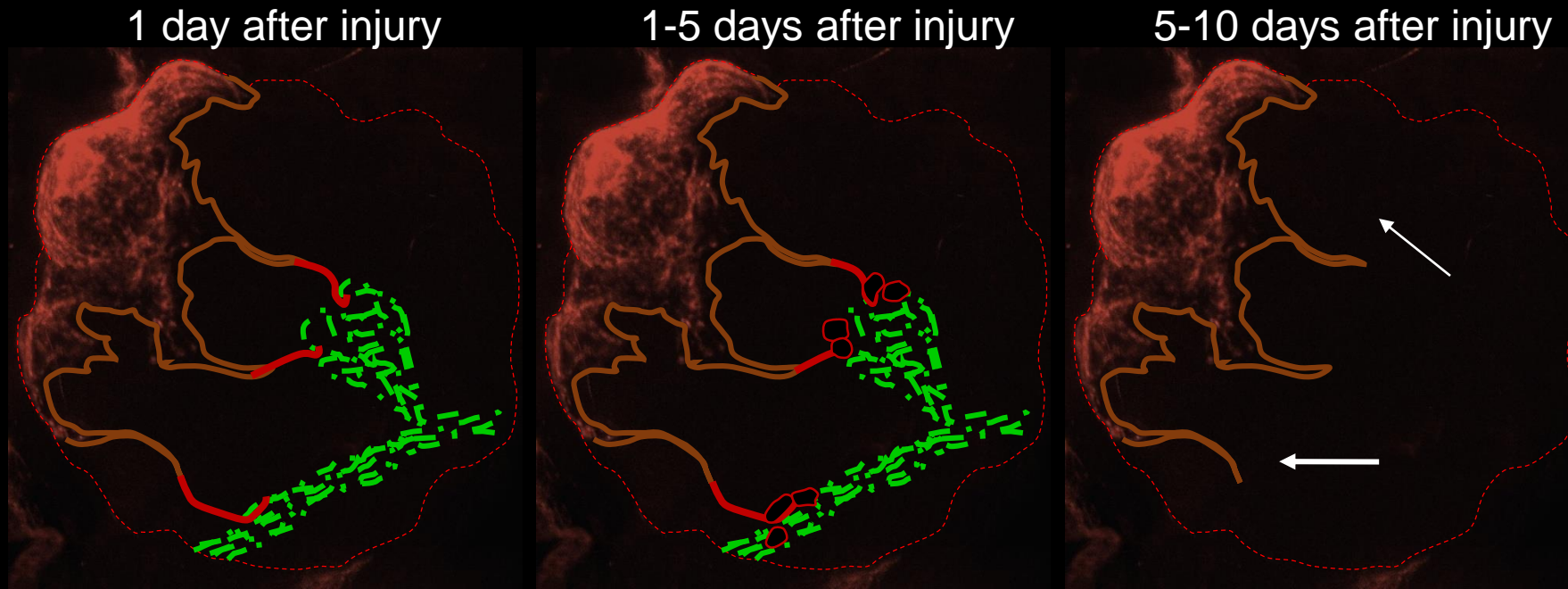
## Step 2: Phagocytosis

- Internalize debris
- Degradation





# Engulfment Steps: Phagocytosis and Termination of response



## Step 1: Glial Activation

- Recognition
- Up-regulate engulfment proteins
- Change morphology

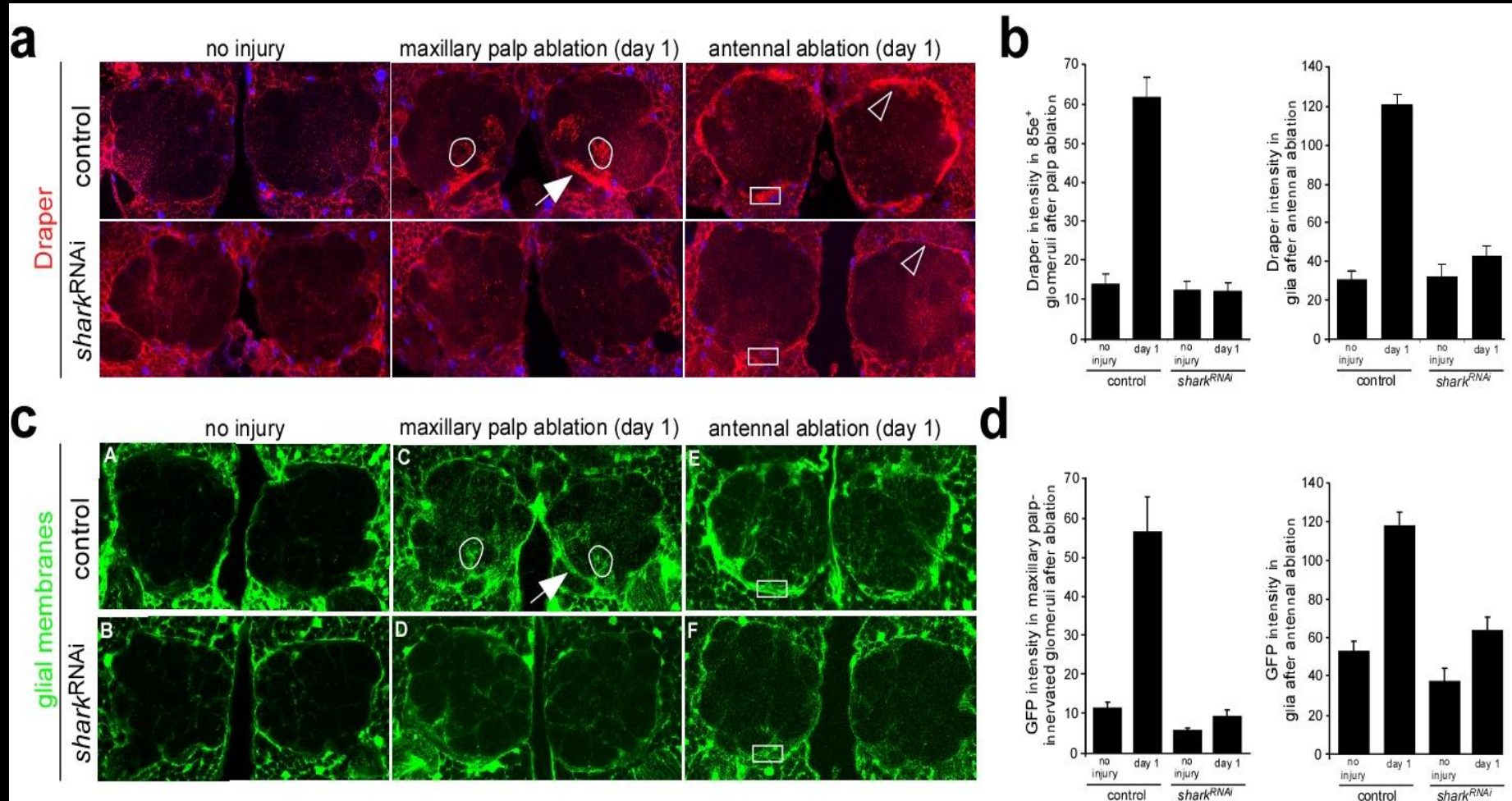
## Step 2: Phagocytosis

- Internalize debris
- Degradation

## Step 3: Termination

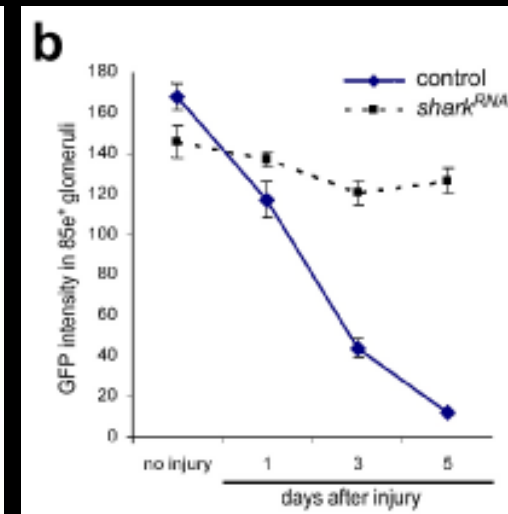
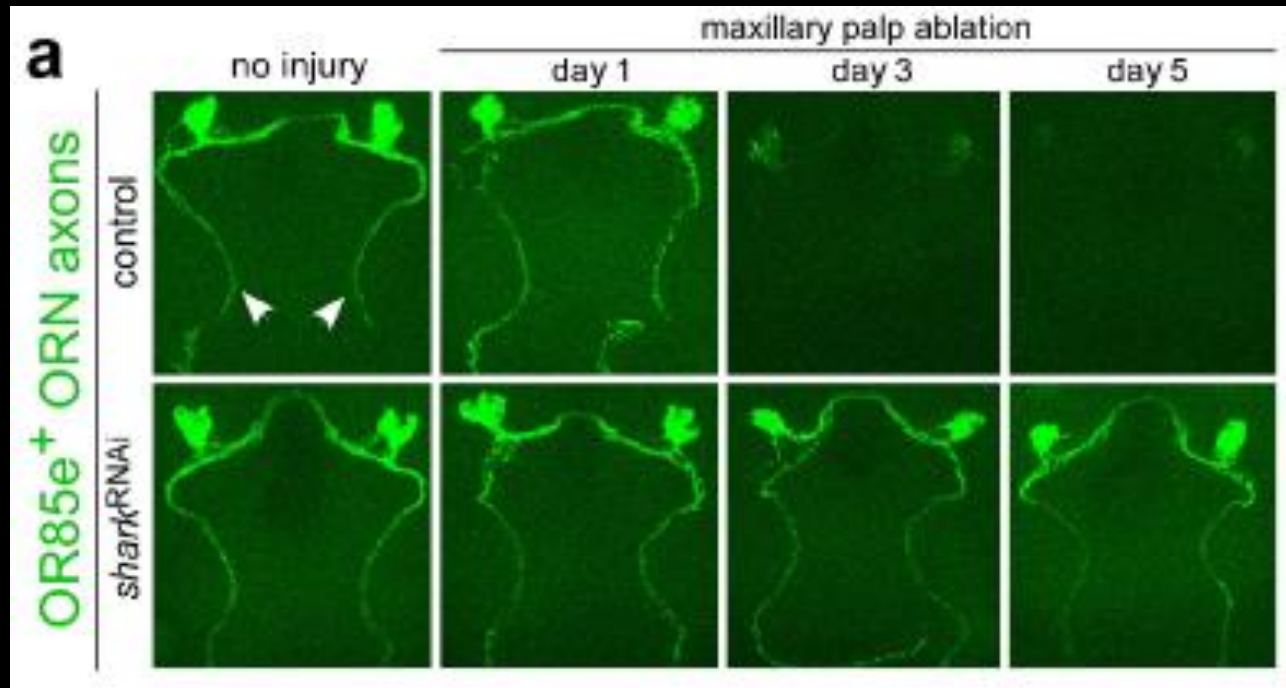
- Down-regulate engulfment proteins
- Return to resting morphology

# Injury induced changes in glial morphology and Draper require Shark



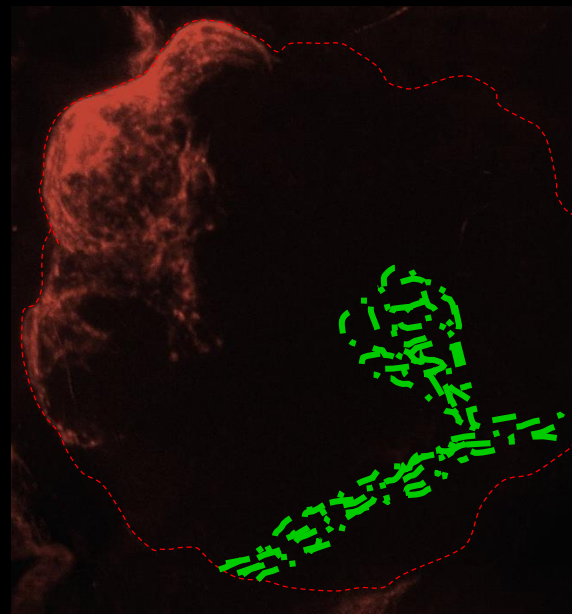
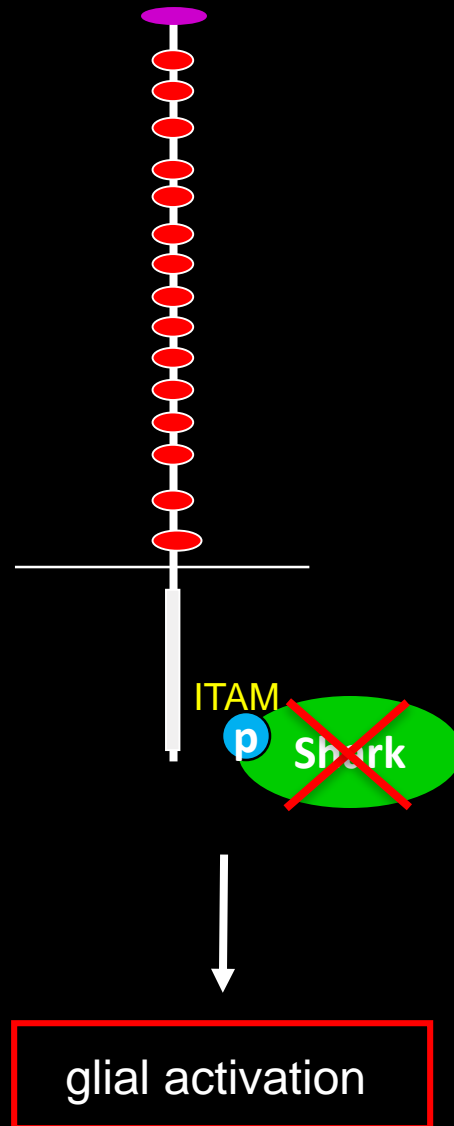
# Severed axons are not cleared from the CNS in *shark* RNAi flies

*shark*<sup>RNAi</sup> driven with pan-glial *repo-Gal4*





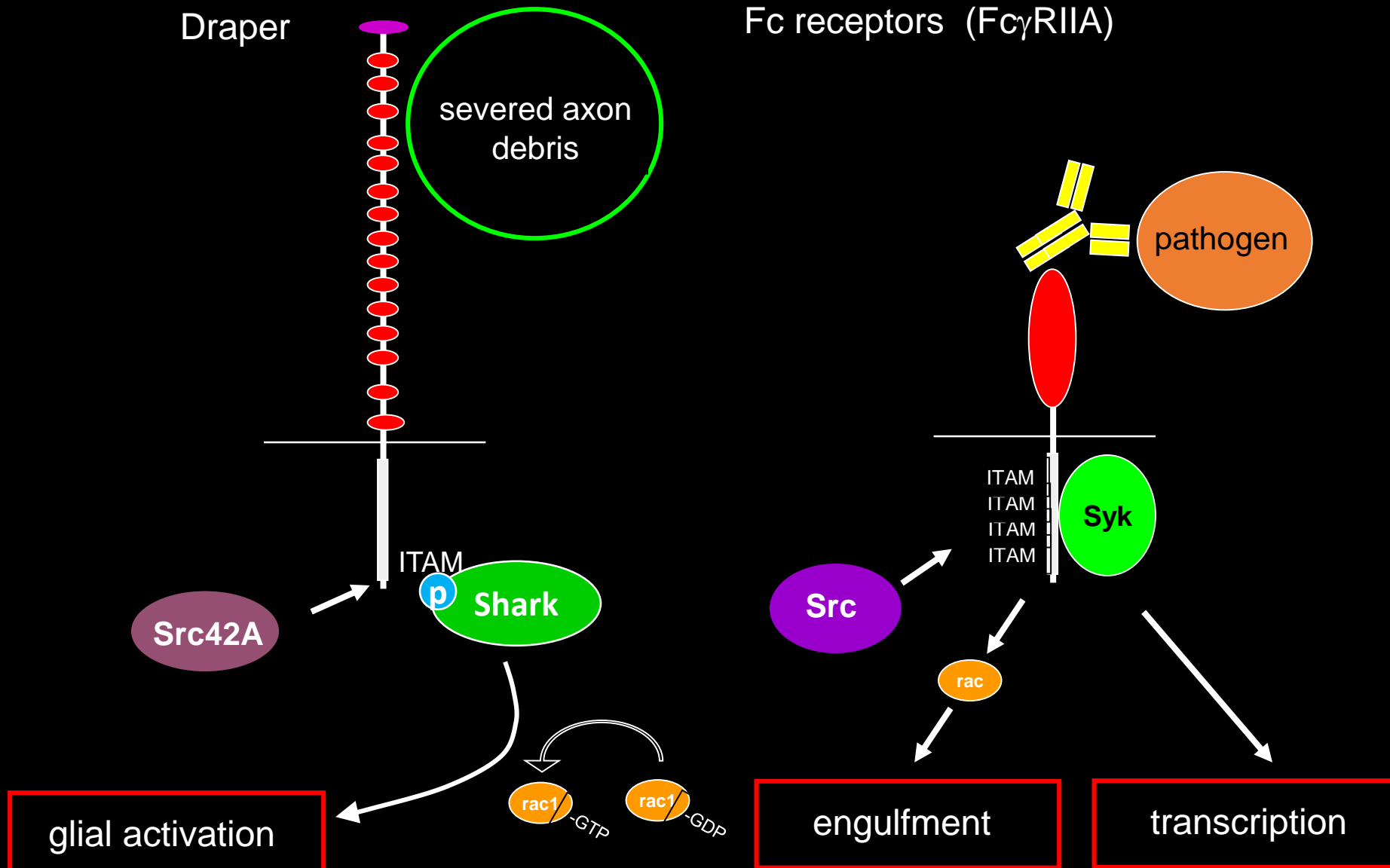
# What happens to severed axons when activation is impaired?



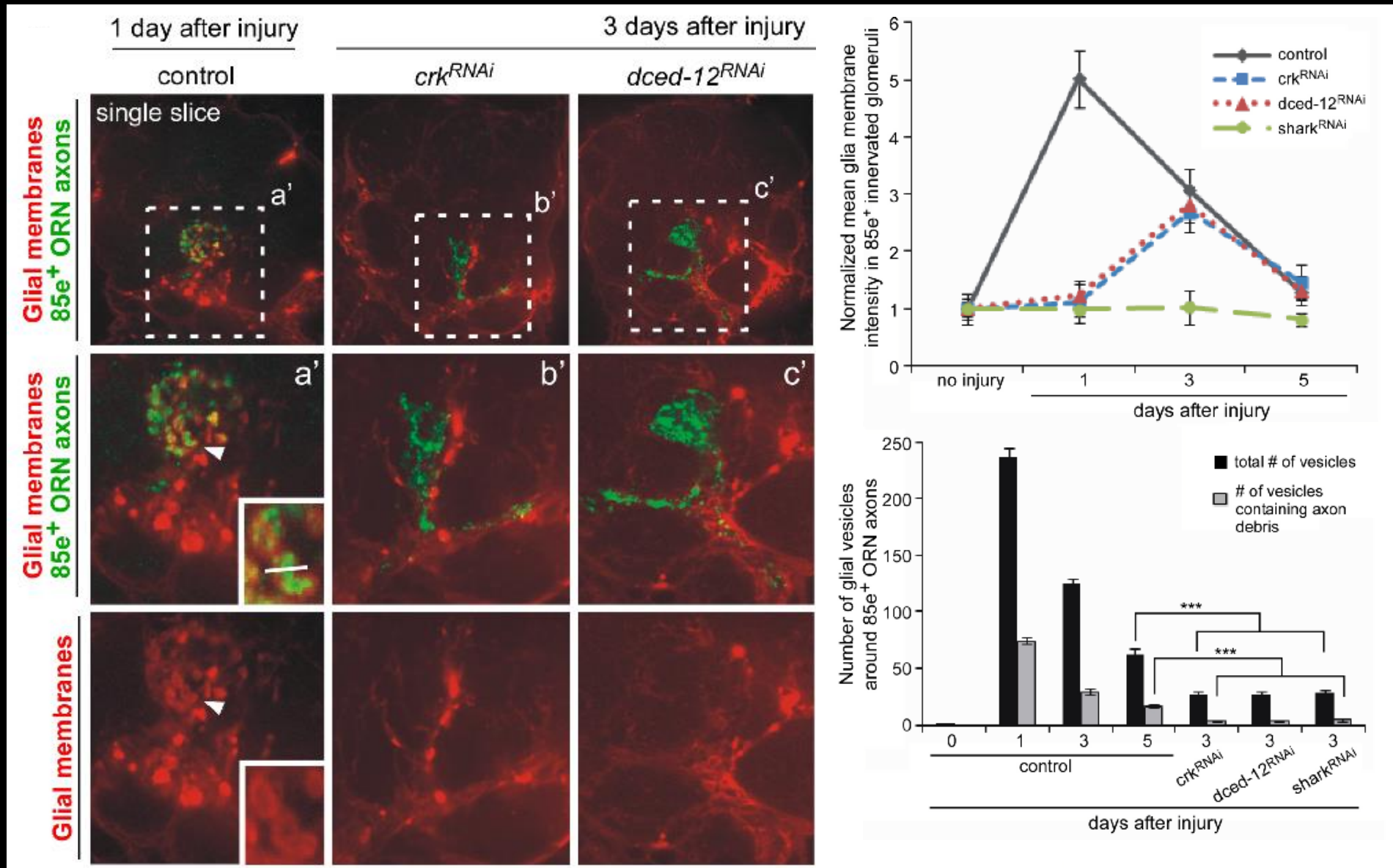
Step 1:  
Glial Activation

- Recognition
- Up-regulate engulfment proteins
- Change morphology

Draper is an ancient immunoreceptor with extracellular domain(s) tuned to “modified self”



# Glia devoid of Crk or dCed-12 still respond but fail to eat axon debris

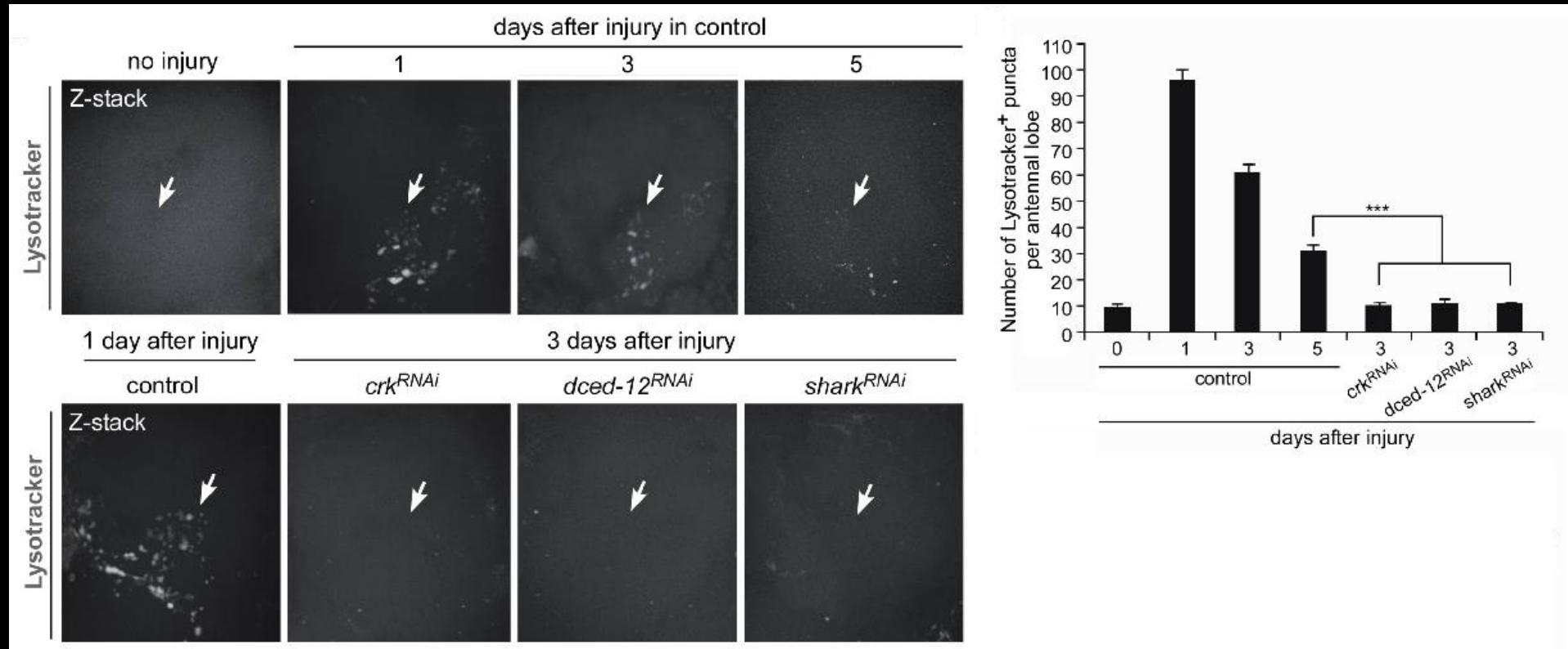




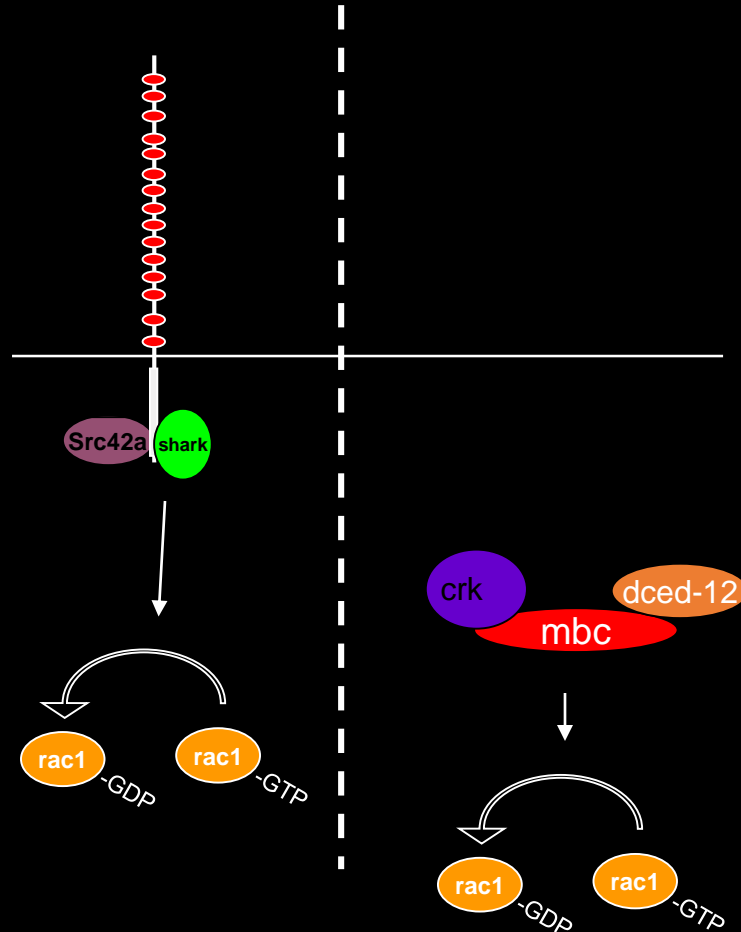
# Glia devoid of Crk or dCed-12 fail to degrade axon debris

Lysotracker: labels acidified mature phagosomes

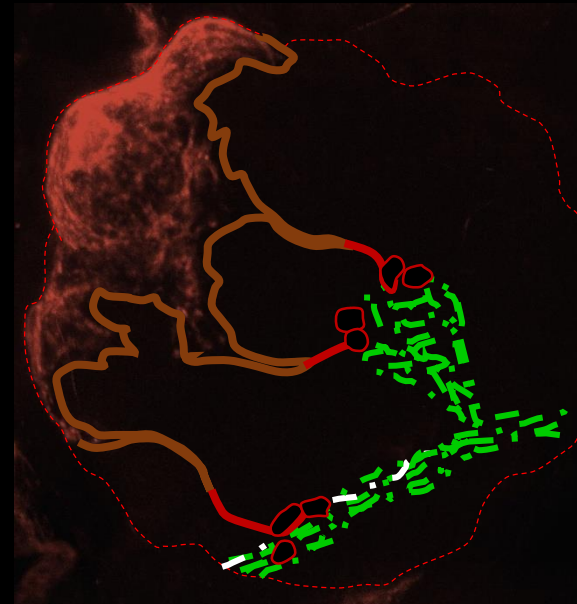
axon debris



# GEF activity essential for phagocytosis of axon debris



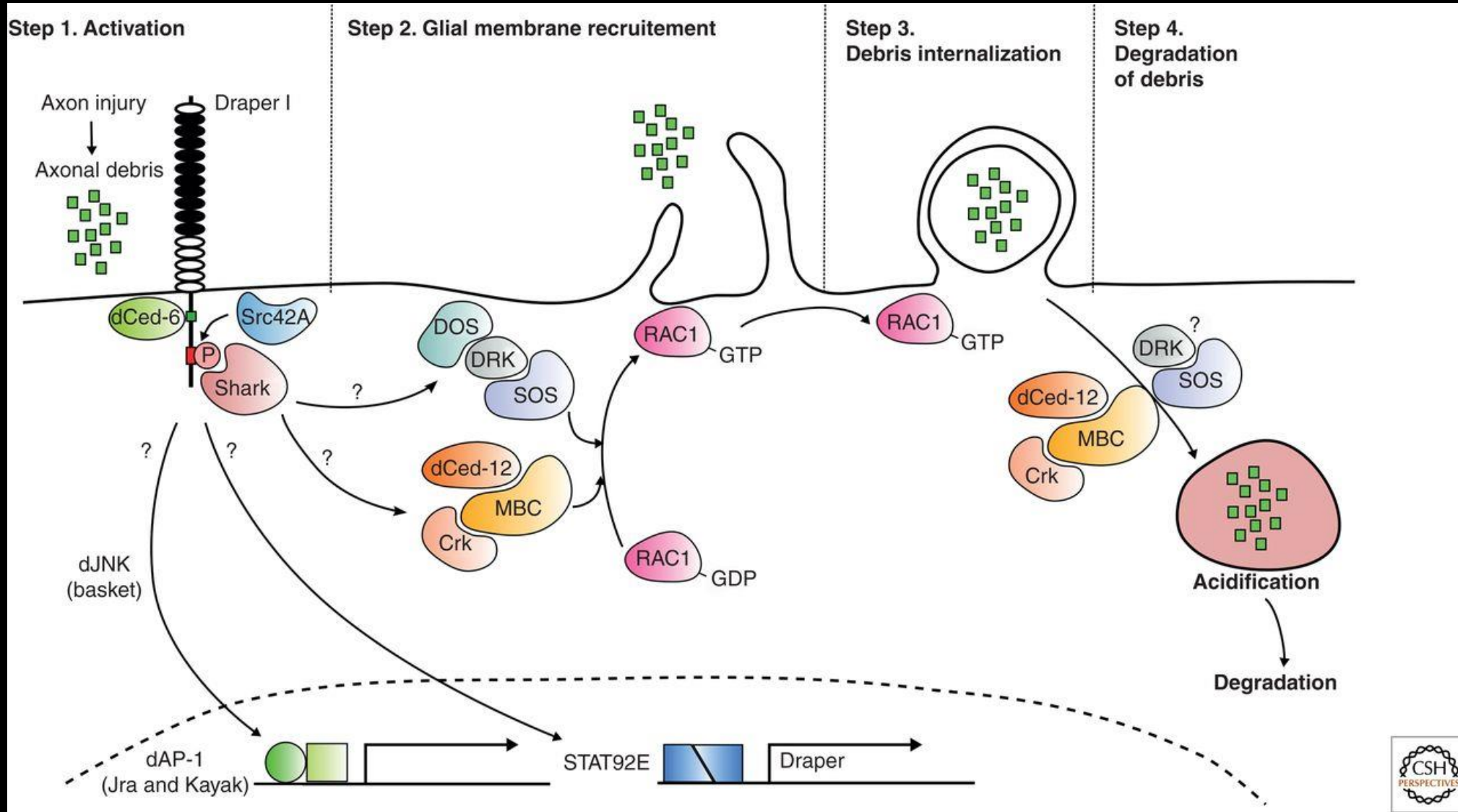
also Rac-mediated phagocytosis? **YES**



Step 2:  
Phagocytosis

- Internalize debris
- Degradation

# Summary of glial engulfment signaling to date





Thank you!  
I hope you are more  
“glia-evangelized”  
to the coolness of glia.

