Neural Development & Regeneration

Development of neural circuits is the earliest form of learning

Building specific connections in the brain requires

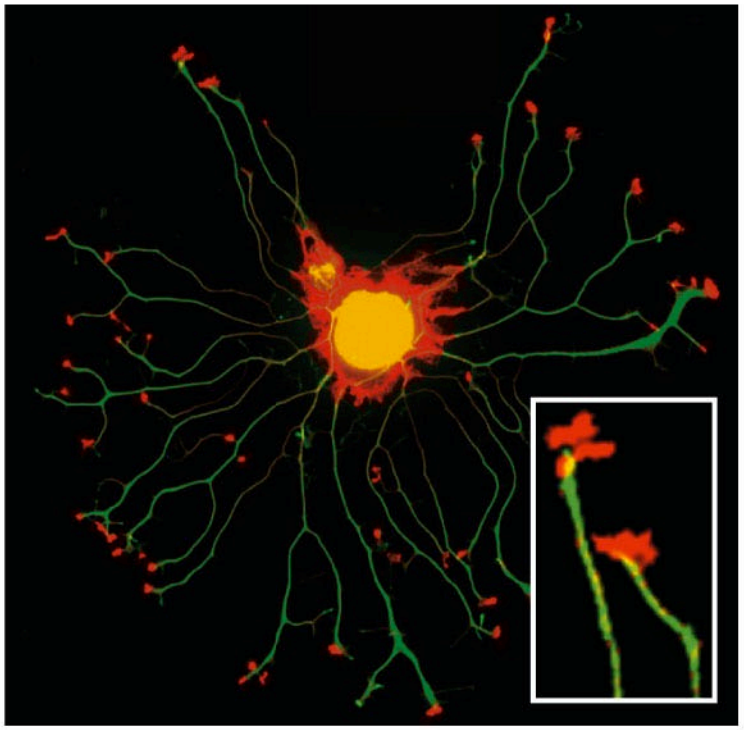
① Neurite growth and axon guidance

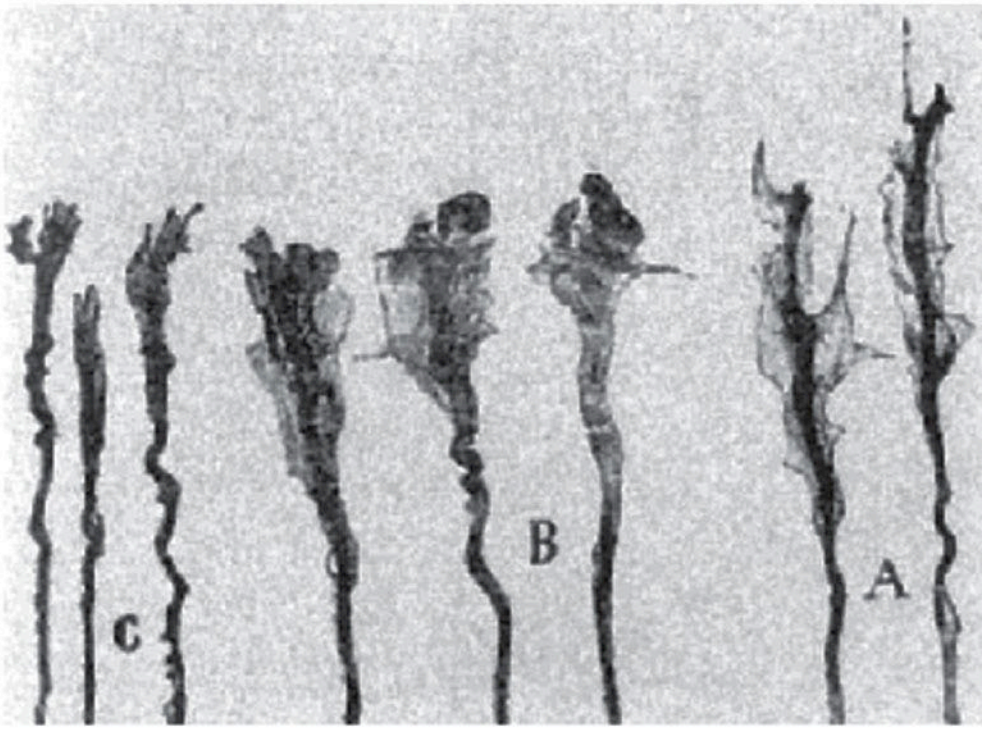
② Adhesion molecules

③ Pruning and maturation

① Neurite growth and axon guidance

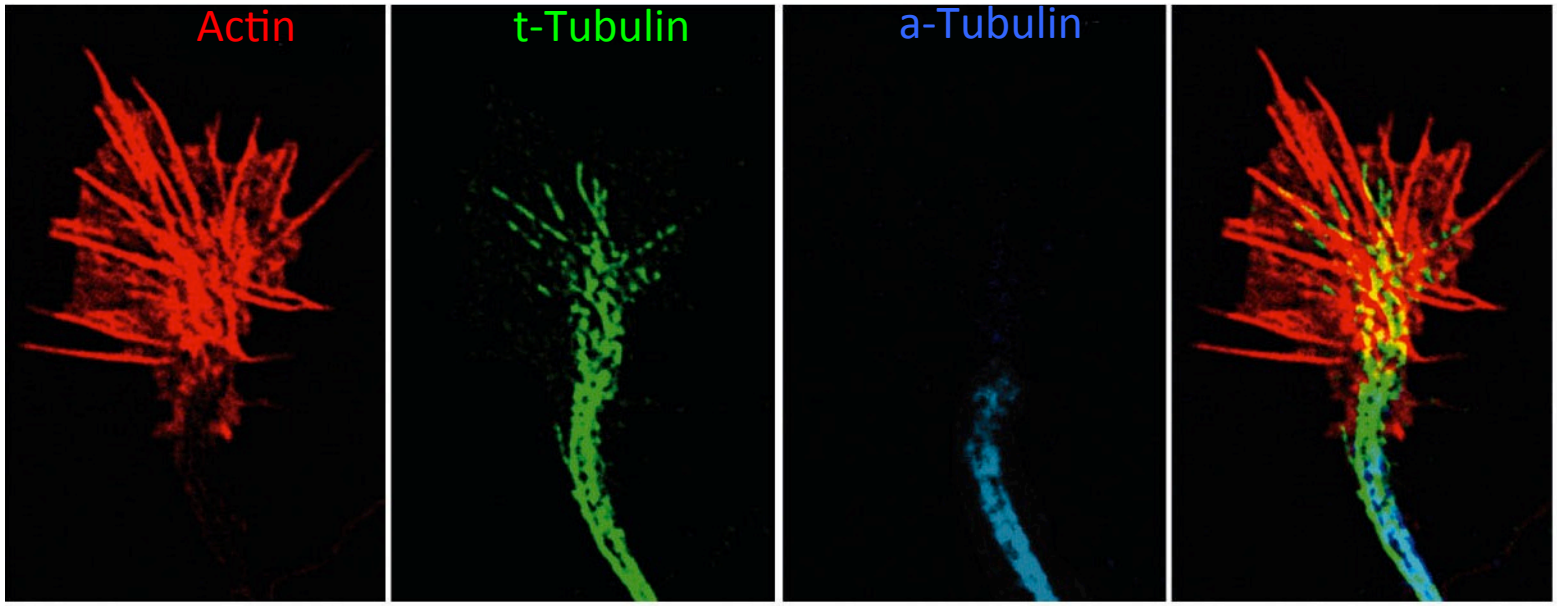
Young neurons sprout axon “growth cones”

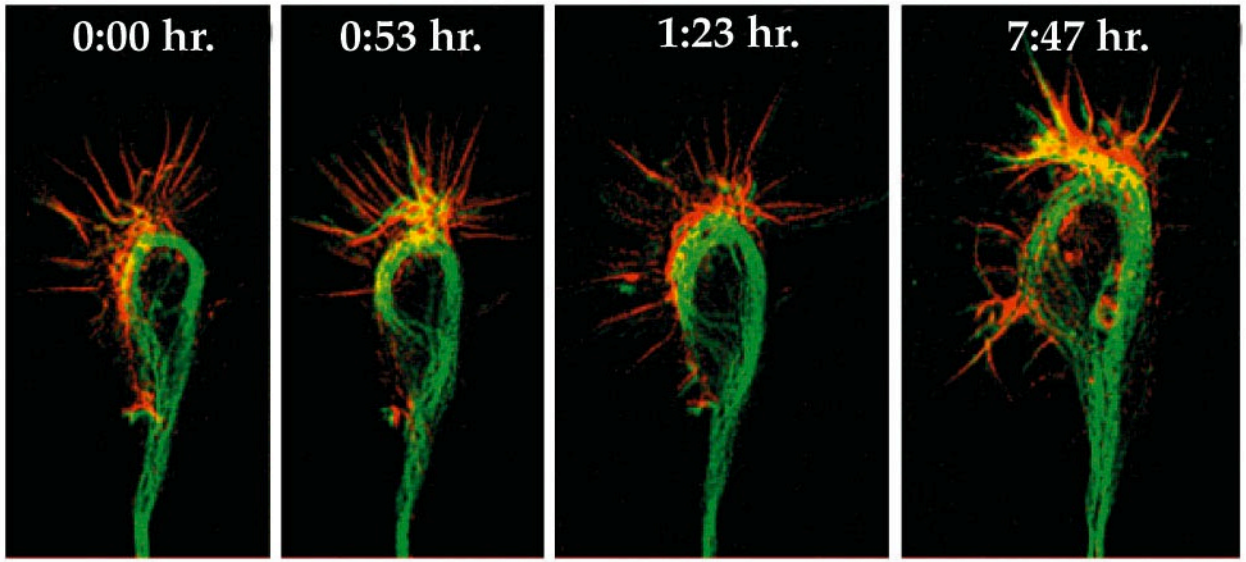




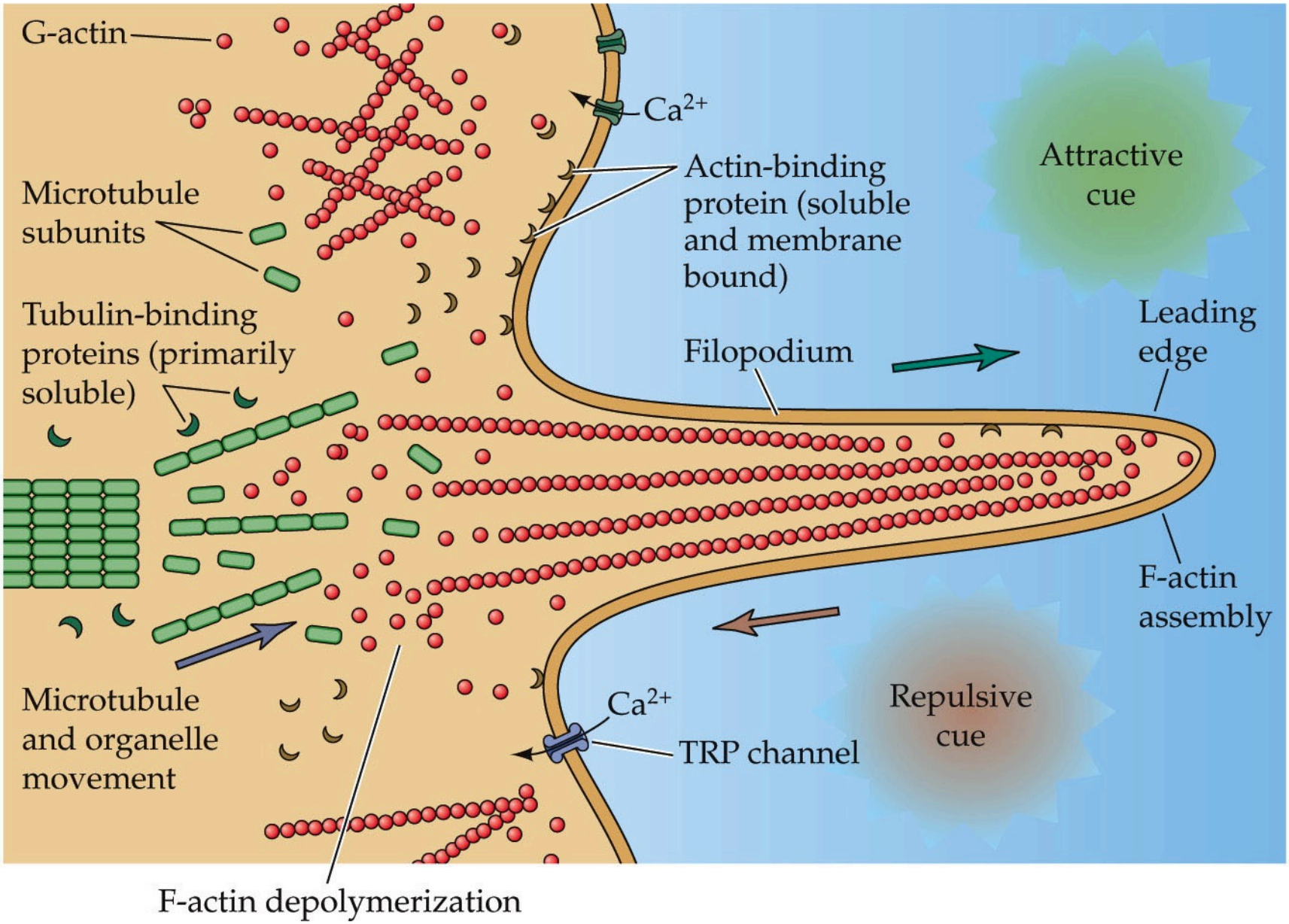
① Neurite growth and axon guidance

Growth Cone

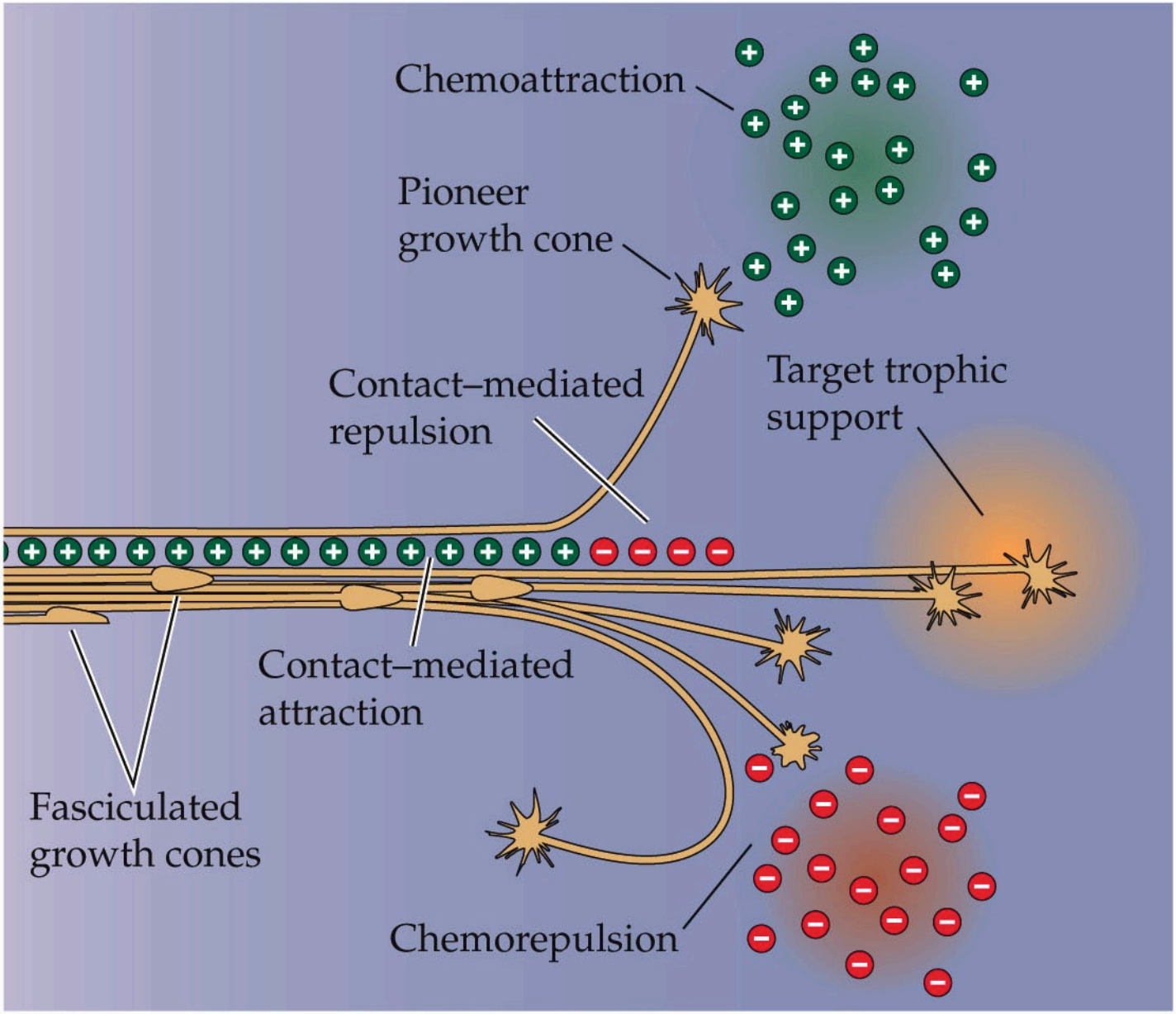




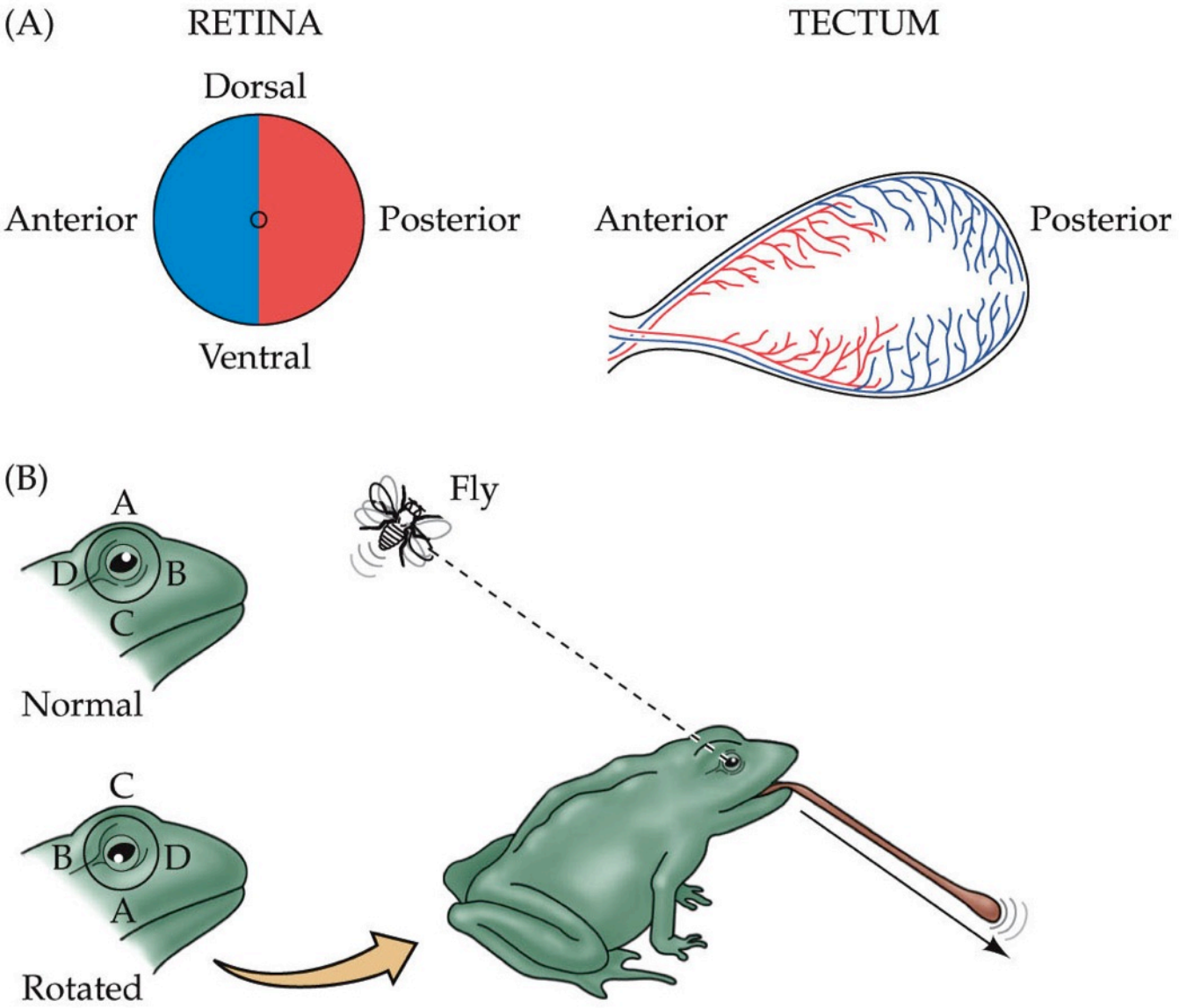
① Neurite growth and axon guidance



① Neurite growth and axon guidance

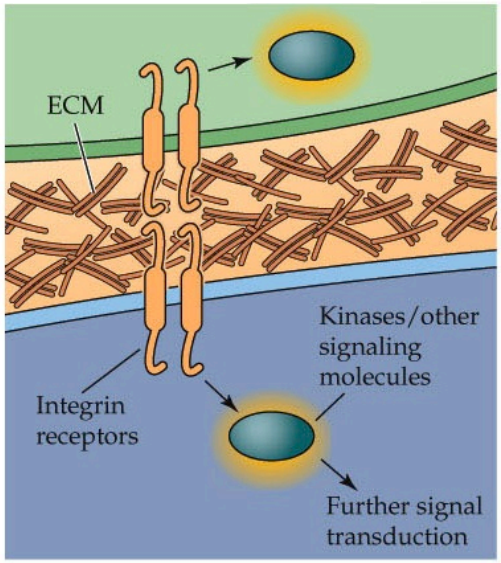


① Neurite growth and axon guidance

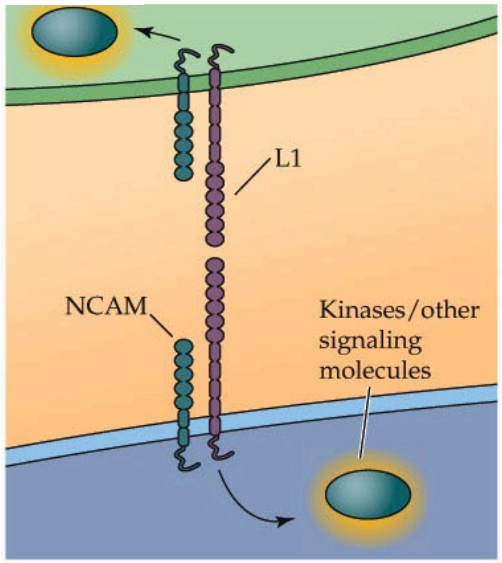


② Adhesion molecules

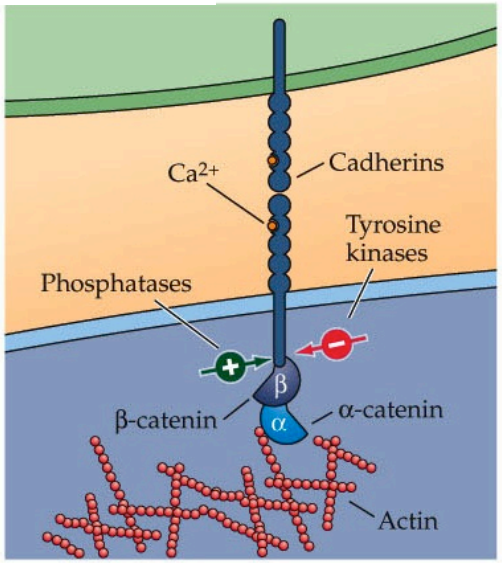
Extracellular Matrix



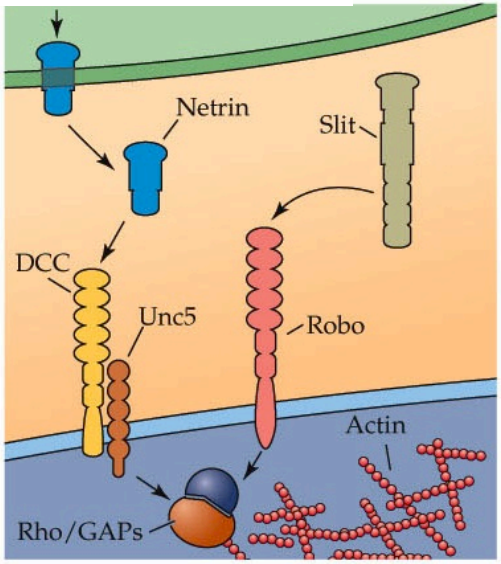
CAMs



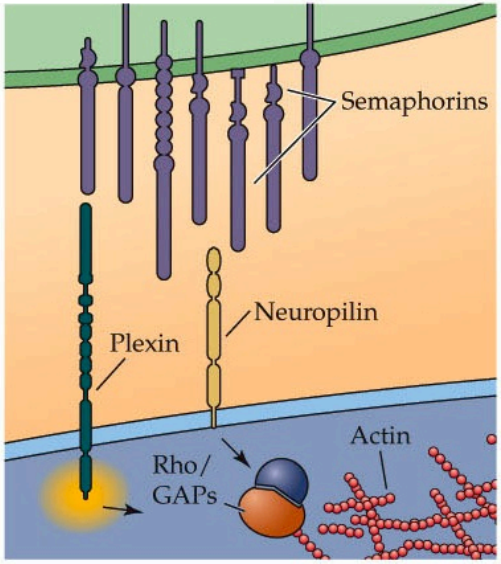
Cadherins



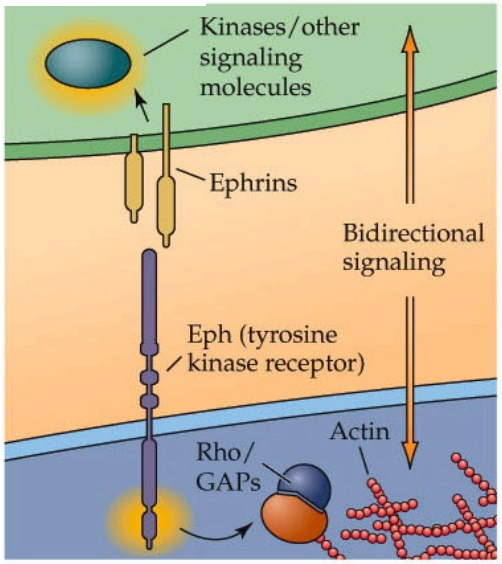
Netrin/Slit Family



Semaphorins

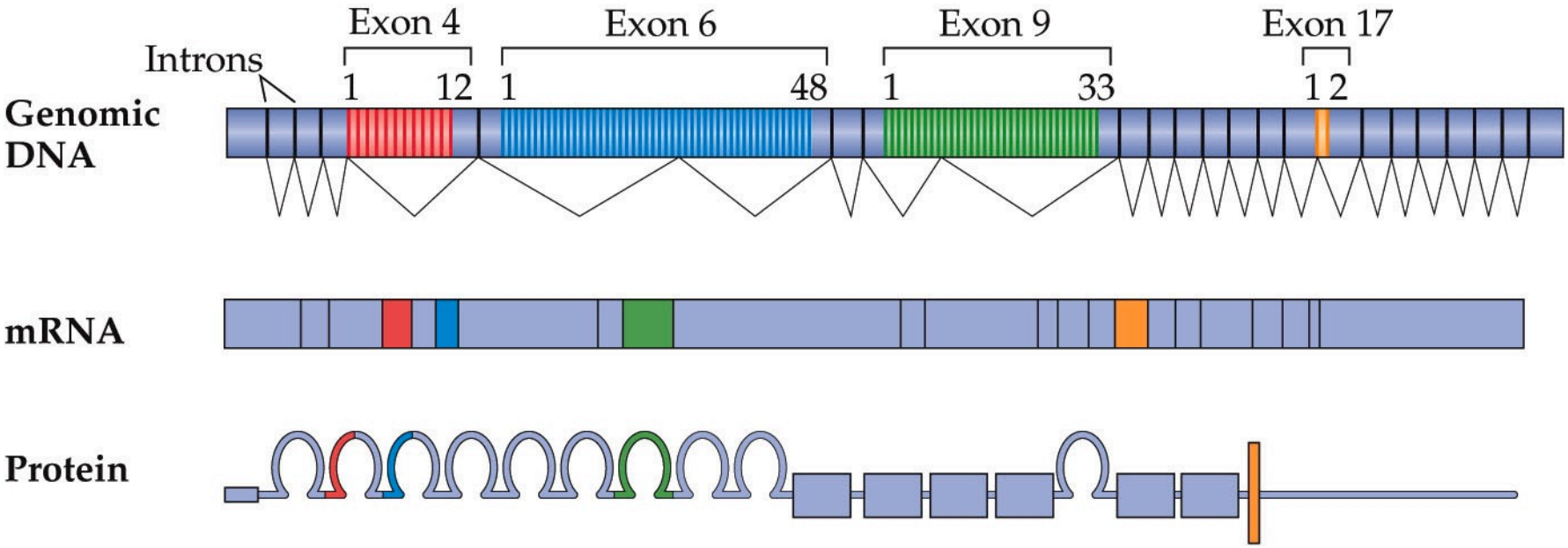


Ephrins

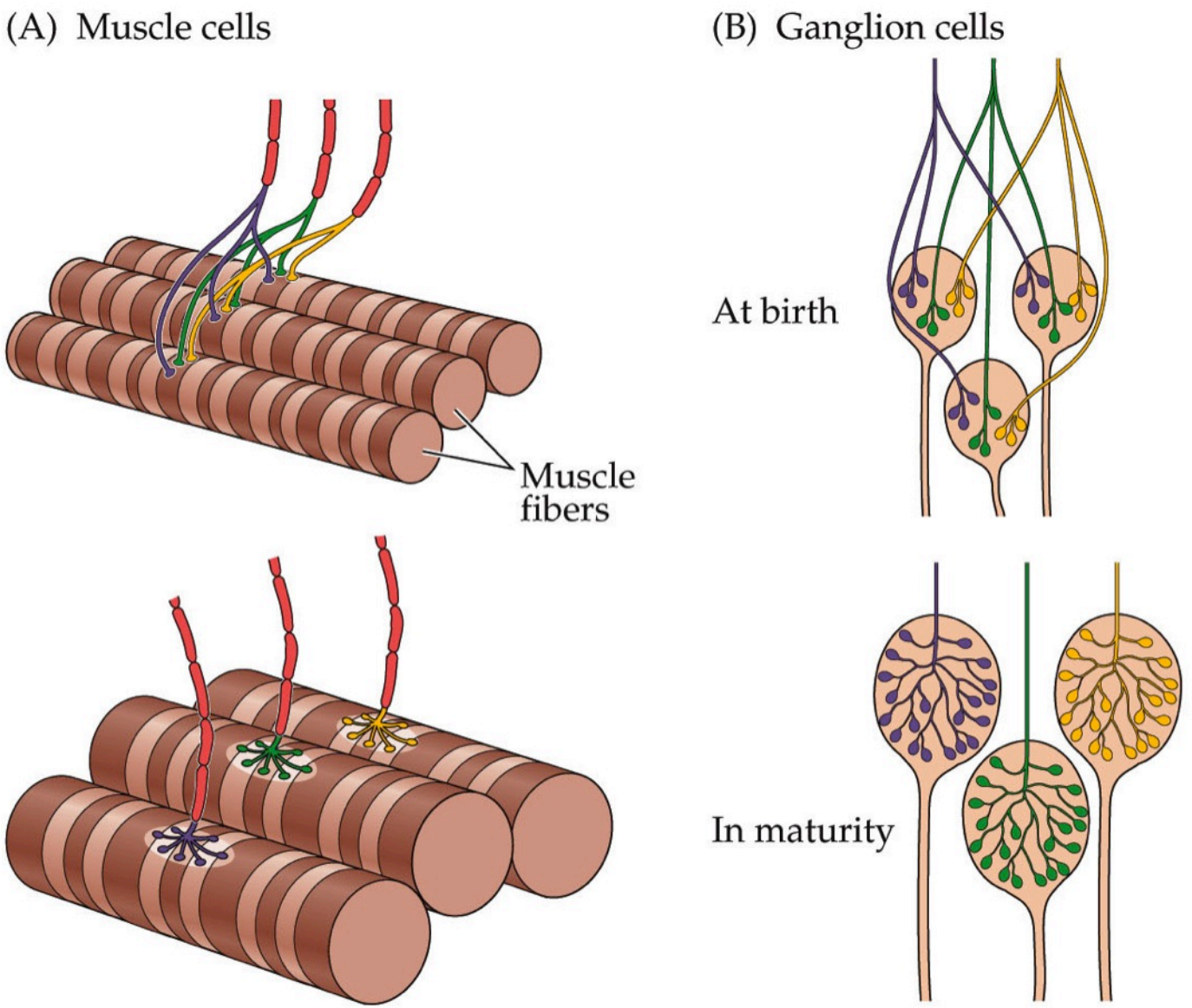


② Adhesion molecules

DSCAMs 37,000 potential forms



③ Pruning and maturation



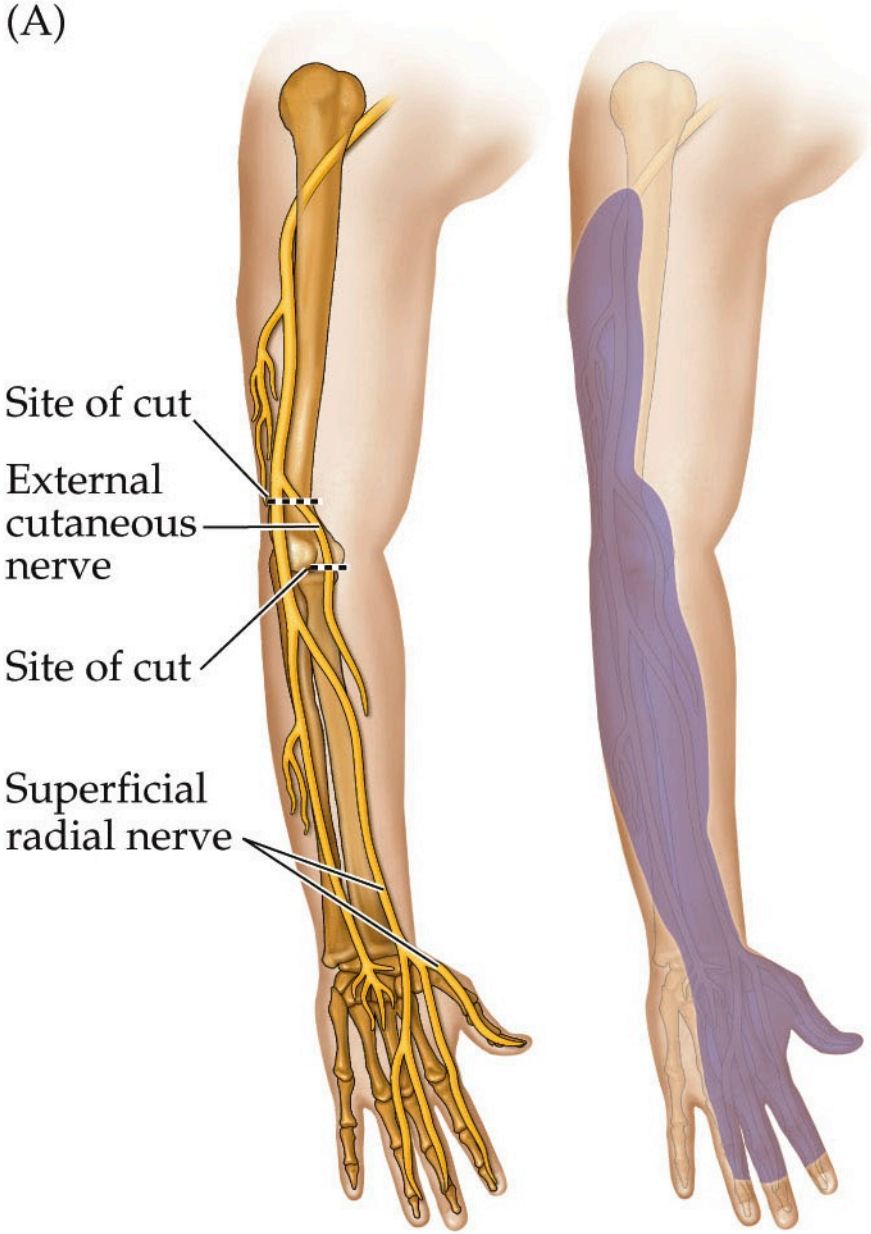
Critical Period

- period in early life when activity in neural circuits is required for their normal development
- occurs when brain is most plastic (most capable of structural and synaptic changes)
- useful connections are strengthened / maintained while weaker ones are lost

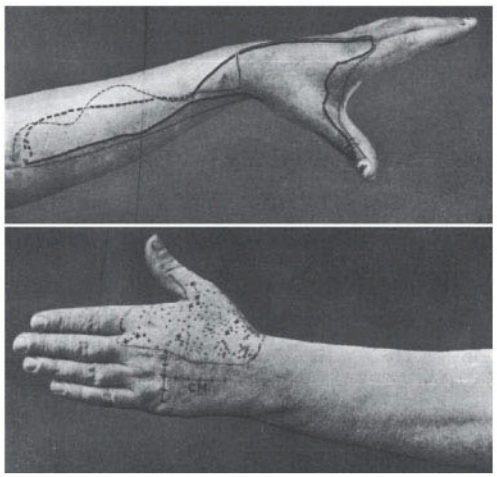
examples?

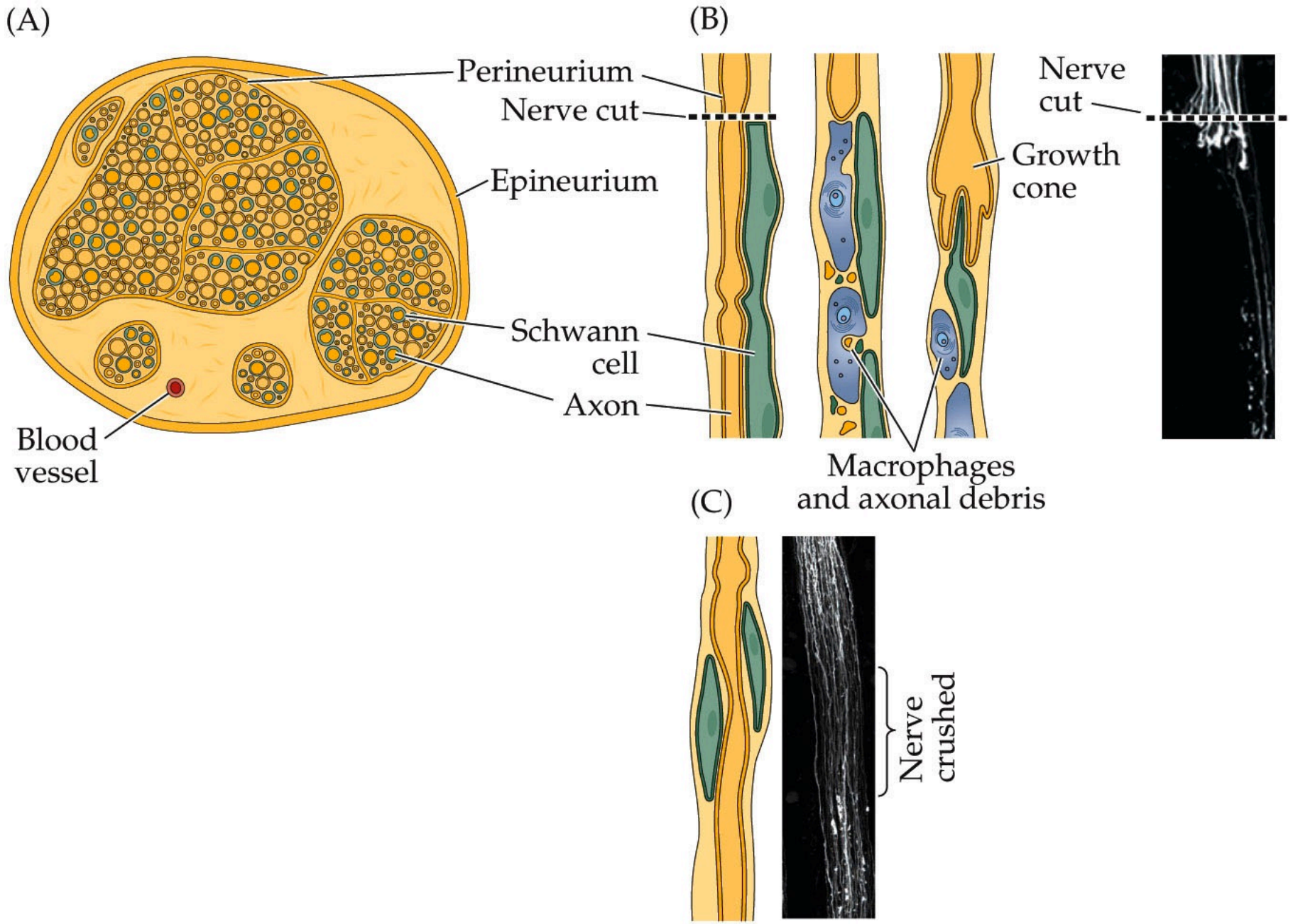
Neural Injury and Regeneration

(A)

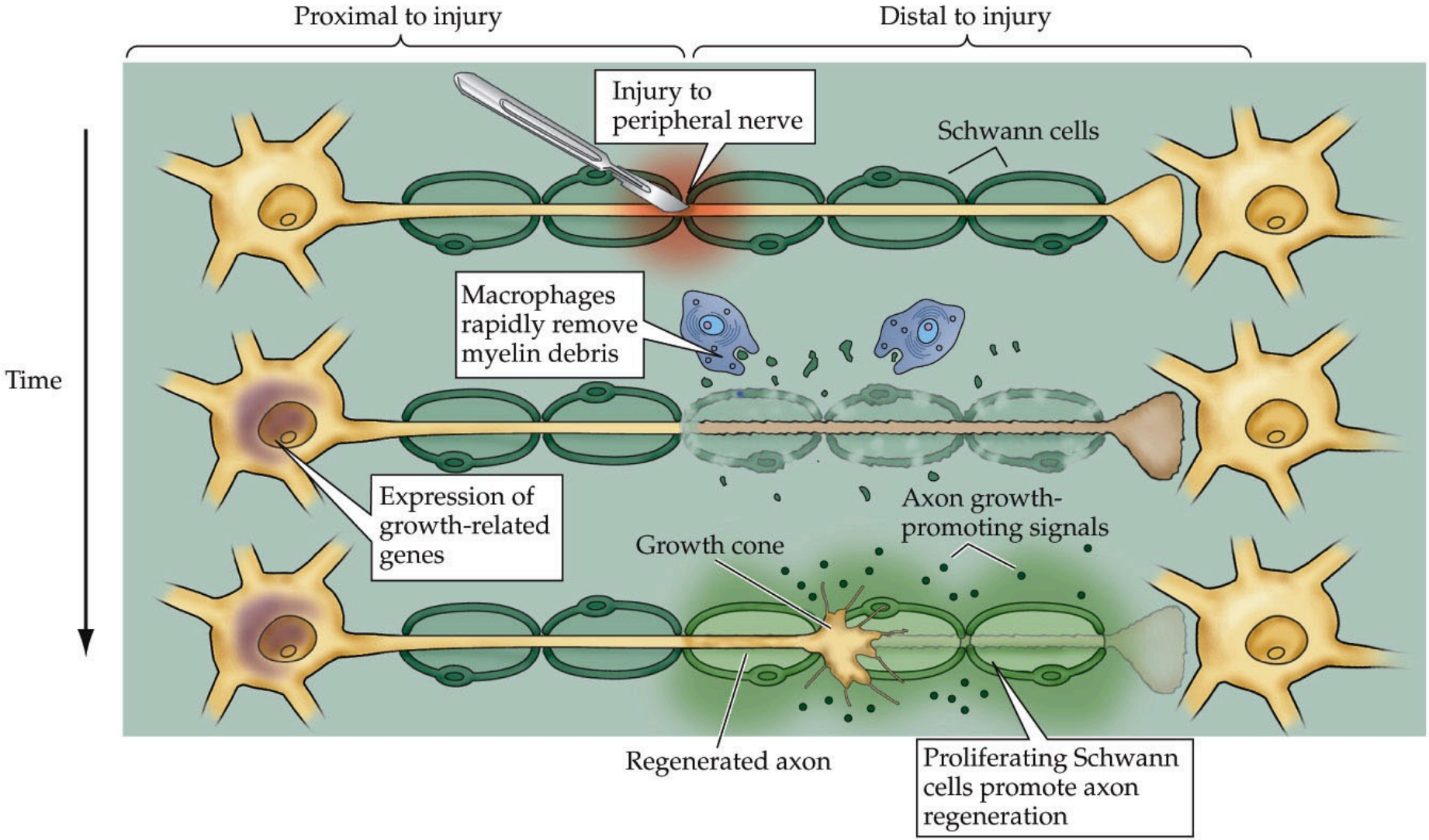

Site of cut
External cutaneous nerve
Site of cut
Superficial radial nerve

(B)

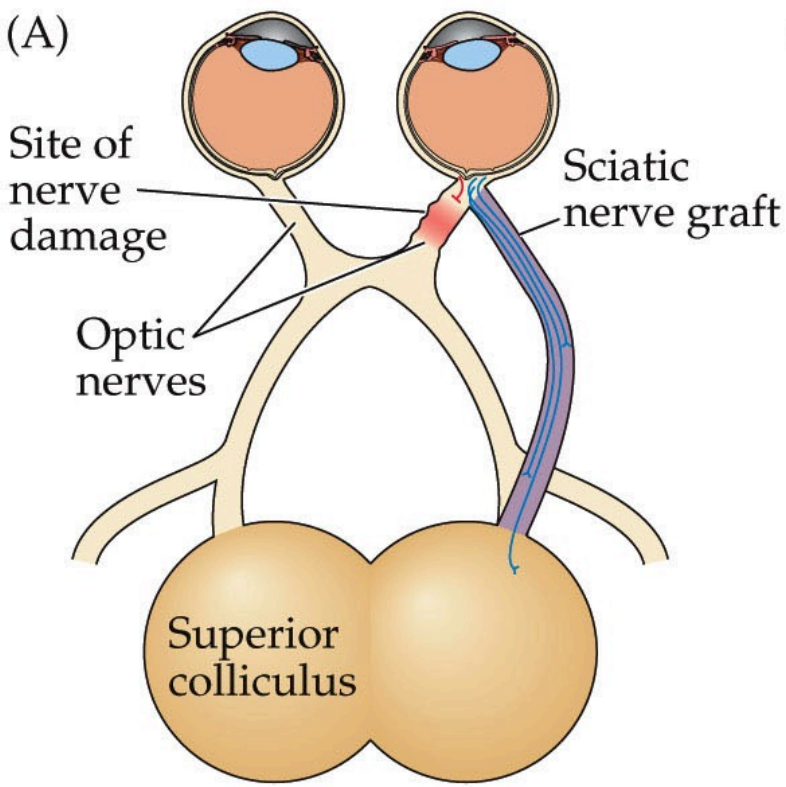


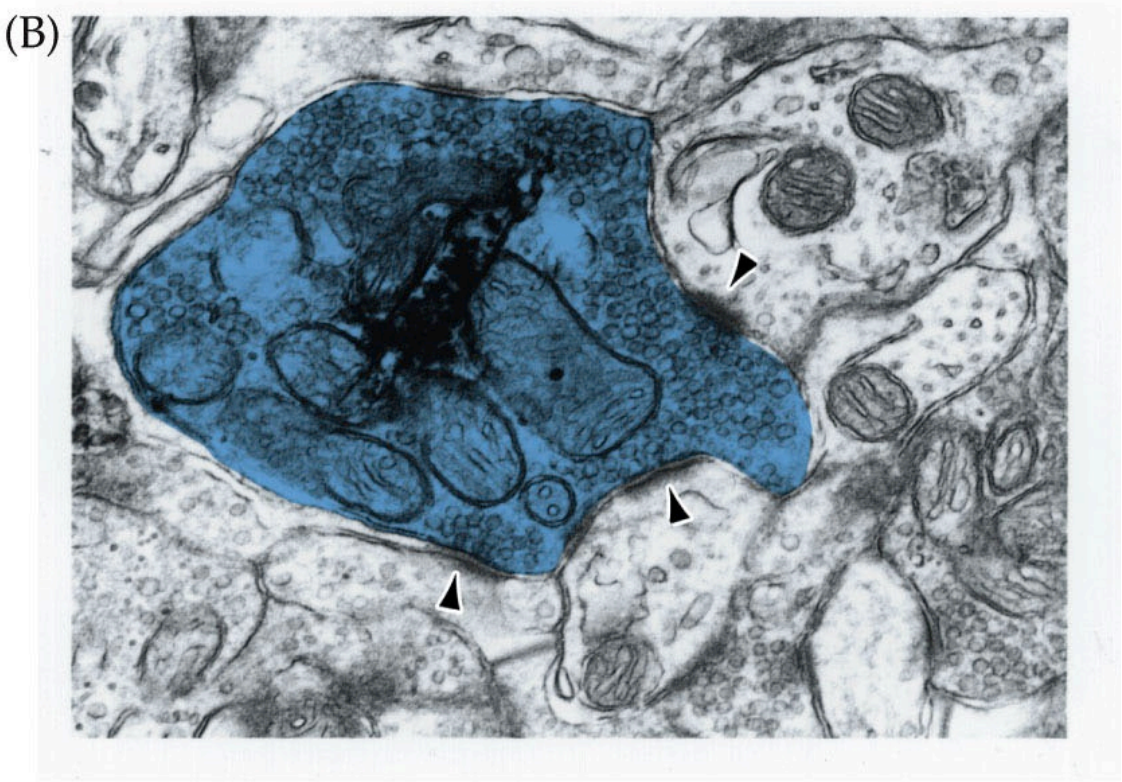

(A)
Perineurium
Nerve cut
Epineurium
Schwann cell
Axon
Blood vessel
(B)
Growth cone
Nerve cut
Macrophages and axonal debris
(C)
Nerve crushed

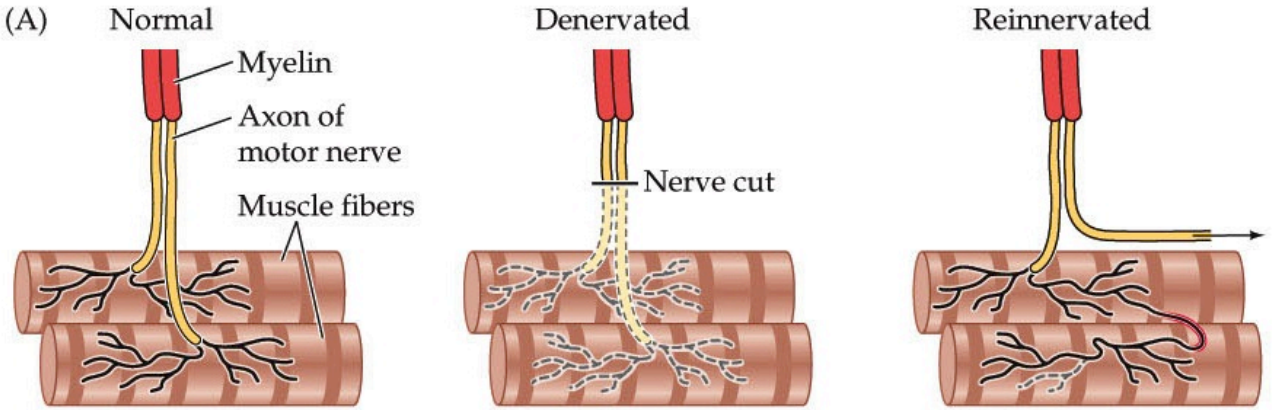
Peripheral nervous system



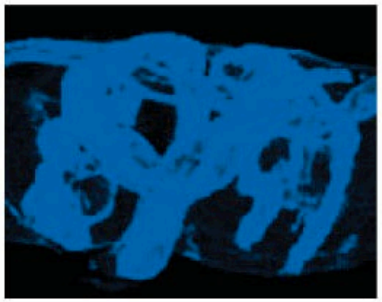
Peripheral nerve sheaths may be used as grafts



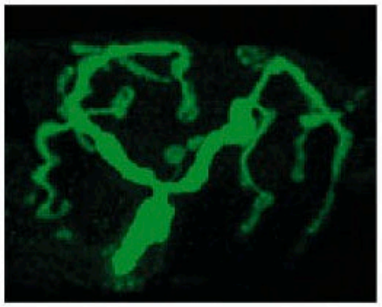




(B)



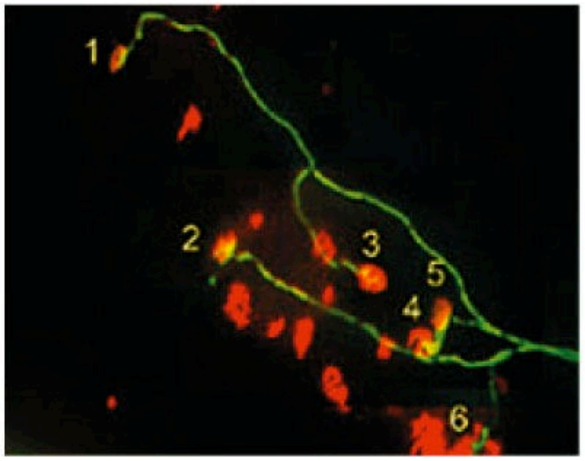
Schwann cells



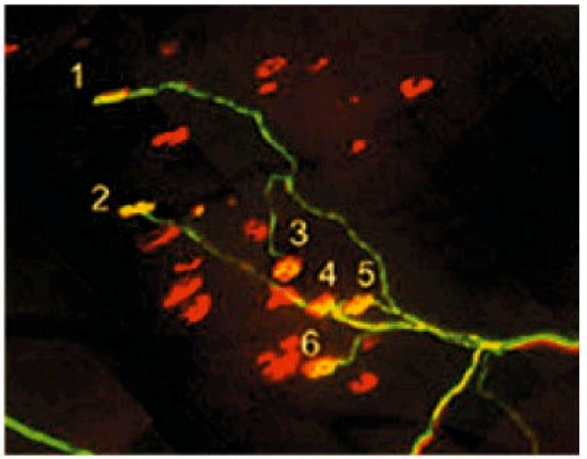
Axons

Acetylcholine receptors

(C)

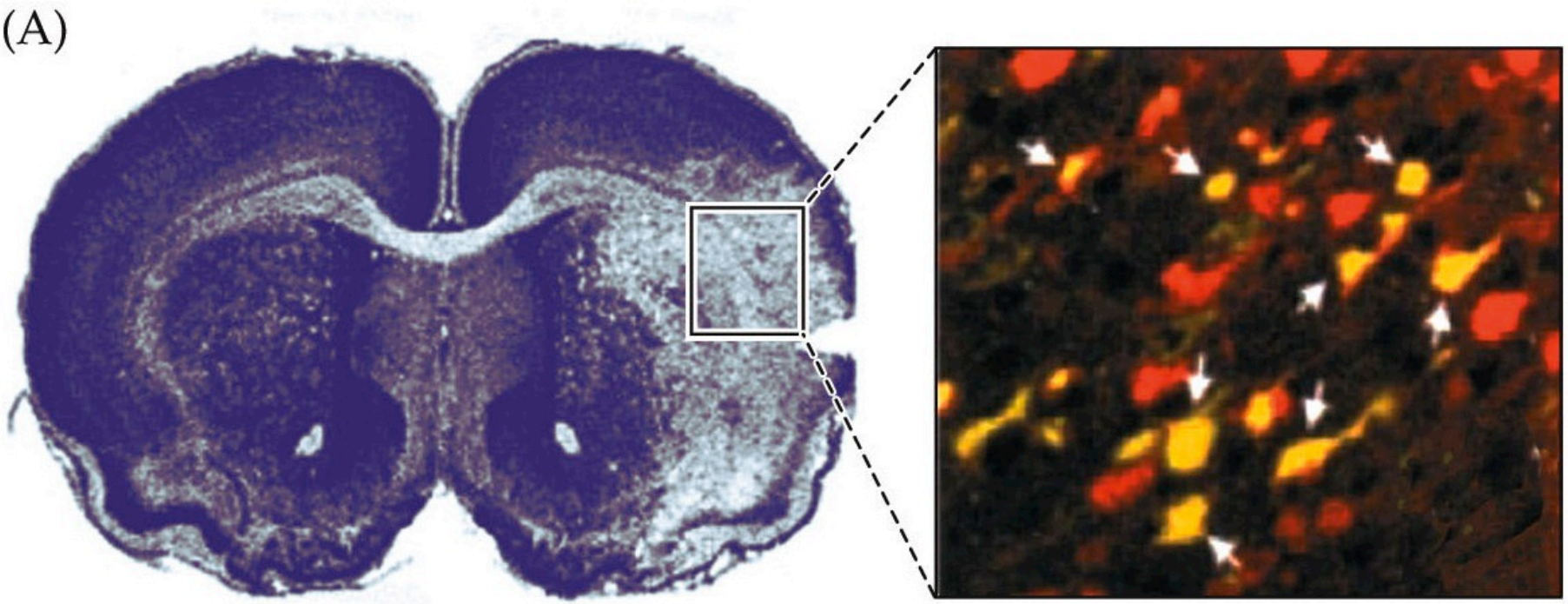


Pre-injury

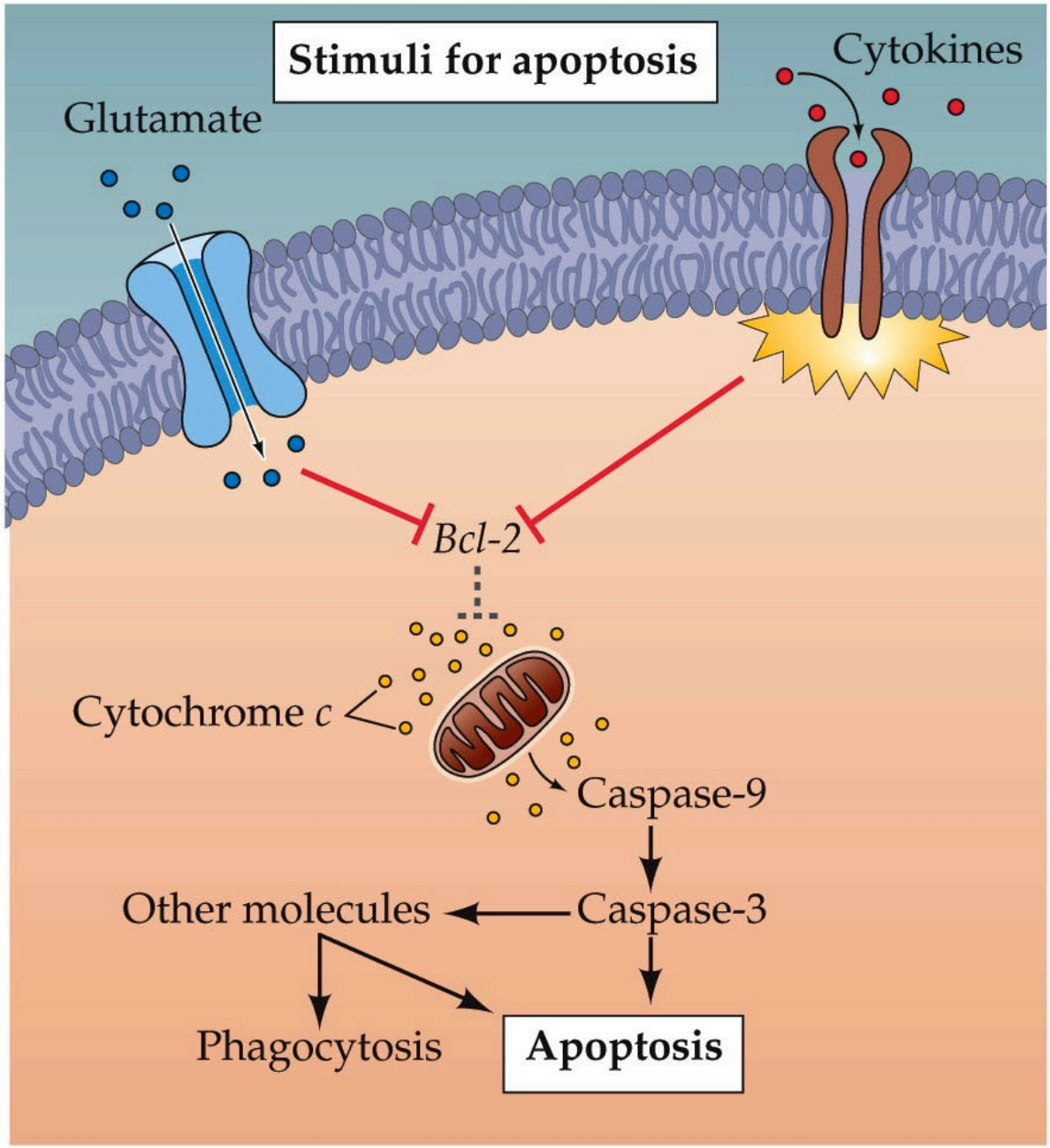


25 days later

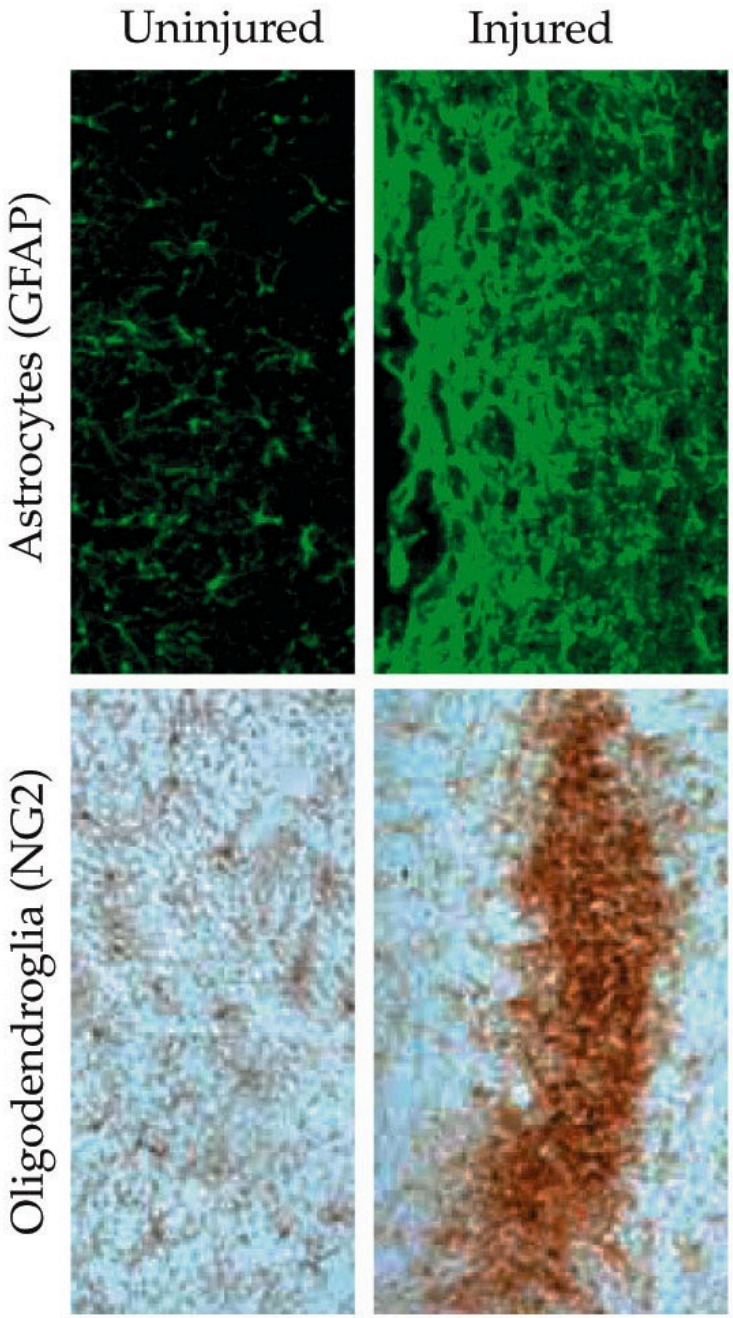
(A)

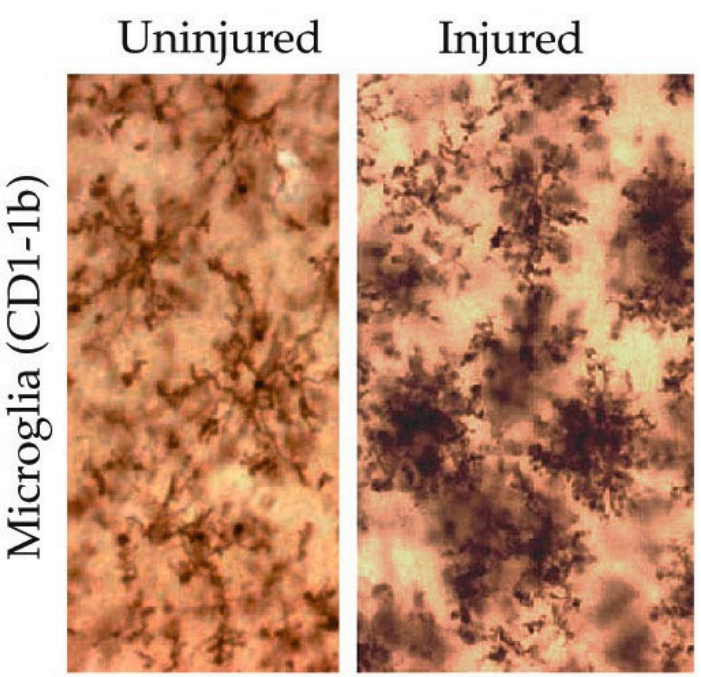


Apoptosis is stimulated by local cytokines and glutamate release

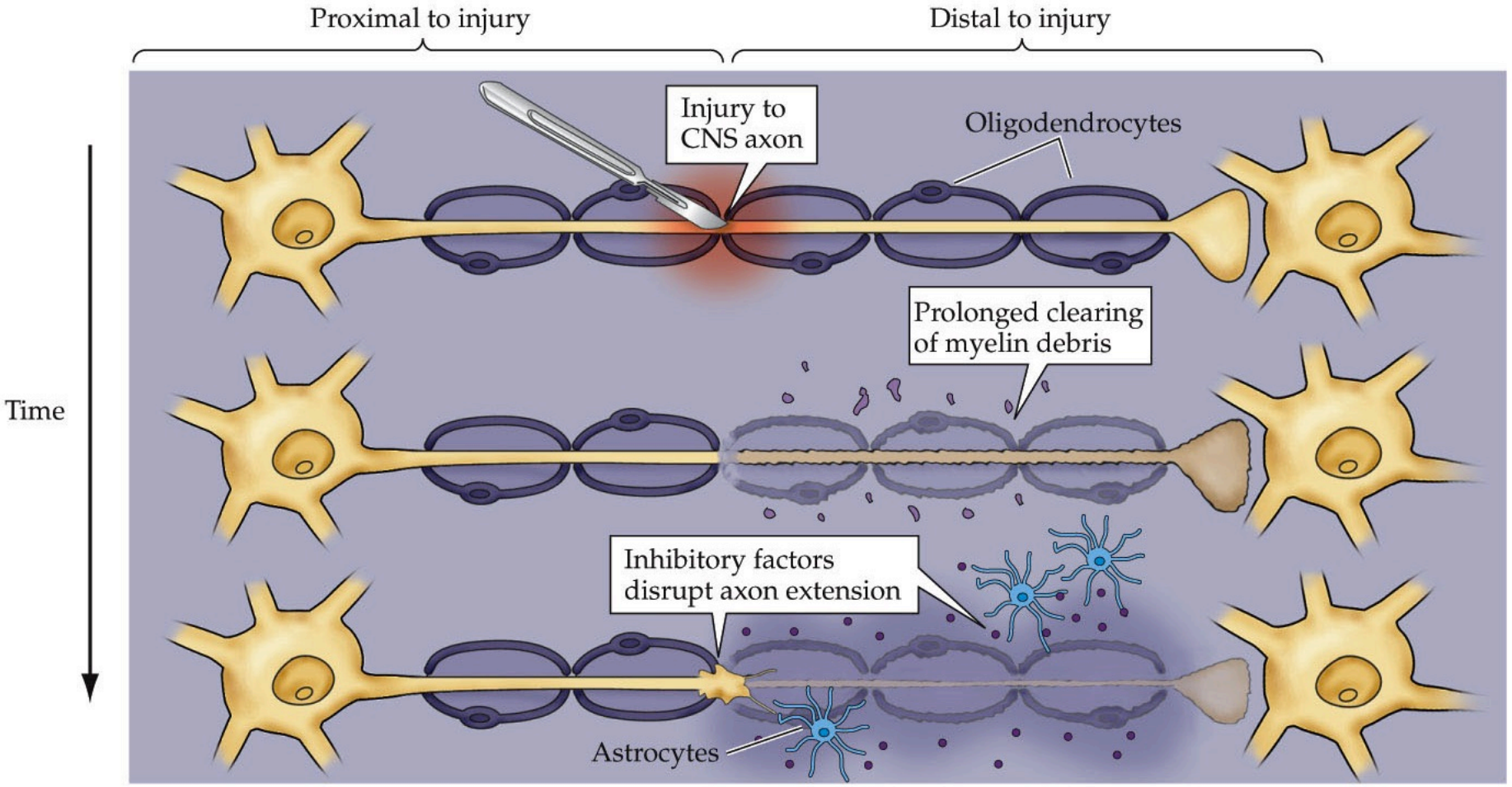


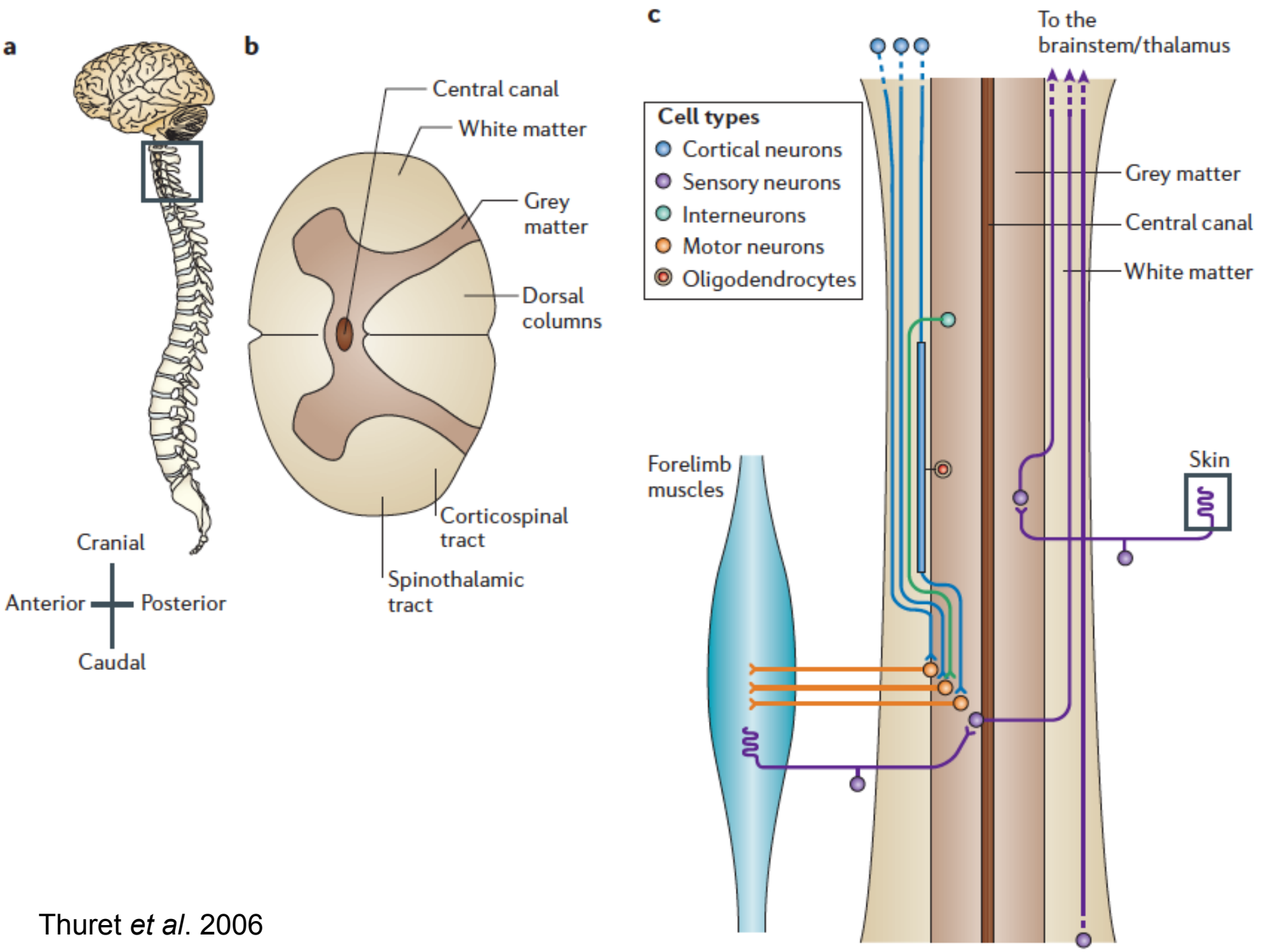
Gliosis


Uninjured
Injured
Astrocytes (GFAP)
Oligodendroglia (NG2)

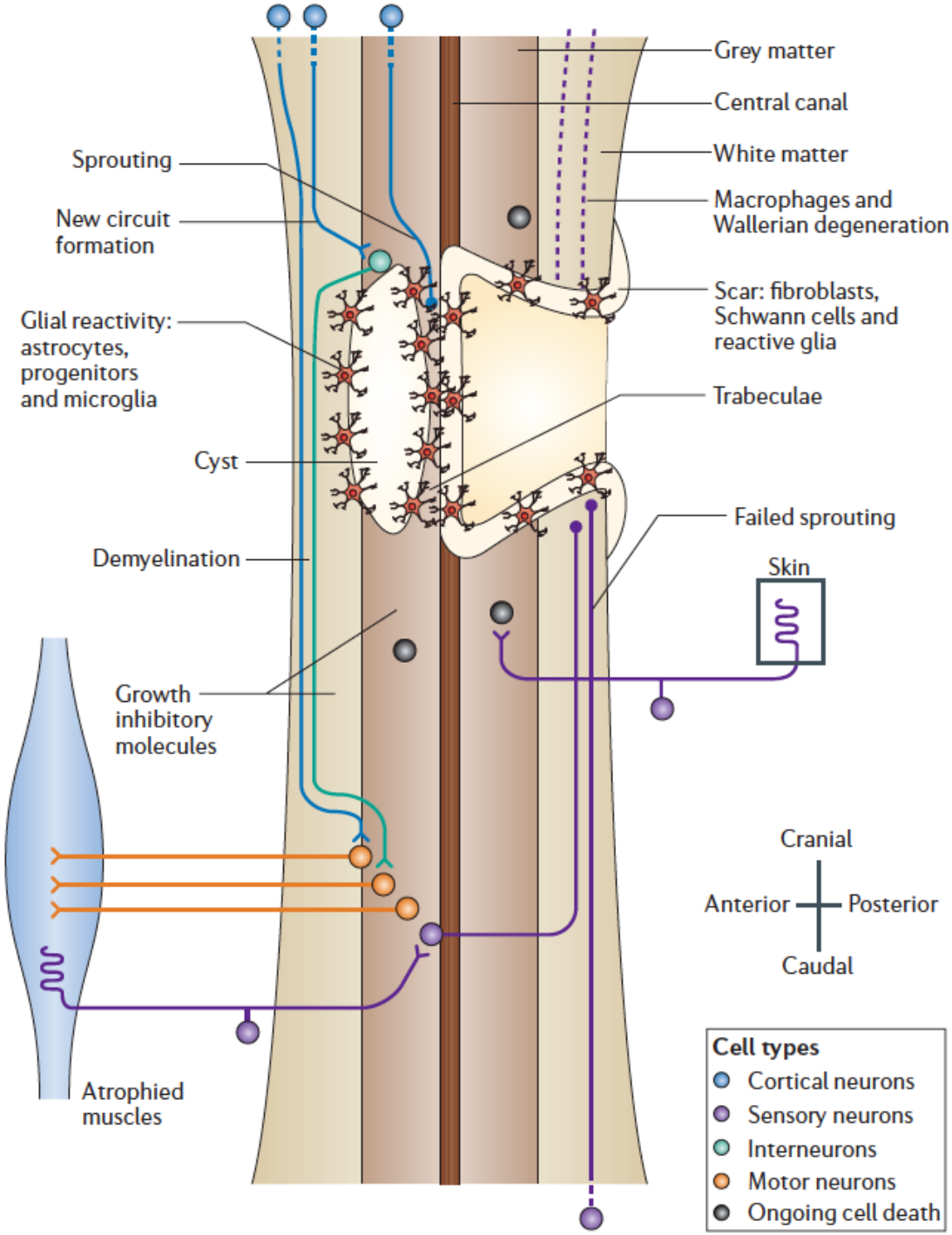

Uninjured
Injured
Microglia (CD1-1b)

Injury to CNS Axons

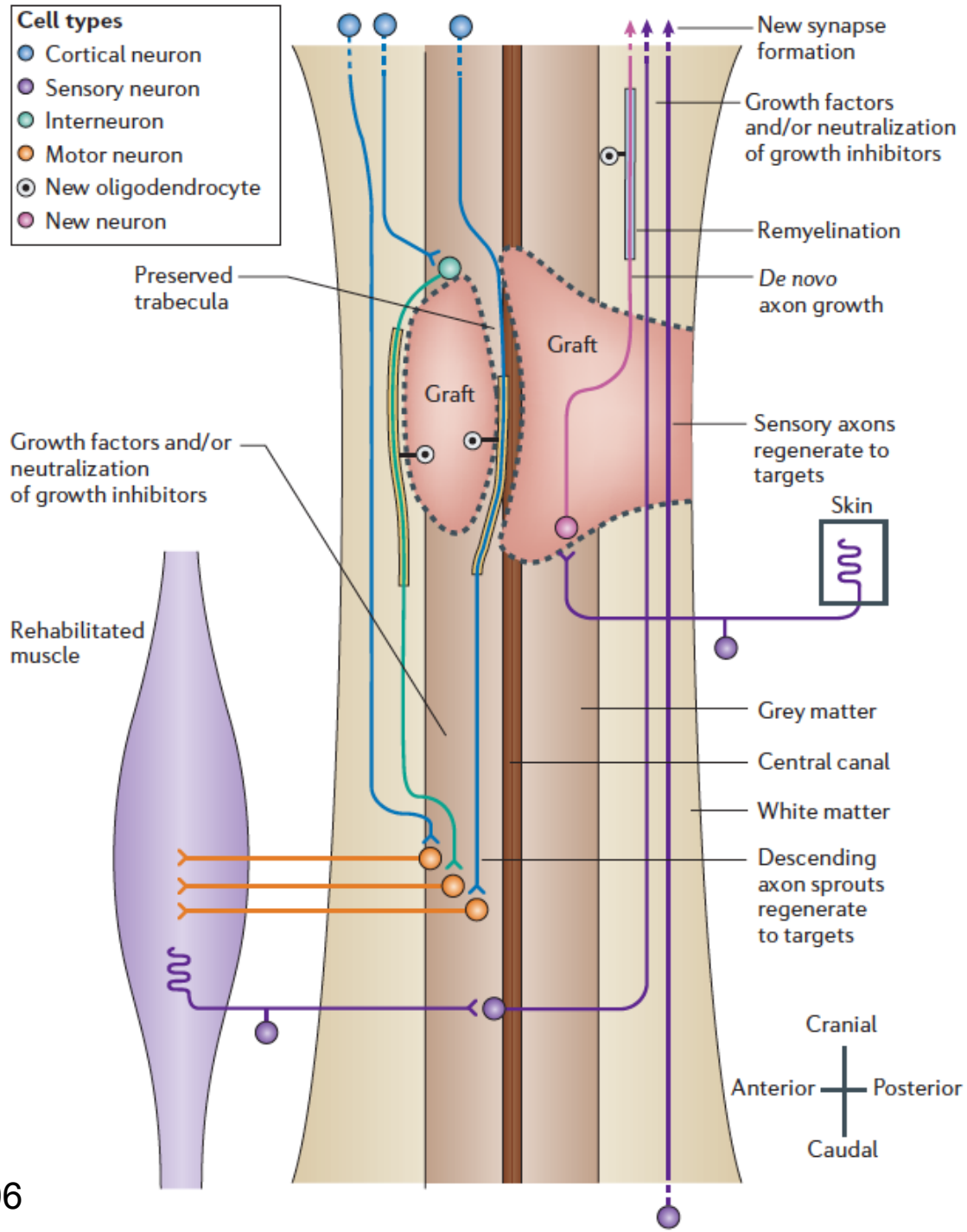




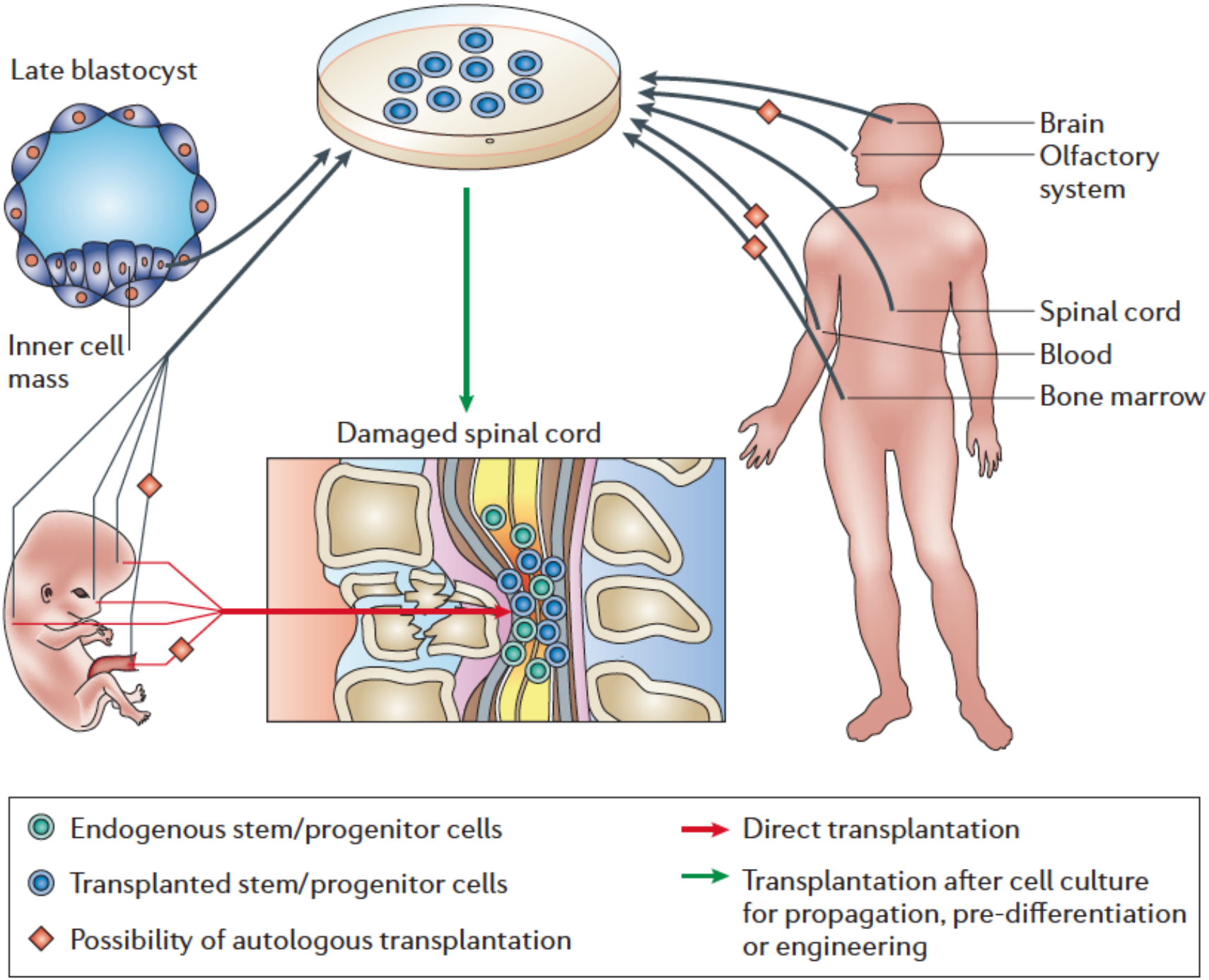
Thuret *et al*. 2006



Thuret *et al*. 2006



Thuret *et al*. 2006



Thuret *et al.* 2006

Neurodegenerative Diseases

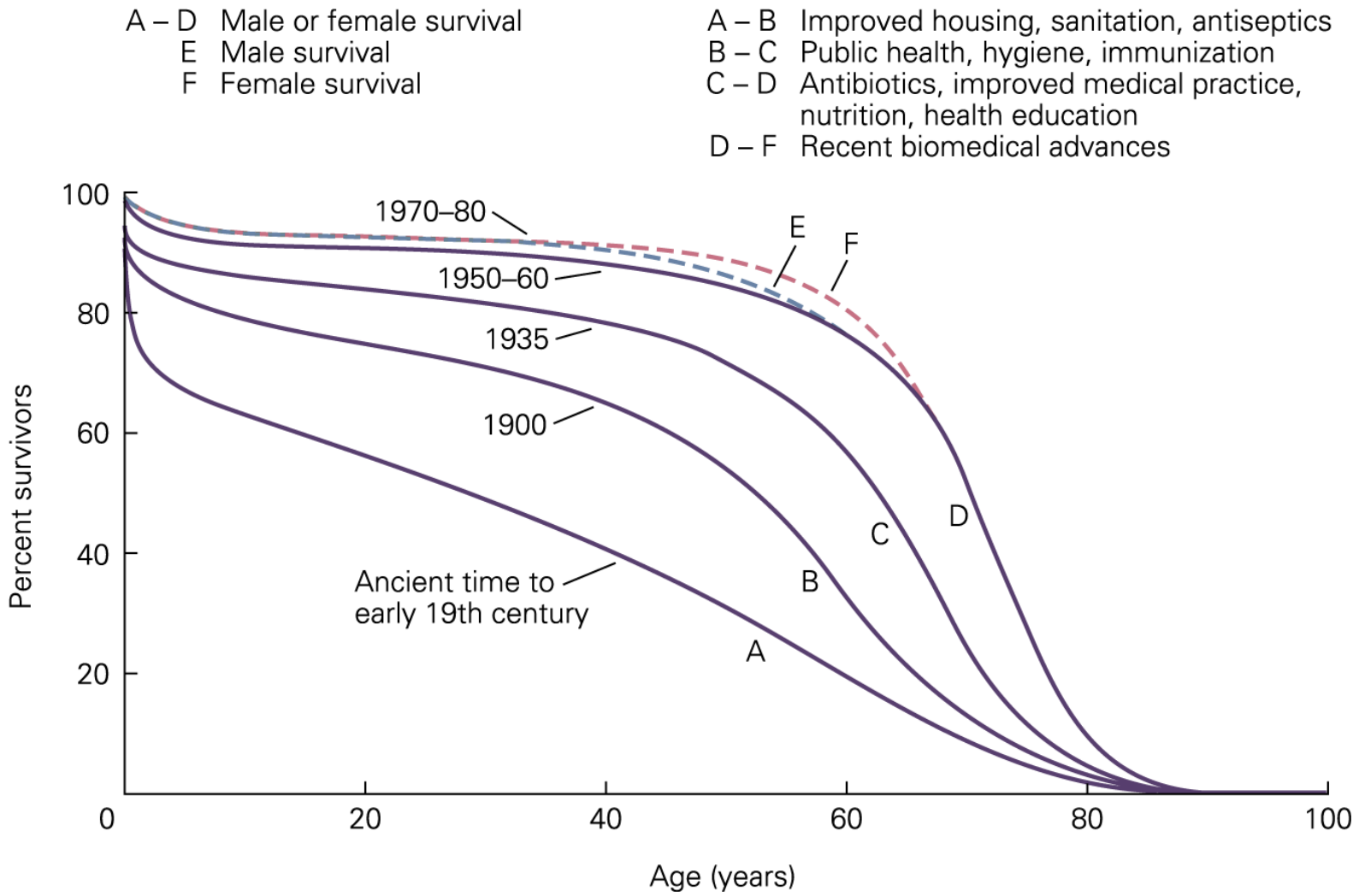
- Alzheimer's Disease
- Parkinson's Disease
- Huntington's Disease
- Amyotrophic Lateral Sclerosis (ALS)
- Frontotemporal Dementia
- Multiple System Atrophy

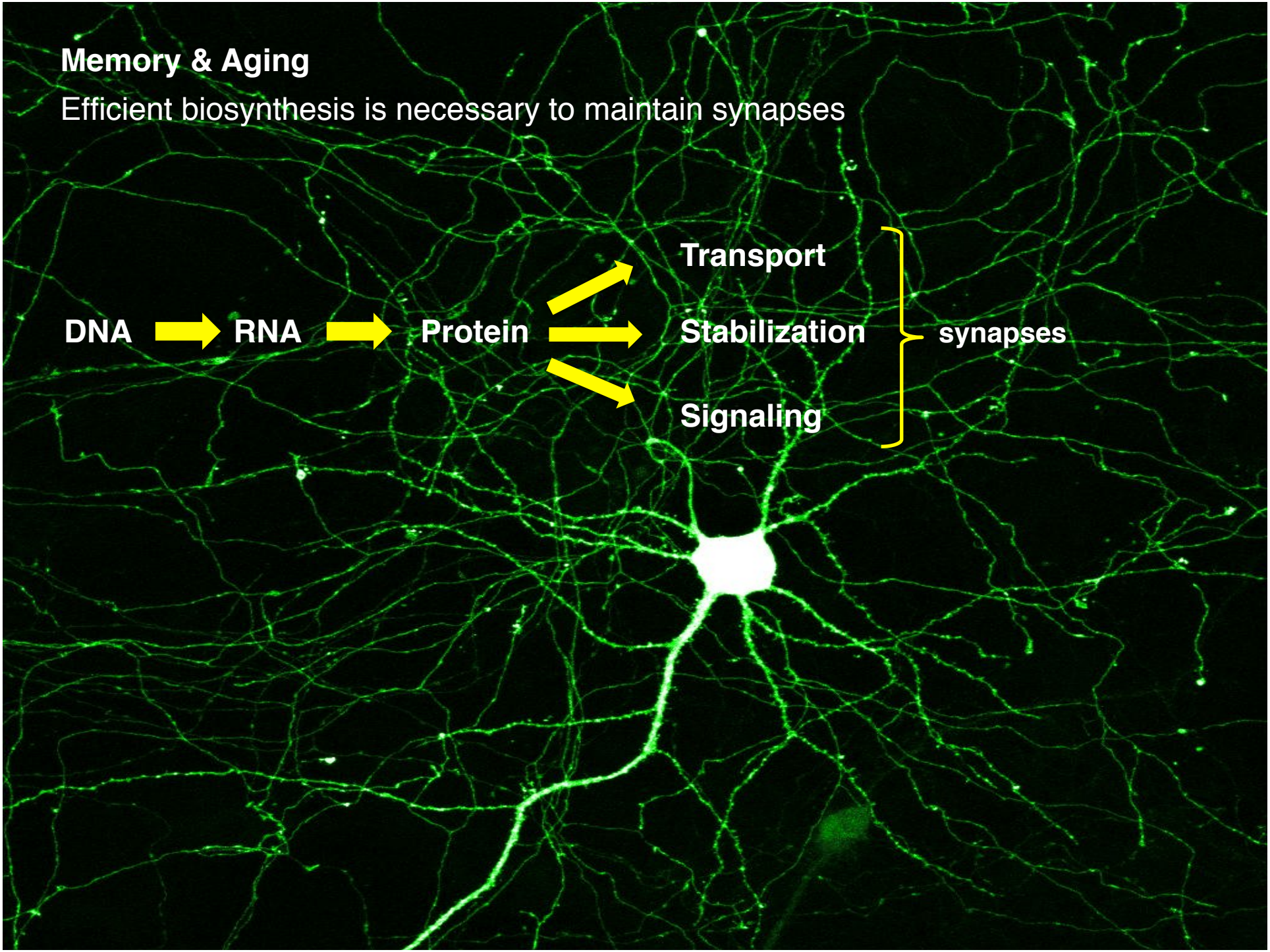
Prion Diseases

- Creutzfeldt-Jakob
- Fatal Familial Insomnia

Memory & Aging

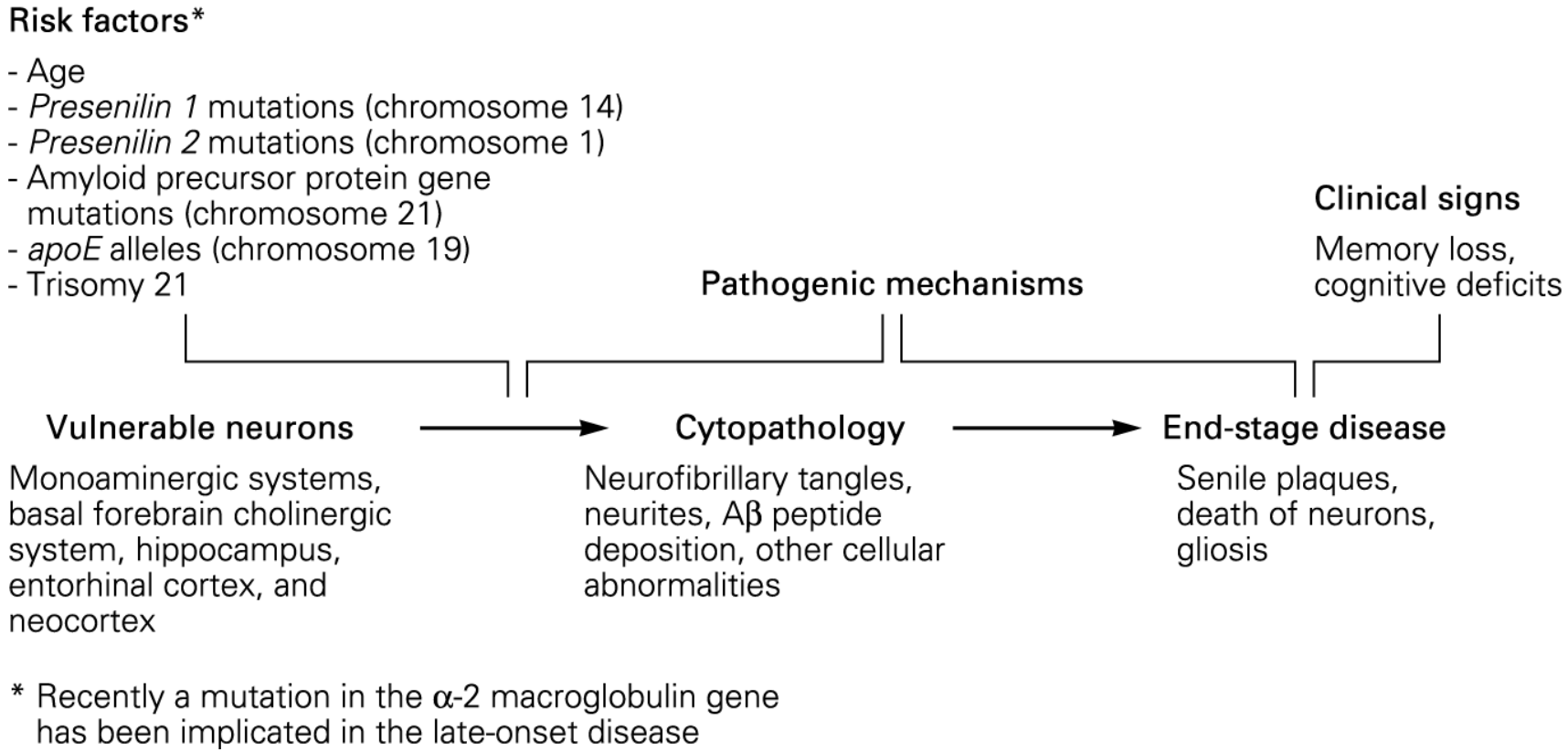
People (and brains) are living longer…




Memory & Aging
Efficient biosynthesis is necessary to maintain synapses
DNA
RNA
Protein
Transport
Stabilization
Signaling
synapses

Memory & Aging

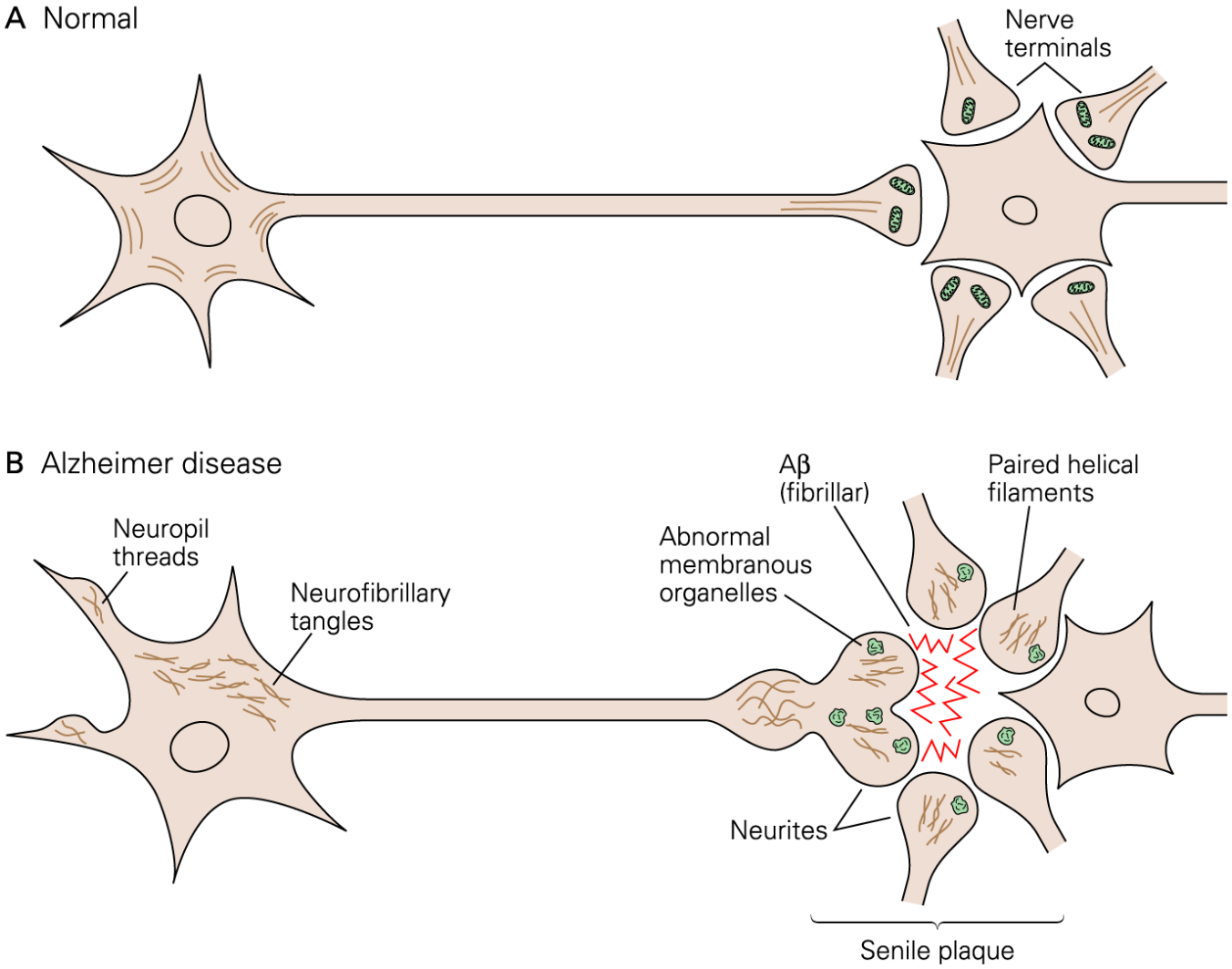
Dementia and Alzheimer's Disease



* Recently a mutation in the α-2 macroglobulin gene has been implicated in the late-onset disease

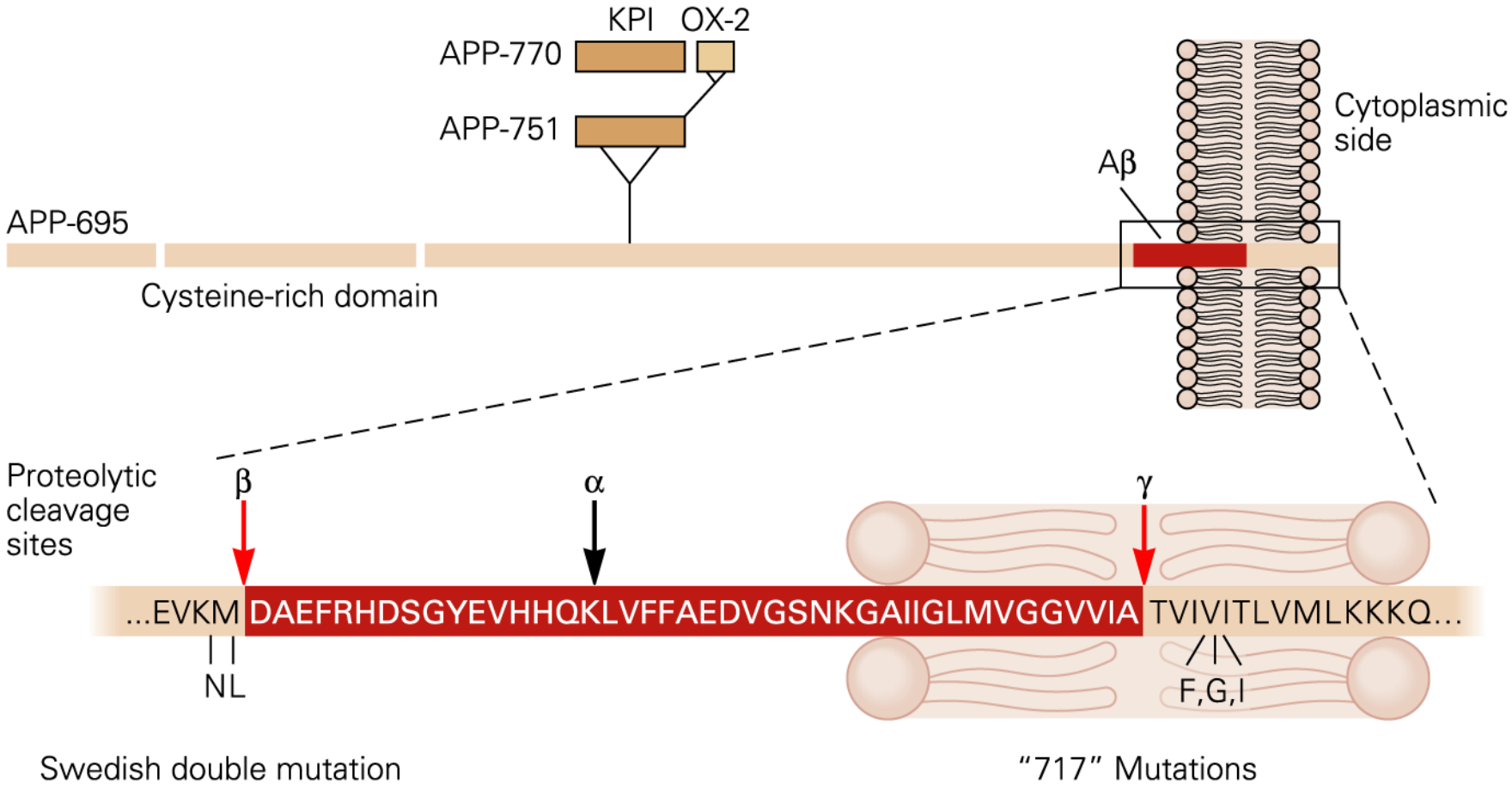
Memory & Aging

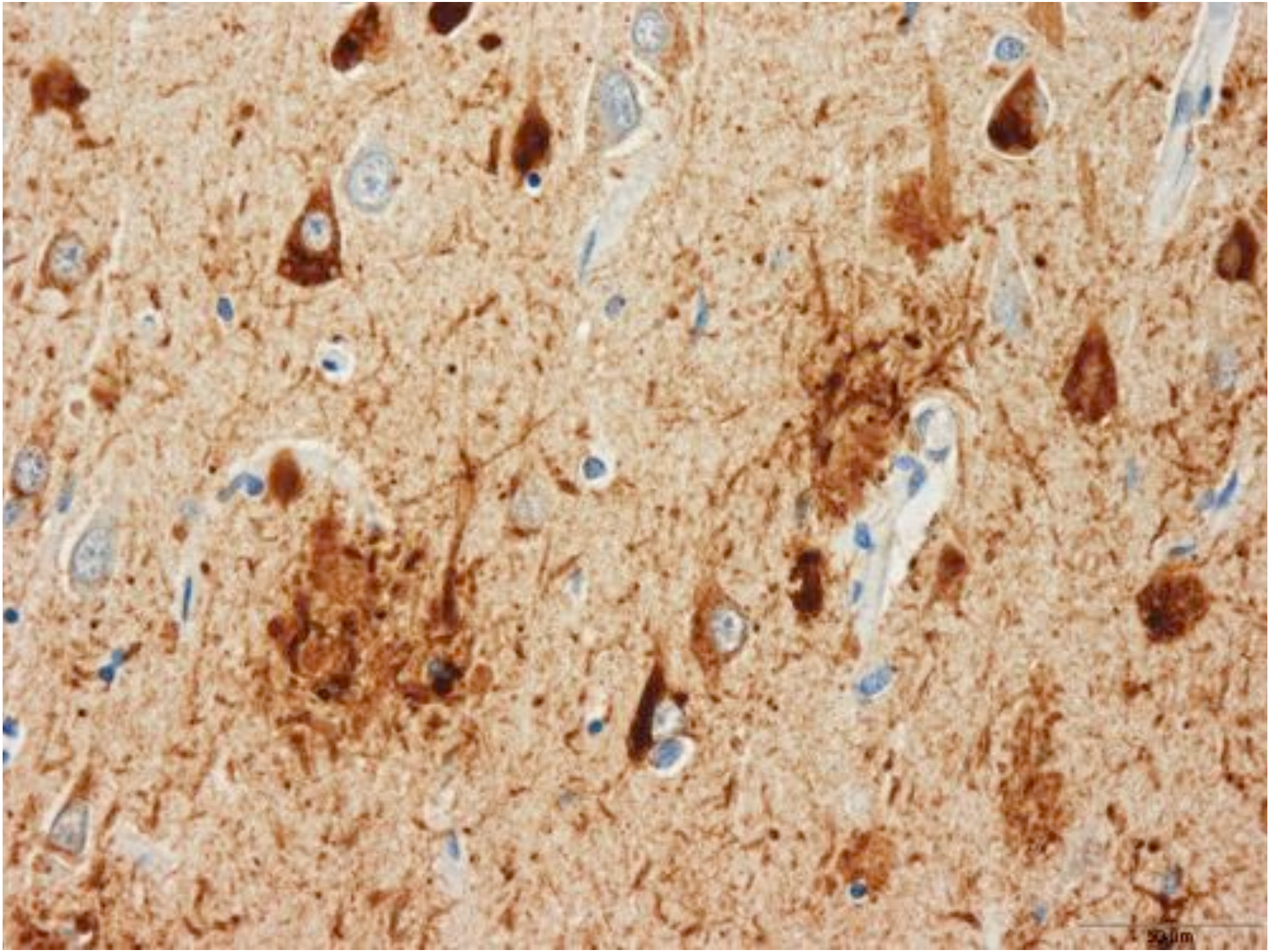
Dementia and Alzheimer's Disease



Memory & Aging

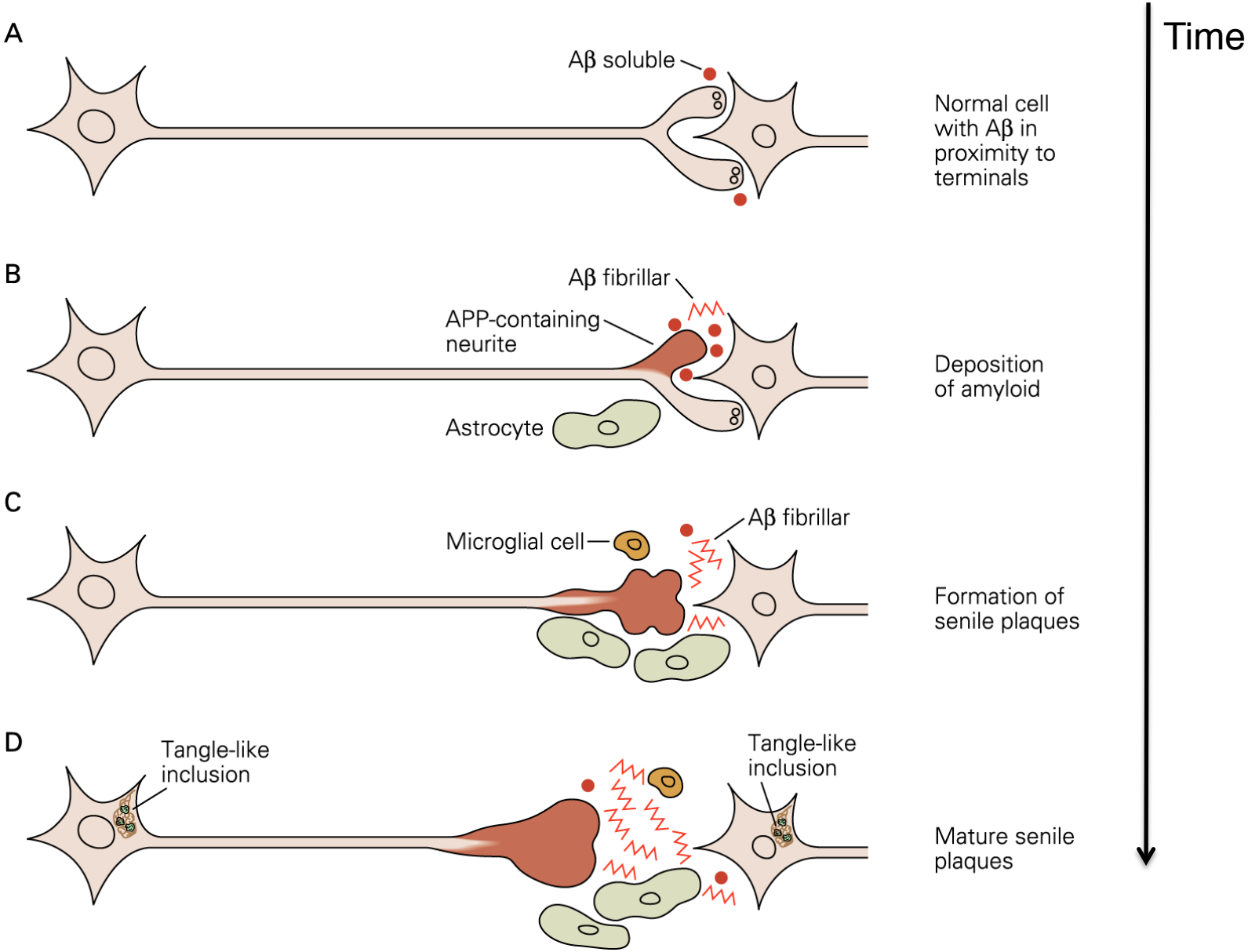
Dementia and Alzheimer's Disease





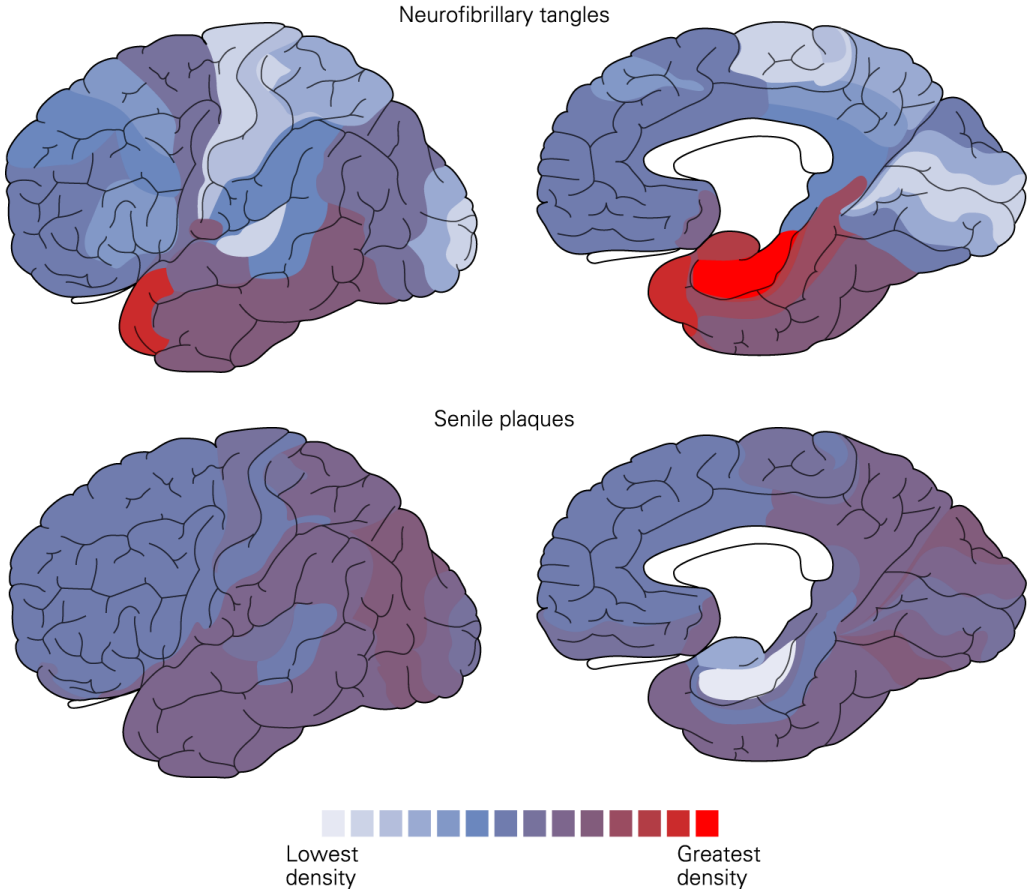
Memory & Aging

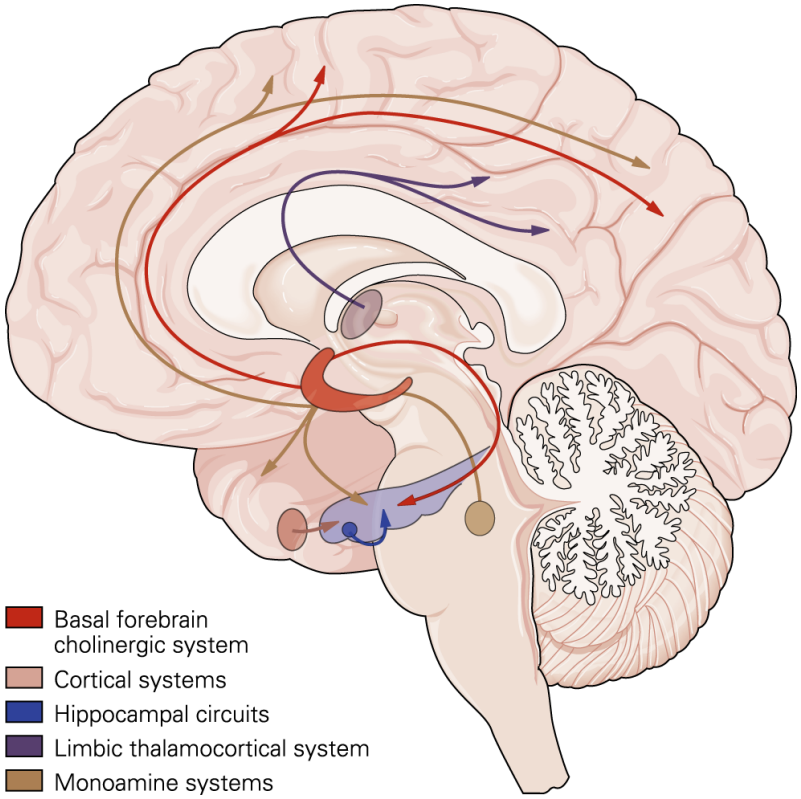
Dementia and Alzheimer's Disease



Memory & Aging

Dementia and Alzheimer's Disease

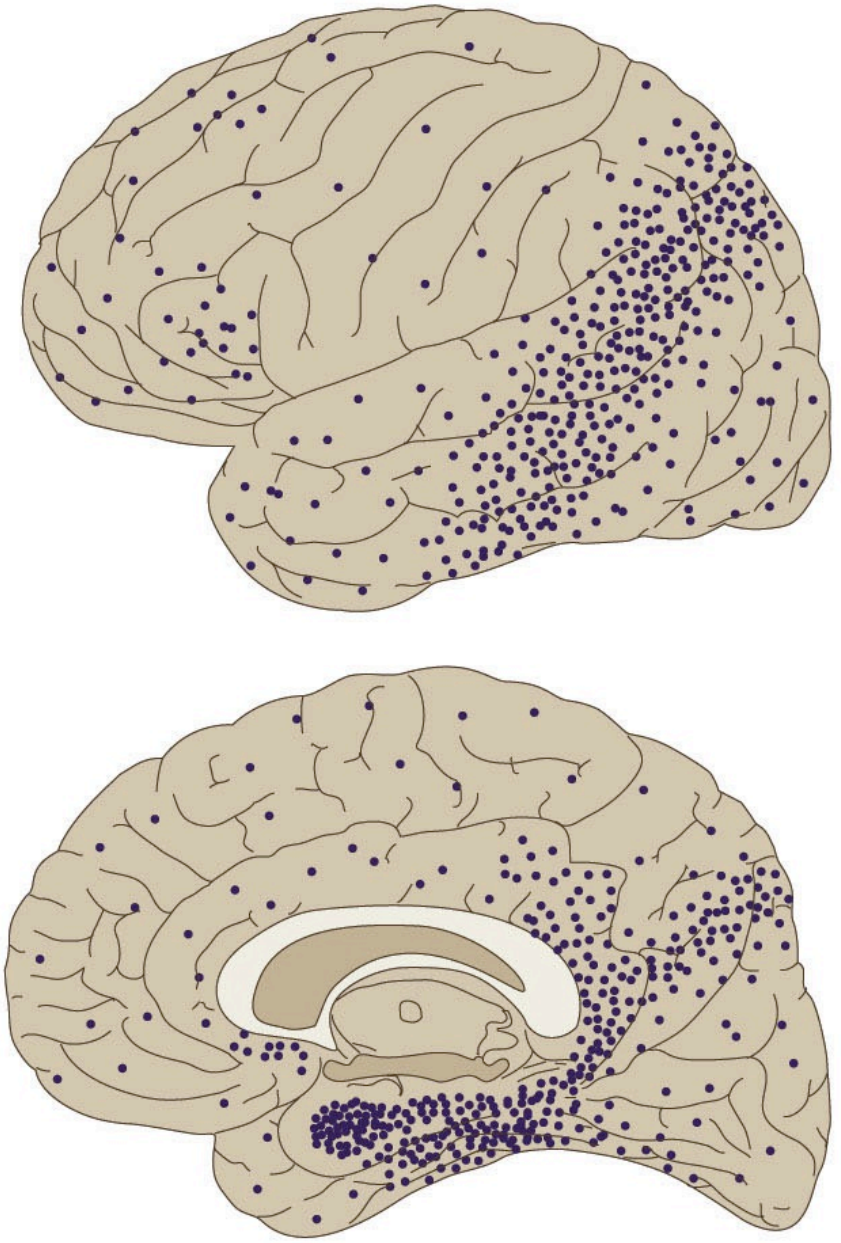




(A) Neurofibrillary tangle

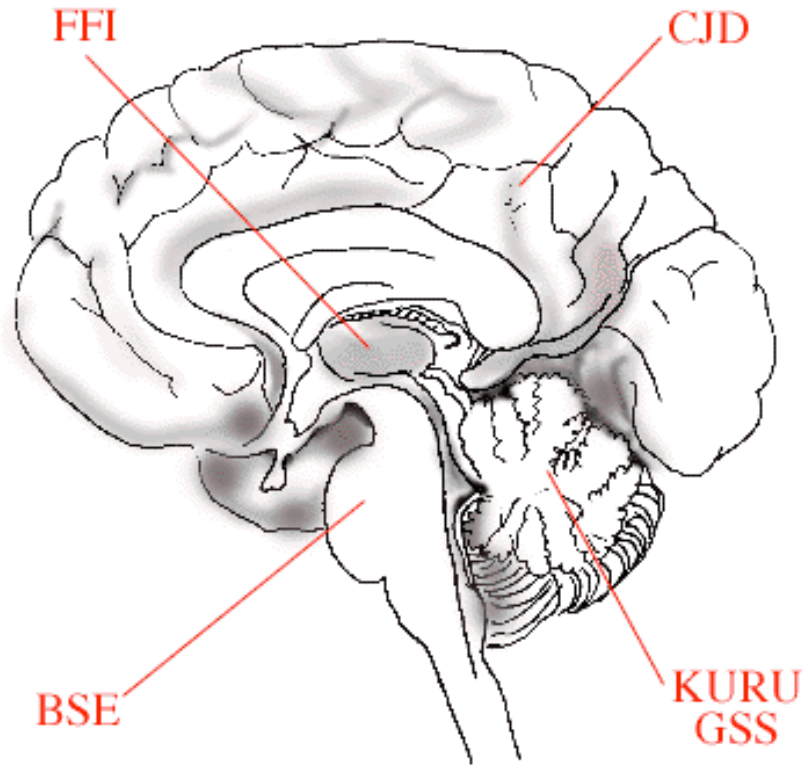
Amyloid plaque

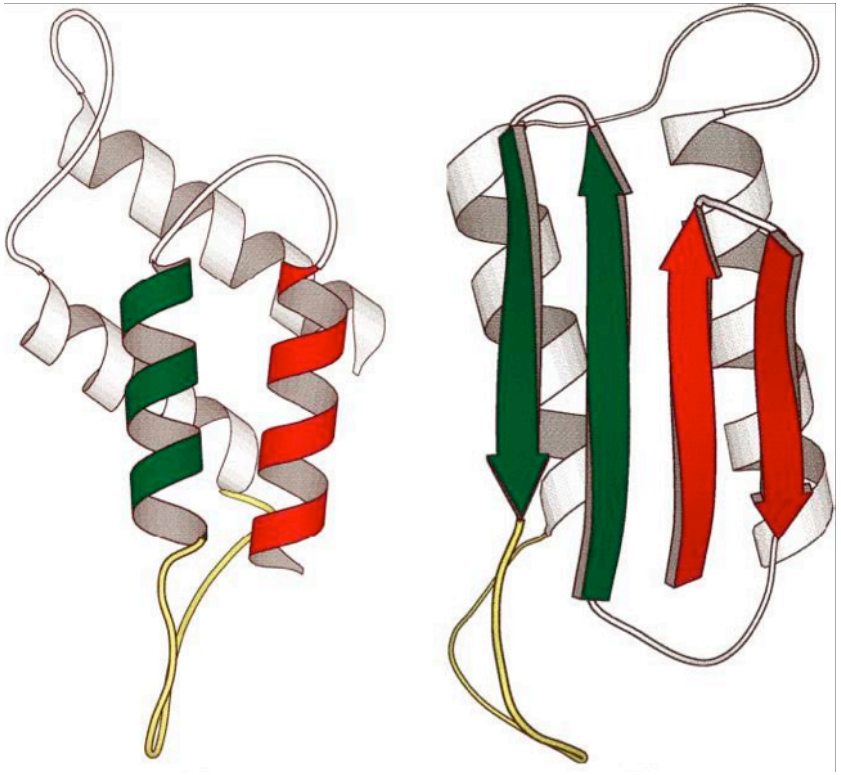
(B)



Prion Diseases

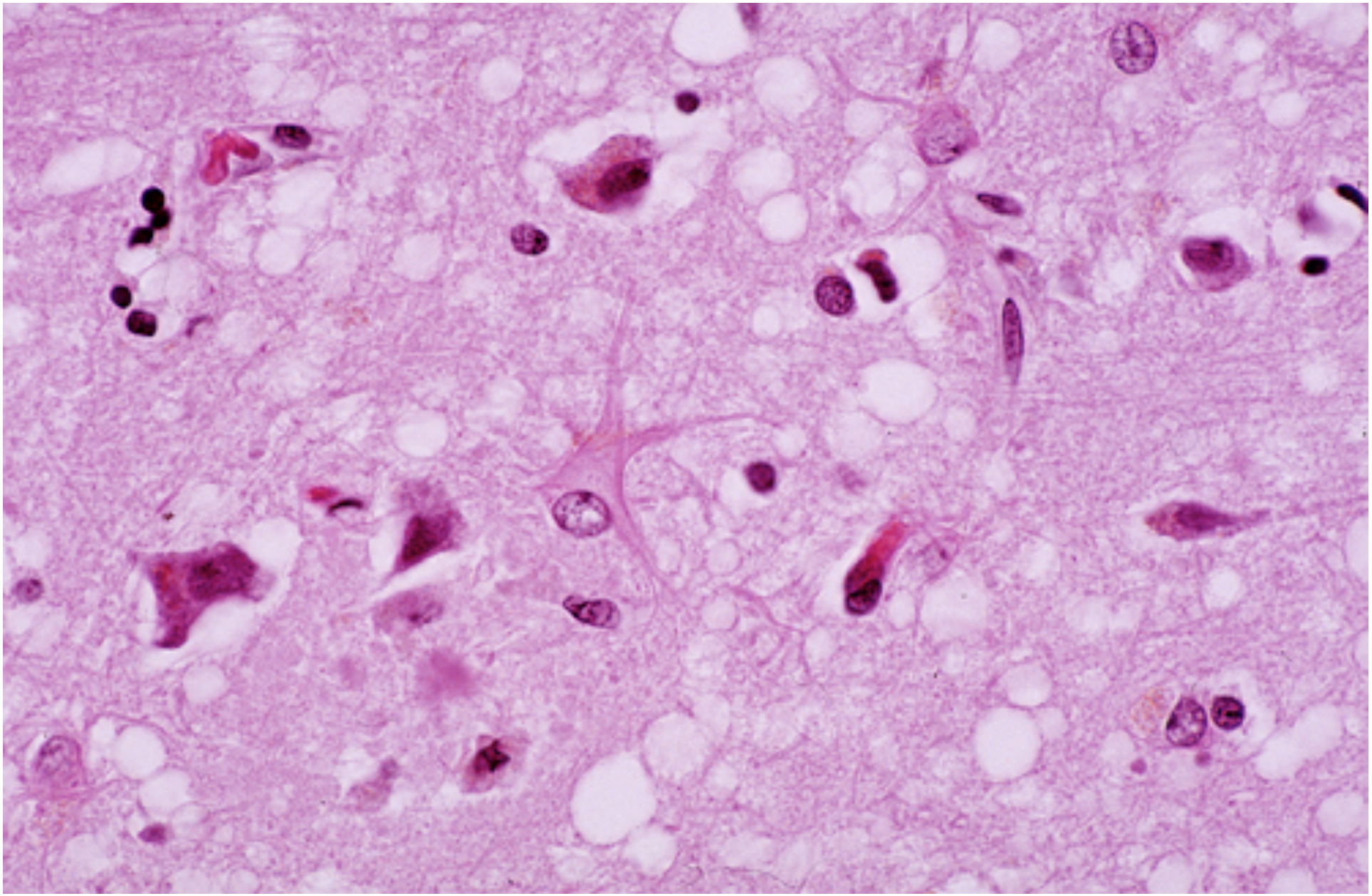
Creutzfeldt-Jakob Disease
Kuru
Bovine Spongiform Encephalopathy
Fatal Familial Insomnia

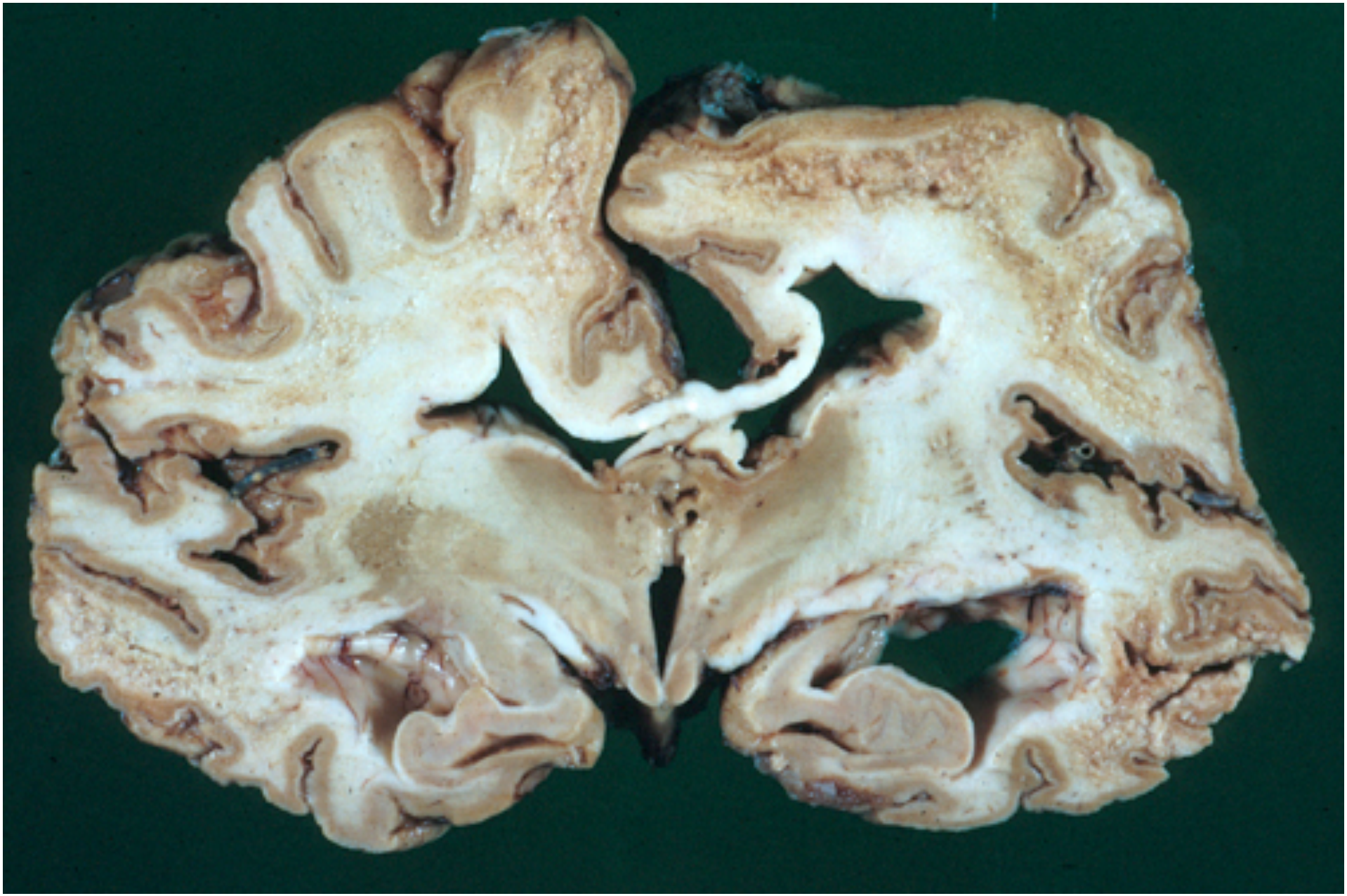




Normal Form

Prion Form





The PKMzeta story

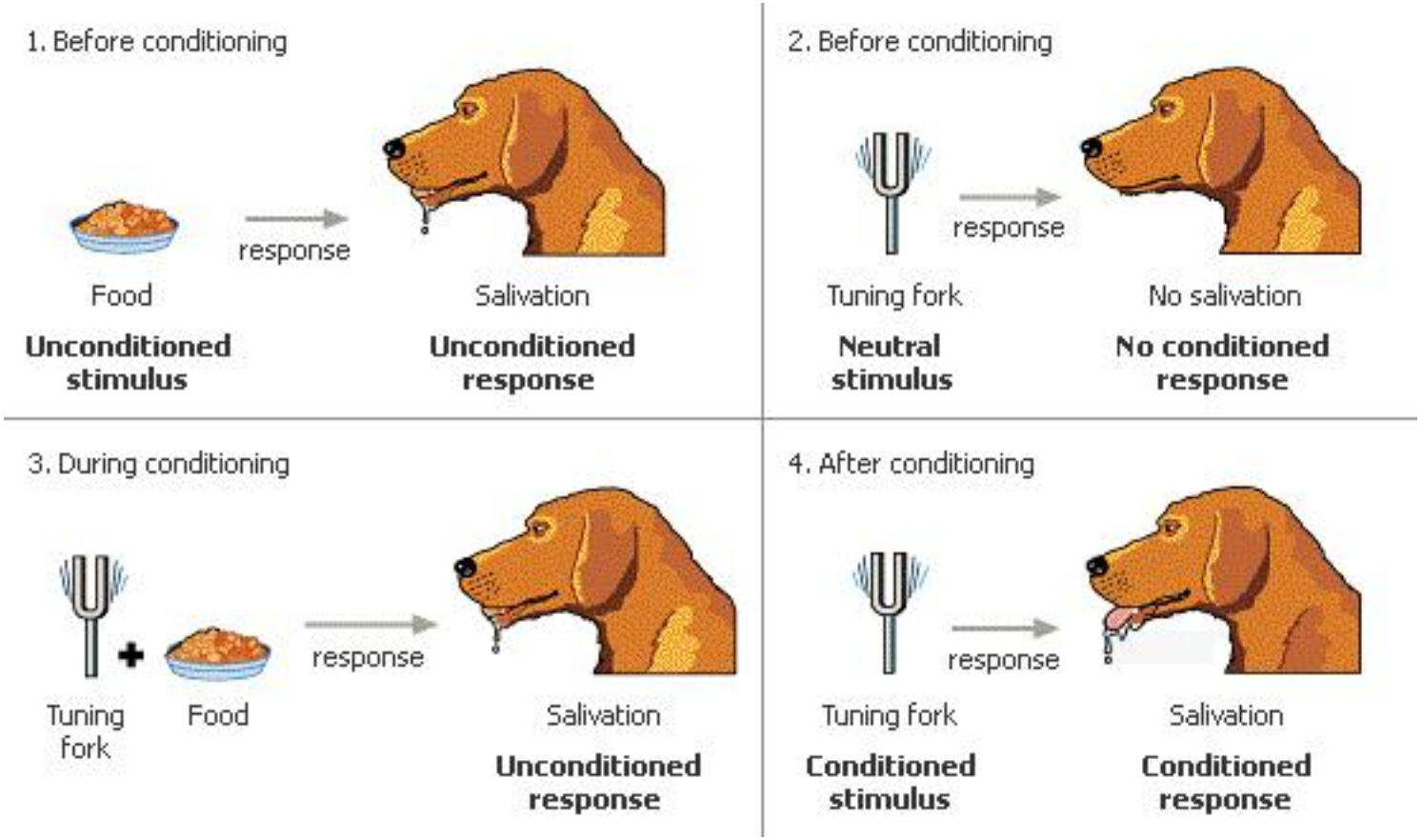
How memory works

Rapid Erasure of Long-Term Memory Associations in the Cortex by an Inhibitor of PKMζ

Reut Shema,[1] Todd Charlton Sacktor,[2] Yadin Dudai[1]*

Little is known about the neuronal mechanisms that subserve long-term memory persistence in the brain. The components of the remodeled synaptic machinery, and how they sustain the new synaptic or cellwide configuration over time, are yet to be elucidated. In the rat cortex, long-term associative memories vanished rapidly after local application of an inhibitor of the protein kinase C isoform, protein kinase M zeta (PKMζ). The effect was observed for at least several weeks after encoding and may be irreversible. In the neocortex, which is assumed to be the repository of multiple types of long-term memory, persistence of memory is thus dependent on ongoing activity of a protein kinase long after that memory is considered to have consolidated into a long-term stable form.

Pavlov's conditioning learning



Conditioned Taste Aversion

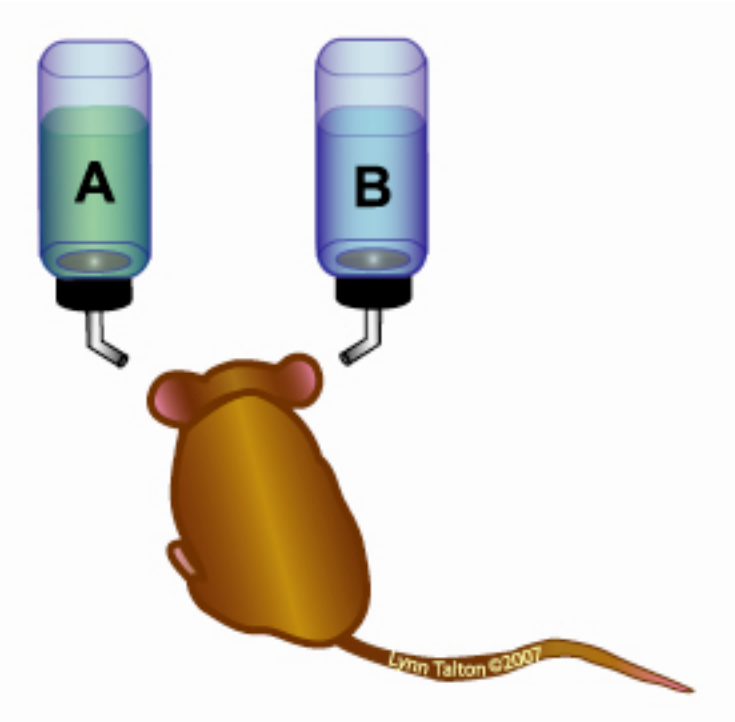
Conditioning

- One day, the saccharine is added to the water the rats are given
- 40min after they drink the saccharine water, they get an injection of LiCl- rat do NOT enjoy this

Conditioned stimulus (CS) = saccharine taste

Unconditioned stimulus (US) = injection

Conditioned Taste Aversion



Testing Day:

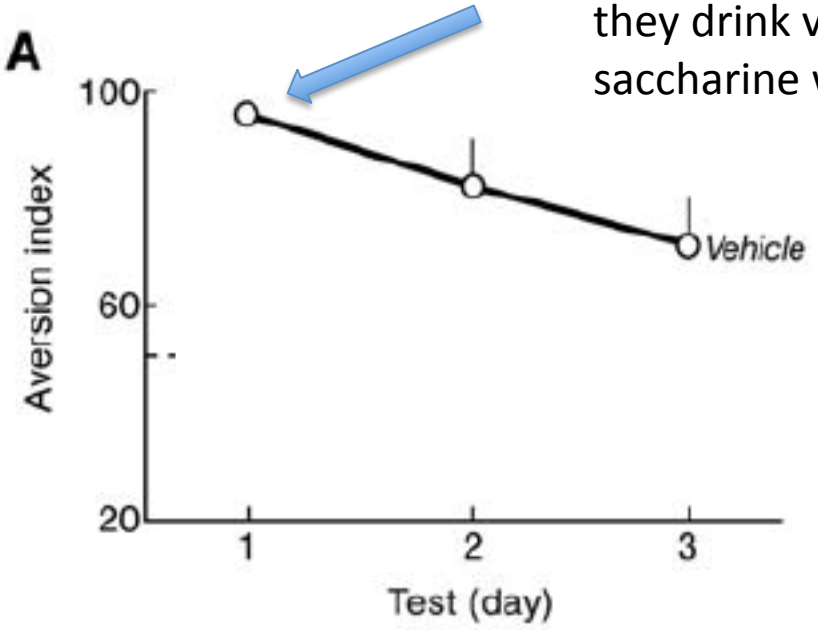
Bottle A contains regular water

Bottle B contains water + saccharine

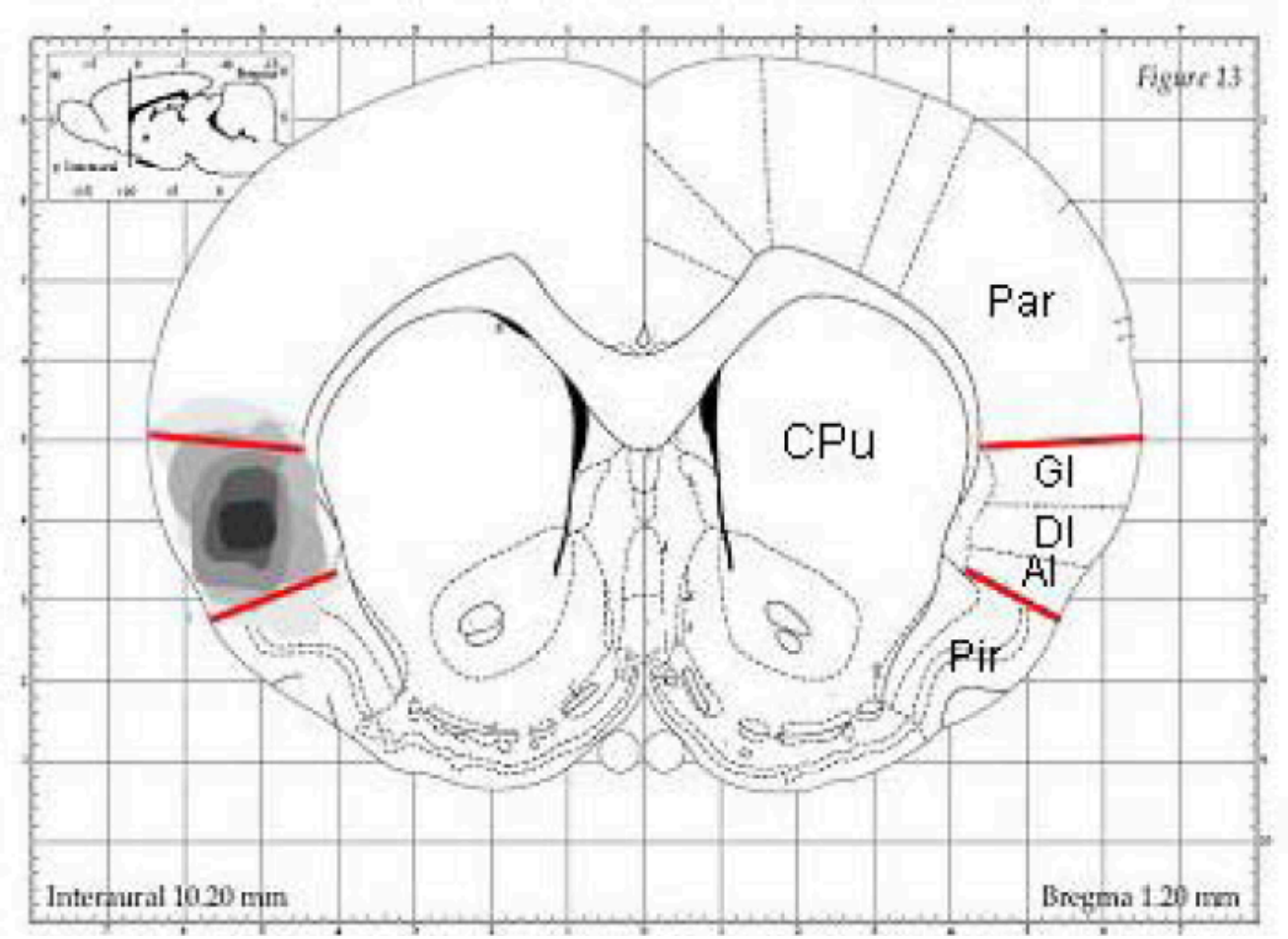
Which bottle will the rats choose?

Animals quickly learn to avoid the saccharine water

High aversion index means they drink very little of the saccharine water

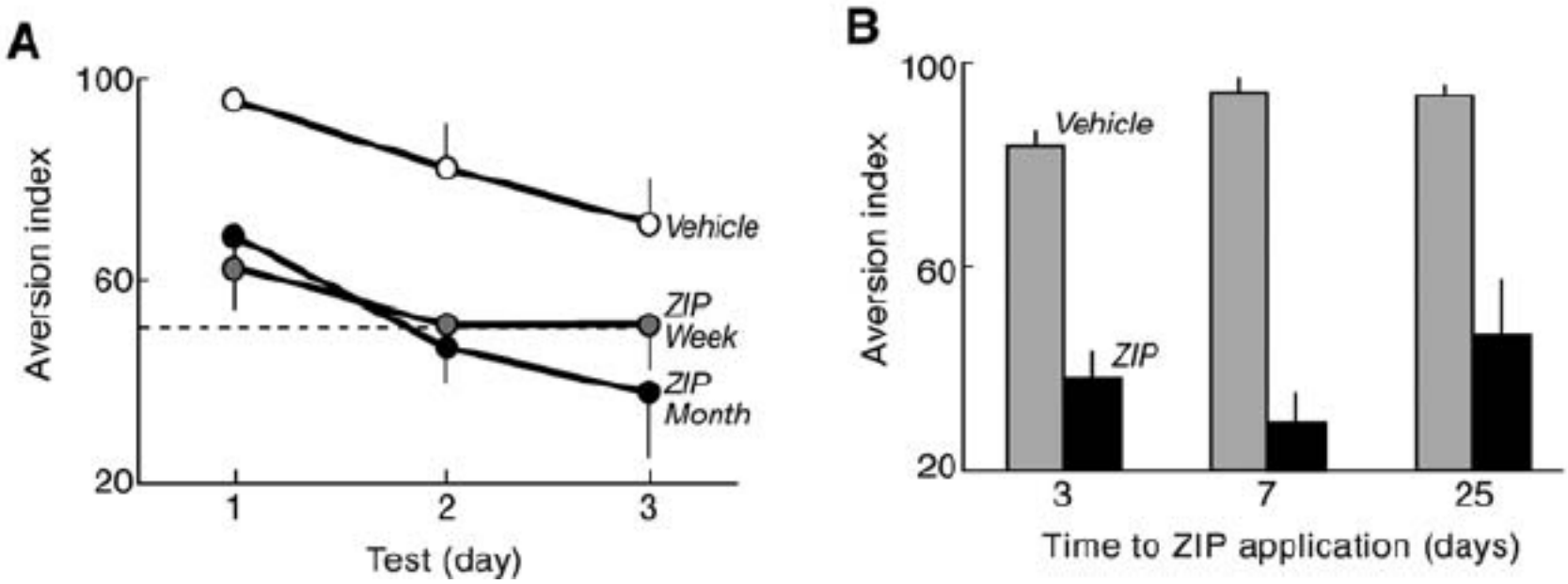


CTA learning requires the insular cortex



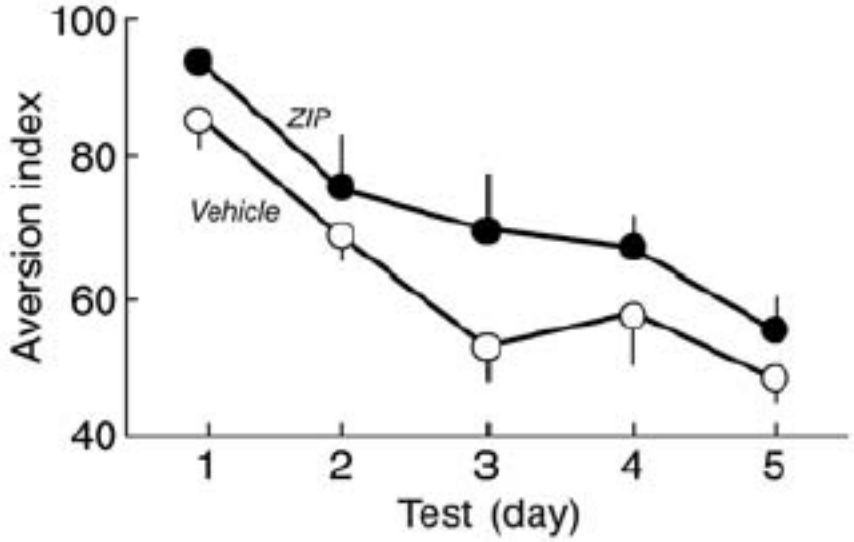
The hypothesis:
PKMζ is required for CTA learning

- To test this:
  - There is an inhibitor of PKMζ called ZIP
  - Inject ZIP into the insular cortex
  - Do the rats still avoid the saccharine water after ZIP injection?



Conclusion: One injection of ZIP into the insular cortex after CTA learning greatly reduces the aversion index

Maybe ZIP is just messing up the whole brain and that's why rats don't remember the CS

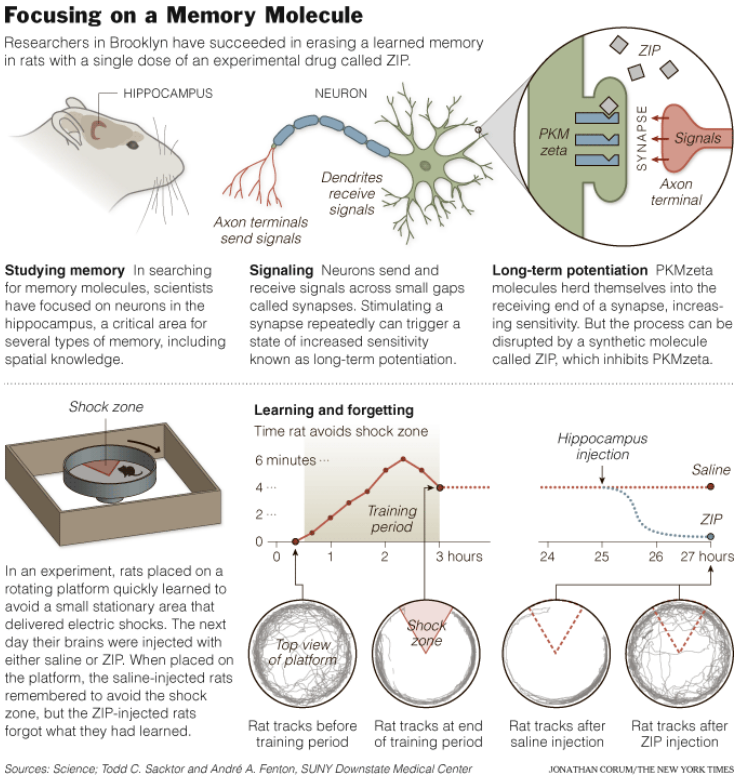


Inject ZIP into a different part of the brain and see if does anything to the CTA memory

Conclusion: PKMζ is a synaptic "glue"

You need it to store memories

Big deal! The press goes wild!



Brain Researchers Open Door to Editing Memory
In fact, the **PKMzeta** molecules appeared to herd themselves, like Army ...In short : **PKMzeta**, a wallflower in the great swimming party of ...
April 5, 2009 - By BENEDICT CAREY - Health / Research - Article - Print Headline: "So You Just Want to Forget? Science Is Working on Eraser"

Erasing Your Memories
This is likely to alter the function of **PKMzeta** and may contribute to the ...These two surprising features are because **PKMzeta** is an enzyme.
April 13, 2009 - By THE NEW YORK TIMES - Health

Focusing on a Memory Molecule
The New York Times. April 6, 2009. Close Window Copyright 2011 The New York Times Company. DCSIMG.
April 6, 2009 - U.S. - Multimedia

Voices: What's Next in Science - Interactive Feature
In just the past few years, Dr. Fenton and other researchers have discovered that one molecule present in those branches, known as **PKMzeta**, ...
November 8, 2010 - Produced by Soo-Jeong Kang, Thomas Lin and Karen Barrow - Science - Multimedia - Print Headline: "Voices: What's Next in Science"

MIND - Consults Blog
The experiments were designed to test the hypothesis that memories are stored by the action of a specific molecule— **PKMzeta**. You should ...
Health

And then……..

LETTER

doi:10.1038/nature11802

PKM-ζ is not required for hippocampal synaptic plasticity, learning and memory

Lenora J. Volk[1]*, Julia L. Bachman[1]*, Richard Johnson[1], Yilin Yu[1] & Richard L. Huganir[1]

LETTER

doi:10.1038/nature11803

Prkcz null mice show normal learning and memory

Anna M. Lee[1], Benjamin R. Kanter[1], Dan Wang[1], Jana P. Lim[1], Mimi E. Zou[1], Chichen Qiu[1], Thomas McMahon[1], Jahan Dadgar[1], Sarah C. Fischbach-Weiss[1] & Robert O. Messing[1]

First up

LETTER

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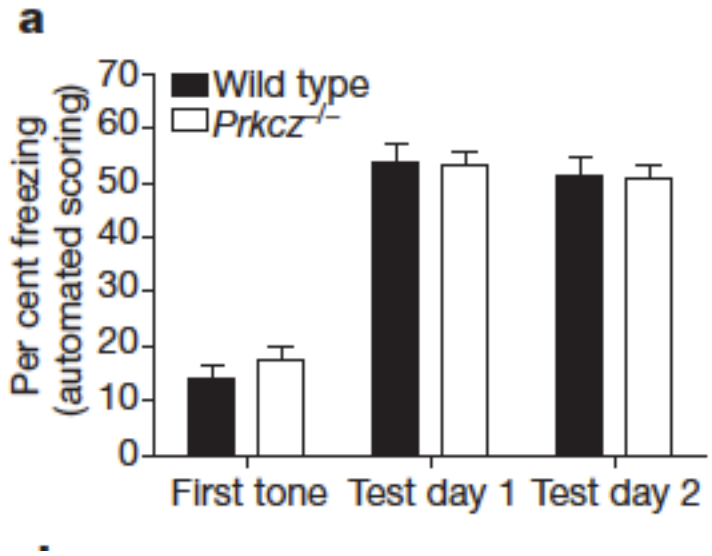
Remember: In the previous paper, ZIP inhibited PKMzeta and that blocked the conditioned taste aversion memory

Messing's group make genetically altered mice that don't have any PKMζ at all

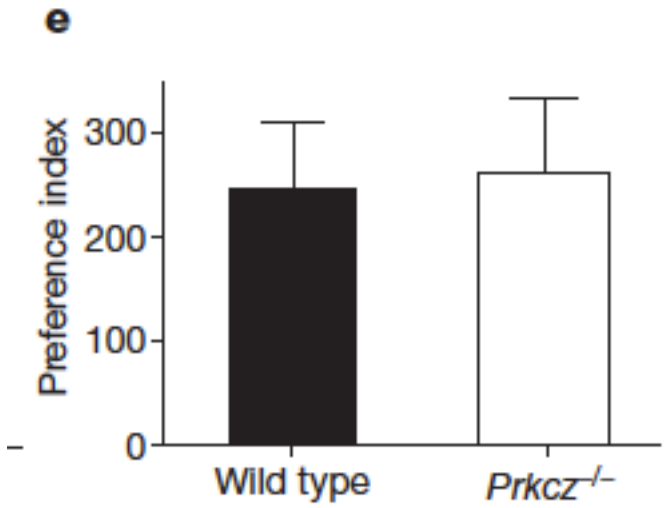
Predictions?

Fear conditioning test

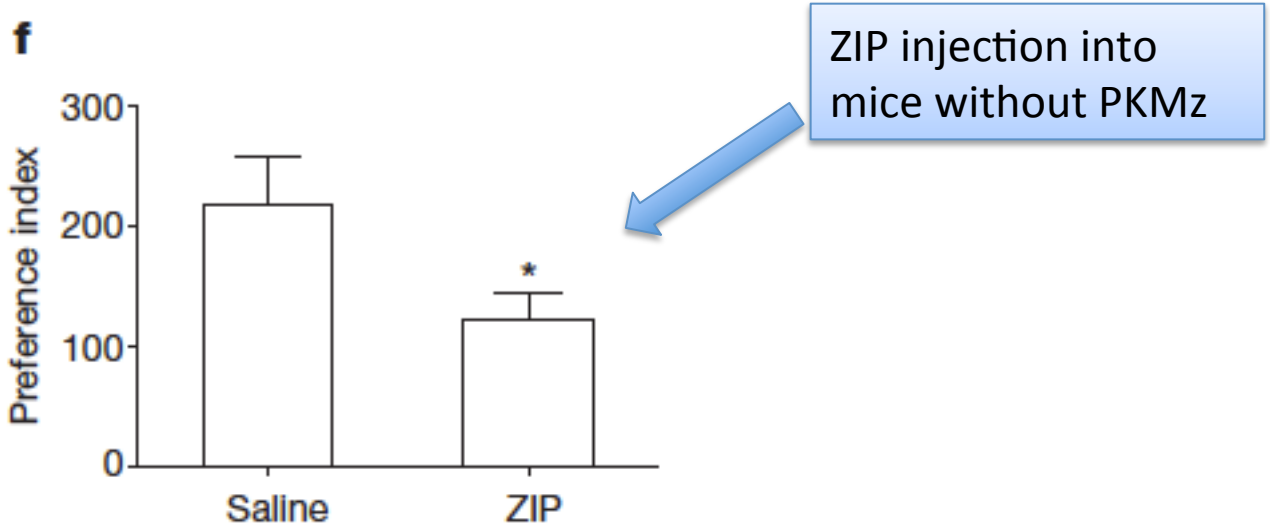


The PKMz knockout mice were totally normal

The PKMz knockout mice were also normal in a (slightly different) preference test



And finally..



In that same preference test, in mice without any PKMz, **ZIP still blocked the memory**!

LETTER

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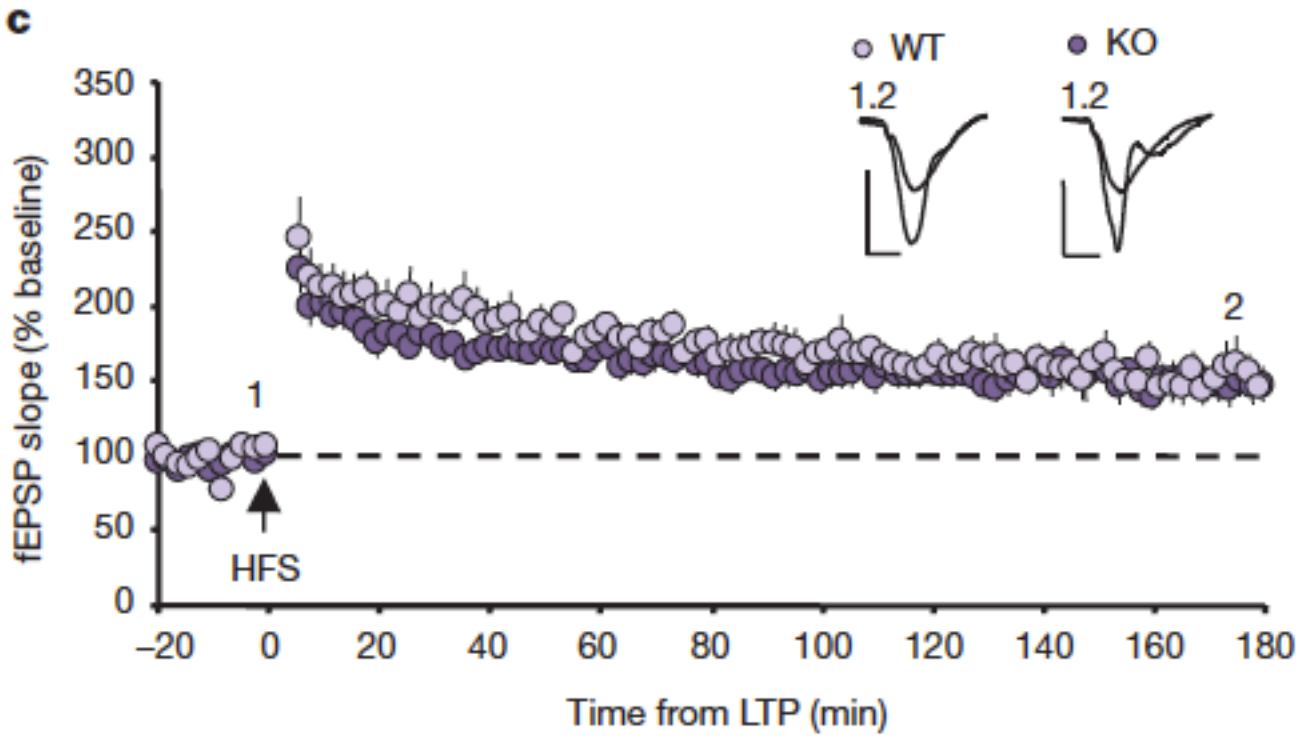
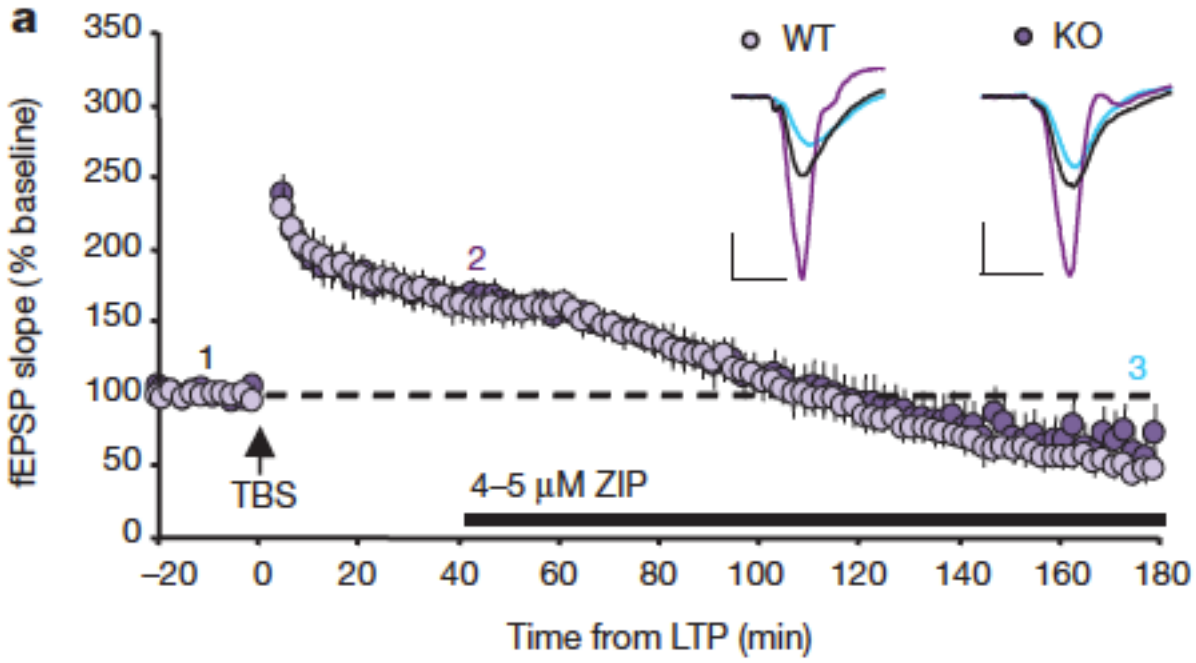
Again, PMKzeta knockout mice have normal long-term potentiation



AND ZIP blocks LTP in normal and PKMz knockout mice

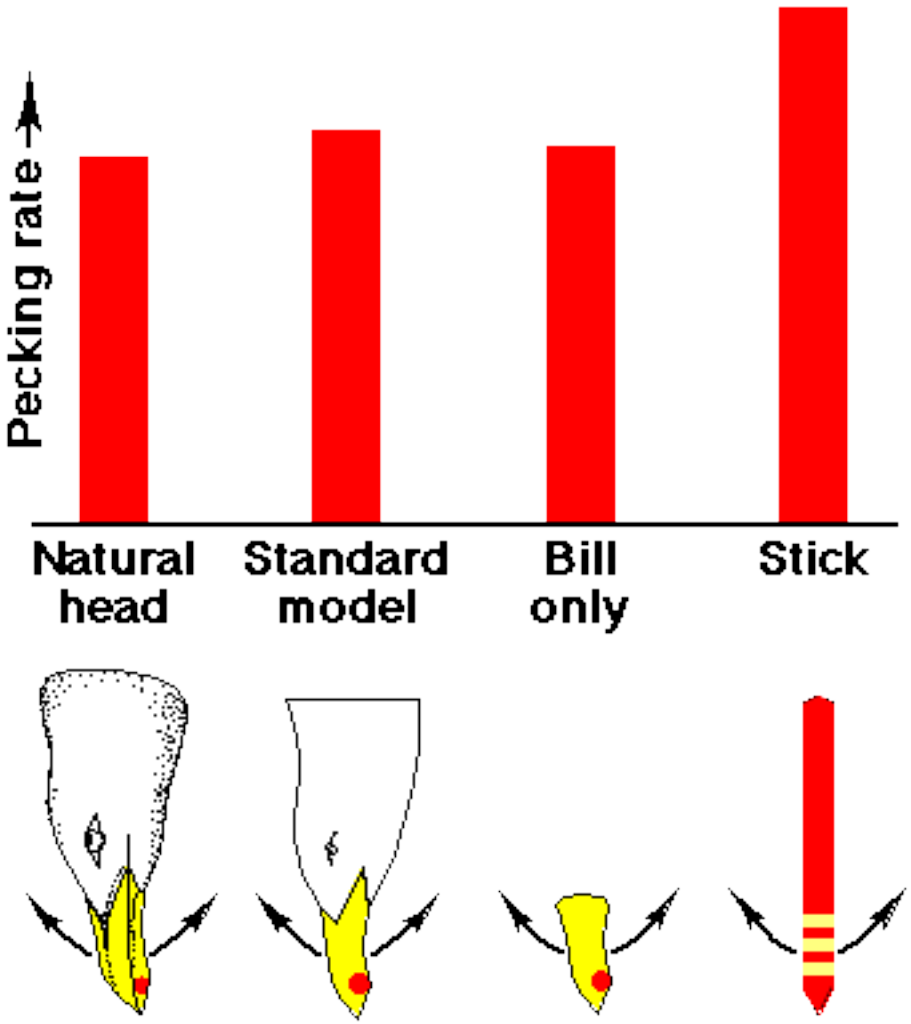


Now let’s speculate wildly…

Art and Neuroscience

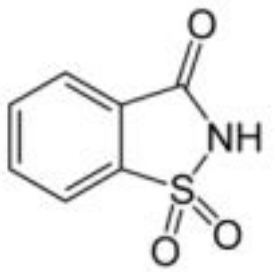
Supernormal stimuli

Which does the chick prefer?



gull babies!

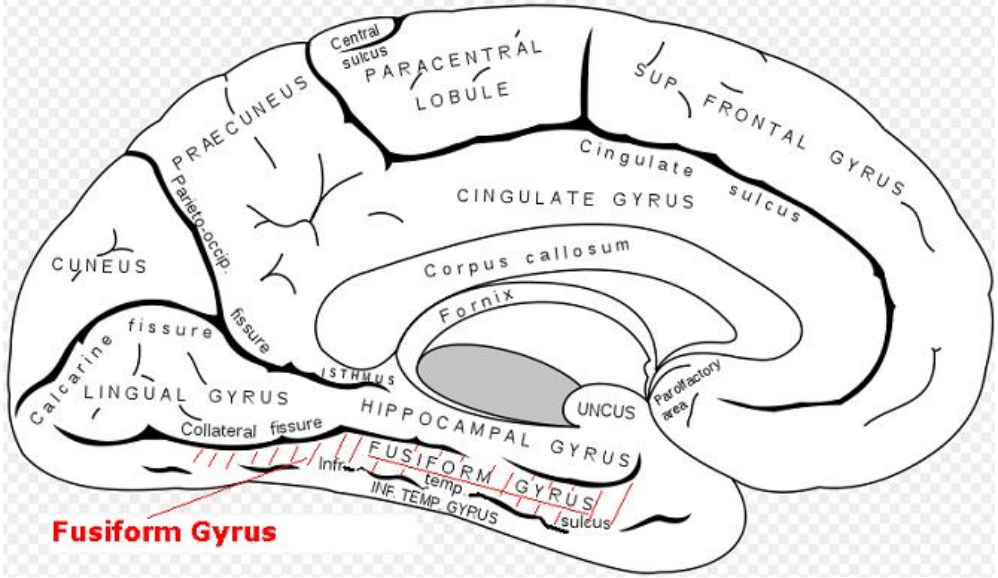
Supernormal stimuli

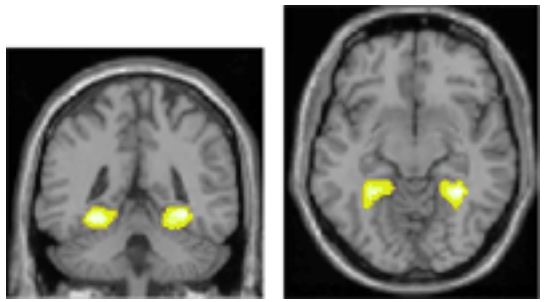


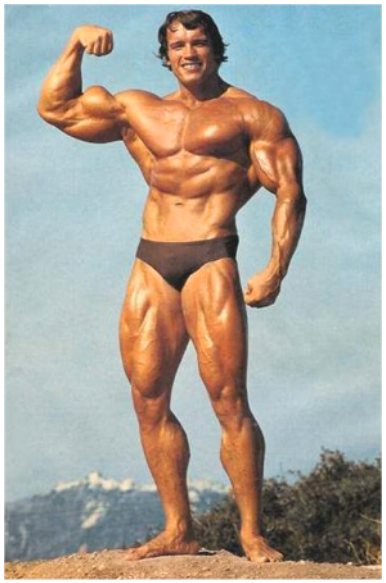
Sucrose is 300X sweeter than glucose, but we don't digest it- no nutritional value

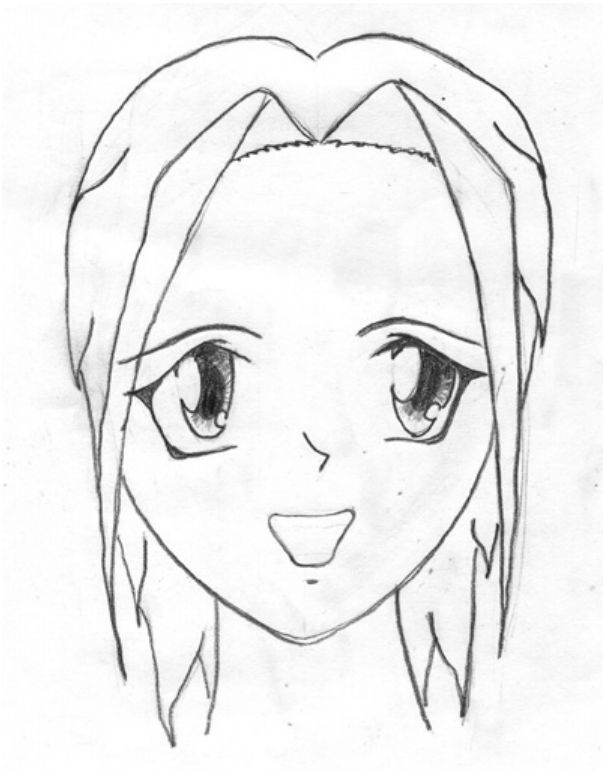
The Big Mac: not normally found in nature

Supernormal stimuli and humans







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